INTRODUCTION TO VOLUME 2: ADDITIONS TO C–X π-BONDS, PART 2

Since the publication in 1991 of Comprehensive Organic Synthesis (COS) Volume 2 on Carbon-Carbon Bond Formation to C=X Bonds, discoveries and applications are much advanced. The carbonyl (C=O) functionality is in the central position of organic synthesis, therefore this is a good time to compile a new volume on this subject. First, the basic knowledge on the formation of enolates from the carbonyl compounds and their aldol reactions of group I-III enolates in particular are reprinted from the first edition. The recent development of aldol reactions of group IV enolates are then reviewed with the following zinc enolates. The chapter on biocatalytic aldol reactions are renewed and the new chapter on the aldol reactions based on the organocatalysis approach (**Figure 1**) is highlighted in this second edition. The related Henri reaction by asymmetric catalysts (**Figure 1**) and metal homoenolates are reviewed on the recent development. The carbon-carbon bond formation of alkenes as nucleophiles to carbonyl C=O bonds is particularly focused on the recent development in asymmetric catalyses of carbonyl-ene reactions (**Figure 1**) followed by the related Prins reactions involving the oxo carbenium ion intermediates. Imine (C=N) analogs are extensively reviewed and the Mannich reactions are revised particularly on the recent topics of the organocatalysis approach using Bronstead acids (**Figure 1**). The carbon-carbon bond formation to carbonyl and imine bonds using allylic organometallic reagents such as allylborons, -silanes, and -stananes are extensively revised. Even on the recent examples, developments and applications of heteroatom-stabilized allylic anions, and propargyl and allenyl organometallics are fully cumulative in their revised chapters. The last but not the least chapter on the classic and basic name reactions, Knoevenagel, Perkin, and Darzens reactions deals with many recent advances particularly on the solid and immobilized reagents and catalysts (**Figure 1**).

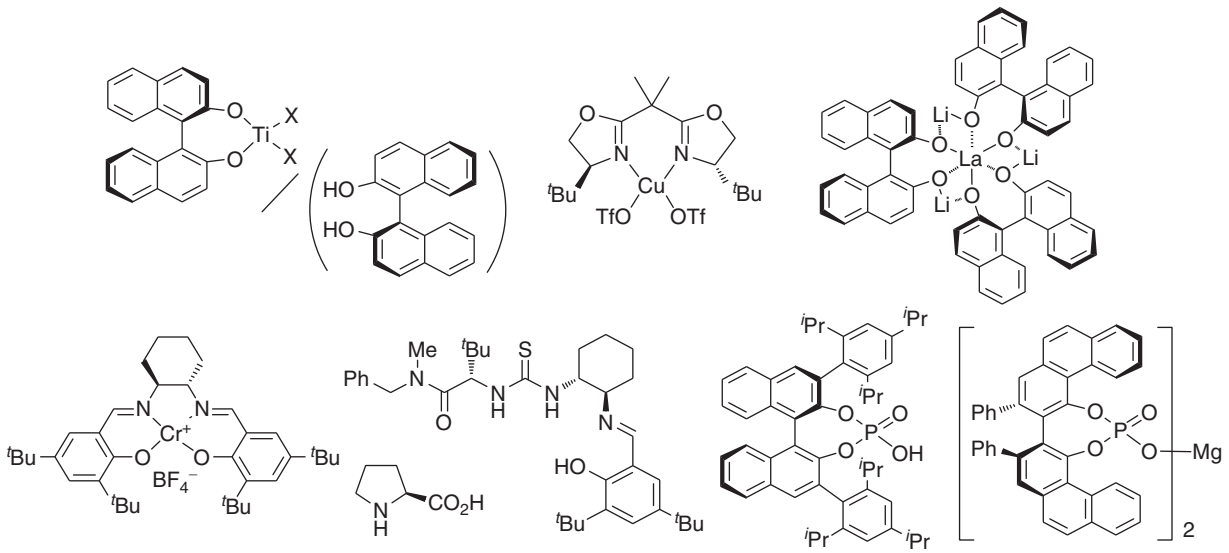

Figure 1

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2.01 Allylborons

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Glossary

Allylborane A derivative of borane (BH_3) wherein one or more hydrogens are replaced by an allyl groups.

Allylboration A carbon–carbon bond forming reaction wherein an allylborane is added across an aldehyde, ketone, or imine.

Allylboronate An allylborane with two alkoxy groups on boron.

Asymmetric allylboration Allylboration wherein a chiral ligand is used to induce chirality in the product.

Crotylborane A derivative of borane (BH_3) wherein one of the hydrogens is replaced by a but-2-en-1-yl group.

Dialkylallylborane An allylborane with two alkyl groups attached to boron.

Homoallylic alcohol Product obtained from allylboration of an aldehyde or ketone.

2.01.1 Introduction

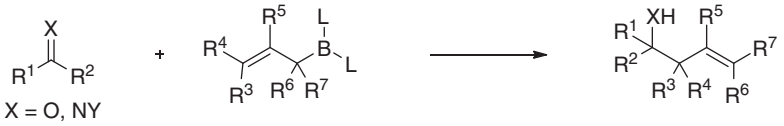
This chapter provides the scope of chemistry of allylboranes as possible and introduces to the reader the general concepts governing their chemistry. Beginning with the physical properties of boron, a transition into the effects of ligands on the Lewis acidity is made. This further segues into the general mechanism of allylboration and into the fine-tuning effect that these ligands play.

Thereafter, the synthesis of allylboranes is thoroughly discussed, including both the historical and newer methods. These methods are explained in the context of a particular example, allowing the reader to understand the practical utility of the chemistry being presented. Thereafter, the extension of these construction methods to the structurally related analogs of allylic boranes is performed.

The reactions of allylic boranes with carbonyls can proceed with relative and absolute stereocontrol, with such parameters being affected by both external and internal controls. During these reactions, substitutions can be incorporated at any of the various positions on the allylborane. Knowing this, the sections detailing the allylation of aldehydes has been broken down into the following classification scheme: without additives, using no stereocontrol, using boron-based stereocontrol, using aldehyde-based stereocontrol, and using mixed stereocontrol; with Brønsted–Lowry acid additives (same breakdown); and with Lewis acid additives (same breakdown).

Continuing from aldehydes, the allylation of ketones is next discussed, followed by those of *in situ*-produced carbonyls. The allylation of simple imines and *N*-substituted imines is then covered, followed by the allylation of other carbonyl derivatives such as esters and amides. Moving away from carbonyl derivatives, the use of allylborane derivatives in the allylation of alkynes and alkenes follows. Next, the allylation of other π-bond systems is discussed, followed by the use of allylboranes in other reactions such as when they are made to serve as coupling partners or in sigmatropic reactions. The simple derivatization of allylboranes is thereafter covered, followed by a select series of synthetic examples.

To date, many scores of allylborane derivatives have been synthesized and used in allylboration. Indeed, specific advancements in this chemical technology have been so profound that allylboration can lead to the formation of several contiguous stereogenic centers, and can proceed with a high level of practical control over both the relative and absolute stereochemistries. Multiple functionalities have been incorporated into all possible positions of the allylborane partner; indeed, α, β, and γ substitutions are well-documented, and include such functionalities as halogens, alkoxys, alkylamines, carbonyl derivatives, heteroatoms, etc. These will be more thoroughly discussed in Section 2.01.3. The incorporation of these varying functionalities at each position can have stereochemical and mechanistic consequences, which, in turn, lead to either advantageous or disadvantageous allylboration characteristics. As a result, these substitutions have led to a general understanding of allylboration, wherein each substitutive element of the allylborane is incorporated into the functionalized product (equation 1).



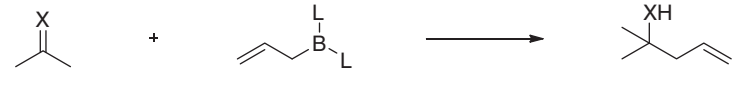
(1)

There have already been several reviews on this topic.[1] However, all efforts have been made to be fully comprehensive with regards to referencing and coverage throughout this chapter. It is impossible to cover all the developments in so vast an area in a single chapter; any omission is unintentional.

This chapter has been produced so as to be different from typical allylboration reviews, wherein the simple concept of the allylation, crotylation, alkoxyallylation, etc. of aldehydes, ketones, or imines to provide homoallylic alcohols or amines is covered in-depth. Instead, the authors have attempted to address the preparation and reactions of many types of allylboranes and structurally-related species as possible. These reactions are presented in such a way so as to demonstrate the ability of the chemistry to provide both common and rare products. In an effort to maintain the natural flow of this chapter, the classification scheme mentioned above has been rigidly followed. Consequently, not all the individual topics have been presented in a strictly chronological order. Instead, the authors have sought to cover as wide a scope of reactions and reagents as possible.

2.01.1.1 Background/History

The utility of allylboron compounds was first described in 1964 by Mikhailov and Bubnov.[2] They observed, from the interaction of triallylborane and carbonyl compounds, the formation of homoallylic alcohols (equation 2, X=O). The natural extension of this transformation was performed thereafter, usually at comparably higher temperatures, with imines, vinylic ethers, and – perhaps less intuitively – acetylenic compounds (equation 3).[3] In 1966, this chemistry was extended to the less reactive allylic boronates by Gaudemar and Favre (equation 2, L=OR).[4] The diastereomeric nature of these reactions was initially explored by Hoffmann[5] et al. in 1979, using γ-methyl-substituted allylboranes (crotylboranes). This subject was exhaustively studied over the next 30 years by Hoffmann, Brown, Roush, Corey, and others.



(2)

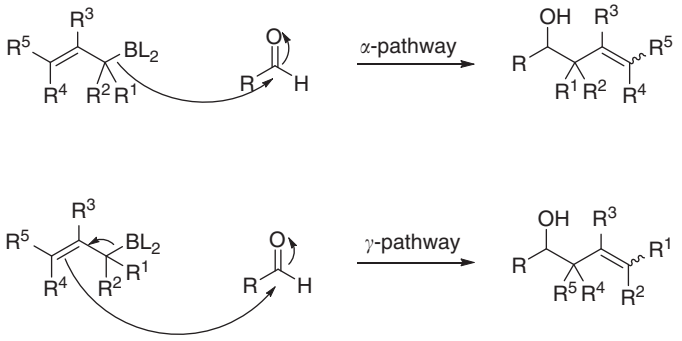
(3)

2.01.2 Overview of Allylboranes

2.01.2.1 Mechanism

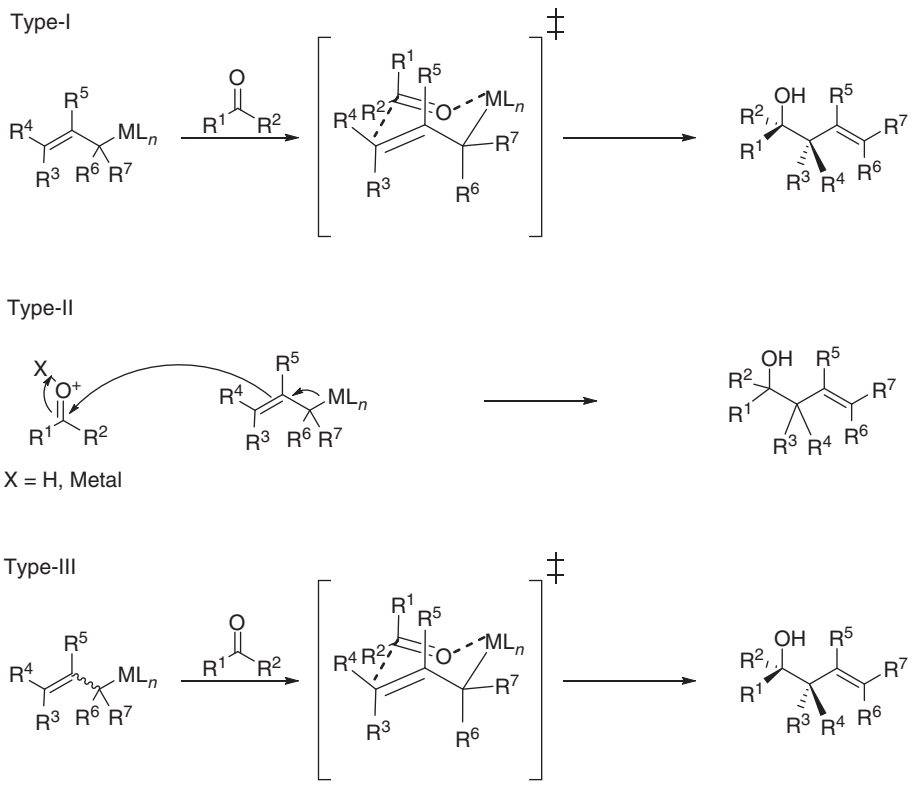
The general pathway for allylation with allylborons is one that occurs with allylic rearrangement. Like most allylmetal systems, allylborons have the potential to undergo reaction at either their α- or γ-position. Generally, boron variants of this reaction occur

exclusively at the γ-position, and are formally considered S_E2' reactions (Scheme 1). Only a limited number of examples of the α-reactivity of boranes have been published in the literature, occurring only in systems of extreme γ-steric demand.



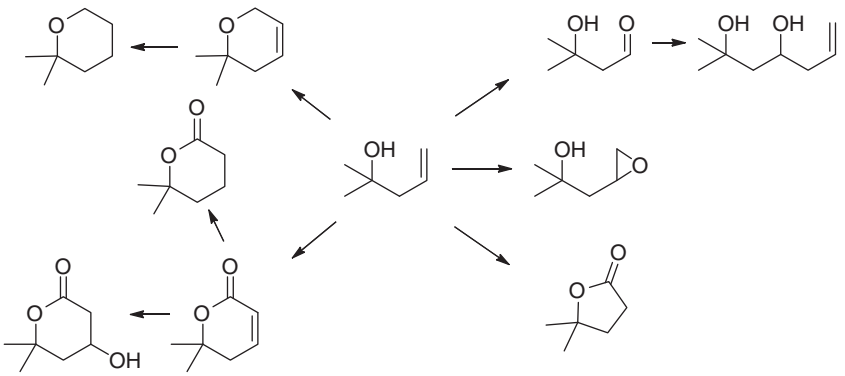
Scheme 1

Although allylmetal systems are known to react with activated π-bonds, the mechanisms of such additions can be quite varied, depending on a number of factors. Denmark et al. have classified the addition of such allylic systems to electrophiles into three distinct groups: Type-I, Type-II, and Type-III.[6] Type-I additions proceed through a six-membered, chair-like transition state, akin to that which was originally proposed by Zimmerman and Traxler (Scheme 2).[7] During this cyclization, the electrophilic partner is coordinated to the metal center, thereby serving to both increase its own electrophilicity, and to activate the nucleophilic allyl group by increasing the electron density on the Lewis-acidic metal center. This type of transition state is good at predicting the relative stereochemistry of the pendent groups at the formed stereogenic centers, as the lower-energy pathway generally proceeds with the maximum number of groups in pseudo-equatorial positions. In contrast, those systems which suffer from a lack of Lewis acidity and cannot readily accept a Lewis basic group, proceed through an open transition state.[8] Such processes, termed Type-II, are performed with a different type of activation – most often by the addition of Brønsted or Lewis acid additives. Generally, Type-II processes offer inferior levels of diastereoselectivity. In Type-III processes, a concomitant stereoscrambling at the prochiral allylic position occurs, and is followed by a Type-I cyclization. Most frequently, allylborations proceed through a Type-I process.[9]



Scheme 2

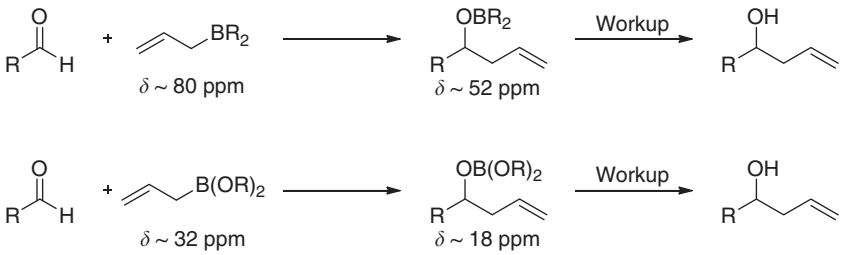
The synthetic utility of the products of allylboration cannot be understated. These polyfunctionalized products have the potential to be derivatized at either or both the formed alcohol or alkene (or equivalent groups) through transformations such as oxidation, cyclization, metathesis, and ozonolysis. Thus, allylboration can provide a route to many important synthons such as β-hydroxy carbonyls, cyclic ethers, and both saturated and unsaturated lactones. As demonstrated in Scheme 3, the inclusion of certain functionalities such as alkoxy, amino, or halo-substituents along the allylic backbone (as R_1–R_5) will produce the expected allylboration products, but with expanded functionality. These can also allow for further derivatization, such as in coupling processes, lactamization, or epoxidation.



Scheme 3

In Type-II processes, the carbonyl (or derivative) electrophile is usually activated by the appropriate selection of a Lewis or Brønsted acid, or, alternatively, the boron center can be activated by the formation of an 'ate' complex. In Type-I processes, the chelation of the electrophile to the boron-based Lewis acid allows both mechanisms of activation to take place simultaneously: the electrophile is formally activated, and the borate complex is formed.

^{11}B nuclear magnetic resonance spectroscopy is especially useful for following the course of allylboration reactions. This is due to the drastic change in chemical shift of the starting and final electronic structures of boron. Relative to a standard sample of BF_3 with $\delta = 0$ ppm, trialkylborane chemical shifts are typically observed to be approximately $\delta \approx 82$ ppm, alkyl borinites approximately $\delta \approx 52$ ppm, dialkyl boronates approximately $\delta \approx 32$ ppm, and borates approximately $\delta \approx 18$ ppm. This is demonstrated in the following two examples (Scheme 4).



Scheme 4

2.01.2.2 Properties of Boron

Elemental boron is an economical and nontoxic metalloid used in a wide variety of chemical technologies. Its atomic electron configuration allows it to form three bonds to neighboring atoms with an incomplete octet, thereby rendering the boron center Lewis acidic. This innate Lewis acidity is that which gives organoboranes their unique reactivity. In compounds containing B–X bonds, where X = O, N, S, a halogen, etc., there can exist a significant amount of π-backbonding to the p-orbital (Figure 1).[10] The extent of this backbonding can be used as a tool in fine-tuning the Lewis acidity of the boron center, thereby modulating its activity.[11]

Due to its moderate level of electronegativity (2.05 on the Pauling scale), boron tends to form strong, covalent bonds to its neighbors, especially carbon.[10] Kinetically, the highly covalent nature of carbon–boron bonds generally makes them comparatively more inert than many other carbon–metal (or metalloid) bonds. Nonetheless, these reagents are still potentially dangerous, and can be highly reactive or even pyrophoric, and must be handled under an inert atmosphere and with extreme caution.

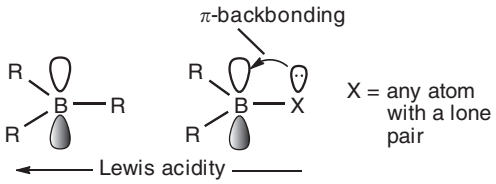


Figure 1 Backbonding in organoboranes: effect on lewis acidity.

2.01.2.3 Nomenclature of Boron Compounds

The nomenclature of boron compounds follows the pattern of IUPAC recommendations. The common allylic derivatives of boron are named according to their structural classes as shown in Figure 2.

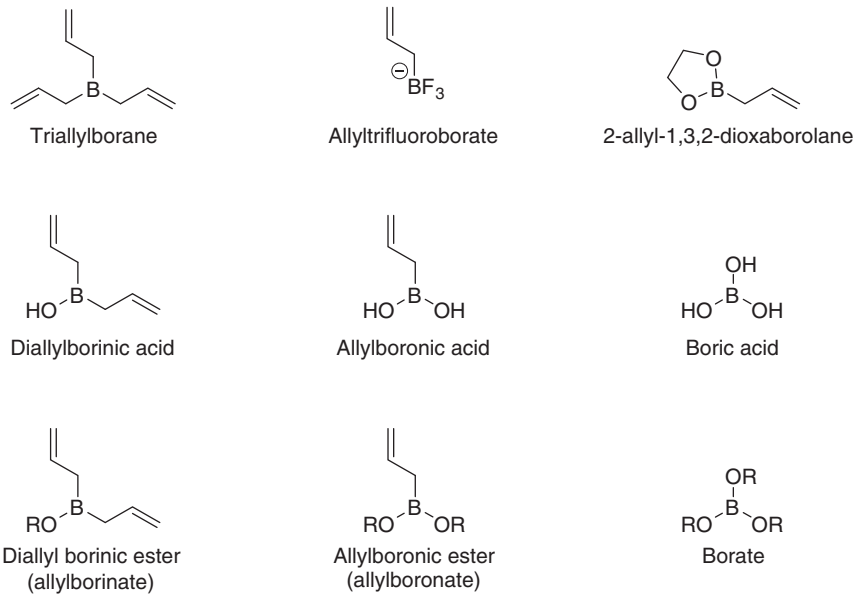


Figure 2 Generic nomenclature of boron compounds.

2.01.2.4 Effects of Boron Ligand Choice

There are a multitude of ligands that can be placed around the boron in allylboron reagents. The three most common choices are those based on carbon, nitrogen, and oxygen connectivities. As described in Figure 1, the ability of the ligands to backdonate into the boron's empty 2p-orbital greatly controls the reactivity of these compounds. Specifically, the greater the ability of the ligand to backdonate into the boron (the mesomeric effect), the greater the corresponding decrease in the Lewis acidity of the boron (Figure 3). This, in turn, increases molecular stability, and can be combined with other factors such as kinetic stability through steric shielding. For example, the bulkier pinacol-derived 1,3,2-dioxaborolanes are so stable that they can usually be chromatographed,

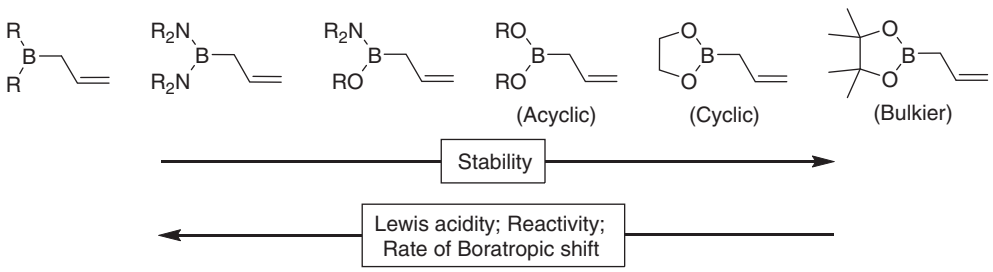


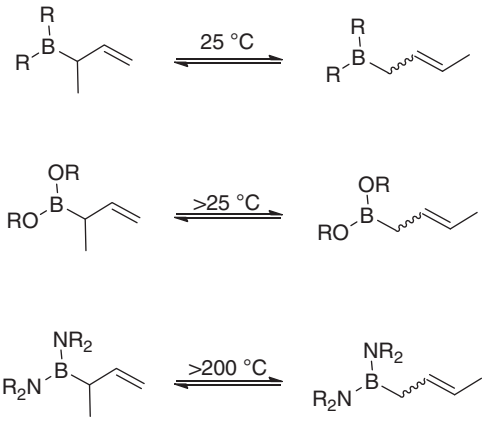
Figure 3 Stability and reactivity of allylborons.

whereas the trialkyl-derived boranes are not.[1f,12] This effect also decreases the rate of reaction with potential chemical partners such as water, molecular oxygen, and Lewis bases such as carbonyls. As discussed in Section 2.01.2.1, Type-I processes rely on the activation of the carbonyl electrophile through the chelation of the oxygen to the metal center. Therefore, it can be presumed that with an increase in the π-backbonding of the boron ligands, there will be a decrease in the rate of allylation. This has indeed been demonstrated to be the case,[13] as the reactivity of allylboron compounds typically obeys the trend shown in Figure 3.

2.01.2.5 1,3-Boratropic Shifts

Although many borane derivatives can be much more stable than other molecules containing heteroatom-carbon bonds, they are not entirely free from problems. Considering the case of η^1-allyl metal systems, which are capable of undergoing a unique 1,3-metallotropic shift,[14] which occurs by the metal changing the ligand's hapticity from 1 to 3 and then back to 1, there is a stereochemical scrambling necessitated for the ligand (Scheme 5). As the hapticity of the ligand must increase from 1 to 3, it must be true that a decrease in the Lewis acidity would necessitate an increase in the activation energy for such a transformation, thereby slowing this interconversion either significantly or altogether stopping it. Exemplifying this fact is the knowledge that dialkylallylboranes, such as *B*-crotyl-9-BBN, undergo rapid interconversion between the *cis*- and *trans*-forms at room temperature, whereas the corresponding *B*-crotyl-1,3,2-dioxaborolane requires prolonged heating to affect the same scrambling.[15] A similar observation has been made when comparing the mono- and diaminocrotylboranes, which require temperatures of ≈150 °C and ≈200 °C, respectively (Scheme 6).[5a,16] As further evidence, the coordination of amines to triallylborane drastically increases the temperature required to force a boratropic shift.[2,3]

Scheme 5



Scheme 6

2.01.2.6 Structural Classifications of Allylborons

Generally, all allyl-style boron compounds can be classified into five broad categories: allylic, allenic, propargylic, homoallenic, and α-ylidenyl(allylic, allenic, propargylic, or homoallenic) (Figure 4).

These five categories are all capable of reacting via the typical allylation reactivity pathway. The distinguishing factor among these five categories is mainly the type of product formed, (Scheme 7). On reacting, the first type, simple allylic systems, gives rise to homoallylic systems. The second type, allenic, produces homopropargylic functionalities. Conversely, starting from a propargylic system will offer a homoallenic product. Homoallenyl boranes give rise to 1,3-butadiene systems. The remaining class varies in its product's structural type.

2.01.3 Preparation of Allylboranes

There are many scores of allylboron systems that have been described to date, with the majority of them being derivatives of the simple allylic system. They have mostly been formed by incorporating various substitutions at the α-, β-, and γ-positions as shown in

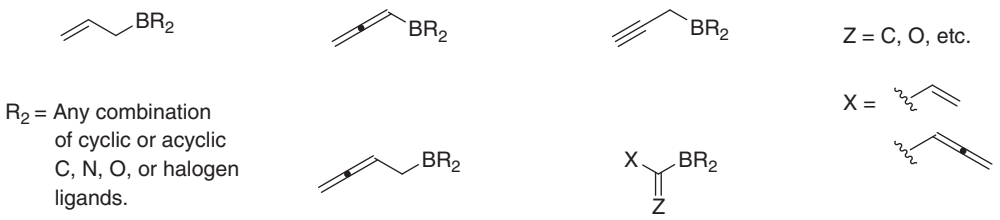
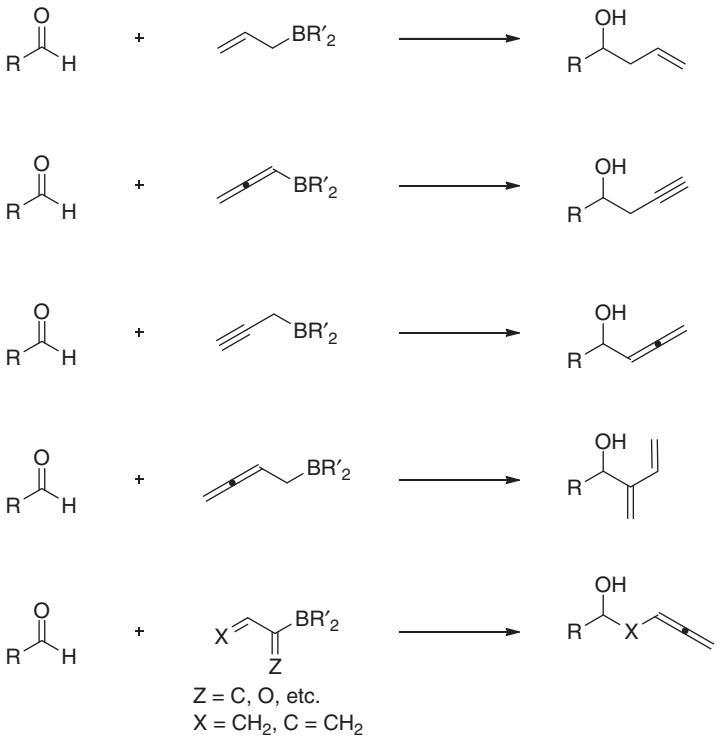


Figure 4 Structural subclasses of allylborons.



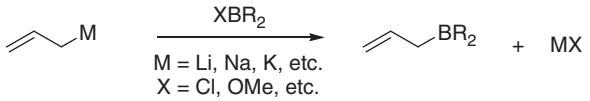
Scheme 7

Scheme 1. Several reviews on the topic of allylboranes, which include their preparation, have already been published.[1] Herein, the authors describe access to these derivatives in a fairly general manner. In lieu of an exhaustive listing of known allylic systems, the authors have chosen to describe the preparation through as many means as possible, to demonstrate the general availability of these useful systems.

The arrangement of the preparation of these borane systems is: allylic, allenylic, propargylic, homoallenic, then finally 'allylic' boranes with cross-conjugation. For allylboranes, a further subdivision into fourteen different manners of preparation is given. Each is shown first as a generic scheme, followed by a few notable examples, along with references to additional preparative examples.

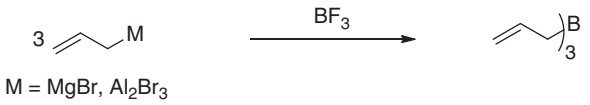
2.01.3.1 Trans-metalation Reaction with Alkali/Alkaline Earth Metal Allyl Systems

In general, the reaction of allylic nucleophiles with boron occurs readily. If an appropriate leaving group is present on the boron, then, with very few exceptions, an exchange process will occur, resulting in the elimination of the leaving group from the boron. This double displacement reaction occurs with the release of a stable salt, most frequently a metal halide or alkoxide (equation 4).



(4)

The first such report of an allylborane preparation was that of triallylborane, as published by Mikhailov et al.[17] It was discovered that the reaction of either allylic Grignards or allylic sesquihalide aluminum complexes with boron trifluoride resulted in an exchange (equation 5). Presently, this has been generalized to many different boron trihalides, with many different allyl group derivatives. This simple exchange methodology has hence been extended to include a variety of other leaving groups on the boron atom, such as methoxy[18] or acetoxy groups (equation 6). In the last few decades, this methodology has been extended as a means to incorporate allyl groups onto borons with stereogenic ligands such as isopinocampheyl[19] (equation 7), isocaranyl,[20] and many others.[21] Metaborates have also been shown to be capable of serving as precursors to triallylboranes (equation 8).[22] Cyclic boronates, in which only one oxygen is part of the heterocycle, have been converted to allylic borinates by this method.[23]



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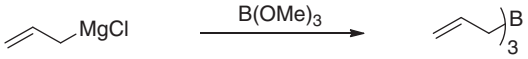

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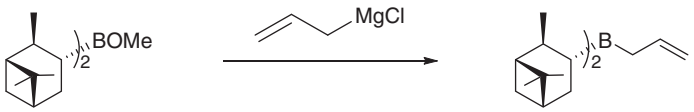

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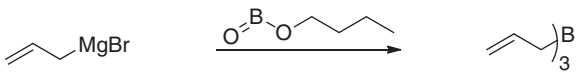
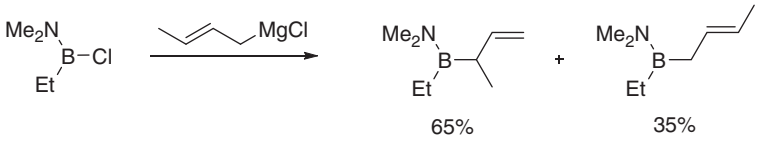


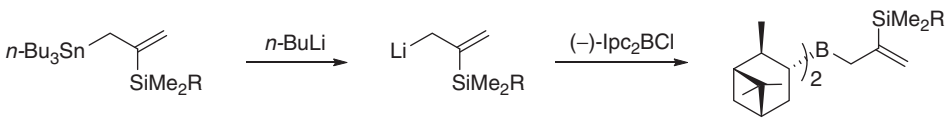
(8)

Substitution at the α-position using this methodology is rare, but has been reported.[16d] The reaction of *E*-but-2-enylmagnesium chloride gives a mixture of the but-1-en-3-yl and but-2-en-4-yl products in a proportion of 65 to 35 (equation 9). Fortunately, due to the decreased Lewis acidity of the boron center (caused by the amine ligand), this molecule is slow to undergo a 1,3-boratropic shift, and so can be used as it is. Actually, the isolation of α-substituted allylboranes is exceedingly rare, as such shifts are typically facile at even lower temperatures. This same report demonstrated that heating the but-2-en-4-yl to 150 °C for 6 h resulted in the completely rearranged product.



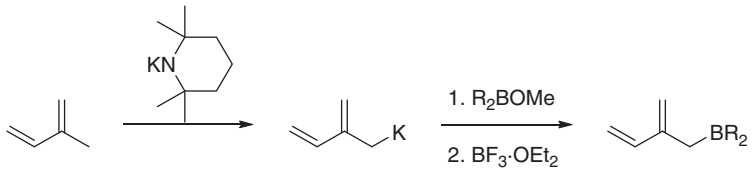
(9)

In contrast, there are many reports detailing the use of a substitution at the beta position. For example, very bulky silyl groups are readily incorporated as shown (equation 10). Starting with the allylstannane, lithium-tin exchange gives silyl-derived allyllithium, which, on quenching with a chiral chloroborane, yields a β-(silyl-substituted) allylborane.[24] Many other groups have been incorporated with similar methodologies, including alkyl groups,[21f,25] boramethyl groups,[26] imines (which serve as masked amines),[27] and chlorides (which can lead directly to allylic epoxides).[28]



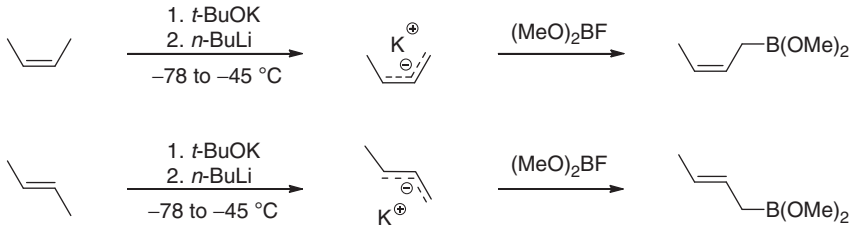
(10)

Brown and Randad developed a method to produce symmetric and asymmetric dialkylisoprenylboranes using this approach.[29] The reaction of potassium 2,2,6,6-tetramethylpiperidide with isoprene, followed by a subsequent reaction with an appropriate alkyl dialkylborinite then boron trifluoride, furnished the desired borane (equation 11).

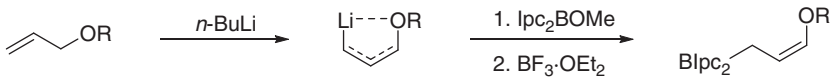


(11)

By far the easiest location to incorporate substitutions is the γ-position. This is likely due to the fact that the thermodynamic sink for 1,3-boratropic shifts lies on the γ-side. What are, perhaps, the three most widely used allylborane derivatives fall into this category: the *Z*- and *E*-crotyl boranes (*cis*- and *trans*-γ-methylallylboranes, respectively) (equation 12), and the γ-methoxyallylborane derivatives (equation 13). The routes to the *Z*- and *E*-crotylboranes were established by Schlosser[30a,d] and coworkers using a modified *n*-butyllithium base, and were later applied by Hoffmann,[30e] Brown,[30b,c] and Roush.[30f] The utility of these two synthons has been firmly established,[30] and will be discussed here.

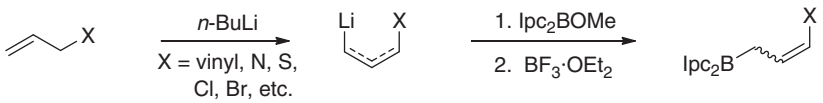


(12)



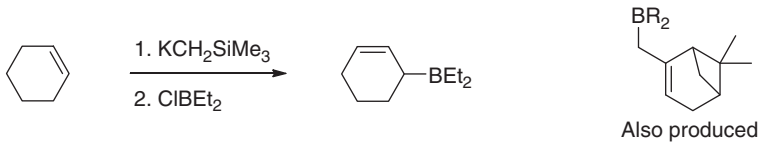
(13)

The production of γ-alkoxy substituted boranes is quite facile.[31] Deprotonation of an allylic ether with *n*-butyllithium gives the *cis*-chelated allyllithium shown.[32] Brown and Narla have shown that, on quenching with alkoxydialkylboranes, the γ-alkoxysubstituted allylboranes are obtained (equation 13). Virtually any alkoxy group can be substituted into the γ-position (equation 14).[31b] Indeed, many other groups have been successfully incorporated into the γ-position, including: vinyl groups[33]; aminols, acetals, and aldehydes[34]; chlorides[28b]; γ-silyl-γ-ethers[35]; amines[36]; thioethers[37]; and silanes.[38]



(14)

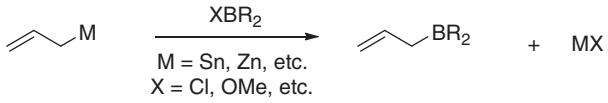
A surprisingly low number of examples have appeared in the literature detailing this same route as a method to incorporate multiple substitutions on the allylic system. As an example of one such case, Zaidlewicz and coworkers[39] demonstrated the formation of a series of β,γ- and α,γ-disubstituted allylboranes, wherein the olefin was internal to either a cyclohexene or pinene ring system (equation 15).



(15)

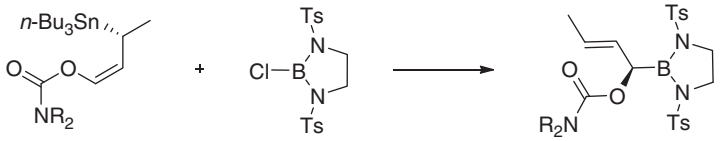
2.01.3.2 Trans-metalation Reaction with Transition/Main Group Metal Systems

Similar to the reactions of allylic alkali and alkaline earths, the use of other allylmetals as a route to produce allylboranes is well-known (equation 16). In general, these types of allyl systems are considered to be 'softer', and are significantly less basic than their group-I and II counterparts. This tends to result in the tolerance of a greater level of functionality. One drawback to the use of these systems is found in their availability. Although most allylic alkali and alkaline earths are either commercially or readily available, many of the softer compounds must be prepared freshly in the laboratory, either directly before use or *in situ*.



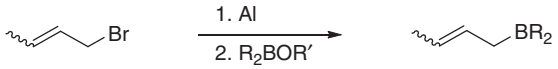
(16)

There are fewer aspects known regarding the production of allylboranes from the softer allylmetal systems. Unlike the 'harder' allylmetals, the softer ones are less prone to perform allylation with the strict inversion seen with the 'harder' metals, and can sometimes proceed through a direct M–C bond reaction. In fact, mixtures are many times observed, but a careful design can give either product. For example, Hoppe and coworkers[40] reported a case wherein allylic inversion takes place. Starting from an enantioenriched allylstannane, the reaction with a *B*-chloro-1,3,2-diazaborolidine resulted in ligand exchange to give the enantioenriched 2-allyl-1,3,2-diazaborolidine (equation 17).



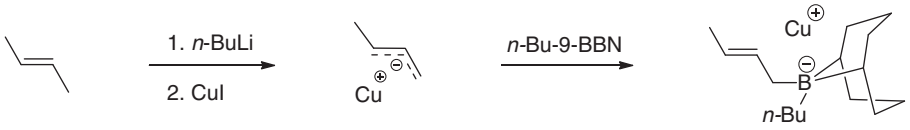
(17)

The reaction of borinic esters with sesquihalide–metalloid complexes is also known (equation 18). A report by Mikhailov et al.[41] originally detailed this methodology. Fundamentally, there is no difference between this route and those of the harder allylmetals.



(18)

Other methods of producing the desired crotylboranes have also been reported. One such report involved the use of *n*-butylithium to deprotonate 2-butene. The allyllithium product was then allowed to react via double displacement with cuprous iodide to give the allyl cuprate.[42] This cuprate, when reacted with *n*-butyl-9-borabicyclo[3.3.1]nonane, formed the ate complex *in situ*, which was then reacted further (equation 19).

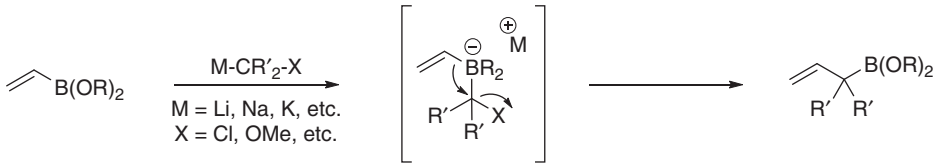


(19)

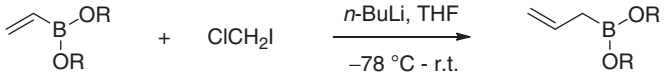
The reaction of triallylborane with cyclic boronates as a means of furnishing cyclic allylborinates has also been described.[23] Similarly, the reaction of allylic trimethylsilanes (and stannanes) to furnish allylic dichloroboranes has been published.[43]

2.01.3.3 Matteson Homologation of Vinyl Boronates

Matteson and coworkers demonstrated[44] that the addition of chloromethyllithium to a vinylboronate resulted in the homologation of the boronate by a methylene spacer (equation 20). Mechanistically, the attack occurs first at the boron center to form the ate complex followed by ^{11}B NMR.[45] On increasing the temperature, the unstable ate complex underwent rearrangement, with the vinylic group forming an incipient anion which attacks the methylene group, and substitutes in place of the chloride. This process has been generalized, and is now referred to as the Matteson homologation reaction (equation 21).

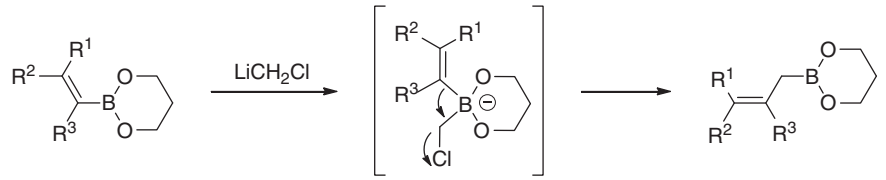


(20)



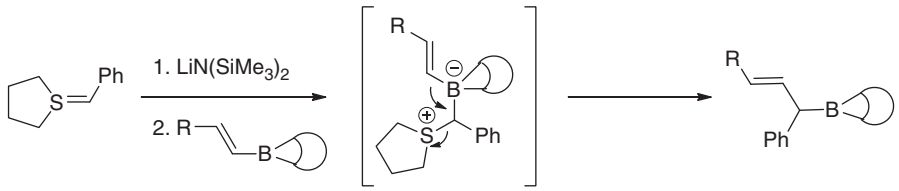
(21)

This highly useful transformation has been used several times since its intial report. For example, Brown et al.[45] used this methodology to produce allylic 1,3,2-dioxaborinanes in both symmetric and asymmetric variants (equation 22). These authors have shown that this reaction functions with both mono- and bidentate boron ligands, and that it is tolerant to a wide range of functionalities. Since then, the use of chloromethyllithium for this transformation has been used many times in the literature.[46]



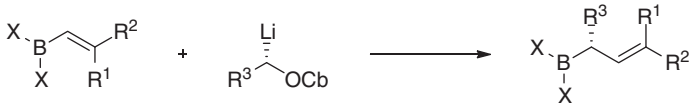
(22)

Another variant of this reaction was described in the use of a sulfur ylide–borate complex (equation 23). The expulsion of a tetrahydrothiophenyl moiety furnished the desired migration product, which was stable at −100 °C. The same work extended this methodology to include chiral sulfur ylides.[47]



(23)

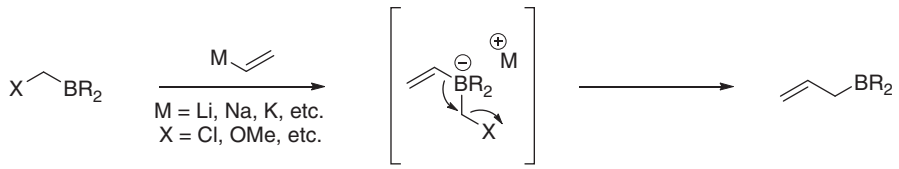
Several examples of an asymmetric Matteson homologation variant are known. One such example involves a homologation wherein the nucleophile is a chiral, α-lithiated carbamate (equation 24). The latter class of reagents, which were first introduced by Hoppe and coworkers,[48] can provide allylboranes with α-chiral centers in very good yields, and with excellent enantio- and diastereomeric ratios.[49]



(24)

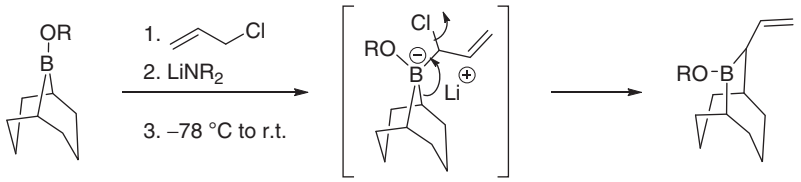
2.01.3.4 Matteson Homologation with Vinyl and Allylmetals

This transformation is quite similar to the preceding preparation subclass, as it proceeds through the same intermediate ate complex. It is different, however, in that either a vinylic or allylic group is made to be the nucleophile, and a ligand other than a vinyl group is already present on the boron (equation 25). Similar to the previous subclass, an ate complex is formed, and the same migration (resulting in homologation) takes place. Due to the mechanistic similarities of this synthetic method to the original work, this transformation has also become known as the Matteson homologation, but the authors leave it separate here, as the starting reagents are quite different from each other.

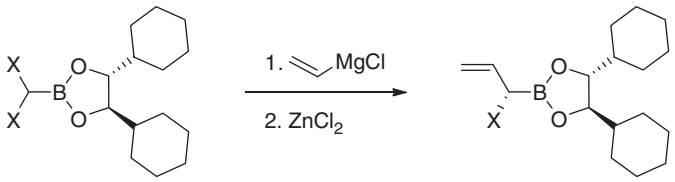


(25)

Brown and Jayaraman[50] reported that the addition or 3-chloro-3-propenyllithium to *B*-alkoxy-9-BBN derivatives gives rise to the ate complex as expected. Interestingly, the suppression of the nucleophilic displacement of the alkoxy group can be performed, depending on the conditions chosen for the reaction (equation 26). Indeed, the migration of the carbon ligand was competitive or preferred; the resulting ring-expanded system has found great utility, and has been carried forward mostly through the work of Soderquist.[21i] Hoffmann has successfully incorporated a chiral 1,2-dicyclohexylethyleneglycolato ligand into the boron to perform this reaction as a means to produce chiral allylboronates (equation 27). The incipient chirality of the bidentate ligand is actually transferred onto the α-position of the allyl group, which retains a single halogen atom, thus creating a stereogenic carbon center. This was used as a means to produce ω-chlorohomoallylic alcohols in virtually enantiopure form.[51] Similar work to incorporate groups other than chlorides has also been performed.[52] Further derivatization of these products to incorporate other groups has also been studied in detail.[1p]



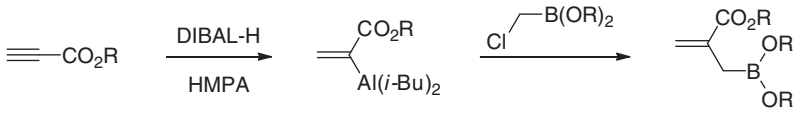
(26)



(27)

Just as both hard and soft allyl groups are known to add to boron in the production of allylboranes, so too can the latter be used for Matteson homologation reactions. For example, the hydroalumination of propiolates leads to vinylaluminates which, on reaction with chloromethylboronate complexes, leads smoothly to the ate complexes which rearrange to give *β*-(alkoxycarbonyl) substituted allylic boranes as shown (equation 28).[53] This methodology has also been undertaken with the analogous vinyl cuprates, the latter being formed from the addition of Gillman reagents to the same propiolate systems.[54] An enantioselective version of this work has also been developed.[55] Similar work has been performed by Ramachandran et al. in the production of *α*-*exo*-methylenelactones.[56]

Returning to vinylic lithiums, several other reports have surfaced which describe such homologation reactions. Brown et al. reported a method that could be used to produce *α*,*α*-disubstituted allylboranes through this same procedure. A simple hydroboration of an appropriate alkene, followed by halogenation alpha to the boron center, provided good yields of the appropriate precursors.[57] Homologation then proceeded smoothly to give the homologated products in mostly excellent yields (equation 29). Products produced through this pathway have been used as reagents in the stereoselective addition to aldehydes.[58] Polysubstituted reagents, including those containing ethers and orthoformates have also been produced.[59] The elusive *β*-vinylsubstituted allylboronates are also readily produced by this methodology.[60] More recently, the Ramachandran group[61] has used this transformation as a means to introduce fluorine substitution into synthons in an asymmetric manner (equation 30). *γ*,*γ*-Disubstituted allylboranes have also been produced by this method.[62] Pendent silyoxy groups have also been shown to be tolerated functionalities.[63]



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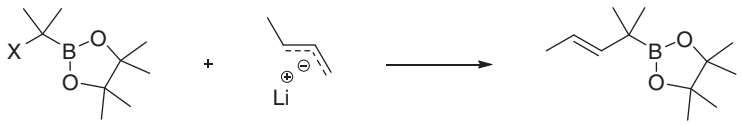
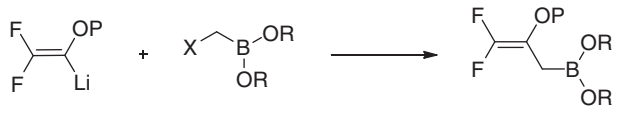
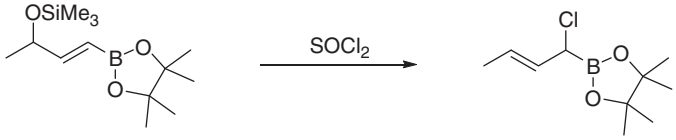


(29)



(30)

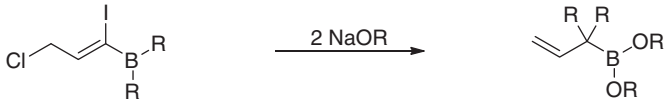
In a publication by Hoffmann and Dresely, the sigmatropic reaction of a starting allylic silyl ether with thionyl chloride was shown to furnish *α*-chlorocrotylboronates (equation 31).[64]



(31)

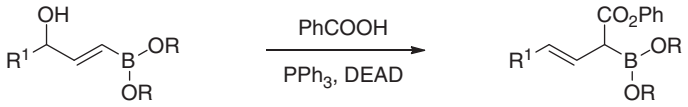
A more unusual vinylic-allylic conversion from the dihalo complex occurs when subjected to conditions of nucleophilic substitution (equation 32). The initially formed chelate complex undergoes alkyl migration to displace the proximal halide.

A second chelate complex causes the migration onto the vinylic group to occur with an S_N2' allylic rearrangement.[65] Several other displacement reactions of chlorides have also been reported by Hall and coworkers.[66] Other direct additions to the allylic system have been reported, including the conversion of allylic acetals to vinylic ethers, which take place with the addition of an appropriate nucleophile.[67]



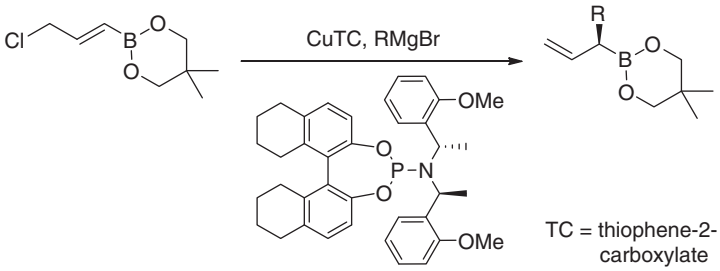
(32)

One clever expression of this sort of inversion came in the form of a Mitsunobu-type reaction.[68] Treatment of an allylic alcohol (equation 33) with benzoic acid, triphenylphosphine, and diethyl azodicarboxylate gave rise to the α-benzoyloxyallylboronates as shown. The mild conditions of the reaction make it an especially attractive synthetic transformation.



(33)

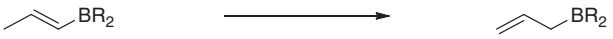
It is also possible to induce chirality while simultaneously building up an organic framework, all during this same vinylic-allylic transformation, at the expense of an allylic chloride.[69] Hall and coworkers have shown that under conditions which generate an appropriate alkyl cuprate *in situ*, and when allowed to interact with an appropriate ligand, the vinylic boronates can give rise to allylic ones (equation 34). The results were generally good, with as high as 96% *ee* being induced. This same ligand, when applied to Tsuji–Trost conditions of iridium(I) catalysis, can induce chirality for the displacement of a carbonate group in favor of a malonate group.[70]



(34)

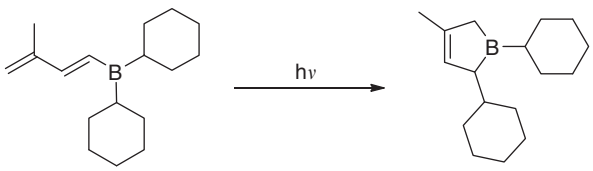
2.01.3.5 Isomerization of a π-System

The constitutional isomerization (equation 35) of a double bond without other accompanying skeletal changes has only been used as a means to furnish allylborane derivatives on a few occasions. Just as with their purely organic counterparts, these olefinic isomerizations are typically either catalyzed by transition metal catalysts, or take place under photochemical conditions.

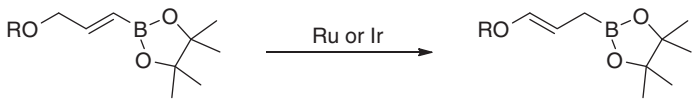


(35)

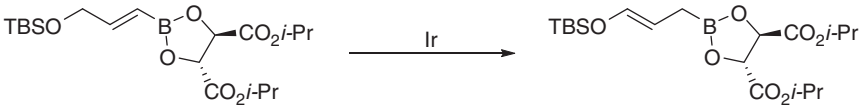
To exemplify such isomerizations, the authors present three examples. First, the irradiation of a butadienyl system can produce a diradical (equation 36). Rearrangement of the diradical will necessarily lead to both a cyclization and a ligand migration from the boron onto the α-radical. Although this process produces a stereocenter, there was no attempted control of the stereogenicity.[71] Second, Miyaura and coworkers reported that both ruthenium and iridium metals are capable of catalyzing the isomerization of vinylic boranes to allylic ones (equation 37). In the demonstrated cases, the thus-formed vinylic ethers remained intact. Although the reaction was tolerant of both organic and silyl ethers, the yields were only moderate, but the reaction occured with good diastereoselectivity.[72] A later publication detailed an attempt to control the absolute stereochemistry[73] through the incorporation of an optically pure diisopropyl tartrato ligand (equation 38). Third, a report of a ruthenium-catalyzed hydroboration, detailed the concomitant isomerization of the double bond along the chain toward the preexisting silyl ether.[74] A selected amount of other work has also been performed.[74]



(36)



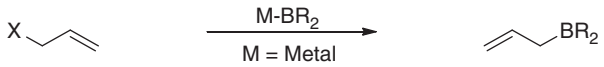
(37)



(38)

2.01.3.6 Displacement of an Allylic Leaving Group

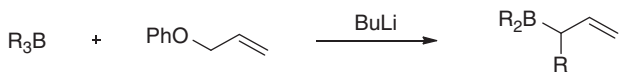
The production of allylborane derivatives at the expense of a different allylic group, wherein boron formally acts as a nucleophile, represents its own category (equation 39). Usually, this is a transition metal-catalyzed reaction, wherein the catalyst undergoes oxidative addition into an X–B bond, followed by a typical coupling reaction. Tsuji–Trost style conditions are known, along with several other related processes. Most commonly, the synthesis of this system occurs with an allylic rearrangement.



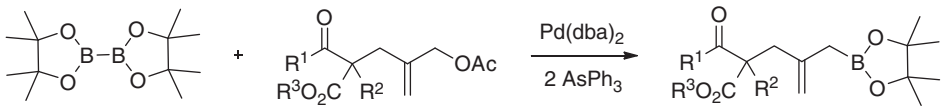
(39)

One example wherein a metal-catalyzed coupling was not used was in the reaction of trialkylboranes with 1-phenoxy-2-propenyllithium, which resulted in the expected ate complex.[75] The migration of the organic ligand from boron to the allylic group then occurs with the expected elimination of the phenoxy group (equation 40). The synthesis of different α-substituted allylic boranes can so be achieved in moderate yields.

The palladium-catalyzed cross-coupling reaction of bis(pinacolato)diboron with allylic acetates has been reported by Miyaura and coworkers (equation 41). The utility of this procedure was made evident by the intramolecular reaction of the allylborane to the carbonyl which took place on heating.[76] An enantiomeric version of this style of conversion has also been developed.[77]

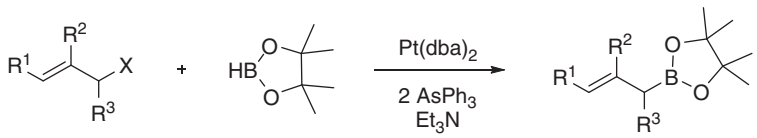


(40)



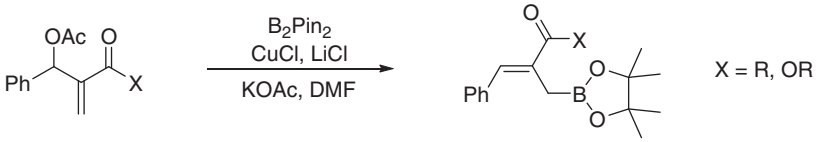
(41)

Platinum has also been used for such a coupling. In this case, the borane itself can be coupled to an allylic halide, which results in the formation of a hydrohalic mineral acid,[78] which is quenched *in situ* by the basic medium (equation 42). As pinacolborane is so readily produced in the laboratory from the reaction of pinacol and borane, this reaction can be performed with common laboratory reagents. A drawback to this methodology is the inclusion of arsenic ligands. However, the high conversion rates for even allylic chlorides may serve to compensate for this.



(42)

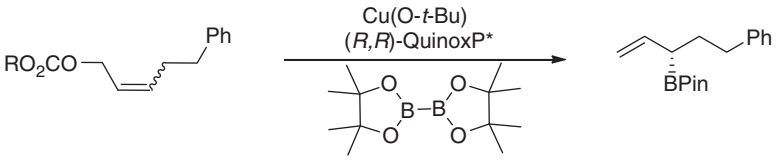
The conversion of allylic acetates into pinacolboronates has been investigated with the acetate derivatives of Morita–Baylis–Hillman adducts (equation 43). Miyaura and Hosomi independently reported the use of catalytic copper to affect this reaction,[79] followed by a report by Szabó and coworkers.[77b] Chiral 1,3,2-dioxaborolanes were introduced in this manner.[80] Related work has been performed by several other groups as well.[76b,81]



X = R, OR

(43)

The displacement of allylic carbonates has also been reported with copper catalysts (equation 44). The reaction is believed to proceed via an exchange process of the copper(I) system to give a pinacolatoborylcuprate. If a stereogenic carbon is produced as a result of the rearrangement, then the inclusion of a chiral ligand can be expected to allow for some level of induction. This has been realized, typically in greater than 95:5 *er*, while proceeding to give good yields.[77a,82] The same group has also reported that simple ethers can serve as leaving groups in place of carbonates. They have further demonstrated that this functions very well with cyclic alkenes (equation 45), giving rise to cyclic allylboranes in excellent *ee* (and *de*, when applicable).[83] Work to introduce chiral 1,3,2-dioxaborolanes via a palladium-catalyzed coupling with allylic acetates has also been reported,[84] including a stereoconvergent conversion of allyl aryl ethers to enantioenriched allylboronates with copper.[85]



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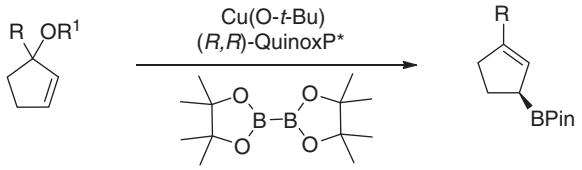
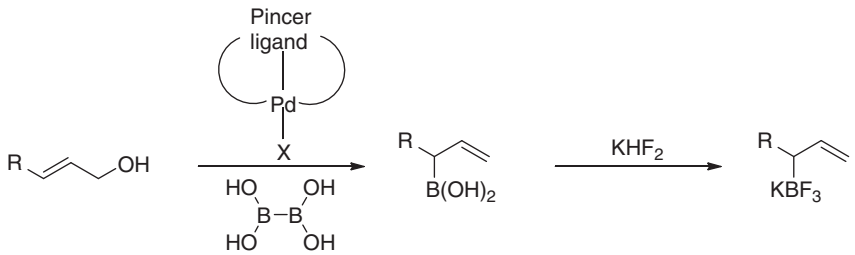


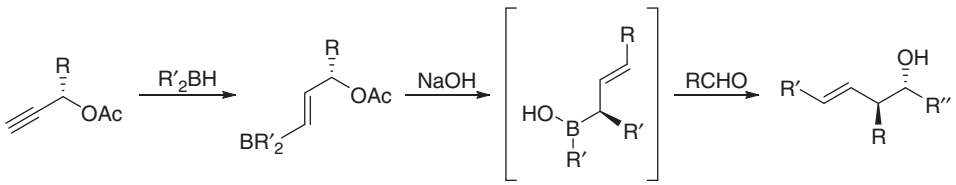
(45)

The work of Szabó and coworkers has led to the direct conversion of allylic alcohols into boronic acids and potassium trifluoroborates through the use of palladium catalysts with pincer complexes. Remarkably, this conversion is entirely fueled by the oxidation of diboric acid. The reaction most likely proceeds through ligand exchange to produce the *B*-borylboronate. This can then undergo a transmetallation reaction with the palladium, which, following formal oxidative addition to form the η^3-allyl complex, eliminates the boric acid (or derivative). Reductive elimination restores the palladium species, and releases the allylic boronate. Subsequent conversion to the trifluoroborate salt can take place on reaction with potassium bifluoride (equation 46). Typically, these conversions take place in very good yields, and with an inversion of the stereochemistry. Perhaps even more amazingly, this reaction can be used to open up allylic cyclopropanes and aziridines, wherein the leaving group is stabilized by attached malonate and sulfonamidate anions. The reaction has been further extended to the elimination of allylic acetates, acetals, and other common leaving groups.[86] A similar work to produce allyldiethylborane from allyl alcohol and triethylborane under conditions of palladium catalysis has also been reported.[87]



(46)

The hydroboration of enantiopure propargylic acetates, when followed by a hydroxide-promoted allylic rearrangement, has been shown to give enantiopure allylborinic acids (equation 47). These can be directly used in a subsequent allylboration reaction.[88]

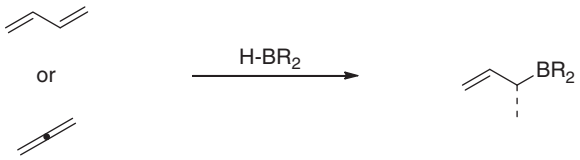


(47)

2.01.3.7 Reaction of H–B with π-Systems

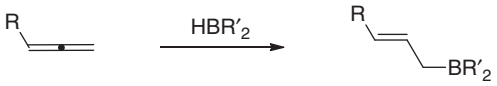
The 1,2-hydroboration of 1,3-butadienes (addition of hydrogen to the terminal position and boron to the internal position) or the 2,1-hydroboration of allenes (addition of hydrogen to the internal carbon and addition of boron to the terminal position) gives rise to allylic borane derivatives (equation 48). Although over-hydroboration and regio- and chemospecificity issues are potential

problems during these reactions, such undesired outcomes can usually be suppressed by the appropriate choice of conditions or hydroborating agent. Given that chiral boranes are readily available, the advantage of this method is that these compounds can be produced in the laboratory quickly, in high yield, and usually in excellent stereoselectivities.



(48)

The hydroboration of monosubstituted allenes with 9-BBN and Chx_2BH was performed in an achiral manner by Brown et al., giving the expected *E*-terminally hydroborated allylboranes (equation 49).[89] An asymmetric version of this reaction was later developed by Brown and coworkers, using $^{d}Ipc_2BH$ (equation 50).[90] Such hydroborations have since been shown to be an incredibly general way to produce an allylborane from relatively simple starting materials.[91] Like most hydroborations, the reaction conditions are mild with high yields. Innate in the hydroboration of allenes, however, is an issue of chemospecificity. When coupled with the potential problem of a lack of regiospecificity during hydroboration, there happens to be a total of four possible products for this hydroboration reaction. However, just as with the case of the hydroboration of simple alkenes, wherein the electronic and kinetic effects typically cause anti-Markovnikov regiochemistry, so too can they in the case of allenes. A common method for controlling the chemospecificity during the hydroboration of allenes is to introduce steric bulk at only one of the two termini, thereby directing hydroboration toward the opposite end (equation 51).[92] Additionally, this bulk tends to assist in the regiochemical specificity during the actual hydroboration, as 1,2-hydroboration (internal) would introduce a high degree of A-1,3 strain that would not be felt during the 2,1-hydroboration (terminal).



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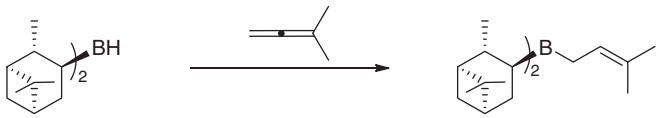


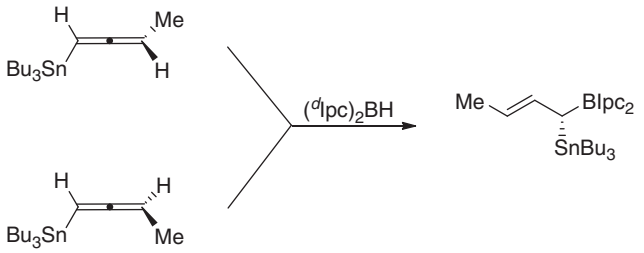
(50)

(51)

Since its inception, the hydroboration of allenes has become quite a commonplace, and many different functionalities have been found to be compatible with the mild conditions. For example, the inclusion of weakly labile groups such as carbon–silicon bonds are readily tolerated (equation 52). This particular example contains the added feature of a coordinating group. Such coordinations can force the thioether and boramethyl ligands of the alkene to be in the *cis*-configuration.[93] This type of silicon-containing hydroboration of allenes was further generalized by the work of Wang and coworkers.[94]

(52)

Other more reactive carbon–metal bonds can be tolerated during this reaction. For example, certain vinylic stannyl groups such as tetraalkylstannanes, which possess virtually no Lewis acidity, can be carried through hydroboration reactions. One particularly fascinating example is in the enantioconvergent hydroboration of a racemic mixture of 3-methyl-1-stannylallenes (equation 53). Roush and coworkers have proposed that the hydroboration of the two enantiomers proceeds through different pathways, and that, after 1,3-boratropic shift, the two pathways stereoselectively converge onto the same product.[95] Such hydroborative stereoresolutions are not commonplace; this represents a very unusual method of resolving enantiomers into one via derivatization. This was actually a natural extension of the earlier work dealing with the simple hydroboration of achiral, monostannylsubstituted allenes.[96] Earlier, they had shown that vinylic boronates are perfectly stable to such hydroboration conditions, and that, on the successful hydroboration of allenic boronates, double-allylboration reagents could be produced (equation 54), wherein the normal usage of the first allylborane functionality would create a second allylborane moiety, which could then be used for a second, subsequent allylation reaction.[97]



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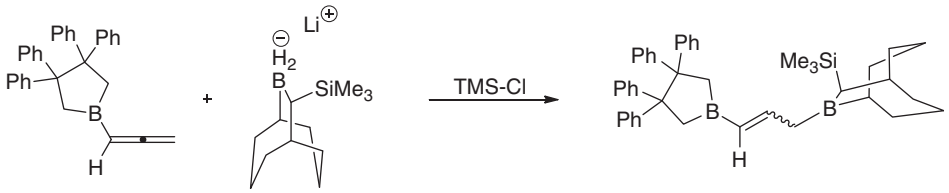
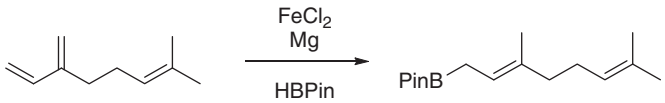


(54)

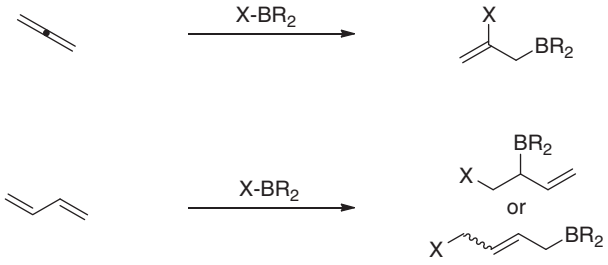
Catalyzed hydroboration is a well-known reaction, of which much research effort has been put forth over the past several decades.[98] Quite recently, Ritter et al. published the first the iron-catalyzed hydroboration of alkenes, and showed therein that 1,3-butadienes were particularly suitable substrates for this reaction (equation 55).[99] The conversion is believed to proceed through a hydroferrylation-reductive elimination pathway. Other metals have also been used for the catalysis of comparable reactions with dienes, such as the 1,4-hydroboration with palladium,[100] and the 1,2-hydroboration with rhodium[101] and nickel.[102] Additionally, the uncatalyzed 1,2-hydroboration of tetralkylammonium trifluoroallenylborates is known to give rise to double allylating reagents.[103] Although not strictly a hydroboration, a report of a copper(I)-catalyzed addition of both a proton and a single boron from methanol and bis(pinacolato)diboron has been reported to give the equivalent of a hydroboration product, starting from 1,3-cyclobutadienes. The reaction can be used to generate nearly enantiopure allylic boronates, wherein the chirality is transferred from any number of mostly bidentate bisphosphine ligands.[104]



(55)

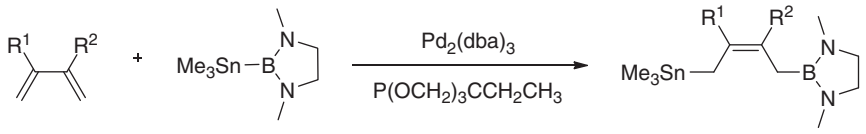
2.01.3.8 Reaction of X–B with π-Systems (X≠H)

Similar to hydroboration, the reaction of X–B with the same species and in the same manner (*vide supra*) can give allylic borane derivatives (equation 56). Most frequently, these 'X' groups are carbon-, silicon-, tin-, or boron-based reagents. Although many of these reagents are not commercially available, their synthesis is usually quite facile, and can be carried out with few problems. Additionally, the added functionality of the products–be it a boron, silicon, tin, or other group offers a great utility for these synthons, and can allow for multiple reactions with nucleophiles or electrophiles, and can be used in cross-coupling methodologies and synthesis.



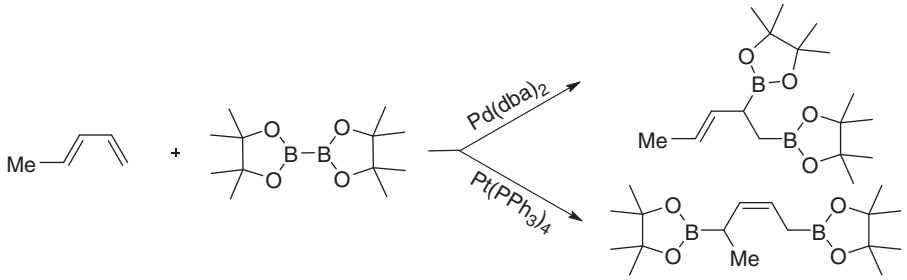
(56)

The palladium-catalyzed 1,4-stannylboration of 1,3-butadienes has been studied by Tanaka and coworkers.[105] They have shown that the stannylboration takes place with the nearly exclusive formation of *cis*-product, and with no detectable level of 1,2-addition product formed (equation 57).



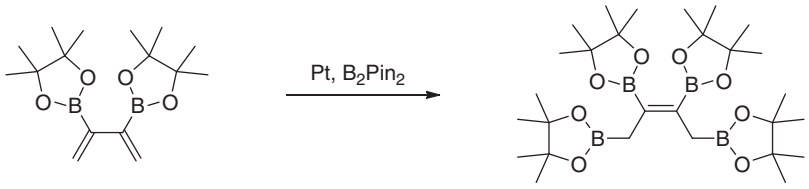
(57)

Another route to diallylating (diboryl) reagents comes from the 1,2-diborylation of a 1,3-butadiene. There has been much research centered around such work; 1,2-diborylation competes with the 1,4-pathway, and both or either product can be observed, depending on the chosen conditions (equation 58). In fact, by simply changing the temperature and catalyst ligand choice, either product can be obtained in very high yield.[106] Many other diborylation processes are also known,[107] including those which produce enantioenriched diboranes.[108]



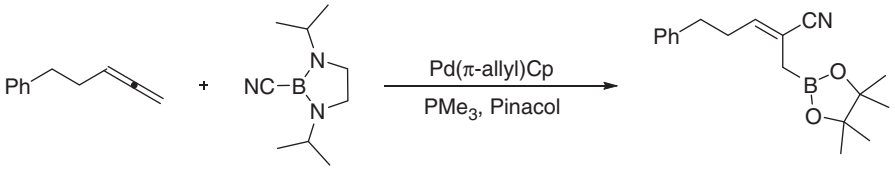
(58)

The formation of some very interesting tetraborylated products through a 1,4-diborylation pathway has been described by Hiyama and coworkers (equation 59). Although these highly versatile synthons have the potential to react with up to four electrophiles, they have only been described to react until the third derivatization, wherein an elimination pathway appears to take precedence.[109]



(59)

The 1,2-carboborylation of allenes is a less well-studied process than some of its counterparts, but nevertheless, enough is known to use it in the preparation of allylboranes.[110] For example, β-cyanoallylic boronates can be produced from the intermolecular reaction of allenes and 2-cyano-1,3,2- diazaborolidines (equation 60). However, the reaction does not proceed as well as the intramolecular reaction, wherein the cyano and boron moieties are delivered from an etheric tether. In this latter method, the desired products could be prepared in near-quantitative yield under conditions of either nickel or palladium catalysis. Similarly, the palladium-catalyzed carboborylation of allenes has been reported.[111] This three-component coupling reaction brings together an acyl chloride, an allene fragment, and bis(pinacolato)diboron to produce β-acylallyl-1,3,2-dioxaborolanes (equation 61).



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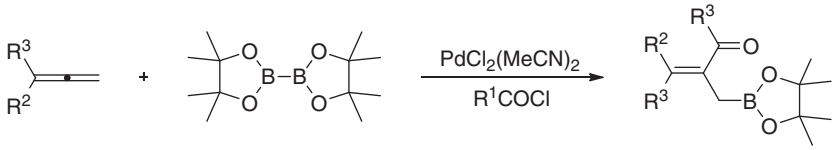
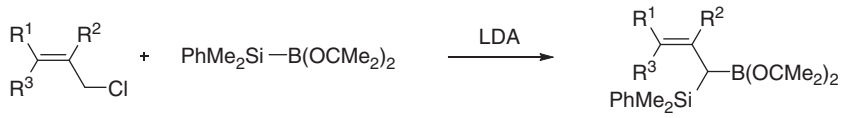


(61)

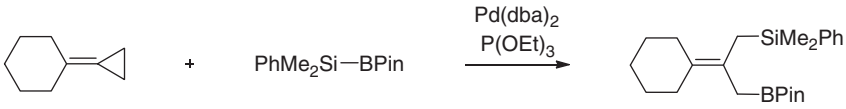
Although not a π-system in the strictest sense, cyclopropanes are said to possess significant olefinic character,[112] and, in certain cases, can react with carbon–boron bonds. For example, bicyclo[1.1.0]butane will react with some trialkylboranes to give α-substituted boranes.[113] Along the same vein, the reaction of triallylborane with allenes occurs via carboborylation to give a series of nonisolable allylboranes.[114]

The nickel-catalyzed 1,4-silaboration of 1,3-butadiene systems is also known, and can lead to allylic boranes in very good yields and selectivities.[115] In general, steric competition leads to the regiochemistry which places the smaller group at the more hindered position. Conversely, the borasilation of silyloxy-substituted allenes leads to a 1,2-silaboration, i.e., a vinyl borane product.[116] A very novel route to the production of α-silylallylic borane derivatives was published by Hiyama and coworkers.[117] The reaction of 1-chloroprop-2-enyllithium with silicon–boron bonds is believed to lead to the ate complex, which undergoes preferential silyl-migration onto the allylic group, necessitating a concomitant chloride elimination (equation 62). These densely-functionalized

synthons are produced in very good overall yields, and without any detectable level of the 1,4-silaborane product. This indicates that at the reaction temperature, the 1,3-boratropic shift was so kinetically deactivated, so as to render it improbable. The silaboration reaction of cyclopropanes has also been studied, and has been shown to function just as well as carboborylation (equation 63). Amazingly, activated cyclopropanes can actually be silaborylated in the presence of olefins, to give α-silylmethylallylboranes.[118]



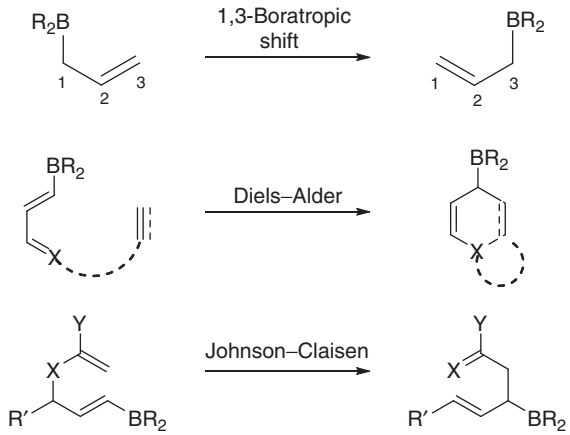
(62)



(63)

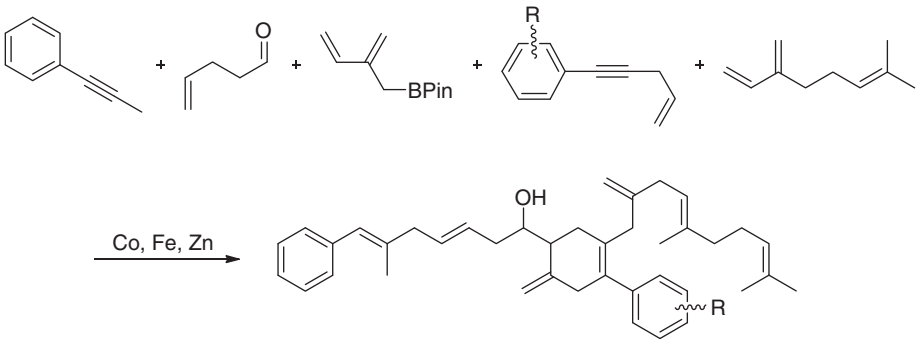
2.01.3.9 Sigmatropic Reactions

The sigmatropic reactions of boron-containing compounds are a natural extension of purely organic-based ones (equation 64). Although many dozens of sigmatropic reaction variations are known with strictly organic-based compounds, there are far fewer reports of such pericyclic processes with boron-containing compounds. Actually, the vast majority of these sigmatropic reactions occur when the boron-containing group is being used as a reagent in the formation of carbon–carbon bonds, such as in the aldol reaction, or during the allylation of carbonyl compounds. In contrast, there are relatively few reactions that use previously-incorporated boron atoms that are used to produce allylborane derivatives. Most of these pericyclic reactions fall into three main categories of preparations. First, 1,3-boratropic shifts (*vide supra*, same title) of allylboranes gives rise to constitutional isomers of the starting allylic system: an allylborane derivative. Although it is many times true that 1,3-boratropic shifts can be the bane of allylborane synthesis, those which are controlled can quite elegantly lead to highly functionalized systems. Second, the Diels–Alder reaction of 1,3-butadiene systems which contain a boron tethered to the 1 or 4 position lead to (cyclohex-2-en-1-yl)boranes. The *exo*-boryl allyl systems produced in this manner are set with all the advantages of Diels–Alder chemistry: high stereocontrol and functionality tolerance. Unfortunately, the difficulty of preparing these systems is evident by their high tendency to homodimerize through the same pathway. More recent is the third method: a boron-containing variant of the well-known [3,3]-sigmatropic Johnson–Claisen reaction.



(64)

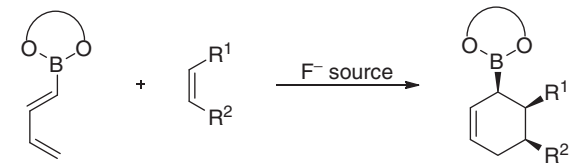
A cobalt-catalyzed, multicomponent four segment coupling reaction of acrylates, β-vinylallylic boranes, γ-enals, and trienes has been shown capable of producing allylic boronates as part of a bicyclo[4.4.0]decane system (alkyl 7-substituted-7-hydroxy-6-methyl-5-methylenehept-2-enoates), or 4-methylene-2,3,6-trisubstituted tetrahydropyrans in a one-pot sequence. Incredibly, the yields for this 4-component coupling are quite high, ranging from 60–99%, and generally give very good diastereomeric ratios.[119] This same methodology was later extended to include a fifth component – an enyne – the one-pot sequence then provided highly functionalized cyclohexene derivatives (equation 65).[120]



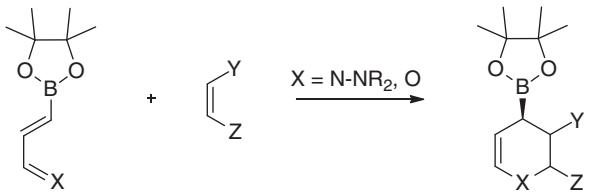
(65)

Perhaps the most famous of the three above-mentioned sigmatropic reactions is the Diels–Alder reaction. The first two laboratory syntheses of 3-borylcyclohexenes via the Diels–Alder reaction were reported by Mikhailov and Hoffmann.[121] The reactions that they reported were performed at the moderate temperatures of 80–100 °C, so a reasonable number of thermally stable functionalites could be expected to be toleratant. It was shown that ethyleneglycolato, pincacolato, and catecholato boronates were all functional. As expected for such reactions, the 1,3-product was not observed, and high *endo*-selectivity for the maleic derivatives was observed.

It was later reported that the same type of reaction with the boron ate complex – formed by activation through fluoride chelation – was not only tolerated, but also greatly accelerated.[122] The acceleration was so great, that the reactions were able to be performed at room temperature, which is desirable for the greater allowance of functionalization of thermally labile groups. This methodology was extended to include the typical dienophiles of Diels–Alder reactions, such as maleimides, acrylates, and diazo compounds. Hall and coworkers[123] further elaborated on this, incorporating 4-isothiazolin-3-one 1-oxides as the dienophile. They also transformed this reaction into a formal hetero-Diels–Alder one, by incorporating different groups at the position labeled 'X', such as oxygens and amines (equations 66 and 67). These amine adducts were then able to be aromatized into pyridine groups through appropriate transformations. Due to the tendency of the products to undergo [3,3]-sigmatropic reactions, and to react as allylboranes toward the starting carbonyl (or derivative) compound, the desired sigmatropic reactivity had to be carried out at a significantly lower temperature than would allow for the allylboration to proceed. To overcome this problem, the development of a catalytic method was undertaken, wherein it was disclosed that a chromium(III) catalyst was capable of solving this reactivity problem.[124]



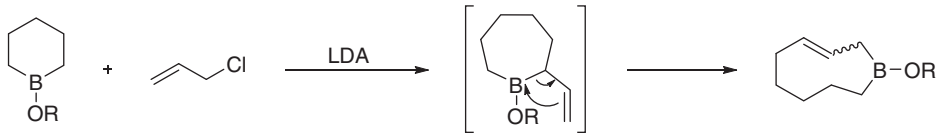
(66)



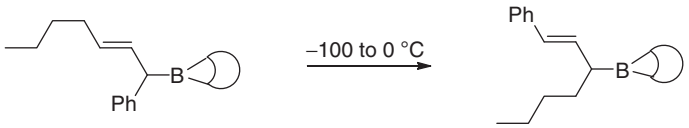
(67)

The utility of the 1,3-boratropic shift can quite easily be overlooked as being considered a synthetically useful transformation, as such shifts were historically problem makers rather than problem solvers. For example, the predictability of these shifts was used by Brown et al.[125] as a tool to expand a ring by a three-carbon segment. The expansion of a borolane to a mixture of the *cis*- and *trans*-isomers of hexahydroborocine was achieved. This methodology was extended from the five-membered borolane all the way to the 12-membered boracyclodec-3-ene, to give hexahydroborocine through boracyclopentadec-3-ene, respectively. Initially, the work was performed with the deprotonation of allyl chloride *in situ* by lithium diisopropylamide. After formation of the ate complex and subsequent ligand migration, the 1,3-boratropic shift gave rise to the propenyl-homologated ring system. The use of lithium 2,2,6,6-tetramethylpiperidide was actually superior, as the *in situ*-formed protic diisopropylamine was found to promote a competing protonolysis reaction (equation 68). As discussed in Section 2.01.2.5, 1,3-boratropic shifts can occur quite readily, depending on the kinetic energy of the beginning allylborane and the energetic barrier to reaction. Although the former can be adjusted through the regulation of the Lewis acidity on the boron center or the imposition of steric constraint, it can only be controlled through a change in the reaction temperature. This is actually a very common tool used in boron; the synthesis of an allylborane at low temperature can isomerize via said mechanism on heating. For example, those allylboranes which were previously synthesized through a sulfur

ylide pathway[47] (*vide supra*) are stable only at low temperatures. On heating to 0 °C (from −100 °C), the initially formed product, which could be used as it is, was made to undergo thermal rearrangement to the more stable styrylic allylborane (equation 69). Several other 1,3-boratropic reactions have been used in the preparation of specific allylboranes.[5b,15a,16d,47,90,126]

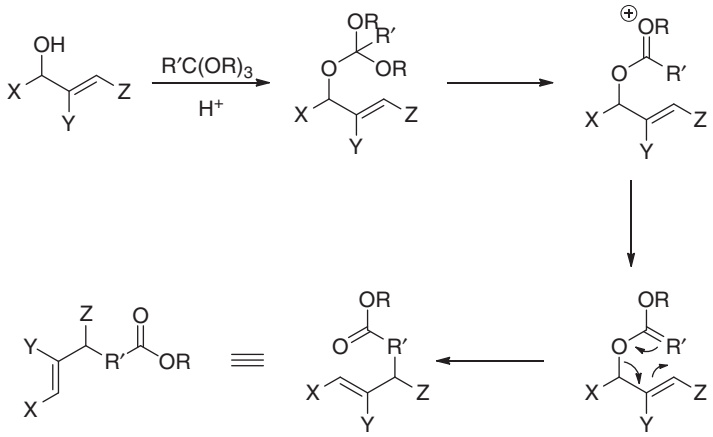


(68)



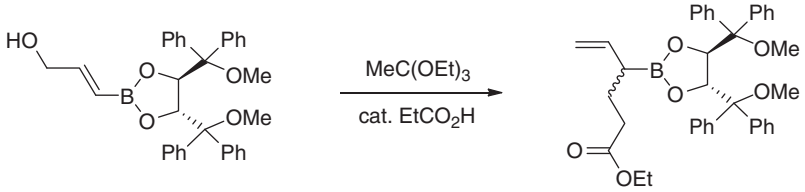
(69)

One of the most synthetically elegant reactions that can be used in the construction and/or skeletal reorganizational procedures of a given molecule is the [3,3]-sigmatropic reaction. Many variants are known, from the original Claisen reaction of allyl phenyl ether, to the Bellus-, Eschenmoser-, Ireland-, Aza-, and Johnson–Claisen variants. The latter rearrangement occurs with the condensation of an allylic alcohol with an orthoester. Slightly acidic conditions will ultimately lead to the divinyl ether, which is followed by cyclization (**Scheme 8**).



Scheme 8

As can be readily seen from the mechanism, the incorporation of a vinylic boryl group as '*Z*' would result, on cyclization, in the formation of an allylic boryl group. This variation of the Johnson–Claisen sigmatropic reaction was first introduced by Pietruszka et al.[127] After regiospecific hydroboration of a silyl-protected propargylic alcohol with catechol-derived boranes, the subsequent exposure to triethyl orthoacetate, along with a catalytic amount of propionic acid, furnished, at 135 °C, the desired allylic boronates in very good yields (equation 70). The use of these reagents for chiral allylboration was thereafter accomplished, and used to demonstrate the stereoselectivity of the sigmatropic process. The Eschenmoser rearrangement, in which the orthoacetate was replaced by an orthoamide, was also successful in producing the expected amides. Further work has since been performed to extend this methodology to chiral substrates,[128] and to perform the reaction under microwave conditions.[129]

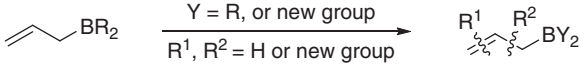


(70)

2.01.3.10 Derivatization of Simpler Allylboranes

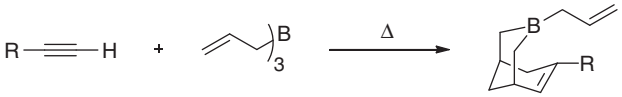
The practice of derivatizing an allylborane (equation 71) at either the α-, β-, γ-, or boron position is fairly commonplace. Perhaps the most commonly used method is through a simple ligand exchange. Other noteworthy methods include olefin and enyne metathesis,

along with nucleophilic substitution at the various carbons. The ability to produce more complicated allylboranes from simpler ones is a simple idea, but this has been used less and less frequently, as better chemical technologies allow for a more convergent approach to the same scaffoldings. Nonetheless, the authors include this section for reasons of history and completeness.



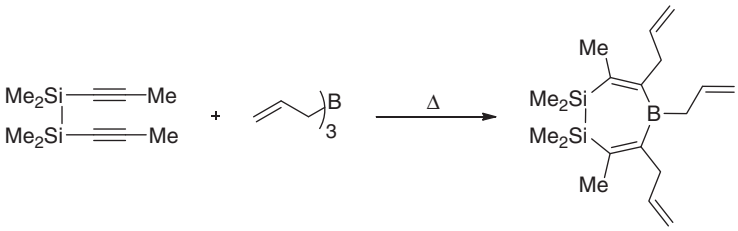
(71)

One of the earliest examples of such a derivation comes from the simple case of triallylboranes. The authors have already introduced the concept of carboborylation, a process which is most typically catalyzed with transition metal chemistry. However, before such developments, carboborylation processes – those such as allylborylations – were typically performed under thermal inducement. In this way, many unusual compounds have been produced. For example, the bicyclic compound shown (equation 72) is produced from two successive allylborations of the alkyne, along with subsequent thermal rearrangement.[23,130] These bicycloborane derivatives have received much attention due to their multitudinous practical utilities.[131]



(72)

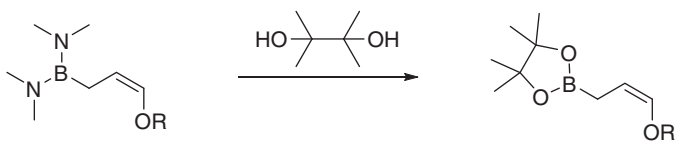
A far more interesting example involving the allylboration of an alkyne was published several decades later.[132] In studying the competition between 1,1- and 1,2-allylboration processes for silanylacetylenes, Bubnov and coworkers reported the preparation of many different vinylsilanes and vinylboranes. It was found, however, that the 1,1-allylboration process is generally the dominant pathway, and that such a process would require the cleavage of the acetylenic-silicon bond. This fact allowed for the rearrangement of the starting materials to some products that were previously difficult to access. For example, the highly functionalized allylborane shown in (equation 73) was produced in quantitative yield.



(73)

The exchange of ligands on the boron center of an allylic borane necessarily falls into this category of preparation. The vast majority of the examples in the literature have to do with the solvolytic removal of ligands. Just as with their organic ester relatives, the reaction of any given set of ligands can take place through a simple exchange, akin to a Fischer-Speier transesterification reaction.[133] Just as is the case for organic esters, wherein a two step process – hydrolysis and then derivatization – is sometimes utilized, so too can be the case for boronic acids. For example, if the preparation of a potassium trifluoroborate salt is mandated by the situation and only a pincacolatoborane is available for building the necessary organoborane scaffolding, then conversion first to the boronic acid is usually the route of choice. The latter would then be reacted with a fluorinating reagent such as potassium bifluoride as a means of obtaining the desired salt.

When designing a synthetic route for placing necessary ligands around a boron atom, the basic principles learned from other systems will many times be applicable. For example, the chelate effect is commonly utilized as a means to place bidentate ligands around boron. Indeed, the literature is replete with such bidentate ligands for boron, such as those made from glycolato, pinacolato, catecholato, and tartrato scaffolds. Furthermore, the Thorpe-Ingold effect can make certain ligands less labile than others.[134] The perfect example is seen in the slower kinetics of the solvolysis of pinacolato than glycolato ligands. A third feature of ligand choice that renders certain groups less prone to hydrolysisis is the question of nucleophilicity. Ligands of higher nucleophilicities (within reason) tend to form stronger bonds to boron, and have a decreased lability to retard hydrolysis. This trend is again mirrored with organic esters: amides are less prone to undergo solvolysis than are comparable esters. The combination of these three factors necessarily dictates that certain ligand exchanges are more facile than others-some exchanges require more than one chemical operation, whereas others can be performed directly. In one such example, the exchange of a pair of dimethylamino ligands takes place in favor of a catecholato ligand (equation 74).[135] In this case, it is the Thorpe-Ingold and chelate effects beating out the better donor ability of the nitrogen ligands. In the second example (equation 75), a combination of the chelate effect and enhanced nucleophilicity can give rise to the ligand exchange product, on azeotropic removal of the water.[13] Countless examples are known in the literature,[53b,136] but they generally follow these above-listed principles.



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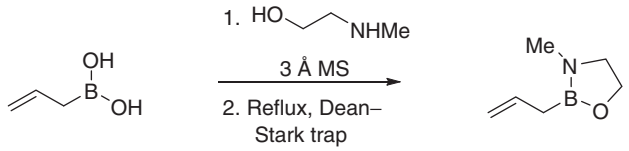
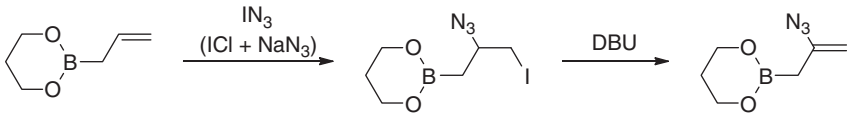


(75)

It is many times desirable to derivatize the boron's allyl group into a more functionalized one, for later use or transformation. Such a strategy is usually more convergent, as the extra functionality does not need to be introduced at a later time in a synthesis. As an example, the reaction of iodine azide (which is generated *in situ* from the reaction of either molecular iodine or a mixed iodo halide with sodium azide[137]) with an allylborane will give rise to the vicinal iodoazide (equation 76). The elimination reaction with 1,8-diazabicycloundecene furnishes *β*-azidoallylborane in 70% yield over two steps.[138] The derivatization of groups already present on the allyl functionality can also be transformed further. For example, the *α*-chloride substituent of certain compounds has been exchanged with groups such as alkoxides and thioalkoxides.[139] In a more complicated example of such a derivatization, a 2*H*-1,3-dioxan-2-yl group has been incorporated into the *α*-position of the allylborane.[140] Such a high degree of functionalization is especially attractive when built through this route, as the starting tosylate is readily derived from glycerol (equation 77).



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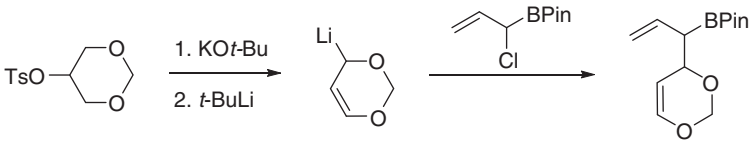
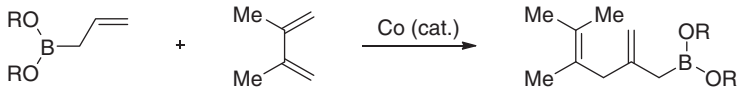


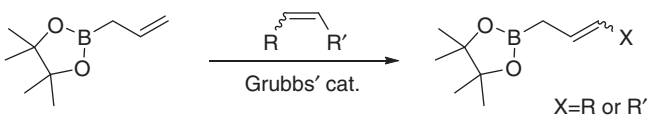
(77)

In a very unusual and almost uncanny manner of transformation, Hilt and coworkers published a most interesting form of derivatizing an allylborane. In what might at first seem to be an ideal situation for a Diels–Alder reaction, a cobalt-catalyzed 1,4-hydrovinylation was instead used.[141] This almost unpredictable outcome has been readily performed in tandem with an allylation sequence to give a series of 1-substituted-5,5,6-trimethyl-3-methylene-hex-5-en-1-ols in a one-pot procedure in mostly excellent yields (equation 78).



(78)

With the newer field of metathesis becoming an increasingly mature chemical technology, the opportunity to derivatize allylboranes directly at the terminal olefinic position with such high levels of atom economy that were before unthinkable have now come within the grasp of the synthetic community. Indeed, the prospects of applying techniques such as ring-closing and cross-metathesis as a means to create novel ring systems and to concatenate two *π*-systems has been reported. The former, was quite separately reported in the same year by both Grubbs and Miyaura.[142] The general schematic of both works is shown in equation 79. The elongation of the chain was shown to function when starting with either terminal or internal olefins, and was demonstrated to be tolerant of silyl- and benzyloxy groups, dioxolanes, halogens, and esters. Typically, a great deal of functionality is expected to be tolerated in these reactions, due to what are usually very mild conditions for metathesis reactions. Indeed, more recent work has demonstrated that both vinylic and allylic silanes can serve as metathesis partners for these reactions, under conditions of ruthenium-hydride based-metathesis. Even reactive silicon–chloride bonds have been tolerated under these conditions.[143] Further advances were highlighted by the production of diborylating reagents by a cross-coupling methodology with Hoveyda–Grubbs' second generation catalyst. Despite the incredibly high steric requirements for such a metathesis, good yields were obtained for a wide range of mostly carbon-based substrates.[144] The ring-closing metathesis to produce cyclic boronates has been reported by Schrock and Hoveyda.[145] Indeed, the reaction of solid-supported, axially-chiral molybdenum-based alkylidene catalysts was shown to successfully form unsaturated cyclic boronates in good yields and excellent enantiomeric ratios (equation 80). Ring-closing metathesis has also been used to create other boron-containing ring systems.[136e] Further work with metathesis has also been beformed.[145,146]



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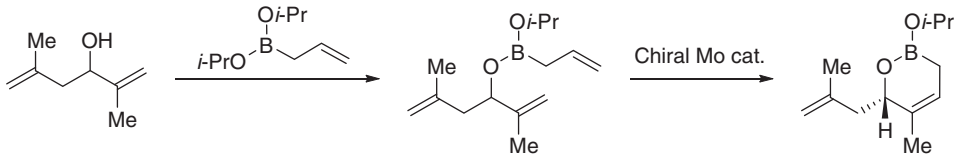
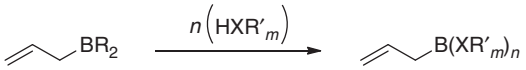


(80)

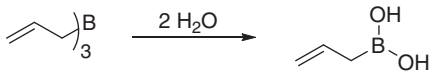
2.01.3.11 Reaction of Boranes with Protic Acids

The slightly polarized nature of a carbon–boron bond results in a small but present inherent basicity. This utility allows for the reaction of alkyl groups with various protic acids such as alcohols, amines, and thiols (equation 81). With little general chemoselectivity available for this reaction, a mixture of products can many times result. A solution to this problem is to begin with triallylborane, which is conveniently prepared from boron trihalides and allylmetals. The introduction of chiral ligands which possess stereogenic carbon atoms can be incorporated in this manner.

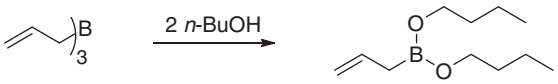


(81)

One of the most rudimentary examples of such a protic acid reaction is that of the solvolysis of triallylborane. In fact, the stoichiometrically controlled reaction of water with triallylborane can readily give rise to allylboronic acid (equation 82). Analogously, the stoichiometrically controlled reaction of alcohols with triallylborane gives dialkyl allylboronates in high yields (equation 83).[17] A similar reaction readily occurs with a single equivalent of thiol, giving dialkyl allyldithioborinates (equation 84), but the reaction with two equivalents is not as simple, as several byproducts form, albeit in minor amounts.[147] The first reagent reported to undergo an asymmetric allylboration reaction was prepared in such a manner. The diol-derivative of camphor dione smoothly reacts with triallylborane to furnish chiral *B*-allyl-1,3,2-dioxaborolanes in good yield (equation 85).[136f,148] Similar reactions with aminols are also known.[13] Other examples include the reaction of the alkyoxy salts of tartramides with allylboron difluoride to give optically pure B-allyl-1,3,2-dioxaborolanes in good yields,[136d] along with several others.[21d,149]

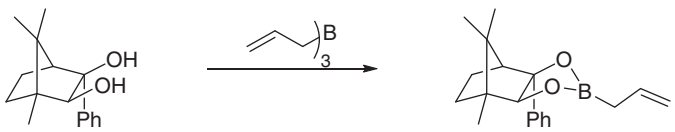


(82)



(83)

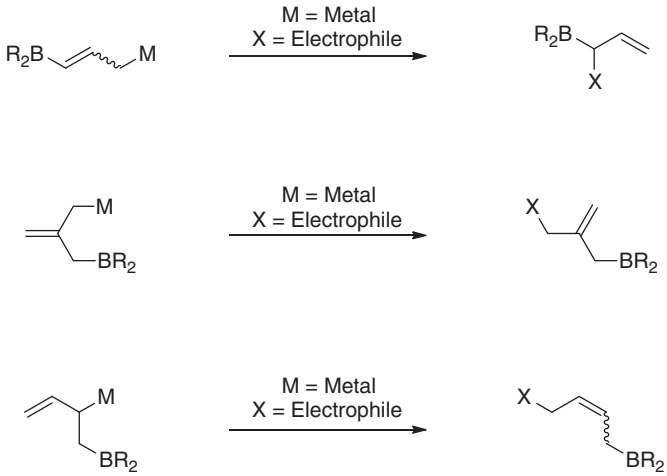
(84)



(85)

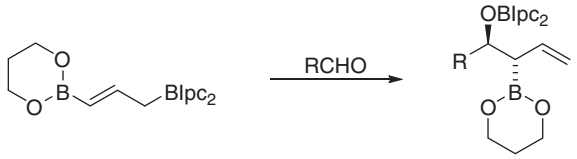
2.01.3.12 Allylmetalation

Many bismetal reagents have been made and characterized till date. They can many times be designed and built in such a way that, on reacting as an allylmetal during a carbonyl allylation reaction, the resultant alkene is allylic with respect to the second metal (equation 86). Indeed, this has been performed with boron as the second metal on a number of occasions, using a metal such as tin or a metalloid like silicon as the first metal.

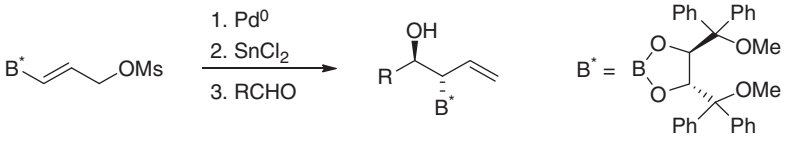


(86)

There are more and more reports surfacing that make use of these 'double allylating' reagents. These reagents typically have a either a 1,4- or a 1,5-dimetal relationship, necessitating a homoallylic/allylic or a vinylic/allylic relationship. Most often, these metals are both reacted *in situ*, so that the formed allylmetal is not isolated, but rather directly reacted. Quite frequently, these systems are found as mixed-metal ones, wherein one partner is a boron and the other a silicon, a stannane, or a comparable atom. For example, Brown and coworkers have reported on such work,[31a] by developing the hydroboration of an allenyl borane to give a diborane (equation 87). Primary allylation gives the allylborane shown which can be used for a subsequent allylation reaction, or further derivatization. Many other examples are known of such diborons and their construction.[103,105–108,118,144] For a case in which the allylation with a stannane is to give rise to an allylborane, the authors look to one which is produced *in situ* (equation 88). During a palladium-catalyzed reaction, tin(II) can undergo an oxidative addition into the allylic carbon–mesityoxy bond, forming an allylic tin(IV) system. The reaction with an aldehyde produces the allylborane as shown.[150]



(87)

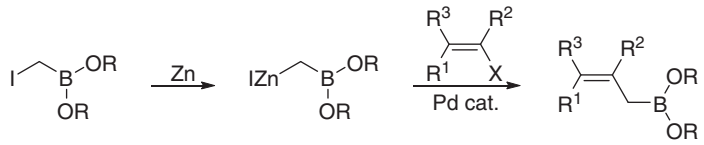


(88)

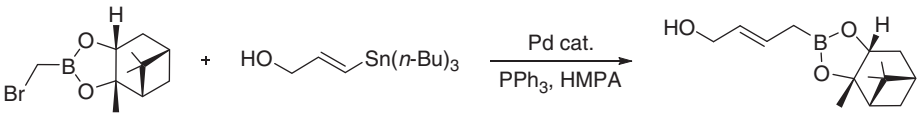
2.01.3.13 Allylboranes Through Other Synthetic Means

All the remaining methods for the preparation of allylboranes have been grouped into this miscellaneous class. Each will be discussed in its own light.

Cross-coupling has been used as a tool in the preparation of allylboranes, but surprisingly little has followed within the typical boundaries of what is considered cross-coupling. As the authors have seen above, most couplings entail the use of diboranes as cross-coupling partners, but only a select number of examples have been published that couple a preformed metal with a halide–conditions used for the more typical cases such as Stille- or Negishi-coupling. The authors present here one example of the latter (equation 89). Given the molecular similarities between the starting materials for this Negishi-style coupling and a Matteson homologation, the consideration of the historical use of the latter makes it simple to understand how such a transformation can be easily overlooked. Nevertheless, the coupling of the boronatomethylzincates with vinyl halides has been demonstrated to give rise to the expected products in moderate yields.[151] This procedure offers a very nice alternative to the Matteson homologation procedure, should a portion of the molecule be incompatible with the (many times) strongly basic and nucleophilic conditions of the Matteson homologation technique. Other work with Negishi-style couplings has been reported.[152] Work with Stille-coupling (equation 90) has also been shown to furnish substituted both chiral and achiral allylboronates in very good yields.[153] A wide range of functionalities was tolerated, including esters, nitriles, alcohols, ethers, and various aromatic groups. As expected, the stereochemical integrity of the starting olefin was maintained during the coupling step.

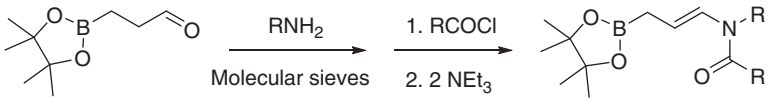


(89)



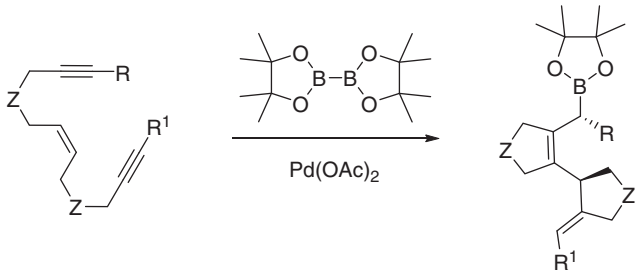
(90)

One method for producing γ-substituted acylaminoallylboronates was described by Hoffmann et al.[154] A β-1,3,2-dioxaborolan-2-yl aldehyde was made to form the corresponding Schiff base. The thus-formed ketimine was acylated with an acid chloride, thereby necessitating an increase in the acidity of the proton beta to the boronate. Deprotonation with a mild base produced the *N*-acyl enamine, whose olefinic moiety formed an allylboronate (equation 91). In one example, the reaction was even tolerant of an acid-sensitive acetal functional group.



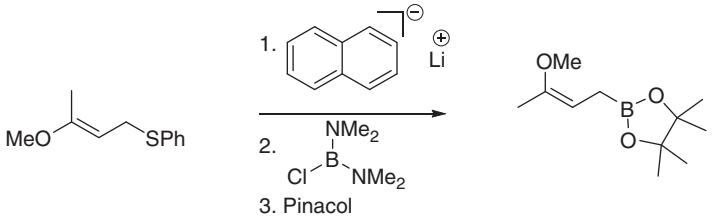
(91)

A route to more complicated but specific allylboronates has been developed by Cárdenasi and coworkers.[155] Using a palladium-catalyzed 'zipper' reaction, they had previously shown that 1,6-enynes can give homoallylic boronates through a formal 1,7-hydroboration reaction,[156] but herein extended this work by tethering an additional alkyne (equation 92). This pendent functionality necessarily formed a pendent cyclopentanyl derivative. This methodology is attractive as it allows for the formation of complex ring systems that would otherwise take multiple, more linear synthetic sequences to build. They have since extended this methodology for the production of complex allylboronates, starting with allenynes.[157]



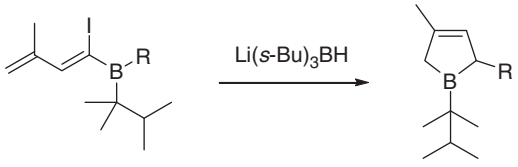
(92)

One unique manner of producing allyl boronates was reported some time ago,[158] in which a lithium naphthalenide reduction of an allyl phenyl thioether produced the allylic anion. Quenching the formed allyllithium species with a chloroborane, followed by ligand exchange gave *B*-allylpinacolatoborane (equation 93).



(93)

The deprotonation of alkynes, followed by the quenching with molecular iodine and subsequent hydroboration, provides α-iodovinyl boranes. The formation of the hydridic ate complex results in the migration of a hydride to the α-position in lieu of the iodide. This migration occurs with an inversion of the pro-chirality of the α-olefinic carbon (equation 94). Thermal rearrangement at moderate temperature (> 50 °C) is believed to initiate a skeletal reorganization to the zwitterionic ate complex. A subsequent 1,2-alkyl migration would then form the borolene shown. This bora-Wagner-Meerwein method for the production of boralenes is unprecedented.[71b,159]

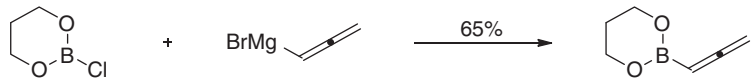


(94)

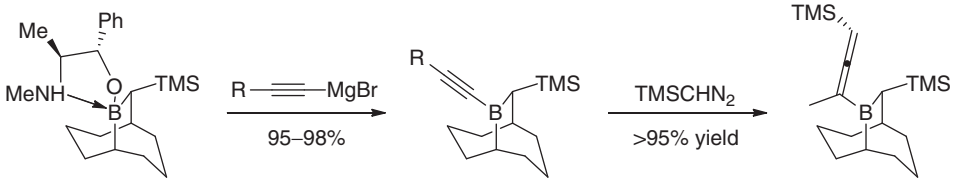
2.01.4 Structural Analogs of Allylboranes

2.01.4.1 Synthesis of Allenylboranes

Perhaps the easiest route to the production of allenylboranes is the nucleophilic addition of allenyl Grignard reagents to boron. This type of reaction generally proceeds in good to excellent yields, so long as a suitable leaving group (Cl, OMe, etc.) is available for displacement. In one example, Brown and Narla produced the simple 2-allenyl-1,3,2-dioxaborinane in good yield (equation 95).[31a,160] Such methods of allene functionalization are commonly used, and can readily tolerate a variety of functional groups. Soderquist and coworkers used this same method of salt metathesis to introduce substituted alkynes which, upon complexation with (trimethylsilyl)diazomethane, readily undergo a 1,3-boratropic shift to give allenylboranes in excellent overall yield (equation 96).[161] These allenylboranes are common reagents which are used in the synthesis of other useful synthons.[97b]

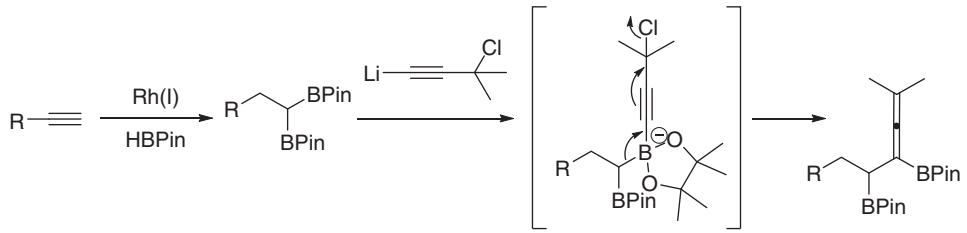


(95)



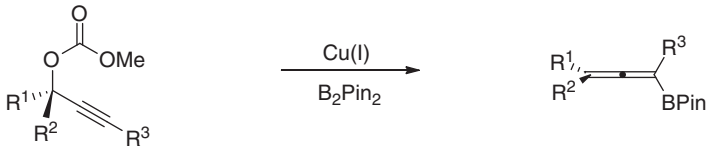
(96)

An interesting approach to the synthesis of α-(boraalkyl)allenyl boranes has been investigated by Shibata and coworkers. Using rhodium(I) complexes, the dihydroboration of alkynes was shown to successfully provide 1,1-diboraalkanes. These methyne-bridged diboranes, when made subject to attack by lithium 3-halobutynides, underwent homologation, with the migrating carbon undergoing an S_N2' reaction, thereby generating the allenic diboranes (equation 97).[162]



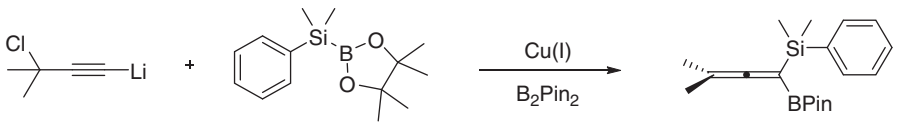
(97)

Along the same S_N2' lines, and very much analogous to the formation of allylic boranes from carbonates, the Cu(I)-catalyzed S_N2' addition to propargylic carbonates has been studied by Ito et al.[163] This methodology leads smoothly to the allenylic boranes in good to excellent yields, with complete regiospecificity, and proceeds without racemization by converting from stereogenic to axial chirality (equation 98).



(98)

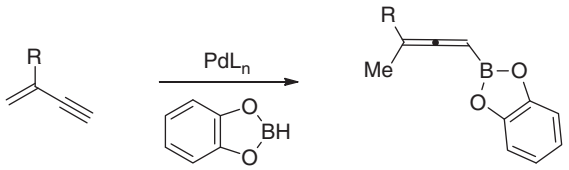
A related methodology has been used to produce the 1,1-silaborylallene scaffolding (equation 99). Reaction of either the same lithium 3-chloroalkynylide with 2-(dimethylphenylsilyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane results in the formation of a similar ate complex, which, on migration of the silyl group in an S_N2' fashion, results in the formation of the 1,1-silylborylallene in moderate to good yields. This reaction also allows for a transfer of stereogenic to axial chirality.[164]



(99)

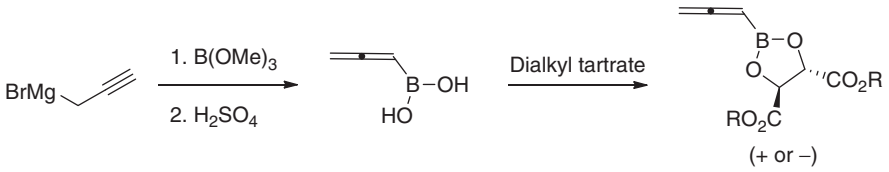
A report by Hayashi and coworkers described the palladium-catalyzed hydroboration of 1,3-enynes with catecholborane.[165] The catalyst system used employed a palladium-phosphine ligand combination (equation 100). Interestingly, the regioselectivity

was entirely dependent on the metal:ligand ratio; the higher this ratio, the higher the 1,4-selectivity. Unfortunately, such selectivity came at the expense of reaction conversion. This drawback is likely to preclude the use of this particular methodology on a preparative scale.



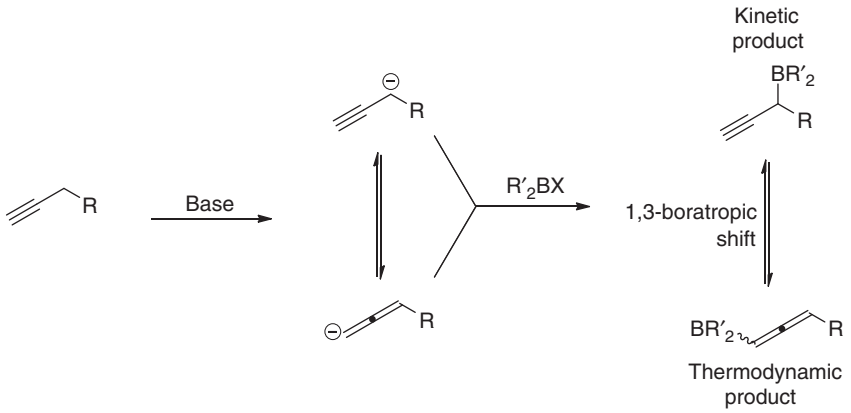
(100)

The introduction of chiral ligands on boron can be used as a means to produce chiral allenylboranes and derivatives. The use of tartrate-based, allenyl boronates was originally reported by Yamamoto and coworkers, wherein they produced either enantiomer of the C2-symmetric, tartrate-derived dioxaborolanes (equation 101). These were used for their ability to transfer chirality in the subsequent propargylation.[166]



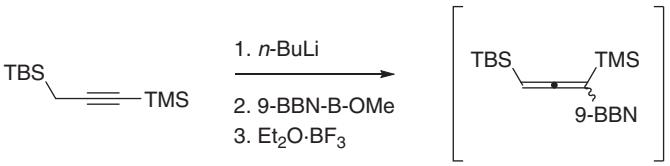
(101)

Just as the strategy of allylic deprotonation-borylation has been investigated for allylic systems, so too has it been utilized for propargylic ones. As propargylic anions can exist as either propargylic or allenic ones, a carefully-controlled derivatization can give rise to either product. Early experiments with the borylation of these anions was shown to be capable of furnishing either product,[167] and that the two constitutional isomers are in rapid equilibrium due to the facility of the 1,3-boratropic shift. However, the thermodynamically more stable allenylic borane can be 'produced' at higher temperatures, whereas the kinetic propargylic borane occurs at the lower temperature (**Scheme 9**).



Scheme 9

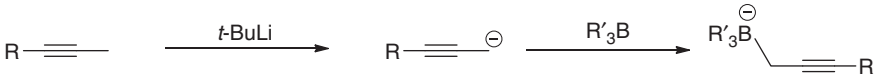
The control of this equilibrium mixture during its reaction has been utilized many times in the literature. For example, Wang has shown that the use of bulkier attachments on the propargyl/allenyl system can determine whether the borylation product will behave as a propargylic or allenic system, and, consequently, deliver allenic and propargylic products, respectively (equation 102).[168] Very similar work has been performed with the use of allenylmagnesium bromide (*vide supra*) which was produced *in situ* from propargyl bromide.[158] Similarly, the use of monosubstituted allenes for the diastereoselective alkylpropargylation of ketones has been described.[169]



(102)

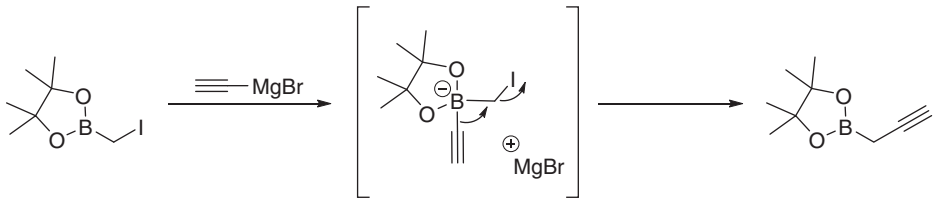
2.01.4.2 Synthesis of Propargylboranes

As discussed in Scheme 9, the use of propargylic anions can give rise to either the allenic or propargylic boranes. Which product is formed (or how it reacts) depends upon the use of specific control features, such as the steric bulk. Grant and coworkers chose a different form of control: if one can prevent entirely the possibility of a 1,3-boratropic shift, then reaction with the propargylic anion must necessarily give the propargylic borate anion (equation 103).[170]



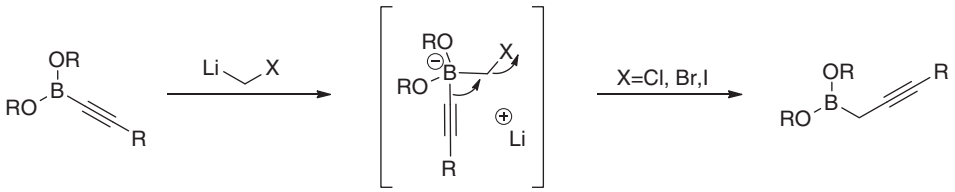
(103)

Another approach to propargylic boranes also involved the formation of the ate complex, this time using an alkynyl anion (equation 104). After it was formed, the high migratory aptitude of the alkyne was used to displace an iodide, giving rise to the propargylic system in good yield.[171] This same methodology has been used to install a terminal trimethylsilyl functionality on the alkyne.[172]



(104)

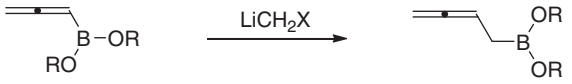
If, in place of attacking the *B*-iodmethyl group with the acetylenic anion, an α-haloanion is used to attack an acetylenic borane, the same method of migration can occur, akin to a Matteson homologation, wherein the migrating group is the acetylenic group.[16a,173] Brown and coworkers reported this work, demonstrating that either chlorides, bromides, or iodides could be used, expectedly, with the latter being the optimum choice (equation 105).



(105)

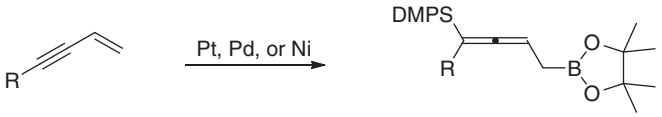
2.01.4.3 Synthesis of Homoallenylboranes

By comparison to some of the other classes of allylboranes, homoallenylboranes and their derivatives have not been studied in great detail. The methods of their production vary from some of the methods used for typical allylic borane systems. The first report of a Mattesson homologation procedure came from Brown.[174] This simple procedure allowed for the formation of these allenes in very good yields, but the reactions time varied from thirty minutes to several days (equation 106).



(106)

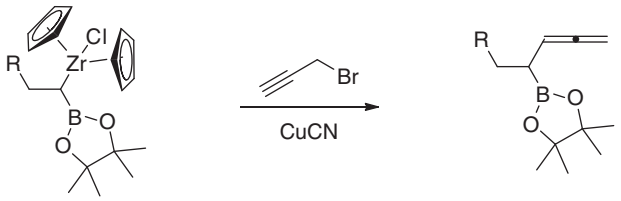
In a 2008 report, Moberg and coworkers demonstrated that the borylsilation of 1,3-enynes can proceed in either a 1,2- or a 1,4-fashion, depending upon the substrate bulk (equation 107). Using platinum, nickel, or palladium, in conjunction with an appropriate phosphine-based ligand, could provide either the 1,2- or desired 1,4-addition product.[175] A similar report allowed for the synthesis of simple allenylboronates from propargyl halides, acetates, and tosylates, which can react with α-(iodozinc) boronates via copper catalysis.[176]



(107)

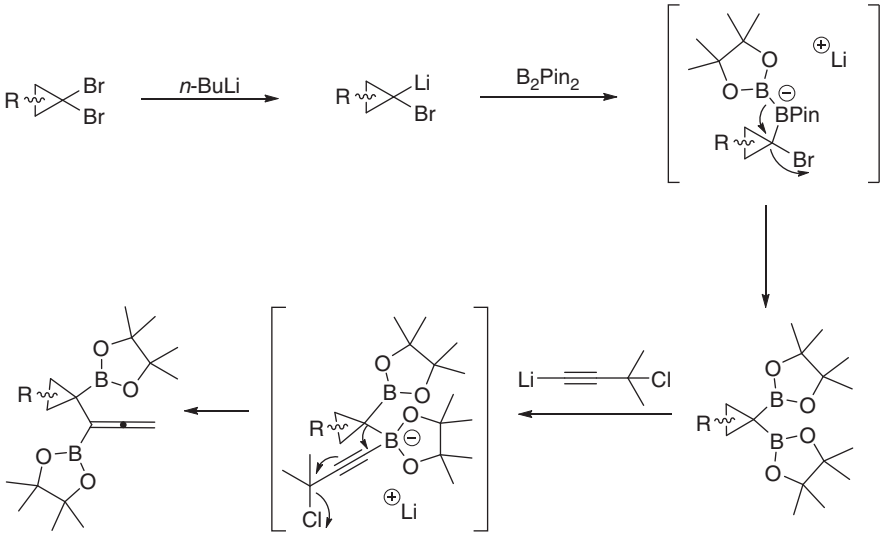
DMPS = dimethylphenylsilyl

An early report by Srebnik and coworkers described the preparation of such homoallenic boronates from α-zirconylboronates.[177] Beginning with vinylic boronates, hydrozirconation, followed by a copper(I)-catalyzed addition onto propargyl bromide provided homoallenylboronates in good to very good yields (equation 108).



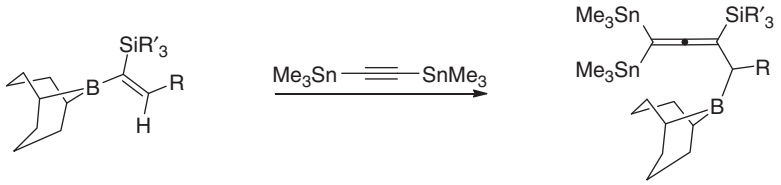
(108)

Homoallenylboronates with a 1,2-diboryl moeity have been produced from 1,1-dibromocyclopropanes.[178] Treatment of these cyclopropanes with *n*-butyllithium forces lithium–halogen exchange which reacts with bis(pinacolato)diboron to give the ate complex. Migration of the boryl group thereafter occurs to substitute the second boryl group in place of the remaining bromide. Treatment of the 1,1-diborylcyclopropane with lithium 3-chloro-3-methylprop-1-ynylide forms a second ate complex, which again undergoes a migration to give allenyl/homoallenyl diboronates in moderate to good yields (equation 109).



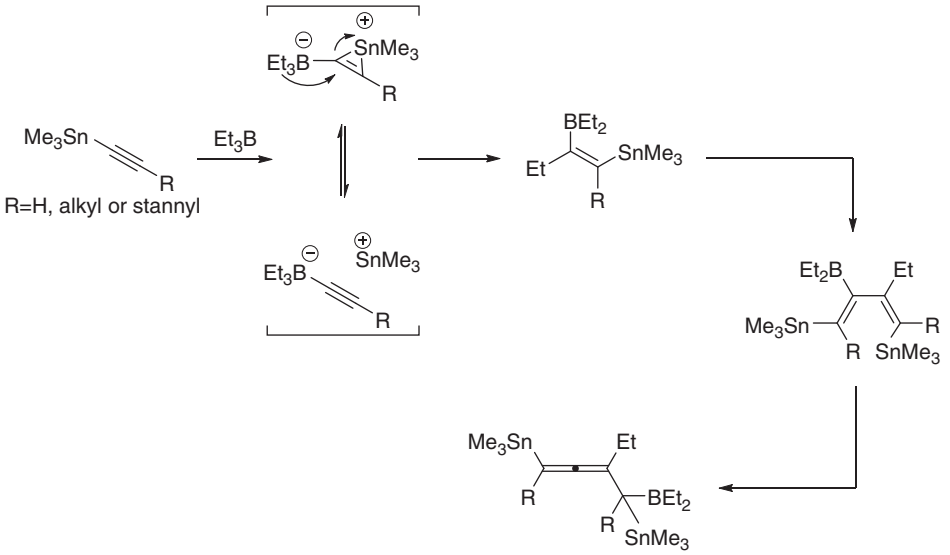
(109)

Highly functionalized homoallenic boranes have also been produced via an unusual rearrangement that takes place *in situ*, following a 1,1-vinylboration reaction.[179] As unexpected as these rearranged products may seem, there is little doubt as to their formation, as these highly functionalized intermediates were fully characterized by their ^{1}H, ^{11}B, ^{13}C, ^{29}Si, and ^{119}Sn NMR spectra. Interestingly, the central carbon of the allenic scaffoldings had surprising ^{13}C shifts, most likely due to the effects of the silicon and stannyl substituent. Nonetheless, further evidence in the form of single crystal X-ray analysis was performed on two of the substrates to unambiguously prove their structures (equation 110). Some very similar work was later performed with lead-based alkynes in place of stannyl acetylenes.[180]



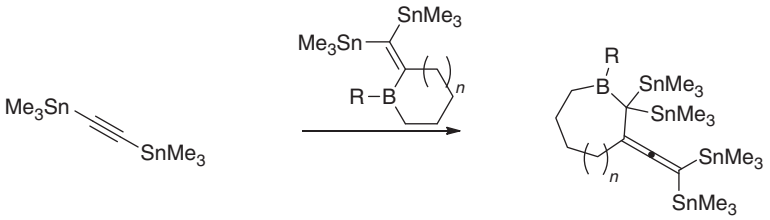
(110)

Similar chemistry had been reported some time before this, in which triethylborane was allowed to react with acetylenic mono- or distannanes.[181] The reaction was believed to proceed by an initial electrophilic displacement of the stannyl moeity, giving rise to the trialkylstannyl borate salt (or possibly the alkynyl-stannane chelate). Migration of a boron ligand to the alkyne occurred with acetylenic–allenic rearrangement to give a 1,2-borastannane. Reaction of this intermediate with a second alkynyl stannane, followed by 1,3-boratropic shift gave α,δ-bis(stannyl)homoallenic boranes as products (equation 111).



(111)

While studying on the ring expansion of boron-incorporated cyclic systems, Wrackmeyer et al. demonstrated the formation of homoallenic boracycles possessing multiple stannyl substitutions.[182] These expansions are believed to proceed through a similar mechanism: boron–tin 'exchange' to obtain the zwitterionic coordinate species, followed by migration of the carbon ligand. Such expansion necessitates the observed ring expansion (equation 112).

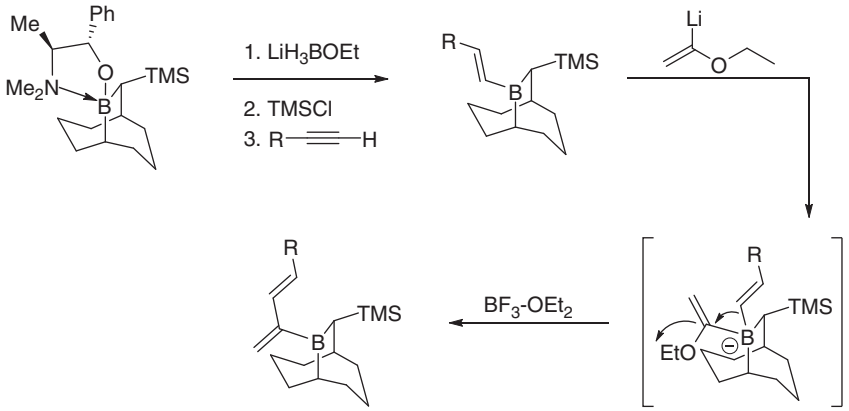


(112)

2.01.4.4 Synthesis of α-Ylidenyl(Allylic, Propargylic, or Homoallenic)Boranes

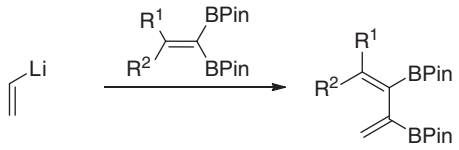
The interruption of the allylic, propargylic, or homoallenic borane functionality with a π-system makes up a unique class of boranes. So long as the local molecular geometry of the molecular scaffolding permits, then there is conjugative overlap of the boron 2*p* orbital with the new π-system; this creates a cross-conjugated system between the boron and the allylic-based π-system. It is perhaps this interaction which causes the many-times-observed enhanced reactivity of these dienes. In fact, so reactive are these species that they many times undergo dimerization via a Diels–Alder pathway.[183]

Soderquist and coworkers reported one such compound which was derived from their 10-TMS-9-borabicyclo[3.3.2]decanes.[184] The reaction of a *B*-vinyl functionality with an alkyl α-lithiovinyl ether resulted in the formation of the expected lithium borate complex. Subsequent migration of the preexisting vinylic ligand occurs with concomitant substitution at the sp^2 carbon (equation 113).



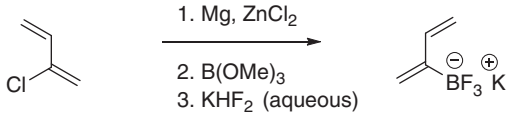
(113)

The interaction of lithium 2,2,6,6-tetramethylpiperidide with vinyl bromide, which results in a lithium–halogen exchange, has been used by Shimizu et al.[185] to provide, on interaction with a 1,1-diborylalkene, a series of 1,2-divinyl-1,2-diboronate species (equation 114).



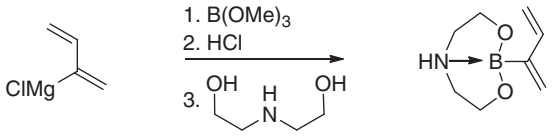
(114)

Welker and coworkers have reported the formation of the trifluoroborate salts of these cross-conjugated allylic systems (equation 115). The production of dienes with these procedures is quite simple, and the resulting products offer the advantage of possessing a significantly enhanced stability, and a lack of propensity to undergo homodimerization via a Diels–Alder pathway.[186]



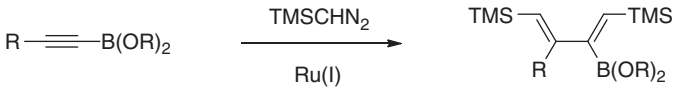
(115)

The same Grignard reagent has been allowed to react with trimethyl borate to give these same dimethyl dienylic boronates.[187] Treatment of the boronic acids (formed by hydrolysis) with diethanolamine formed the amino–boron chelate complex. These were reported to be even more reactive in Diels–Alder reactions than the analogous potassium trifluoroborates, and were also quite stable (equation 116).



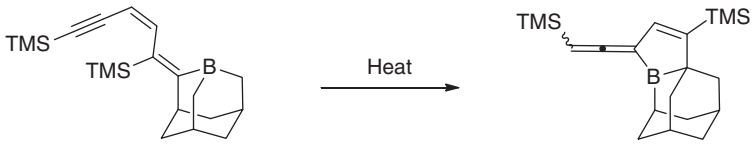
(116)

Shirakawa and coworkers have reported that Dixneuf reaction conditions,[188] when applied to alkynylboronates, can produce these allylic systems in very good yields.[189] An added advantage of this methodology is the enhanced functionalization, which comes in the form of a pair of vinylic trimethylsilyl groups (equation 117).



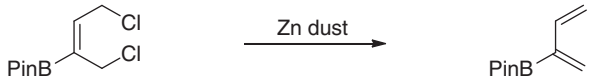
(117)

In a study of the borylation of bis(trimethylsilyl)enediynes, Bubnov and coworkers demonstrated the formation of a very unusual allenylboraadamantane structure (equation 118). This compound is the very first of its structural type reported.[190] There was no stereodefinition given for the axial chirality.



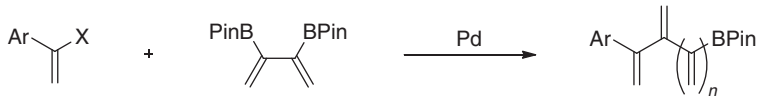
(118)

The facile production of simple 2-(buta-1,3-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane from 1,4-dichlorobut-2-ene was described by Suzuki and coworkers (equation 119). The sequence used: hydroboration, oxidation by acetaldehyde, ester exchange, then reduction with zinc dust, produced the desired compound. Rapid purification by cold trap distillation allowed for the isolation of almost pure compound.[191] If not used rapidly, however, the compound would undergo pericyclic dimerization.



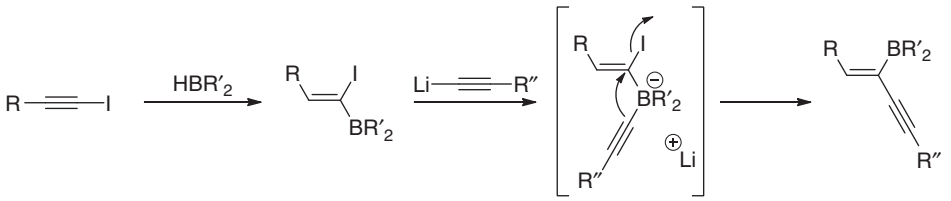
(119)

Shimizu and coworkers have extended the use of their methodology (*vide supra*) in the production of dendralenes that structurally terminate with pinacolatoboryl functionalities (equation 120). These couplings were performed under typical Suzuki cross-coupling conditions with palladium.



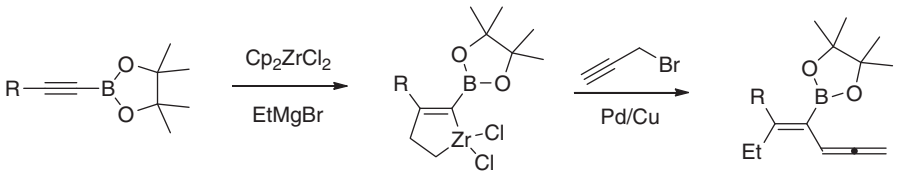
(120)

The related cross-coupled system involving propargylic boranes has only been scarcely reported. Arase and coworkers reported that α-iodoborylalkenes can undergo complexation with acetylenic anions.[192] Migration onto the vinylic position, which occurred with substitution of the iodide, gave rise to this highly functionalized synthon (equation 121).



(121)

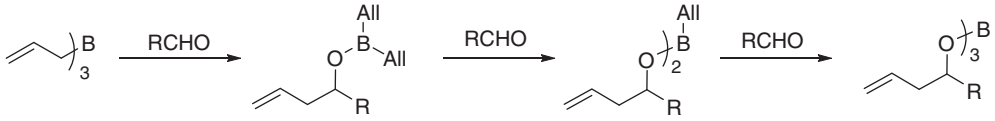
The preparation of the similar cross-conjugated homoallenic boranes was reported by Srebnik and coworkers.[193] Ethylzirconation of 1-boryl substituted alkynes gives rise to cyclic zirconates. They have shown that these cyclic zirconates are incredibly useful synthetic intermediates, and can be converted into a range of functionalities. Under conditions of copper/palladium dual catalysis, these cyclic zirconates can be converted to α-alkylidenylhomoallenic borates (equation 122).



(122)

2.01.5 Allylation of Aldehydes

The first allylboration was reported by Mikhailov and Bubnov in 1964,[194] in which the allylation of aldehydes with triallylboranes was demonstrated (equation 123). In accord with the principle discussed above (see Section 2.01.2.4, **Figure 3**), the decrease in Lewis acidity from borane (to borinate to boronate) to borate decreases the rate of each subsequent reaction, which, in turn, necessitates an increase in the reaction temperature for the second and third allylborations.

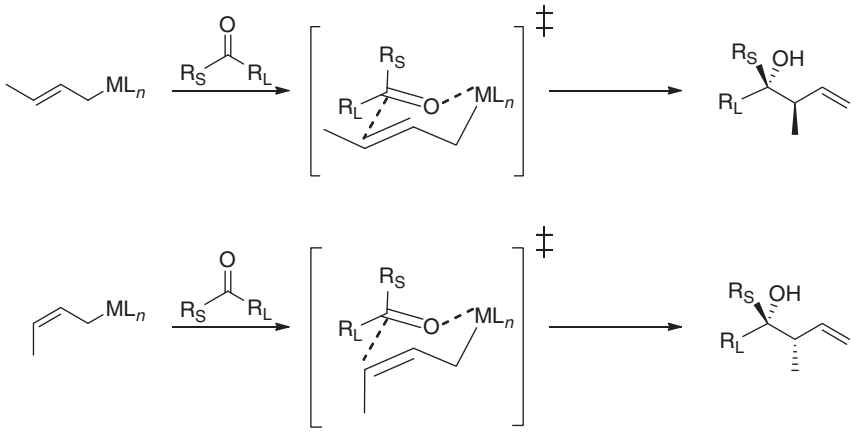


(123)

Since its inception nearly half a century ago, this allylation reaction with borane derivatives has been extended to many functionalities. Incorporation of substitutions – including those which offer further functionality – have been incorporated into the α-, β-, and γ-positions. In those cases wherein only a single stereogenic center is produced in the reaction, the issue of absolute stereochemical control over that center arises. In those cases in which two or more stereogenic centers are formed, the question of the relative stereochemistry between them arises, as does that of the absolute stereochemistry defining them. Many elegant approaches to the solution of stereoselectivity have been taken over time. The question of the absolute stereocontrol is necessarily addressed by borrowing from the chiral pool in one of three manners: the use of an asymmetric allylborane derivative, an asymmetric electrophilic partner, or an asymmetric additive such as a Lewis acid–ligand combination. The question of relative stereochemistry was introduced earlier; the authors finish the discussion here.

The allylboration of most π-systems is believed to proceed through a Type-I mechanism, which necessitates the use of a Zimmerman–Traxler transition state argument as a means to predict the relative stereochemistry (**Scheme 10**).

The explanation of the relative stereochemistry of such reactions has been given as follows: When two groups, one large and one small, are attached to a π-system such as a carbonyl, then a transition state structure is posited to exist akin to those shown in **Scheme 10**. The larger group attached to the π-system will be oriented in the pseudo-equatorial position, whereas the smaller takes on a pseudo-axial orientation. In the case of an *E*-configuration, such as that of the crotyl group shown in the upper pathway of **Scheme 10(a)**, a *syn*-relationship will be formed between the smaller group and the substituent. In the case of an aldehyde, the smaller group is a hydrogen atom, and the resulting product is referred to as the *anti*-product, as the hydroxy and γ-substituents are

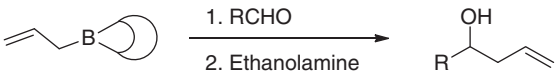


Scheme 10

oriented *anti* to each other. Conversely, when starting with the *Z*-configuration, the final product has the alkyl and hydroxy groups *syn* to each other.

2.01.5.1 Unsubstituted Allyl Groups; No Absolute Stereocontrol

The simple allylboration of aldehydes has advanced in leaps from its infancy nearly five decades ago. Shortly after the report by Brown and coworkers[195] which detailed the allylboration of aldehydes, ketones, acid chlorides, anhydrides, esters, and amides with *B*-allyl-9-BBN and derivatives, they further demonstrated a superior workup technique in the form of an ethanolamine quench (equation 124). This allylative chemical technology was superior in that the issue of stoichiometric control to avoid multiple allylations became more readily controlled.



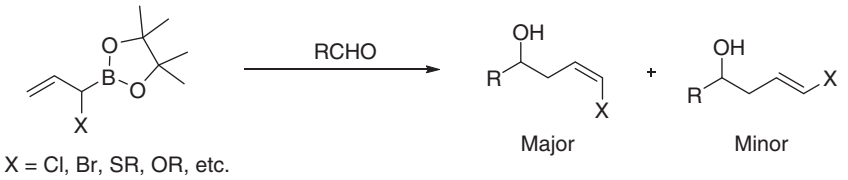
(124)

Experimental evidence for the proposed mechanism of the reaction has been gathered over time.[9a,c,d,196] The effects of typical reaction parameters such as solvent and temperature selection have been well-studied.[13] Furthermore, the intermediate boron-oxygen chelates have been isolated and fully characterized.[23] All collected data have pointed to the pericyclic pathway shown above as being the correct mechanism. This understanding has led to a great generality of the reaction, and has helped to explain its high tolerance for pendent functionalities. For example, the tolerance for allylation to occur with an endocyclic allylborane to give a product of ring cleavage would be difficult to explain without this postulated mechanism.[125] Indeed, the utility of the mechanism in predicting the product of many different skeletal classes of allylboranes in their conversion to products is evident, as a wide variety of structural moieties, including complicated ring systems,[50] can be produced through a simple retrosynthetic analysis.

Many advances have been made over the years with this methodology. Most of them will be discussed in the following sections. In the case of unsubstituted allylboration, several recent advances are worth highlighting. For example, the use of ionic liquids in synthesis is becoming a more commonly used technique.[197] Their use in the allylboration of carbonyl compounds is warranted but understudied. Due to chelative competition, more highly coordinating solvents inhibit the allylboration reaction of carbonyl compounds.[13] As ionic liquids are typically very poor Lewis bases, their use as solvents for this reaction seems natural. Kabalka et al. has investigated this idea, and found that the expected conversion to product occurs in very high yields.[198] The use of Ring-Opening Metathesis Polymerization Gels (ROMPGels) as solid supports for allylation reactions has recently been developed.[199] The biggest advantage of such a procedure is in the ease of product purification; as the products are organic solvent soluble, and the resultant boronates are not, the purification is simply a matter of filtration. Such facility is always a desirable quality for organic transformations. As a converse strategy, the allylation of solid-supported electrophiles has been reported.[200] More recently, an *in situ* enzymatic oxidation–allylation strategy for the synthesis of benzylic alcohols was reported.[201] Allylboration in aqueous media has also been reported.[202]

2.01.5.2 α-Substituted Allyl Groups; No Absolute Stereocontrol

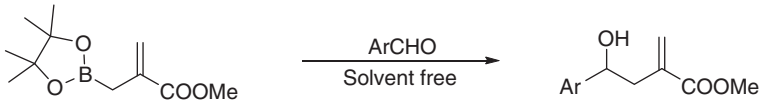
The reaction of α-substituted allylboranes with aldehydes has been scarcely reported in favor of asymmetric variants. However, a few reports do exist of such an allylation. In general, these reactions proceed with very good yields.[140,203] Perhaps unexpectedly, the reaction of α-substituted allylboranes proceeds to give a *cis*-disubstituted homoallyl alcohol (equation 125). The obtained *Z*-stereochemistry is difficult to explain, but it is likely a combination of steric and electronic considerations such as the anomeric effect and molecular dipole considerations.[201]



(125)

2.01.5.3 β-Substituted Allyl Groups; No Absolute Stereocontrol

Similar to α-substituted allylation of aldehydes, the β-substituted allylboration with no stereocontrol has only been reported a few times.[53a] In one such example, the reaction of of β-methoxycarbonylallylic boronates with aldehydes was described (equation 126). As the reactions were performed under mild conditions, several sensitive groups such as dioxolanes were tolerated. Unfortunately, this noncatalyzed reaction was very slow, taking several days to go to completion. In a different example, the incorporation of an azido group at the β-position was described by Brown and coworkers.[138] Nitrile incorporation at the β-position has also been developed.[110]

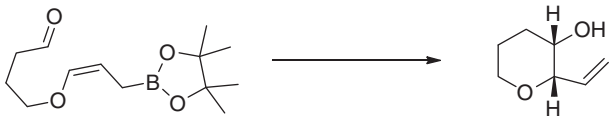


(126)

2.01.5.4 γ-Substituted Allyl Groups; No Absolute Stereocontrol

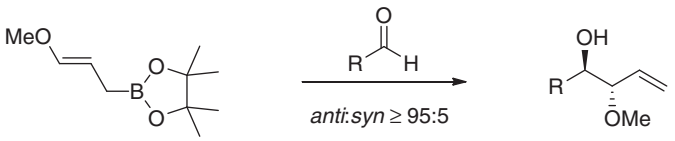
There are countless reports on the use of γ-substituted allylboranes in the literature. As the use of a γ-substituent in the reaction of an allylborane with an aldehyde necessitates the formation of two contiguous stereocenters, the control of diastereoselectivity must be taken into consideration. As mentioned earlier, a *Z*-allyl derivative will give a *syn*-product, whereas an *E*-relationship will give the *anti*-product.

As an example of *syn*-selectivity, the authors consider the case of an intramolecular cyclization.[204] The reaction of the vinylic ether with the tethered aldehyde gave rise to the *cis*-tetrahydro-2*H*-pyran in good yield. The aldehyde, which was producible *in situ* from either an acetal or aminal, reacted cleanly to give >95% *cis*-selectivity (equation 127).



(127)

In contrast to the above example, the intermolecular reaction of the γ-methoxy substituted allylic boronate furnished, upon triethanolamine workup, the *anti*-homoallylic alcohols in good yields and excellent diastereoselectivities (equation 128).[31b] Other work by Hoffmann and coworkers has addressed this diastereoselectivity for similar allylic borane derivatives.[135,154,158]



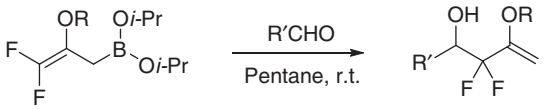
(128)

Many different functionalities have been incorporated into the γ-position, such as alkyl groups,[30a,202,205] halides,[206] and thioethers.[37,207] In one more recent case, the addition of an allylborane as a γ-substituent led to the formation of a diallylating reagent.[208]

There are also many cases of γ,γ-disubstituted allylation reactions. For example, the use of an *exo*-cycloalkanylidenyl fragment as the allylic portion of an allylborane derivative furnished the expected ring system beta to the alcohol residue in resonably good yields.[91] Many times, a silyl moiety is attached, along with another group at the γ-position. Upon allylboration, a vicinal relationship exists between the boryloxy and silyl groups. While the carefully-controlled workup of the reaction can furnish the β-silyl alcohol, these molecules are typically not isolated. Instead the ability of the functionality to undergo a one-pot Peterson elimination through either an acidic or basic pathway, depending upon the workup conditions chosen. The inherent beauty of such a system is that either the *Z*- or *E*-olefin can be produced during the elimination step, thereby correcting for any lack of stereoselectivity that resulted from the γ,γ-disubstitution.[35,93,94,209]

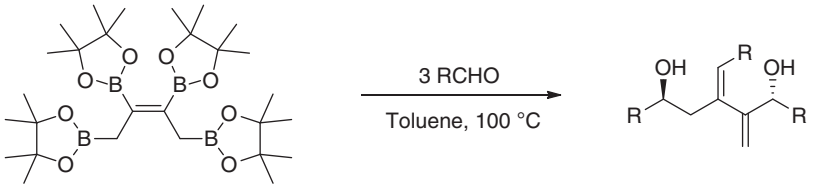
2.01.5.5 Polysubstituted Allyl Groups; No Absolute Stereocontrol

As discussed earlier, the mechanism of allylboration is expected to allow for the polyfunctionalization of the allyl group. Indeed, the incorporation of many different substitutions simultaneously has been performed on a large number of occasions. For example, Ramachandran and coworkers have investigated the allylboration of aldehydes with γ,γ-difluoro-β-alkoxyallylic boronates (equation 129). They have shown that the incorporation of the difluoromethylene into synthons is quite feasible, and proceeds very rapidly at room temperature and in reasonable to very good yields.[61]



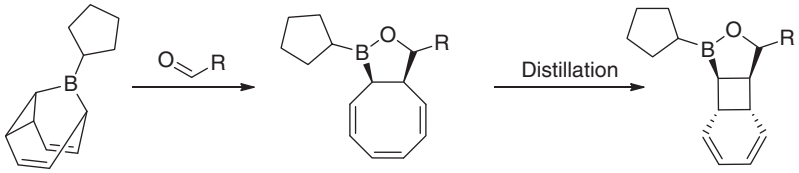
(129)

One very nice example of the use of a polysubstituted allylic borane makes use of the presence of a pinacolatoboryl substituent at each of the three possible positions. This tetraallylating reagent was subjected to an attempted tetraallylboration reaction. While the authors had no difficulty in reacting the reagent with three equivalents of electrophile, an elimination reaction took place in preference to the last allylation (equation 130). Nonetheless, a very simple allylation system was shown to give rise to some very highly functionalized products in very good yields.[109]



(130)

One report of an unusually-structured diallylborane has been shown to give, upon reaction with several different classes of electrophiles, the cyclooctatriene derivates shown.[210] Upon distillative heating, the products undergo a [3,3]-sigmatropic reaction to give tetrasubstituted cyclobutane derivatives. Subsequent oxidation provided the expected diols (equation 131). The original reaction likely occurred through either an allylboration or homoallylboration reaction, and occured with concomitant cyclopropyl ring-opening.



(131)

The incorporation of groups into two or more positions is also a common theme seen in the literature. Perhaps most commonly used are those at the α- and γ-positions simultaneously. For example, carbon and carbon,[30c,211] carbon and nitrogen,[123b,c] nitrogen and carbon,[68] and carbon and silicon[117] have been reported. Some examples of symmetric allylborations with β- and γ-substitutions are also common.[63a,159,212] The incorporation of three or more groups into allylboranes without any level of stereocontrol is relatively rare, but has been reported.[54a,213]

2.01.5.6 Unsubstituted Allyl Groups: Boron-based Absolute Stereocontrol

The allylation of aldehydes with chiral groups present on the boron atom was first reported by Hoffmann and coworkers in 1978.[148b] Since that seminal report, the practice of asymmetric induction through the use of chiral ligands (**Figure 5**) on the boron atom became further advanced. Subsequent reports came from Hoffmann and Landmann, wherein an α-chiral α-chloroallylboronate was reported,[214] along with derivatives formed from that synthon. A report focusing on the promise of tartrate-based ligands was published by Yamamoto and coworkers,[166] then popularized by further reports by Roush et al.[215] Corey and coworkers promoted the use of chiral 1,3,2-diazaborolidines for asymmetric induction.[21g] While each of these chiral borane derivatives has been demonstrated to offer great utility, perhaps none has been found to be so very general as that published by Brown and Jadhav, in which the use of chiral isopinocampheyl ligands for asymmetric allylation was reported.[19] This ligand has taken on such widespread use in synthetic chemistry that a comprehensive review of its reports would extend beyond the scope of this review. Important, however, is the understanding that its use for asymmetric induction in simple allylation reactions provides very high enantiomeric ratios (equation 132). Fortunately, both isopinocampheyl enantiomers are relatively inexpensive, as they are abundantly available from natural sources.

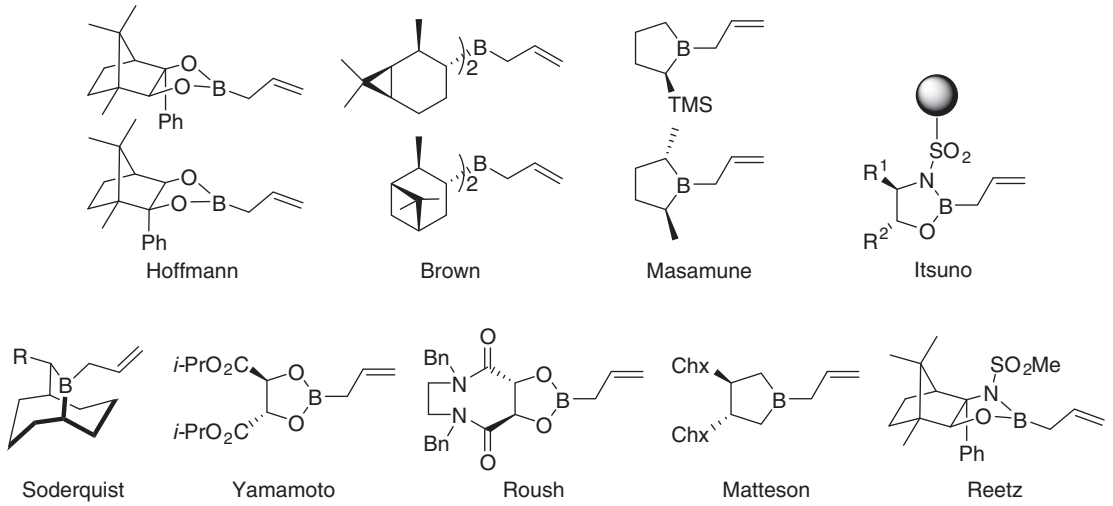
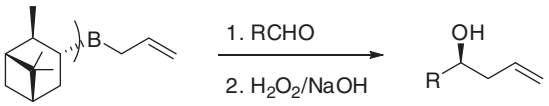


Figure 5 Chiral allylborons.

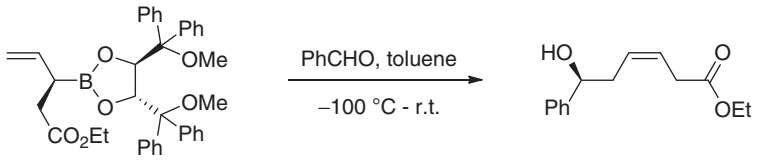


(132)

The use of Brown's asymmetric allylboration reagent has become widespread, and, although limited by its stoichiometric nature, is still many times the reagent of choice for allylations of simple aldehydes,[25,216] heteroaromatic aldehydes,[217] dialdehydes,[218] and those tethered to metal complexes,[219] and is used in the synthesis of important synthetic building blocks such as amino acids[220] and lactones.[221] Much work from others has appeared over the years,[21g,136g,222] including more recently with Soderquist and coworkers and their use of 10-TMS-9-borabicyclo[3.3.2]decane derivatives.[21i] Many other chiral ligands for boron have appeared during this time; their use in allylboration has had varying results.[20,21f,51,136a,c,d,h,223] The use of cyclophanes as asymmetric inducers has also been investigated.[224] The use of solid supports as an anchor for the aldehyde and allylating agent have also both been reported.[136f,225]

2.01.5.7 α-Substituted Allyl Groups: Boron-based Absolute Stereocontrol

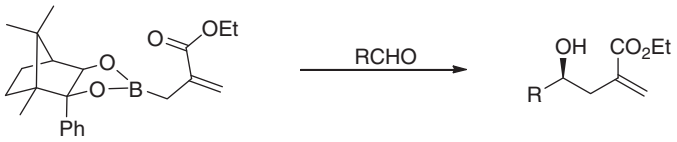
Few reports have appeared that detail the use of chiral borane derivative bearing an α-substituent for allylation of an aldehyde. Most of these have been discussed already, vis-à-vis those derivatives of α-chloroborane derivatives. However, one particular work stands out. The use of a boron variant of either the Johnson–Claisen or Eschenmoser–Claisen sigmatropic reaction to product α-carbon-chiral allylic boronates was described.[127] The use of this reagent in reacting with aldehydes offered excellent yields and diastereoselectivities (equation 133). (The term diastereoselectivity is used here as the molecules produced were possessing of a *cis*-olefin, and the possibility for geometric isomerism existed. The stereogenic carbon was produced with a 98:2 ratio of optical isomers.)



(133)

2.01.5.8 β-Substituted Allyl Groups: Boron-based Absolute Stereocontrol

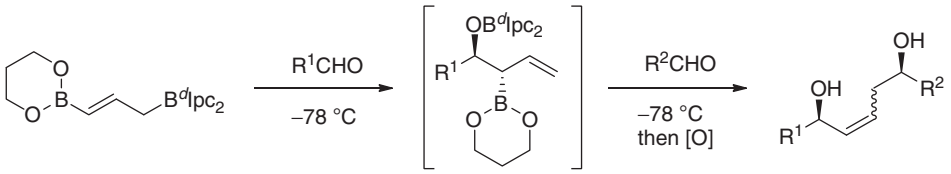
Camphor-derived, β-substituted allylboronates have been used as a means to produce geminally-disubstituted alkenes (equation 134). This particular chiral auxillary was introduced by Hoffmann;[148a] a later synthesis by Hall has offered improved access to this structure.[148c] The conversions and enantiomeric ratios were generally quite good. Villiéras and coworkers have also reported on several other unique, asymmetric borane derivatives for allylboration.[53b,55] Many other substituents have been incorporated into the β-position, such as alkoxymethyl groups,[226] borylmethyl groups (for double allylation),[227] silicon-based groups,[24] and alkyl groups.[228]



(134)

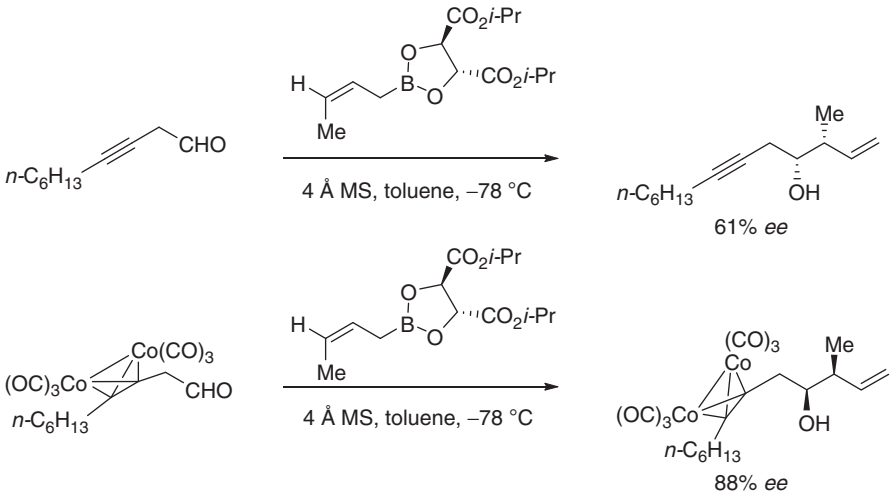
2.01.5.9 γ-Substituted Allyl Groups: Boron-based Absolute Stereocontrol

There are many reports of absolute stereocontrol during the allylboration reaction of an aldehyde with chiral γ-substituted allylborane derivatives. For example, Roush and coworkers have reported on the use of diallylating reagents in which a boronate and a borinate are both present (equation 135). The borane is fitted with two isopinocampheyl groups which are used to induce asymmetry in the reaction. Indeed, the diallylation with two aldehydes was shown to proceed in moderate to excellent yields and with excellent stereoselectivities.[97d] They have actually performed a large amount of work in this area, focusing mostly on further developments with chiral induction through the use of either a diisopropyl tartrate-derived chiral boronate,[229] or with Brown's diisopinocampheylborone derivative.[95a,96,97a,230] They have applied this work in synthesis as well.[97b]



(135)

The Brown research group was one of the largest contributors to the study of γ-substituted chiral borane derivatives, focusing mostly on the allylboration variant now termed crotylboration. These reactions have proven immensely important in organic synthesis, as the β-hydroxymethyl moiety is nearly ubiquitous in natural products. There are two aspects that make his crotylboration highly useful. First, additional reports have shown that the enantio- and diastereomeric ratios remain nearly unparalleled and as consistently high as those given in the original reports. Second, they showed that the enatiomer of the chosen ligand will determine the absolute stereocontrol of the formed stereocenters, and that the geometric isomer chosen could determine the relative stereochemistry of the two stereogenic groups. Thus, the appropriate crotylborane precursor can give rise to any of the four possible stereoisomers.[30b,c,231] Brown and coworkers have also incorporated other groups into the γ-position.[45b,92a] Work with other chiral ligands has appeared in the literature,[21c] as has the incorporation of other γ-substitutions such as amines,[36] alkoxy groups,[232] and halides.[233] Alkyl, alkyl disubstituted allylborane derivatives have also been reported.[234] Roush and coworkers have also shown that certain α,β-unsaturated aldehydes, when allowed to react with the Pauson-Khand catalyst dicobalt octacarbonyl, form the dimetal complex (equation 136). The latter gives the opposite stereochemistry when subjected to asymmetric allylboration conditions with chiral crotylboronates.[235] Similar work was subsequently investigated by other groups.[236]

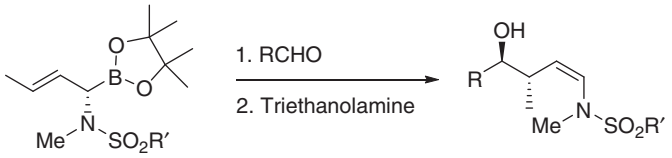


(136)

2.01.5.10 Polysubstituted Allyl Groups; Boron-based Absolute Stereocontrol

Chiral allylboration, wherein the chirality stems from an asymmetric feature on the boron reagent, has been utilized as a means to produce very complicated and highly functionalized adducts. The combination of different substituents can lead to a diverse array of molecular skeletons with differing isomerism. For example, α-chiral-α-sulfonimidocrotylboronates, which are formed by an

allylic displacement of a silyloxy group with concomitant rearrangement from a vinylic to an allylic borane, have been shown to react with aldehydes in good yields, with excellent geometrical stereocontrol, and with superb stereogenic control (equation 137). This transformation proceeded with the expected *cis*-stereochemistry, as was demonstrated above. It was further used for a simple synthesis as an exemplification of its high diastereoselectivity.[237]



(137)

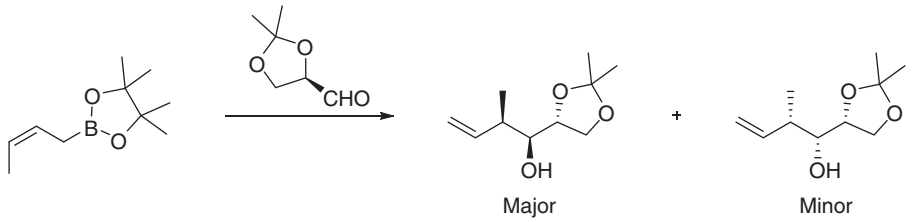
There are many other examples of multiple substitutions being incorporated in such reactions. For example, the use of carbon–boron,[144] acyclic carbon–carbon,[129] cyclic carbon–carbon,[126c] carbon–nitrogen,[238] carbon–oxygen,[123f] oxygen–carbon,[40] and silicon–carbon[239] groups as α-γ-substitutents has been reported. β,γ-disubstituted[80,136b] and polysubstituted allylic systems, including those allowing access to perfluorinated systems have also appeared in the literature.[61a,240]

2.01.5.11 Allyl Groups: Aldehyde-based Absolute Stereocontrol

As an alternative to chiral induction through the use of an asymmetric allylborane derivative, stereoselectivity can be dictated through an asymmetry already present in the aldehyde. The advantage of such a pathway lies in the fact that synthetic routes to chiral aldehydes are well-established, and many are either synthetically or commercially available. Most typically, chiral induction is preferred with the use of α-chiral aldehydes, as chirality transfer from remote stereocenters is more difficult.[241]

The nature of the chiral induction during attack onto aldehydic electrophiles is usually explained through the use of the Cram, Felkin-Ahn, or Karabatos models. As a first approximation, the use of the Felkin model is many times accurate enough for allylboration reactions. However, as such allylboration reactions proceed through a closed, Type-I mechanism, these models can be misleading. Roush and coworkers proposed one simplified explanation of the stereochemical outcomes of these reactions, in which the preferred transition state will be that in which the minimal level of pseudo-*syn*-pentanyl interactions between the aldehydic α-substituent and the γ-position of the allylic system exists.[242]

One of the most commonly used α-chiral aldehydes is the acetonide-protected glyceraldehyde, which is derived from the enantiopure and inexpensive D-mannitol. The crotylboration of this aldehyde in the absense of other chiral agents has been studied by Roush and Walts.[243] They showed that the use of the *cis*-crotyl reagent gave the *syn*,*anti*-diastereomer as the major product, whereas the *trans*-crotyl furnished the *syn*,*syn*-diastereomer (equation 138).

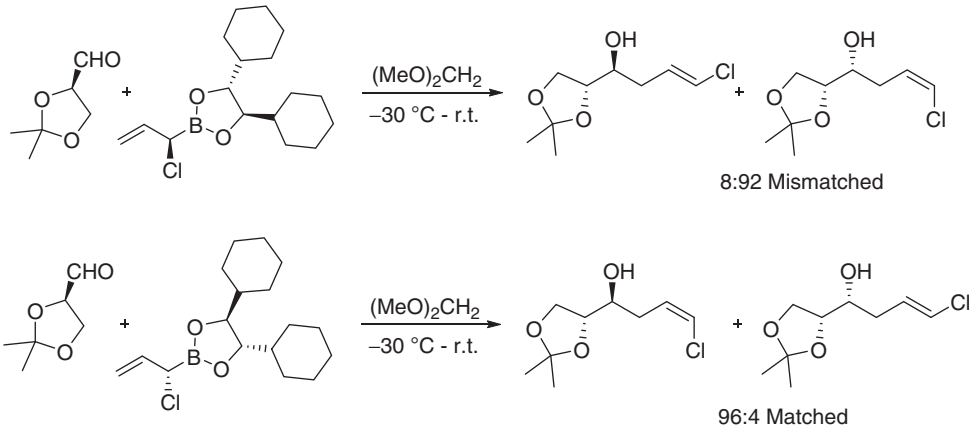


(138)

Many different types of chiral aldehydes have been used for induction, but the same basic models usually apply to their stereoselectivity. A variety of different α-, β-, and γ-chiral aldehydes has been used with a wide range of results, as have aldehydes with multiple stereocenters. Additionally, chirality stemming from other structural types such as cyclophanes has been studied.[38,58,244] The multitudinous amounts of data have typically shown that, as expected, the closer the preexisting chiral center is to the aldehyde, the higher the degree of influence.

2.01.5.12 Allyl Groups: Mixed Stereocontrol

The combination of two or more chiral reagents in allylboration leads to one of three possible stereochemical outcomes. The first, and least likely outcome, is that there is little difference in the stereoselectivity when compared to using only a single chiral reagent. The second possible stereochemical fate of these reactions occurs when the geometry of the aldehyde and that of the nucleophilic borane derivative compliment each other. This so-called 'matched chirality' usually enhances the selctivity, as the two species' steric bulk (or other factors) work together to more kinetically shield either the *re* or *si* prochiral face of the aldehyde from attack. The third possible outcome occurs when the combination of the two chiral reagents work to shield the opposite sides of the electrophile. This last case, usually termed 'mis-matched chirality', does not favor either side of the aldehyde, and will typically lower the selectivity, or sometimes reverse it entirely, depending on which other factors are actively affecting the orientation of the molecular collisions.[136c,245] For example, Hoffmann and coworkers reported[51] that the use of a chiral glyceraldehyde, in combination with the two possible enantiomers of the 4,5-dicyclohexyl-1,3,2-dioxaborolane shown, could give rise to either diastereomer, depending upon the state of matching (equation 139).



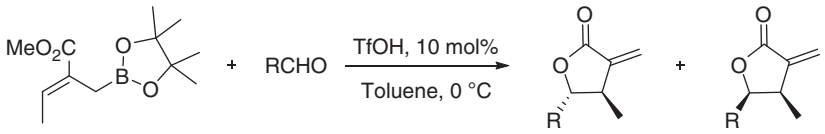
(139)

Unfortunately, modeling the combination of matching and mismatching reagents typically reduces down to simple experimentation, as the typically high cardinality of the set of degrees of freedom for these complex systems allows too much opportunity for reorientation, and many times an unexpected geometrically optimized pathway results, thereby rendering computation a moot point. As a result, most research will attempt to use both possible combinations (i.e., a fixed chiral aldehyde and either enantiomer of the chiral borane, or vice versa). As expected, the closer the aldehyde's stereogenic center is to the aldehydic carbonyl, the larger the possible effects of matching and mismatching. Many cases of α-,[128b] β-,[136b] γ-chiral[21c,246] aldehydes have been reported with incidences of matching. Issues of matching also arise when aldehydes with multiple stereogenic centers are used as electrophiles.[38,244f,247]

2.01.5.13 Allyl Groups: Brønsted–Lowry Acid Catalysis

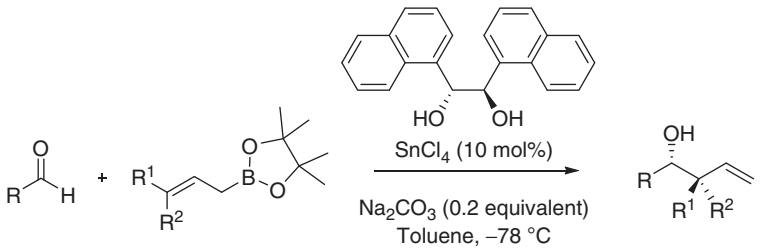
The idea of using a catalyst to accelerate an allylboration rection is seemingly counterintuitive, as such allylboration reactions proceed by means of a Type-I process. Additionally, the notion of coordinating an aldehyde (or other equivalent electrophile) to two different acid catalysts – be they of the Lewis or Brønsted–Lowry type – is generally considered unlikely. In fact, an improper coordination may result in a change in the reaction's pathway from a Type-I to a Type-II process. As the latter typically occurs with diminished stereocontrol, such a pathway change is seemingly undesired. Luckily, the mode of coordination for catalyzed allylboration reactions has been shown to occur at the boronate site. Actually, the coordination of one of the oxygen's lone pairs to the catalyst minimizes the mesomeric effect, thereby rendering the boron center more Lewis acidic. As discussed earlier, this necessarily increases the rate of allylation.

Recently, Hall and coworkers demonstrated that several different superacids could catalyze the allylation of aldehydes with sterically encumbered allylic boronate derivatives (equation 140). Interestingly, the acid catalyst was likely being used for several different purposes at once. For example, the acid not only catalyzed the allylboration reaction, but also catalyzed the lactonization. Depending on the electronic nature of the aldehydic 'R' group, a carbocation could form, and stereochemical rearrangement could take place.[248] This concept has been extended by Rychnovsky to permit the allylboration of aldehydes and ketones with the trifluoroacetic acid-catalyzed activation of allyldiethanolaminoboronate complexes.[249] Also, the use of chiral 1,1'-bi-2-naphthol (BINOL)-derived phosphoric acids has been shown to activate allylpinacolboronates sufficiently for the catalytic allylation of aldehydes. Additionally, the axial chirality has been shown to translate efficiently into the product, providing excellent enantiomeric ratios without the expense of yield.[250]



(140)

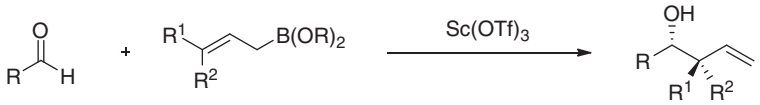
In certain cases, the use of a Lewis acid can serve to activate a Brønsted acid, thereby drastically decreasing the *p*Ka. This idea has been extended by Hall and coworkers to include the atropisomerically chiral Brønsted–Lowry acid derivatives (equation 141). The *in situ*-produced, chiral superacids can be used in the activation of allylic boronates for their reactions with aldehydes. Good to excellent levels of chiral induction have been demonstrated with this method; most of the reactions reported were nearly quantitative in both conversion and isolated yield. This has been extended to other chiral pro-protic catalysts as well.[251]



(141)

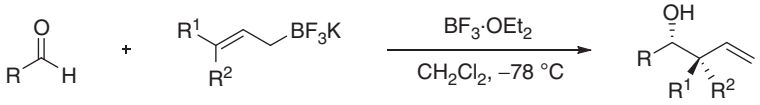
2.01.5.14 Allyl Groups: Lewis Acid Catalysis

Identical to catalysis with protic acids, Lewis acids are known to activate allylboronates through a coordination of the boron's alkoxy ligand to an external metal center. The first clear examples of this type of Lewis acid catalysis were reported nearly simultaneously by Hall[252] and Miyaura.[253] In Hall's case, the use of catalytic scandium triflate was shown to be capable of furnishing either the *syn*- or *anti*-product without epimerization (equation 142).



(142)

As a different manner of Lewis acid activation, the authors consider allyltrifluoroborate salts. The reaction of these salts with aldehydes does not proceed, even at elevated temperatures.[254] However, simply removing one of the fluoride ligands allows for the reaction to proceed, due to the highly reactive nature of the allyldifluoroborane. This method of activation is arguably not catalytic, as a stoichio- or even superstoichiometric amount of additional fluorophilic borane must be added, but it is, nonetheless, a Lewis acid-promoted reaction, and deserves mention (equation 143).



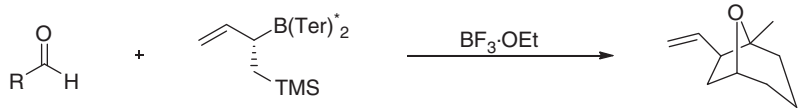
(143)

The use of Lewis acids as promoters and/or catalysts for allylboration has grown rapidly, more so in recent years. For example, boron trifluoride, either naked or in combination with silica gel, has proven to be a very effective catalyst.[81a,b,255] Silica gel alone has also been demonstrated to catalyze such additions,[256] as has cobalt,[119,141] rhodium,[257] and indium and ytterbium.[56,123f,258] There are many reported examples of allylborations that take place in tandem with other reactions; the complex nature of the transformation makes it unclear whether the Lewis acid plays a direct role in the allylboration.[107b,151b,259] The use of Montmorillonite K10 as a catalyst for allylborations has also been investigated.[260]

2.01.5.15 Asymmetric Allylation with Chiral Allyl Groups: Lewis Acid Catalysis

The idea of extending chirality into the allylboration transformation, in conjunction with that of an acid catalyst, is a natural extension of the above idea. And, just as with the above, the chirality may stem from a chiral borane, Lewis acid, or aldehyde.

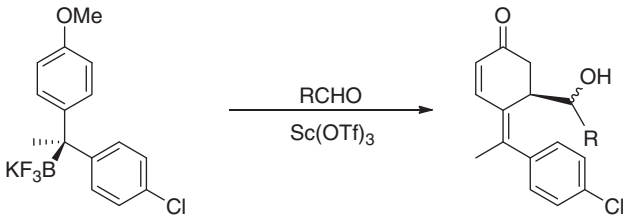
Many of the reports in this area have stemmed from the boron trifluoride-promoted allylation of aldehydes with diallylating reagents. For example, Hall has shown that α-silylmethylallylboronates will undergo double allylation in the presence of boron trifluoride (equation 144).[261] The reaction proceeds through the promoted allylboration, followed by the promoted allylsilation. This work has since been extended to include polysubstituted tetrahydrofurans.[262]



(144)

This work has since been pursued by Roush and coworkers for the formation of *E*-homoallylic alcohols, as well as several other molecular moieties. Unlike the earlier reports which detailed the formation of *Z*-disubstituted olefins, the obtained *E*-alkenes were believed to be formed preferentially as a result of the avoidance of sterically-demanding A-1,3 interactions in the transition state. The latter would be formed as a result of the α-substituent and the Lewis acid sharing pseudo-axial positions in one possible pathway, but not in the other.[103,263] Work towards the use of asymmetric allylboration, starting from chiral boranes, under the conditions of scandium-catalysis, has also been explored;[264] platinum has also been used, although whether it acts as a catalyst for allylboration is unclear.[265]

One very interesting report of a rhodium-catalyzed allylboration was that of a benzylic trifluoroborate, in which a dearomatization was found to take place (equation 145). It was shown that this reaction of 4-methoxyphenyl derivatives proceeded to give cyclohexenone derivatives, with demethylation and attack into an electrophilic aldehyde.[266] While the reaction did not occur with appreciably high yields, levels of diastereoselectivity, or even transfer of stereogenicity, the dearomatizing nature of this reaction is quite unique.



(145)

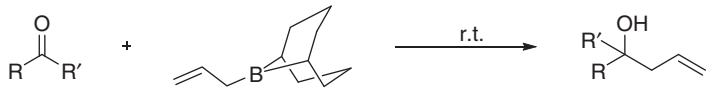
The use of chiral Lewis acid–ligand combinations can theoretically provide for a level of the control of absolute stereochemistry. Thus far, this reaction remains a sought-after goal, with only moderate levels of success having been found. For example, BIPY-derived zinc[267] and aluminum–BINOL complexes have been shown to induce reasonable levels of chirality during allylboration reactions. There are also many reports of allylation catalysis which appear to be allylboration reactions, but which, on closer examination, are seen to not actually be allylboration catalyzed by a chiral Lewis acid. For example, allylation reactions which start with an allylborane, but undergo transmetallation followed by allylation are known.[268] As another example, the use of chiral Lewis acids to form a chiral allylborane has been reported. The latter, which is produced *in situ*, undergo subsequent allylation.[83,84b,123d,e]

2.01.6 Allylation of Ketones

2.01.6.1 Unsubstituted Allyl Groups; No Absolute Stereocontrol

Virtually all of the effects and principles that dictate the reactions of allylborane derivatives with aldehydic substrates can be applied in the analogous reactions with ketones. As such allylation reactions of ketones are more difficult than for aldehydes, fewer examples have appeared in the literature. When they have appeared, the conversions are typically poorer, and the selectivities lower, due to a decreased disparity of the steric demands of the two ketonic alkyl groups.

Just as with their aldehydic counterparts, some of the earliest research on the allylation of ketones was performed by Brown.[195] For example, *B*-allyl-9-BBN was shown to react very rapidly with aldehydes, but far more slowly with ketones (equation 146). Even very hindered ketones (such as *tert*-butyl isopropyl ketone) were suitable substrates, as were cyclic ketones such as cyclohexanone.

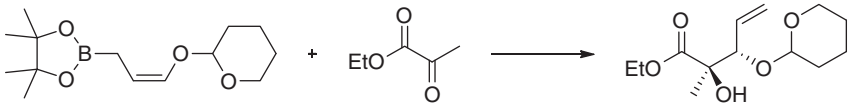


(146)

This simple allylation has since been extended to a wide variety of ketones, but is most frequently used in activated cases such with isatins and isoquinolines,[269] and α-[270] and β-carbonyl ketones.[271] Just as with aldehydes, the use of directing groups can dictate the relative stereoselectivities of the allylation.[272] Furthermore, this reaction has been developed to include the less reactive boronates and borinates,[23] and has been performed with other reaction mediums such as ionic liquids.[198]

2.01.6.2 Substituted Allyl Groups; No Absolute Stereocontrol

The allylation of ketones has been shown to be quite tolerant of substitutions, along with poly- and heterofunctionalities, just as is the case for aldehydes. For example, the moderately acid-sensitive γ-(tetrahydropyranyloxyallyl)boronates have been shown to react with pyruvic ketones under high pressures and at moderate temperatures to give very good yields of the expected product (equation 147). The labile THP-group was surprisingly inert to the reaction conditions.[273]

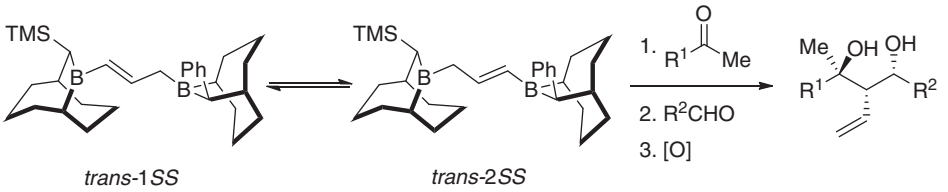


(147)

Most of the substitutions reported to date are carbon-based ones,[274] but others such as silicon[209b] have been incorporated. There are also reports of polysubstituted allyl groups in the allylboration reaction of ketones.[275]

2.01.6.3 Allyl Groups; Boron-based Absolute Stereocontrol

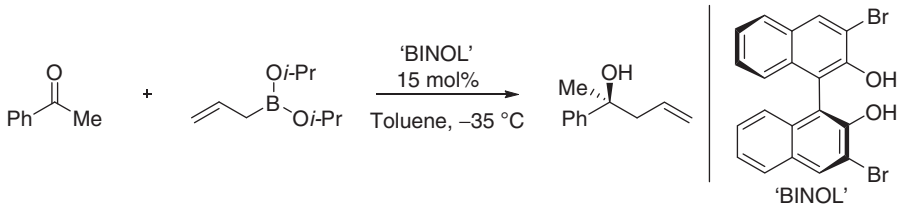
The use of chiral borane derivatives to control the absolute stereochemistry in ketone allylation reactions has been developed, although not as fully as that of aldehydes. The first report of the asymmetric allylation of ketones was made by Brown and Jadhav,[25] and proceeded with only moderate levels of stereoselectivity. Significant improvements have since been made by Soderquist and coworkers, who have demonstrated that the use of diallylborating reagents can react first with a ketone, and then an aldehyde to give the homoallylic bis-alcoholic product.[97e] This three-sequence reaction was reported to occur with a variety of ketones, with generally good yields and exemplary enantiomeric ratios (equation 148).



(148)

Only a few other reports have surfaced in the literature reporting the attempts to control the stereochemistry of these ketone allylboration reactions through use of a chiral borane derivative. Atropisomeric BINOL derivatives,[276] 9-BBN-derived functionalities,[277] and glycol derivatives such as tartrates[278] have appeared, but mostly reporting only moderate success.

Several interesting reports have been published which demonstrate that the inclusion of a chiral, BINOL-derived pro-ligand can affect the chirality during the allylation of ketones (equation 149). Mechanistically, the reaction has been postulated to proceed by asymmetric allylation with a boron complex consisting of a single isopropanol ligand and the mono-chelated BINOL-derivative. Thus, a single exchange takes place, giving an active species which is the actual allylation reagent. In this manner, near-perfect levels of enantioinduction have been shown to take place.[279] This chiral ligand can actually be recycled in the reaction medium, thereby allowing it to serve as a formal catalyst. Similar work has been reported in the context of a 1,2-allylation of α,β-unsaturated ketones to give, on oxy-Cope reaction, a 1,4-addition product.[280]



(149)

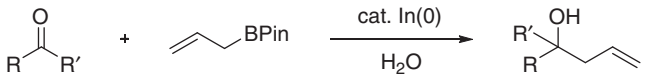
2.01.6.4 Allyl Aroups: Brønsted–Lowry Acid Catalysis

To date, there has been very little published on the use of a protic acid as a catalyst for the allylation reaction of ketones. In one report,[281] the use of *p*-toluenesulfonic acid monohydrate was demonstrated to serve as a suitable surrogate for the Lewis acid-promoted defluorination of allyltrifluoroboronates. Unfortunately, little evidence was presented by the authors to indicate that the allyldifluoroborane species was actually being formed.

2.01.6.5 Allyl Groups; Lewis Acid Catalysis

The use of Lewis acids as catalysts for the allylboration of ketones has been more well-studied than their protic acid counterparts.

In one report, the use of indium metal was shown to allow for the allylation of alkyl aryl ketones in water with pinacolato allylborane (equation 150). This reaction is especially interesting, as it makes use of several facets of less-frequently seen chemistries, such as the partial stability of allylboranes toward protic solvents, the use of indium metal as a catalyst, and the low reduction potential of indium metal in water. This reaction was extended to α-methyl substituted allylic boranes without any detectable level of expected γ-adduct.[282] This result, although not directly interpreted by the authors as such, is possibly indicative of the formation of an allylindium species as being the active one. This report was published subsequent to an earlier work by the same author in which indium(I) was thought to be the active catalyst.[283] Another work, in which an allylboration of ketones was performed, the active species was postulated to be an allyliridium complex, as reported by Jarvo and coworkers.[284]



(150)

Just as with aldehydes, the use of either Montmorillonite clays or boron trifluoride can produce, *in situ*, allyldifluoroboranes from trifluoroborate salts. The former can be used for the allylation and crotylboration of a variety of ketones in excellent yields and generally very good diastereoselectivities.[285] One report, in which allylboronates were produced under conditions of

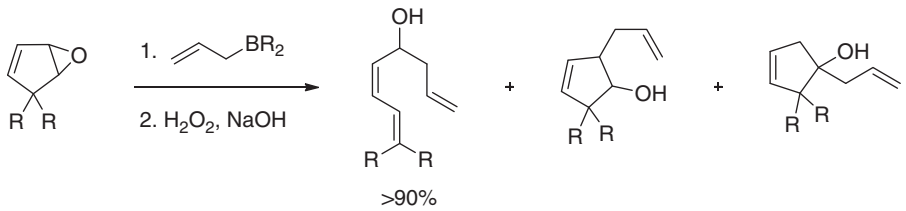
palladium catalysis, demonstrated the intramolecular cyclization in a one-pot method, furnishing cyclic compounds. Although it is not clear, palladium may be playing a role in the cyclization.[76a]

2.01.6.6 Asymmetric Allylation with Allyl Groups; Lewis Acid Catalysis

Chiral ligands, in the context of Lewis acid catalysis, can induce absolute stereocontrol in the course of ketone allylation. Early results have been mostly promising, providing very good levels of enantiomeric excesses. Most of these reports have detailed the use of iridium, copper, or lanthanum-based Lewis acids in combination with BINOL, DuPhos, or other ligands.[286]

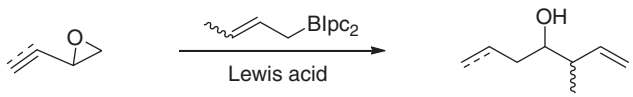
2.01.7 Allylation of Carbonyls Produced *In Situ*

The reaction of epoxides with allylboranes has been reported only in the context of a concomitant Meinwald rearrangement. For example, cyclopentadiene monoxide derivatives react with allyldialkylboranes to give acyclic trienes (equation 151). Most likely, the reaction occurs through a Zwitterionic sigmatropic reaction to give an aldehyde, followed by allylation.[287] Similar chemistry was reported around the same time by other research groups as well.[288]



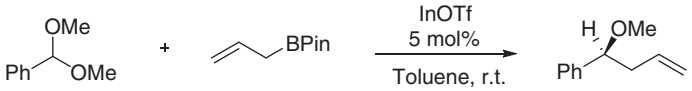
(151)

Chiral examples of this reaction have also been reported. Starting with either propargylic or allylic epoxides, a Meinwald rearrangment provides the corresponding terminal carbonyls, which react *in situ* to produce the expected homoallylic/homopropargylic and bishomoallylic alcohols (equation 152). The use of both scandium triflate and boron trifluoride has been described as effective for this Meinwald rearrangement. With chiral allyldiisopinocampheylborane serving as the nucleophile, the reactions proceeded with excellent enantiomeric ratios and very good yields.[289]



(152)

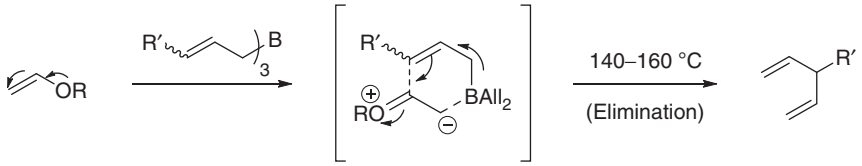
The reaction of oxycarbenium ions with allylborane derivatives is well-documented. Most oxycarbenium ions for these reactions are generated from the decomposition of acetals, ketals, orthoformates, orthoamidates, or other related species. For example, the use of catalytic indium to produce oxycarbenium ions from acetals, followed by allylation to give homoallylic ethers in excellent yields has been reported (equation 153). This methodology is generally very tolerant of multiple and different types of functionalities.[290] Other methods of preparation include the use of *p*-toluenesulfonic acid,[291] and trimethylsilyl trifluoromethylsulfonate.[292]



(153)

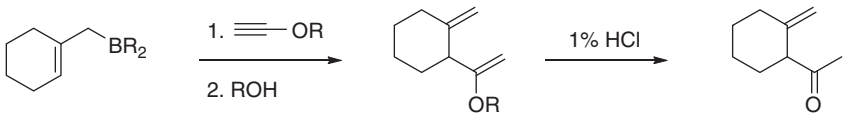
The reaction of allylboranes with vinylic and acetylenic ethers has also been documented. As the regioselectivity of the reaction is dictated by the contribution to the molecular structure by the Zwitterionic oxycarbenium resonance structure, the reaction can be readily understood by considering a chelation to the boron at the oxygen's beta position, followed by allylation of the resultant oxycarbenium ion.

Many times, the resultant α-allyl-β-borylether will undergo elimination followed by protonation to give dienic products. For example, the reaction of triallylic boranes with vinylic ethers was shown to furnish 3-substituted-1,4-dienes in reasonable yields (equation 154). There are only a few reports of such elimination reactions.[43,293]



(154)

The analogous reaction with acetylenic ethers has also been reported. Typically, these reactions are more facile than their vinylic counterparts. This fact is mostly attributable to an increase in the electron density of an acetylenic system when compared to a simple olefin. Unlike their vinylic counterparts, a final elimination is not usually observed. Instead, a protic acid workup is usually prescribed to provide the vinylic ether.[294] In one such example, the final product was subsequently hydrolyzed as a means to produce the β,γ-unsaturated ketone (equation 155).



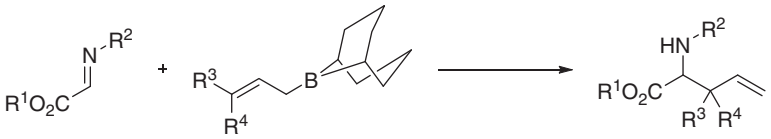
(155)

2.01.8 Allylation of Imines

2.01.8.1 Without Additives

The allylboration of imines is very well known, and has been reviewed recently.[295] As such, the authors only briefly cover them here. In general, aldimines are produced with the *E*-geometry. The consequence is the necessity of a *cis*-coordination of the boron relative to the alkyl group of the original aldehyde precursor. This results in a higher energy and therefore more selective transition state. Many times, aldimine and ketimine allylation reactions occur to give homoallylic amines with the near-exclusive formation of a single diastereomer, and in higher stereoselectivities than with their aldehyde and ketone counterparts.

In one case, the reaction of α-alkoxycarbonyl imines was shown to furnish α-alkoxycarbonyl homoallylic amines in good yields. The reactions proceeded in very good diastereoselectivities (equation 156).[296]



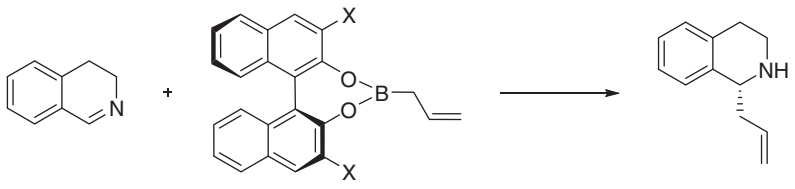
(156)

The use of more complicated allylic derivatives, including those with extra functionalizations such as silanes has been reported. In most cases, very good yields and excellent diastereoselectivities are typically observed.[297] Free N–H imines are more difficult to synthesize, so their use typically requires their *in situ* production. The use of either very unstable α-aminols[298] or liquid ammonia[299] can give rise to such systems.

2.01.8.2 Asymmetric Allylation Without Additives

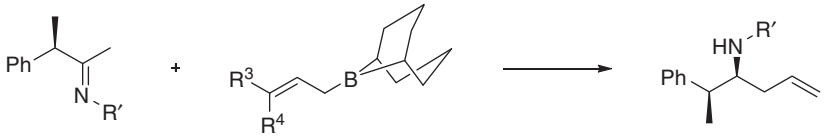
The same basic strategies have been employed in the achiral allylation of imines that were applied for aldehyde and ketone allylation. For example, the use of chiral boronates, such as those derived from BINOL, camphor, and tartrate diols have been shown to induce mostly moderate levels of enantiomeric excess and generally good yields.[21i,300] The best results have come mostly from a phenyl-substituted, camphor-derived bidentate ligand on boron.[301]

In one other report of very good enantioinduction, the use of a bi(3,5-bis(trifluoromethyl)phenyl)-BINOL derivative was shown to provide excellent levels of enantioinduction in the allylation of endocyclic imines (equation 157, X = CF_3). The reaction of several different endocyclic aldimines provided excellent levels of enantioselectivities and generally very good yields in their allylation reactions.[302]



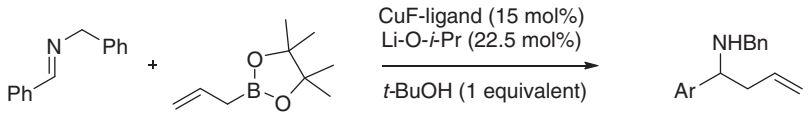
(157)

Similarly, the chirality during such allylation reactions can be transferred from a chiral imine. Just as with aldehydes and ketones, the closer to the electrophilic center that is the stereogenic center, the greater its level of influence (equation 158). The use of a chiral group on the *N*-alkyl group (instead of on the alkylidenyl portion) can also be used to induce excellent levels of diastereomeric excess.[303] Further work to include α-iminoesters as electrophiles has been performed.[304]



(158)

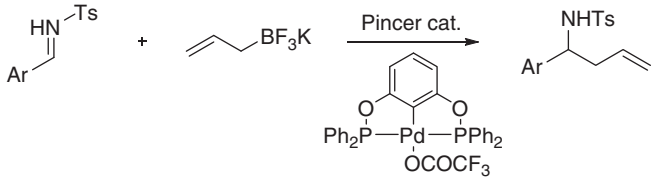
Shibasaki has shown that the use of a catalytic amount of copper, when used in conjunction with the chiral DuPhos catalyst scaffolding, can provide very good levels of enantiomeric induction in the allylation of *N*-benzylimines (equation 159). The reactions proceeded with very good yields and were tolerant of both aldimines and ketimines.[305]



(159)

2.01.8.3 Additives

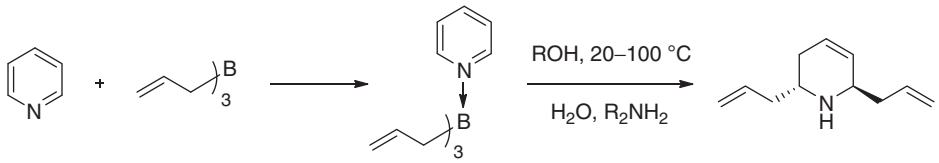
The use of Lewis acids to facilitate the allylation reaction of imines with allylboranes has been only moderately studied. In one example, the use of palladium–pincer complexes has been shown to catalyze the reaction of allyltrifluoroborates with tosylimides (equation 160). In general, the reactions were tolerant of a variety of functional groups, and proceeded in excellent yields.[306] The use of a combined copper/lanthanum catalyst has also been reported to give excellent conversion to homoallylic amines.



(160)

2.01.8.4 Concommittmant Dearomatization

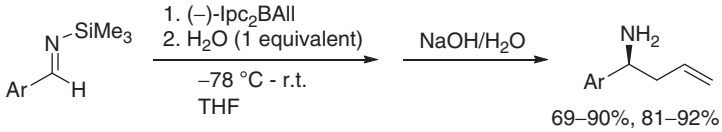
Bubnov and coworkers have reported on a wide variety of the reactions of aromatic imines such as pyridine with triallylborane. Such reactions are believed to proceed through the initial formation of the B-N adduct, which serves to activate the imine-like structure. Subsequent heating allows for the successive allylation of the ring (equation 161). This methodology has been further extended to include the concomittant formation of aziridines; ethanolamine derivatives; and fused, spiro-, and *N*-spirocyclic skeletons. It has been applied to many different heterocycles such as indoles, quinolines, isoquinolines, phenanthridines, indolenines, pyrroles, and pyridines.[1i,307]



(161)

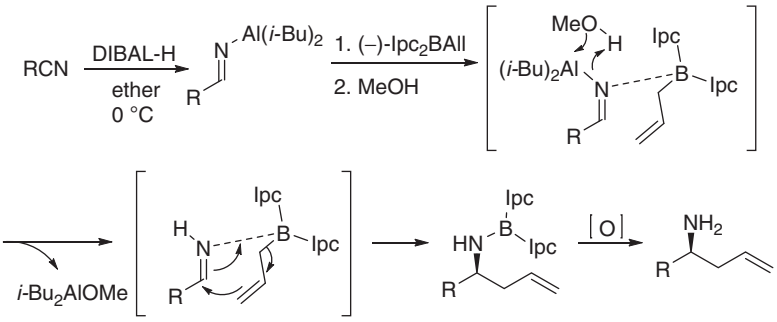
2.01.8.5 *N*-silyl and *N*-aluminoimines

Changing the nitrogen substitution can have a profound effect on the reactivity of imine allylboration reactions. For example, several reports were released by Itsuno and coworkers that described the allylation of *N*-silyl and *N*-aluminoimines with optically active dialkylallylboranes.[308] Later ^{11}B NMR studies by Ramachandran and Brown and coworker demonstrated that the expected allylation was not actually occuring until the workup stage.[309] They then optimized this procedure to include an *in situ* protonation with methanol or water that allowed the reaction to occur with superior yields and stereoselectivities (equation 162).



(162)

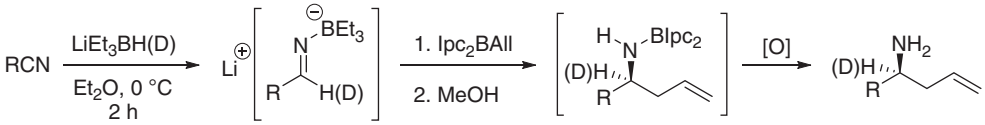
This change is quite unexpected, when compared to simple aldimines. However, with that reaction obstacle removed, both silyl- and aluminoimines, which serve as a masked type of free imine, have been extensively used in the formation of C_2-symmetric diamino aromatics, tetrahydropyridines, amino acid homologs and various lactams.[310] The aluminoimines are usually produced from the reduction of nitrile compounds with diisobutylaluminum hydrides (equation 163). Soderquist and coworkers have applied it to the allylboration of silyl enamine precursors with their *B*-allyl-10-phenyl-9-borabicyclo[3.3.2]decanes.[311]



(163)

2.01.8.6 *N*-boryl Imines

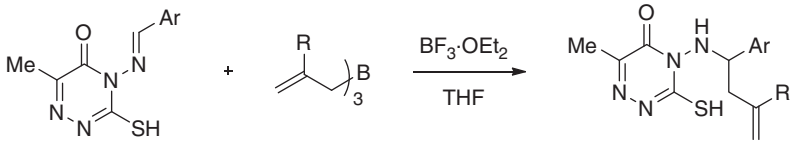
The allylation of isoelectronic (to *N*-alumino) *N*-borylimines has also been briefly described. Similar to those reactions of aluminum-based imines, boron-based imines have been reported to proceed by way of the protonolysis of the iminoborane with stoichiometric methanol (equation 164). Ramachandran and coworkers used this procedure, and made use of a chiral allylating agent as a means to furnish, after subsequent hydroboration–oxidation, enantioenriched δ-amino alcohols from simple nitriles in very good yields.[312] Work by Itsuno et al. to produce the homoallylic amines, without the subsequent conversion to carboxylic acids, has also been performed.[313] Again, the reaction does not proceed without the addition of an appropriate proton source.



(164)

2.01.8.7 *N*-amino Imines

The allylations of hydrazine-derived imines (hydrazones) have been fairly well-studied. In general, the reactions proceed in excellent yields and selectivities, despite the fact that they have lower levels of electrophilicity than do simple imines. In one example (equation 165), the use of boron trifluoride as a director to ensure chemoselectivity toward the exocyclic hydrazine functionality was demonstrated.[314]

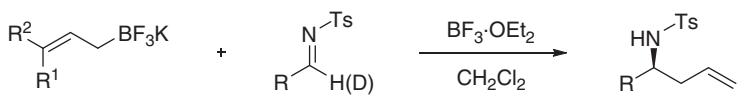


(165)

The low electrophilicity of hydrazones may be partially attenuated by their activation through conversion to acyl derivatives. Indeed, this has been realized several times, and has been combined with the use of either zinc or indium catalysis for both allyl- and crotylboronate additions.[315] The same idea of activation has been extended to the chiral allylation of simple acylimines.[305b]

2.01.8.8 *N*-sulfonylimines

Similar to the activation of hydrazones by acylation, the activation of imines by sulfonation has been used as a tool for allylation chemistry. One such report was made by Batey and coworkers,[316] in which tosylimides were allylated with simple allylic or crotyltrifluoroboronates under conditions of boron trifluoride promotion (equation 166). The reactions proceeded in near-perfect yields, and with excellent relative and absolute stereocontrol. Allylpalladates, which are generated *in situ* from the reaction of an allylborane and a palladium–pincer complex, have also been shown to be effective 'allylborating' catalysts for imine allylboration.[317]



(166)

2.01.8.9 Other Imine Derivatives

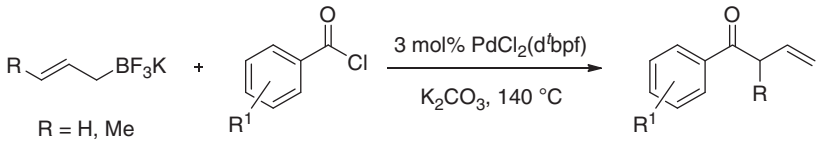
A few other classes of imine derivatives have been used as electrophiles in allylboration reactions. However, their reports appear only sporadically, and very little information is available about their reactivities. For example, the reaction of phosphinoylimines with allylic boranes has been scarcely described. Hoveyda and Snapper have reported that this reaction is indeed feasible and in a chiral fashion, using a copper catalyst and an appropriate choice of *N*-heterocyclic carbene. The resulting products, which are likely obtained through an active copper species, are formed in virtually quantitative conversion and near-perfect enantiomeric ratios.[318] The use of allylboronates in the allylation of nitrones has also been reported.[319] This methodology, which was performed in conjunction with an organometallic addititve, attempted to obtain diastereoselectivity through a preset stereogenicity. The allylation of both oxime ethers and sulfenimines has also been reported.[308a,d,320]

2.01.9 Allylation of Other Carbonyl Derivatives

2.01.9.1 Esters, Amides, and Related Functional Groups

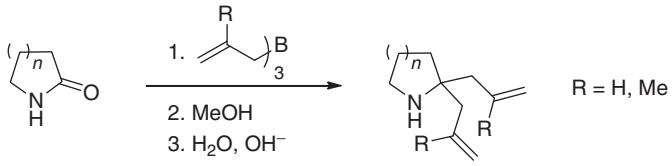
The allylboration of esters, amides, anhydrides, acid chlorides, carboxylic acids, and other related compounds has been reported on multiple occasions.[195,321] These reactions typically follow the patterns observed for the addition of other allylmetal systems to these same groups. And, just like their organic counterparts, they may be catalyzed or not, and may also undergo multiple additions.

For an example of the former, the authors consider the reaction of highly reactive acid chlorides. Palladium has been shown to catalyze the cross-coupling reaction of allyl- and crotyltrifluoroborates with acid chlorides (equation 167). The reaction occurs within twenty minutes at elevated temperatures under microwave conditions. The issue of 1,3-boratropic shifts was not a concern, as trifluoroborate salts do not possess the Lewis acidity necessary to allow for a 1,3-boratropic shift to take place. The reported examples included a variety of different acrylic chlorides, which were transformed with almost all excellent yields.[322] The allylation of acylsilanes with chiral allylboranes has also been reported.[323]



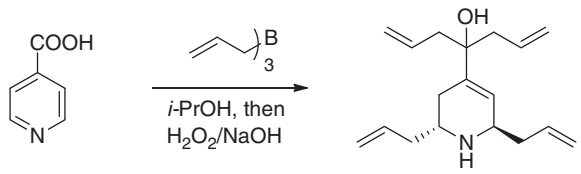
(167)

The allylation and 2-methylallylation of amide compounds was reported by Bubnov and coworkers.[324] They showed that the allylation of lactams with triallylborane and derivatives proceeds entirely to the diallylation product in very good to excellent yields. Although the scope of the reaction was only demonstrated through the variance of the lactam ring size and the chemoselectivity toward simple lactams versus the more sterically-demanding trifluoroacetylamides, the route offers, in conjunction with a ring-closing metathesis, a very nice way to produce spirocyclic compounds in very good overall yields (equation 168).



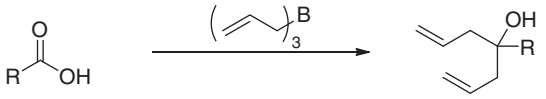
(168)

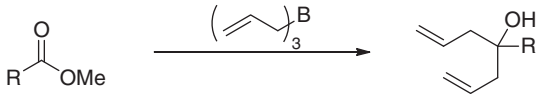
The reaction of allylboranes with carboxylic acids has also been reported.[325] This reaction is a fascinating one, as, unlike alkyllithium compounds, not even Grignard reagents will add to a carboxylic acid, but instead undergo an acid–base reaction, to give an acetate salt. In the case of a boron-based allyl group, the release of propene occurs as expected, but the acetate can bond in a much more covalent fashion, producing the acyloxyborane derivative, thereby drastically enhancing the nucleofugacity of the carbonyl group. Such an activation renders the carbonyl group more reactive, thereby allowing for allylation to occur. This effect parallels the propensity of borane to reduce carboxylic acids more rapidly than esters and other acid derivatives. In one such example, the reaction of triallylborane with pyridine-4-carboxylic acid has been reported, wherein the allylation of the carbonyl takes place. If this reaction is performed in the presence of proton source, a 2,6-diallylation reaction of the pyridine also takes place as discussed in Section 2.01.8.4,[1i,326] giving the tetraallylated product in (equation 169).

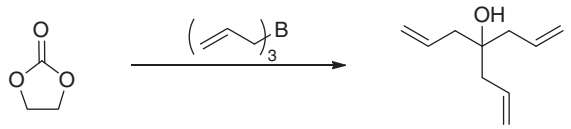


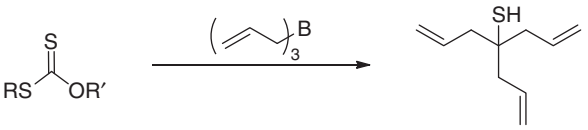
(169)

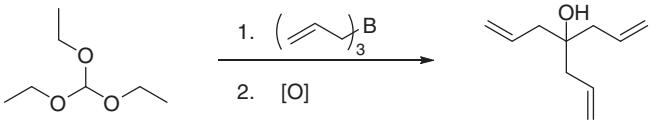
The highly reactive triallylborane has also been shown to be be capable of allylating functional groups of even low reactivity, such as carboxylic acids and esters, carbonates, xanthates, and orthoformates (equations 170–174).[131,327]


(170)


(171)


(172)

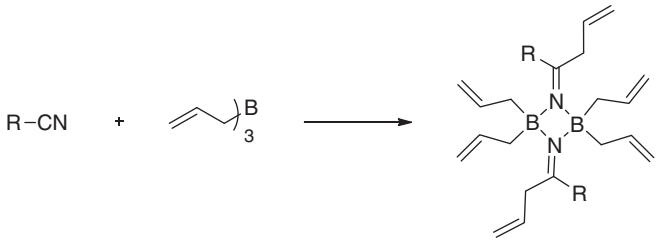

(173)


(174)

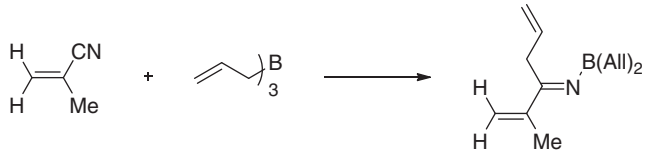
2.01.9.2 Cyano Derivatives

The reaction of nitriles and derivatives with allylboranes has been scarcely reported. Expectedly, the reaction proceeds to furnish the *N*-boryl imine, which can be converted to the carbonyl product on hydrolysis. As is typical of nitriles, the decreased electrophilicity relative to other carbonyl derivatives necessitates an increase in reaction temperature for conversion, unless an especially reactive allylborylating agent is employed.

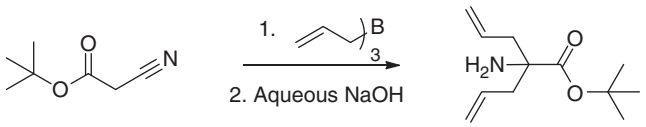
Bubnov and Mikhailov[328] have shown that the reactions of nitriles with triallylborane gives the dimer of *N*-(diallylboryl) imines (equation 175). These reactions occur first by formation of the ate complex, which are stable at low temperatures. Allowing the solution to warm causes the allylation to occur. They also showed that the dimeric iminoborane complexes are not stable, and that on heating to approximately 100 °C, undergo a further allylation to give the diallylated amine.


(175)

This polyallylation of nitriles is readily overcome, however. For example, Meller and Gerger reported that the reaction of methacrylonitrile with triallylborane could provide the desired homoallylic imines (equation 176). Interestingly, this reaction proceeded with an unexpectedly high level of 1,2-addition, despite the lack of steric bulk at the β-position.[329]

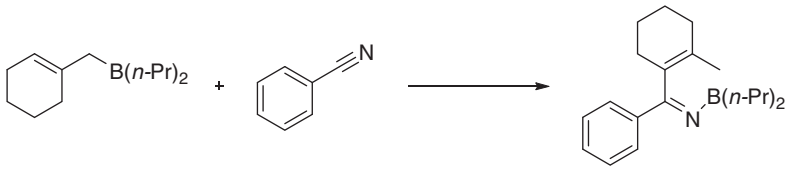

(176)

If, however, the diallylated product is the desired one, then the use of triallylborane at higher temperatures can furnish it. For example, Bubnov and coworkers[324c] have shown that such diallylations can occur in very good yields, even in the presence of a more reactive ester, a result, which is likely attributed to the steric shielding of the *t*-butyl group (equation 177).



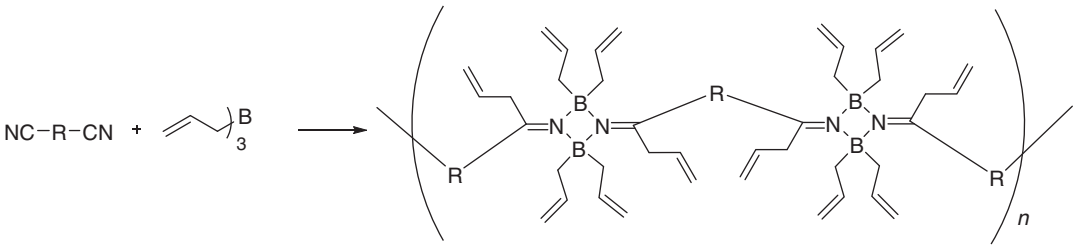
(177)

One very interesting report of a nitrile allylboration came from Bubnov, in which the allylation occurred to give the expected imine.[330] In this particular case, olefin isomerization was also observed, in which the α,β-rather than the β,γ-unsaturated system was obtained (equation 178). Little work on this tandem allylation-isomerization has since been reported.



(178)

The reaction of dinitriles with triallylborane has also been described.[331] The result of these reactions is the formation of several boron-containing polymers (equation 179) with the monomeric unit being isostructural to those dimers described by Mikhailov and Bubnov. In this case also, these unusual species can be further reacted on heating to 100 °C to have an additional allylboration of the isoelectronic imines occur.

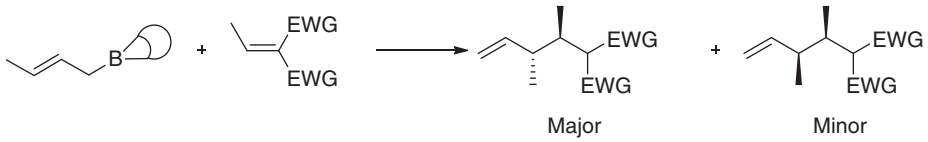


(179)

2.01.9.3 α,β-Unsaturated Systems via Conjugate Addition

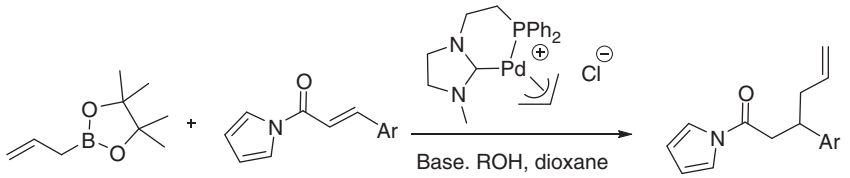
In general, allylboranes are very capable Michael-donors. Their ability to selectively add at the 4-position in lieu of the 2-position can depend on many factors, including the Lewis acid strength of the boron, the Lewis basicity of the unsaturated bond, the relative steric requirements of the two possible attack positions, and the geometrical question of chelative ability. In most cases, a combination of the attenuated reactivity of allylboranes, when combined the fact that their chemoselectivity can pale in comparison to other methods, vis-à-vis, cerium and copper for 1,2- and 1,4-additions respectively, has likely contributed to their general curtailment as a choice in allylative Michael reactions.

Despite this, their utility as allylating groups has been demonstrated. They have been shown to add to malonate and malononitrile groups with relative ease and at ambient temperatures. Naturally, the extension of their reactivity to substituted groups such as crotylboranes has been studied (equation 180). In general, the selectivity remains good, although the isolated yields are not generally as high as those obtained from the analogous reactions with Grignard reagents, titanates, zirconates, or stannanes.[332]



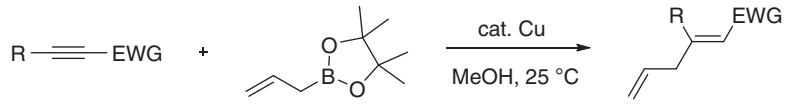
(180)

Most of the more current methods for allylation of Michael systems with allylborane derivatives are now catalytic, thereby removing some of the difficulties previously observed with selectivity. For example, palladium-based *N*-heterocyclic carbenes have been found to catalyze the reaction between allylboronates and Michael acceptors (equation 181). The advantage of the very mild reaction conditions are the tolerance of a wide variety of functional groups, including imidazoles, alkyl halides, nitro compounds, nitriles, and esters.[333]



(181)

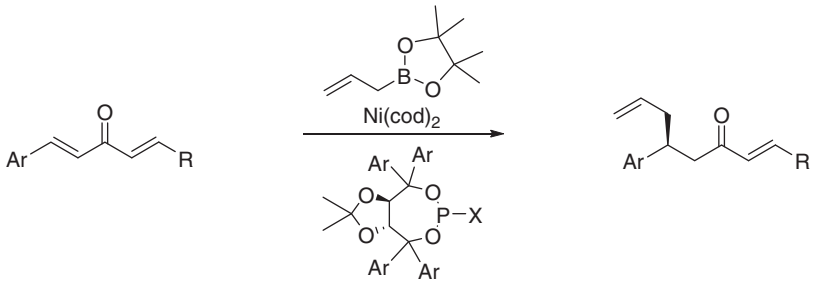
The use of the less expensive metal copper can also catalyze the addition of allylboronates to Michael systems. For example, catalytic amounds of copper(II) acetate have been found to smoothly catalyze the reaction of pinacolato allylboronate to the β-position of β-substituted propiolates, acetylenic amides, acetylenic nitriles, and acetylenic sulfones in very high yields (equation 182). The reaction was also demonstrated to be tolerant of substitution at the β-position of the allylboronate.[334]



(182)

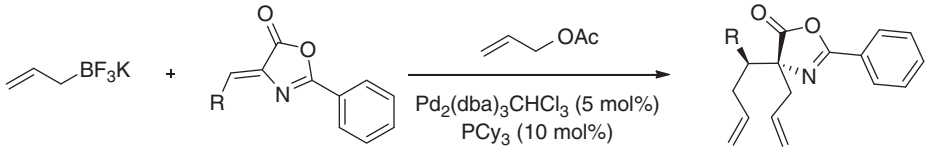
EWG = COOR, COR, CN, $CONR_2$, SO_2R

The use of nickel as a catalyst in the addition of allylic boronates to bisalkylidenyl ketones has also been described.[335] The chemospecificity of the cinnamic Michael acceptor is excellent; the use of a chiral ligand can induce stereogenicity in excellent enantiomeric ratios. The ambient protocol allowed for the incorporation of many different functionalities without significant alteration of the reaction's fate (equation 183). Interestingly, the use of a chelating, triaryl phosphine ligand tethered to the Michael acceptor allowed for a chelation to the nickel metal, in a *P*,allyl-bidentate fashion. Such a chelation forced the allylation at the distal site, whereas the use of a nonchelating moiety gave a mixture of allylated products. This was logically ascribed as an indirect evidence for a 3,3′-reductive elimination.

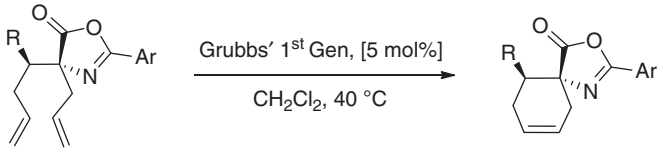


(183)

Another coupling of allylborane derivatives has been reported by Nakamura and coworkers.[336] Preactivated potassium allyltrifluoroborates, under conditions of palladium catalysis, undergo conjugate addition to *exo*-methylene oxazolones, to give palladium-enolates which can couple with allylic acetates in the preparation of spirocyclic precursors. This proceeds in moderate to good yields and reasonable diastereomeric ratios (equation 184). The same paper further detailed the ring-closing metathesis of these compounds to furnish the corresponding spirocycles in excellent yields (equation 185).



(184)



(185)

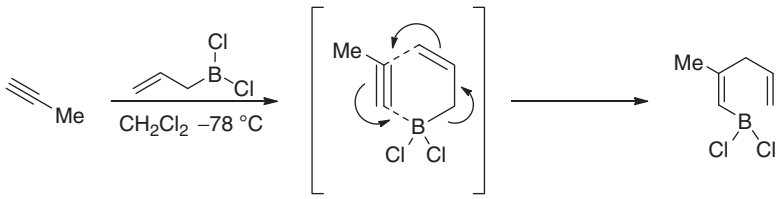
2.01.10 Allylation of Other π-Systems

2.01.10.1 Alkynes

The allylboration of alkynes is typically a very facile process which occurs at low temperatures and can occur in the absence of any added catalyst. The transformation occurs to add an allyl group to one of the carbons, and the boron to the other. The addition

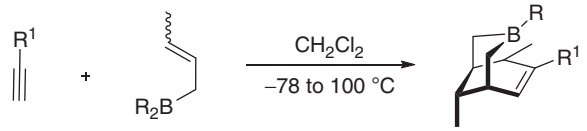
necessitates a conversion from an alkyne to an alkene, so further reaction can be possible (see Section 2.01.10.2 for discussion). As expected, an issue of regiochemistry is present for these additions. In the absence of any external electronic factors, steric grounds usually dictate that the boryl substituent adds to the terminal position, and that the allylic group adds to the internal position. As with most allylborane additions, the reaction is believed to occur through a six-membered transition state. When using a poly (allyl)borane, the monoallylation reaction can many times be difficult to control, as multiple allylborations can take place.

A simple solution to this problem is the use of only one allyl group on the boron center. For example, Bubnov and coworkers described the use of monoallyldichloroborane in the allylation of monosubstituted alkynes (equation 186). The resulting vinylic dichloroboranes could then be further derivatized to boronates or other compounds.[337]



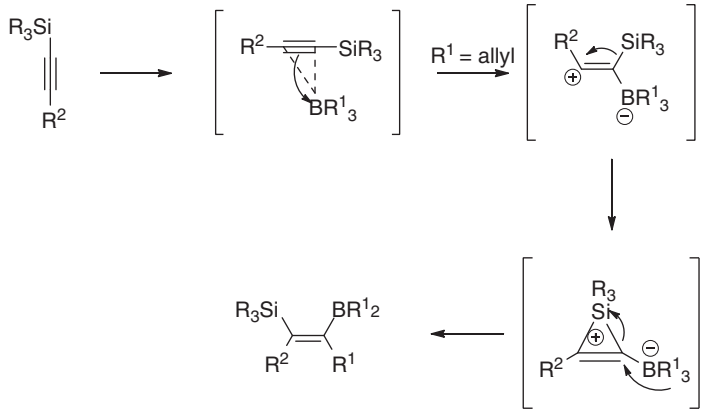
(186)

If the chlorine substituents are replaced with allyl groups, or if a triallylborane derivative was initially used, then further reaction at elevated temperatures can lead to an additional allylation of the homoallylic alkene.[338] A further rearrangement to fused bicyclic compounds can subsequently take place (equation 187). These compounds have been shown to possess much synthetic utility.[131,339]



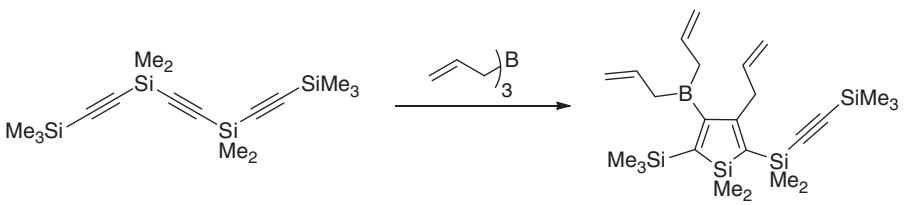
(187)

In many cases, the electronics of the alkynyl system can promote rearrangements, so long as a rearrangement partner with a sufficiently high migratory aptitude can be utilized. Silyl and stannyl moieties are perfect examples of such groups. Due to the α-effect of silicon and tin, the reaction of 1-silyl(stannyl)alkynes with allylboranes will principally give a product that occurs through the addition of boron onto the silicon(tin)-bonded alkyne position, and force a rearrangement to give a silyl(stannyl)cyclopropenium-borate zwitterion. Alkyl migration then occurs to open the ring, resulting in the equivalent of a 1,2-silyl(stannyl) migration and the 1,1-carboborylation of the alkyne. As a result of this process, the latter is converted into an alkene (equation 188). The regiochemistry of the initial chelation to boron is explained by the strong propensity of silyl groups to stabilized β-carbocations and α-carbanions.



(188)

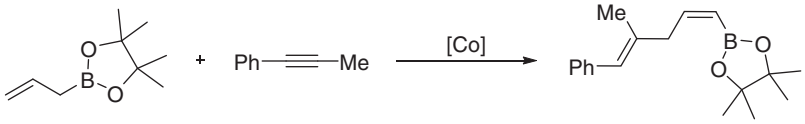
This type of rearrangement has been used in the production of polyallylated silols (equation 189). This product is believed to arise from the 1,1-allylboration of the internal alkyne, which proceeds with the expected silyl migration. 1,1-vinylboration, again with 1,2-silatropic shift, can lead to the expected product, which was fully characterized by ^{1}H, ^{11}B, ^{13}C, and ^{29}Si NMR spectroscopies.[340]



(189)

Such fascinating rearrangements can lead to many different types of products. Indeed, many ideas for complex and highly functionalized molecular scaffoldings have been attempted, with a large number of them being characterized and reported to date.[132,341]

One rather uncharacteristic behavior of an allylboronate derivative was reported by Hilt and coworkers, in which what is formally a cobalt-catalyzed coupling reaction took place, with the resultant product being that which is expected for an Alder-ene reaction (equation 190). Beginning with an allylboronate and a disubstituted alkyne, the formed vinylic boronate product can be formed through a pathway which begins with a coordination of both the alkyne and alkene to the cobalt metal center. A formal oxidative [2+2+1] sigmatropic reaction can then take place, giving the cyclopentacobaltacene. Dehydrocobaltation, followed by reductive elimination would then give the observed product. These reactions, which typically proceeded in very reasonable yields, were tolerant of both silyl groups and silanes, along with ketones and esters.[342]

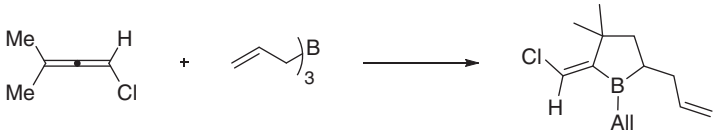


(190)

2.01.10.2 Alkenes

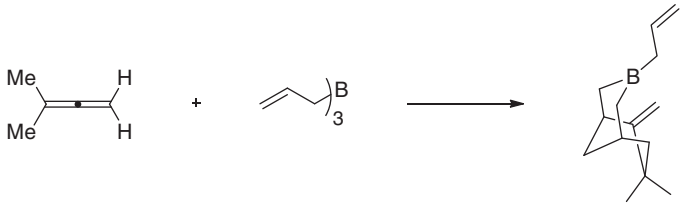
By comparison to alkynes, the allylboration of alkenes is a moderately difficult endeavor. Due to enhanced Lewis-basicity of alkynes, their coordinative ability toward Lewis acids such as boron is typically far greater than that of alkenes. A consequence of this decrease in Lewis basicity for the latter is the necessity for higher reaction temperatures and slightly lower chemical conversions. Although the allylboration of alkynes is typically performed at temperatures at or below −78 °C, the analogous allylation of alkenes is too sluggish, and typically requires temperatures between 0 and 100 °C to undergo appreciable conversion. Just as with their alkyne counterparts, the allylboration of alkenes typically undergoes borylation at the side of lower steric requirement, unless there is a significant electronic alteration of the π-system. Typically, the allylboration's regiochemistry can be predicted in the same way as that of alkoxymercuration.[343]

In the case of allenes, it is many times true that the site of least steric hindrance is at the central carbon atom. As such, a 1,2-allylboration may occur to give vinylic boranes. If a second allylboration of the transferred allyl group takes place, then poly-substituted borolanes can be produced (equation 191). The initial allylation appears to take place primarily at the location of the most highly substituted allenic carbon.[344] This is a reasonably-supposed idea, as a higher degree of substitution would necessarily be the site of the most stable carbocation.



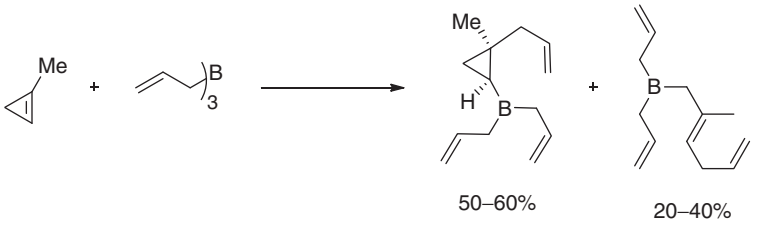
(191)

In some cases, borinanes can be formed instead of borolanes. For the production of such a ring system to take place, the above pathway must be followed, however the regiochemistry of the final allylboration must be switched (equation 192). Indeed, if the allylation occurs internally, and the borylation terminally, then borinanes can be produced.[345]



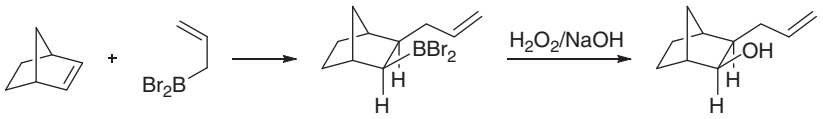
(192)

In the above two cases, the polarization of the allene by the chloro substituent is believed to activate the allene. This method of activation is not the only reported one, however. For example, ring strain can be used as a means to activate olefins. In fact, the allylation of 1-methylcyclopropene with triallylborane is very facile, and proceeds at temperatures as low as −70 °C (equation 193). Two major products are formed; the first is the expected allylboration product, with allylation taking place at the expected position (the more highly substituted carbon); the second is formed from a simple rearrangement.[346]



(193)

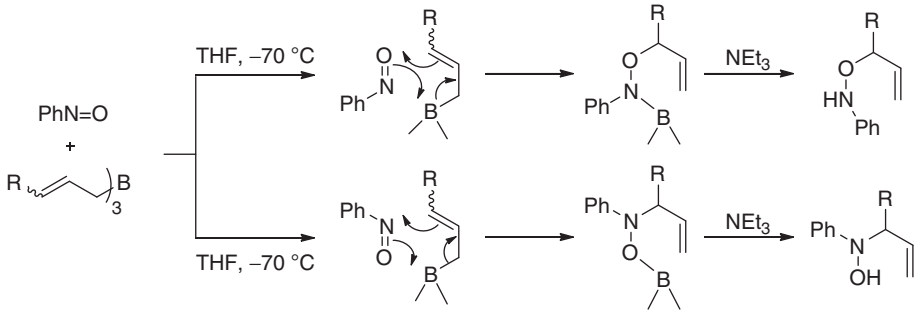
A different strategy in the activation of allylboration of alkenes has been used by Singleton and coworkers.[347] Instead of activating the alkene, the use of a more Lewis acidic boron can accelerate the reaction. This idea is identical to the strategy taken for the allylboration of aldehydes (*vide supra*). By changing the extra two ligands on the boron atom to bromide ones, the Lewis acidity is increased as per that dictated by an increase in the ionic character and bond length of the boron–bromine connectivity. With this approach, the allylation of several simple alkenes was described as a means to obtain a 1,2-hydroxyallylation product from simple alkenes (equation 194).



(194)

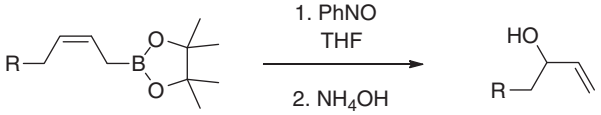
2.01.10.3 X═Y Functionalities

The reaction of an allylborane with any polarized double bond may – in theory – occur to give an allylated product. The extent to which such a reaction occurs depends entirely upon the kinetics and thermodynamics of the reaction. In practice, the attempted reaction of many different X═Y bonds with allylboranes has been attempted, but with only mixed results. Many times, the results of these reactions are quite unpredictable, and occur with rearrangements or unexpected hydrolysis products. For example, the reaction of nitroso compounds and allylboranes has been reported by Bubnov and coworkers[348] to proceed through either an *N*- or *O*-allylation, depending upon the conditions. They have further shown that the reaction can be used for the *in situ* production of allylic alkoxyamines, allylic amino ethers, allylic amines, allylic alcohols, nitrenes, and imines (equation 195).



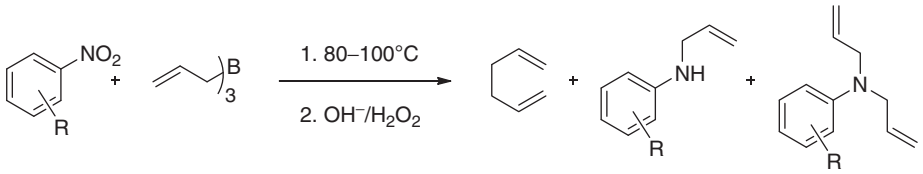
(195)

More recently, Morken and coworkers have shown that the reaction of nitroso compounds with allylboranes can be controlled to give almost exclusively *O*-allylation.[349] The nickel-catalyzed 1,4-hydroboration to give terminal allylboronates was earlier presented. This work demonstrated that the reaction with nitrosyls likely proceeds first through a coordination of the amine group to boron, followed by allylation. Subsequent hydrolysis with either an additive such as a base, or through an oxidative workup provided the simple allylic alcohols with allylic rearrangement in mostly very good to excellent yields (equation 196).



(196)

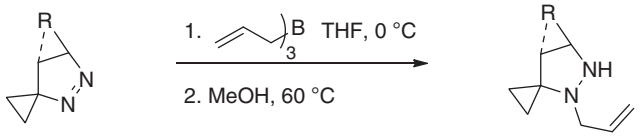
If the reaction as described by Morken and coworkers indeed proceeds through an intial *N*-chelation, then further amine oxidation to the nitro compound should prevent such chelation, and *N*-allylation should occur. In agreement with this, Bubnov and coworkers demonstrated this allylation with simple nitroarenes.[350] By heating nitrobenzene derivatives with triallylborane, they demonstrated that allylation could occur, with the monoallyl product being the dominant one. Some amount of diallylated and fullly reduced compounds were isolated, however (equation 197).



(197)

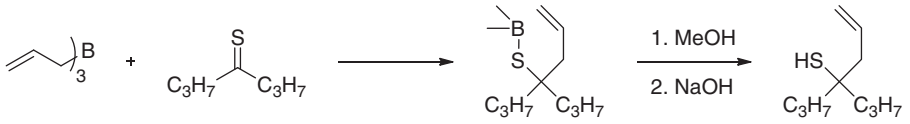
Bubnov and coworkers have further extended this allylation of N═X bonds to include pyrazoline derivatives and diphenyldiazene.[351] Without the competition of *O*- vs. *N*-allylation, such chemistry is more straightfoward, although in the former case,

an issue of regiochemistry must be addressed (equation 198). While the desired products were successfully allylated with the expected stereochemistry, the products were not entirely stable. In the case of R = Ph, the product was found to oxidize rapidly to the aza-styrenyl product in air. When R = dimethylcyclopropyl, the product would undergo a slow 1,2-hydride shift to give a pendent isopropyl group, with concomitant formation of a carbon–nitrogen double bond.



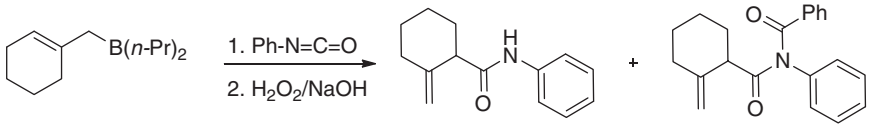
(198)

Perhaps surprisingly, there has been very little work on the allylation of thiones with allylboranes.[352] A report by Bubnov and coworkers has appeared in the literature, in which the reaction of dipropylthione with allylboranes was demonstrated to occur in good yields (equation 199).

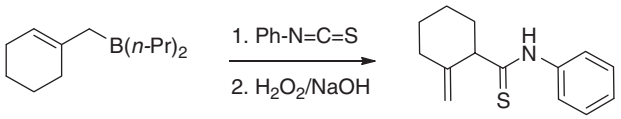


(199)

Allylboranes have also been shown to add readily to more reactive species that are isoelectronic with allene, such as isocyanates and isothiocyanates.[330,353] These highly reactive functional groups react to give allylation exclusively at the carbon atom, keeping intact the repective carbonyl and thionyl groups, giving rise to the respective amide and thioamide functionalities (equations 200–201). Unlike their cyano counterparts, these additions occurred without an olefin isomerization.



(200)

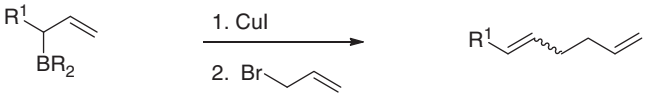


(201)

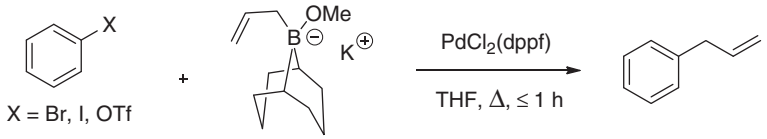
2.01.11 Other Reactions of Allylboranes

2.01.11.1 Coupling Reactions

The coupling reactions of allylborane-derived compounds have been known for several decades, and have been used for many syntheses and methodologies during this period. One early example of such a coupling was published by Suzuki and coworkers.[354] While the transformation was not noted as a coupling at the time, it was such, nevertheless, by manner of it being a stoichiometric addition of allyl cuprates to allylboranes (equation 202). While this reaction allowed for the formation of elongated dienes in only moderate yields, this represented a significant advancement in the coupling of an allylborane group to an allyl halide.[75a] This transformation made use of a dialkylborane as the coupling metal. The use of the 9-BBN ligand, which has a much lower migratory aptitude than simple alkyl groups, can offer significant improvement over this methodology.[355] For example, a palladium-catalyzed coupling of aromatic bromides, iodides, and triflates with potassium *B*-allyl-*B*-methoxy-9-BBN ate complex gives rise to the expected allylarenes in very good yields (equation 203). While these mild conditions were quite tolerant of many funtionalities, aldehydes were not well-suited to this chemistry, probably due to a competitive electrophilicity.

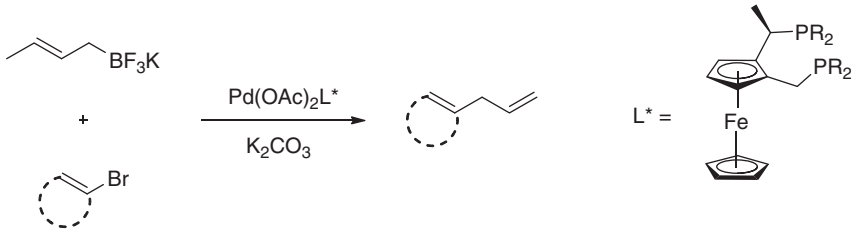


(202)



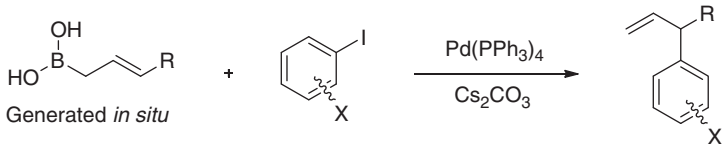
(203)

These coupling reactions require an activation of the allyl group for the transformation to take place. The chelation to boron of an additional ligand, as was seen in the previous example, serves to activate the boron through a decrease in the Lewis acidity, and increases the nucleophilicity of the allyl group. This renders addition processes, such as those necessary for cross-coupling reactions, significantly faster. This knowledge has pushed many research groups to investigate which types of ligands can function in these transformations. Perhaps the two most generally used combinations of ligand-boron complexes thus far discovered are trifluoroborates and boronic acid/ester ate complexes. The reported uses of trifluoroborate salts, and their utility in cross-coupling has grown almost exponentially in the last decade or so. For example, a palladium-catalyzed cross-coupling of potassium crotyltrifluoroborates with arylic and vinylic bromides has been reported by Yamamoto and Miyaura, and has been further developed to the point of asymmetric induction through the use of chiral ligands such as those in the Josiphos series (equation 204).[356] Notably, these methodologies are tolerant of ketone functional groups. More recently, these reactions have been shown to be capable of being run under microwave-irradiation conditions.[357]



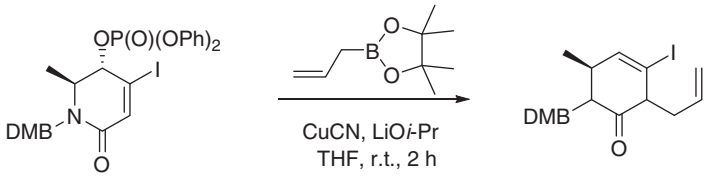
(204)

An interesting coupling methodology has been developed by Szabó and coworkers in which many different allylic groups – such as alcohols and cyclopropyl derivatives – are cross-coupled with diboric acid by the action of palladium–pincer complexes, gives allylic boronic acid derivatives.[358] These species, which do not need to be isolated, are activated by hydroxide ion under basic conditions, and can be reacted *in situ* with arylic iodides under conditions of cross-coupling with tetrakis(triphenylphosphine) palladium(0) to give polyfunctionalized alkene chains in excellent yields (equation 205). Similarly, an enormous amount of work toward the cross-coupling of allylic boronate esters-especially, pinacolato-derived ones-with different partners has been performed over the past few decades.[359]



(205)

One fairly unusual form of coupling has been reported, in which an allylboronate can serve as an allyl donor which exchanges, under conditions of copper(I) catalysis, for an allylic phosphonate leaving group (equation 206). This formal S_N2' reaction generally occurred with good yields. In all cases, a minor amount of the S_N2 product was formed, and even some levels of reduction were found. Although this methodology is not as clean a conversion to the desired products as would be hoped for, it nonetheless offers a simple route to dipeptide mimickers with defined stereochemistry.[360]



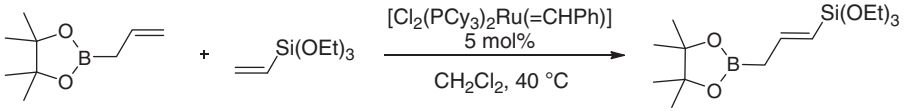
(206)

2.01.11.2 All Others

Outside of allylboration chemistry, there are many other uses for allylboranes, coming mostly in the form of derivatization, chain-elongation, and coupling. Coupling reactions are most typically metal-catalyzed ones, in which the allyl group is attached to a molecule in lieu of a leaving group such as a metal halide or metal trifluoromethanesulfonate moiety. Most chain-elongation reactions fall under the category of Matteson homologation or metathesis reactions, wherein the allylic group is converted into a homoallylic or a substituted one, respectively. Those other remaining derivatization reactions are of many classes, and include reactivity at either the boron center, the α-position, or the olefin group.

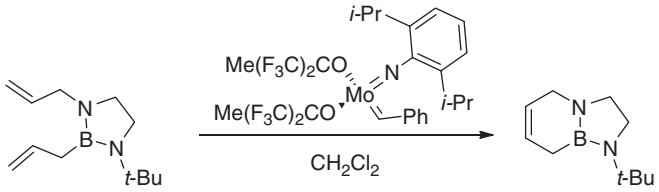
The authors begin their discussion of these reactions with an overview of chain-elongation reactions. There have been a limited number of reports on the metathesis of allylborane compounds. Some of these were introduced in the synthesis of allylboranes (*vide supra*). The authors reintroduce it here, along with a few other examples. Zaidlewicz and coworkers have shown that the

functionalization of allylboranes through cross-coupling with vinylsilanes can give valuable double allylation reagents (equation 207). Incredibly, several very reactive silanes can be coupled this way, including those bearing ethoxy and chloro substituents.[143]



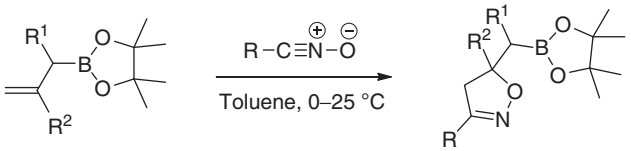
(207)

The cross-coupling of allylboranes is not limited to the use of Grubbs' Gen-I catalyst. For example, the use of Schrock's catalyst has been shown to furnish so-called 'BN type indolanes' with good conversion levels (equation 208). Aromatization of this molecule to the indole analog showed that it is actually more reactive than indole in electrophilic aromatic substitution reactions.[136e]



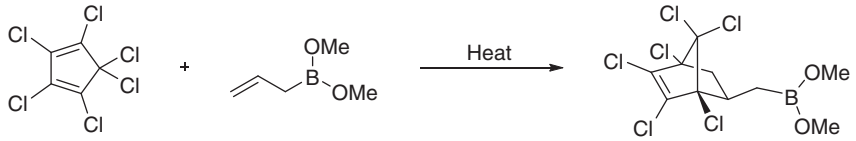
(208)

Although many other reactions of organic allylic groups can be performed with allylboranes, there is still much to be explored. The authors offer a sample of some of the transformations that have been reported with allylborane-derived groups. Organic olefins can undergo thermal [3+2] reactions with appropriate dipolar compounds, such as nitrile oxides. This very transformation with pinacol allylboronate esters has been reported.[361] The resulting 5-(boronatomethyl)isoxazoline products were produced in good to very good yields under these mild conditions (equation 209).



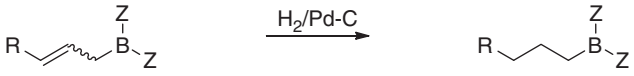
(209)

As another example of a sigmatropic reaction employed with allylboranes, the authors consider [4+2] additions. Very little work has been reported on the Diels–Alder reaction of allylboranes. One example of an inverse-electron demand Diels–Alder was reported by Mikhailov and Bubnov,[362] in which perchlorocyclopentadiene was reaced with dimethyl allylboronate to give the expected Diels–Alder adduct (equation 210).



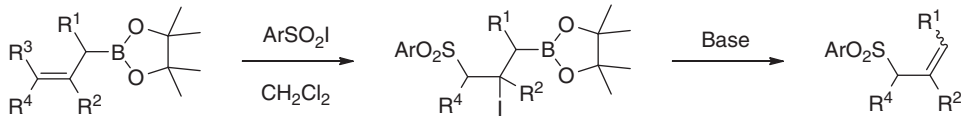
(210)

Many of the simple, elementary organic reactions can be applied to such systems. For example, the simple hydrogenation of allylboronates, which furnishes propyl-derived boronates, has been reported by Brown.[60,126a] This methodology offers a simple route to chain-extended, boron-functionalized alkanes (equation 211). The combination with cross-metathesis is an unexplored yet promising route to produce highly complicated boranes.



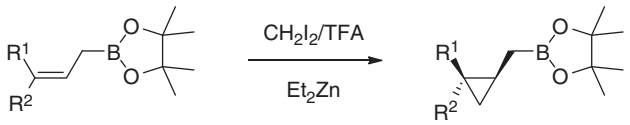
(211)

Allylboranes have also been used as a means to produce allylic sulfonates.[363] By reacting the alkene as an electrophile with an appropriate sulfonyl iodide, the vicinal iodosulfonate can be produced (equation 212). Subsequent reaction with a base such as sodium hydroxide will serve to remove both the boronate and iodide moieties in hydrolytic and elimative fashions, respectively, leaving behind an allylic sulfonate in very good overall yields. The same report also detailed the reaction of allylic boronates with molecular bromine, leading to 1,2-dibromo-3-borylalkanes in high yield.



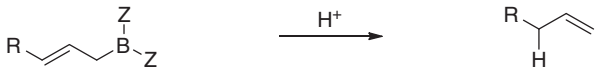
(212)

Based on a literature precedent[364] describing the preparation of cyclopropylic boronates, Krauss and coworkers[365] described the cyclopropanation of allylic boronates via a modified Simmons–Smith reaction (equation 213). Both the initial and product boronates were not reported to be unstable to the trifluoroacetic acid additive. These species offer great utility in the homoallylation of electrophiles such as aldehydes.



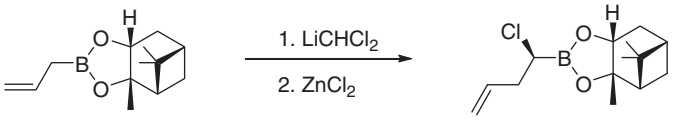
(213)

The reaction of allylboranes with protic acids was introduced earlier as a means of synthesizing allylic boranes with different ligands around the boron atom. As a generality, any carbon-based ligand attached to a boron can be protonated with an appropriate acid. The rate of protonolysis usually follows the reactivity pattern discussed above. As such, triallylboranes are readily transformed into borinates then boronates, but further any reaction with acid is significantly slower. Protonolysis of an allylic borane can take place, and usually does so via a six-membered protonolysis pathway,[41,366] which forces an allylic rearrangement to take place (equation 214).



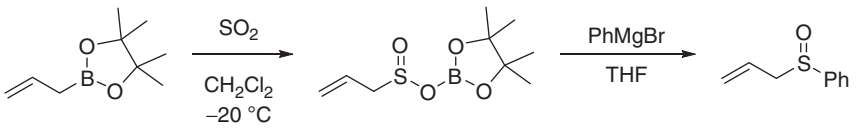
(214)

Just as the authors saw that vinylic borane derivatives can be converted into their homolouges via a Matteson homologation, so too can allylic boranes be converted into their homoallylic counterparts.[21h] Such reactions can also be performed with a transfer of chirality from the boron ligand onto the new carbon, thereby inducing the formation of one enantiomer in significant excess (equation 215).



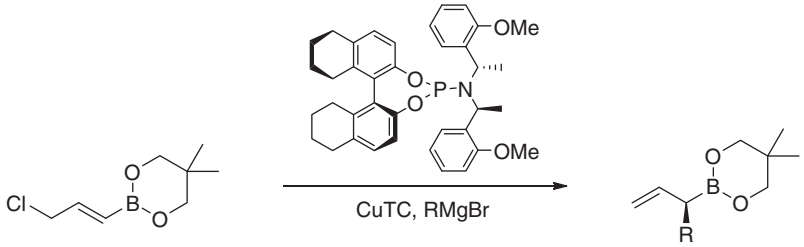
(215)

Occurring through chelation and a sigmatropic reaction, the bora-ene reaction with sulfur dioxide[367] allows for the conversion of allylborane derivatives into dioxaborolan-2-ylsulfinates in excellent yields (equation 216). These valuable synthons can then react with appropriate nucleophiles to give difunctionalized sulfoxides in very good overall yield.



(216)

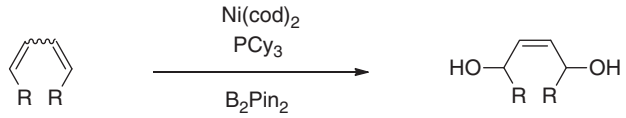
The reaction of B–C bonds with an appropriate oxidizing agent such as alkaline hydrogen peroxide will necessarily lead to the formation of an organic and borylic alcohol. This reaction has probably been made most famous by the discovery of the hydroboration reaction by Brown, wherein an alkene can be made to undergo anti-Markovnikov hydration by way of an organoborane intermediate. Nevertheless, there are cases in which a borylic group has been used as a means to introduce a hydroxyl functionality on an organic framework. For example, Hall has used prochiral γ-chlorovinyl boronates to produce chiral carbamates (equation 217). By allowing an S_N2' reaction to take place onto the allylic system in the presence of a chiral copper catalyst, the oxidation of the borane furnishes the chiral allylic alcohol.[69] Reaction with an isocyanate provides chiral carbamates with very good enantiomeric ratios.



(217)

Morken has described the conversion of 1,3-butadiene systems into *cis*-but-2-en-1,4-diyl systems (equation 218). By means of forming the 1,4-diboryl olefin, subsequent oxidation can provide the 1,4-diol in very good yields. They also showed that this can

be readily scaled up to a multigram level, without loss of conversion. A periodative workup was found to facilitate purification by removing any formed 1,2-diol.[107d] Many other examples of such conversions for purposes of installing a hydroxy group have appeared in the literature.[45a,65]



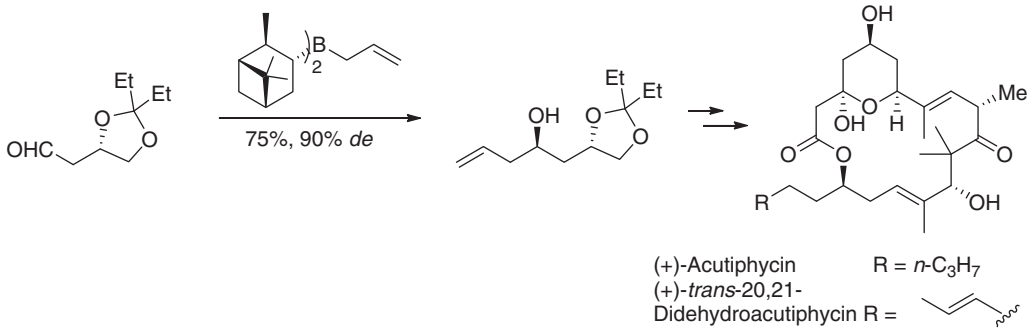
(218)

2.01.12 Allylboranes in Total Synthesis

Allylboranes have been used extensively in organic synthesis, starting only shortly after the discovery of their high synthetic utility. Virtually every structural class of compound has been produced through a route that has incorporated some aspect of allylborane chemistry. The choice to include allylborane chemistry, no doubt, stems from the very high yields and enantio- and diastereoselective nature of their reactions. Hereafter, the authors present several representative syntheses that illustrate the great utility of these allylborane reagents as an attempt to demonstrate several of the fundamental uses and abilities that have been described herein.

2.01.12.1 (+)-Acutiphycin and (+)-*trans*-20,21-Didehydroacutiphycin

The title compounds, which are highly potent against murine Lewis lung carcinoma, as well as being cytotoxic toward the KB and NIH/3T3 cell lines, were synthesized by Smith et al.[368] Both compounds were synthesized from a common intermediate which had been built through the use of a chiral allylboration of the diethyl ketal-protected homoglycolic aldehyde (equation 219). The use of chiral ligands on boron were sufficient to overcome the remote chiral induction from the aldehyde substituent.

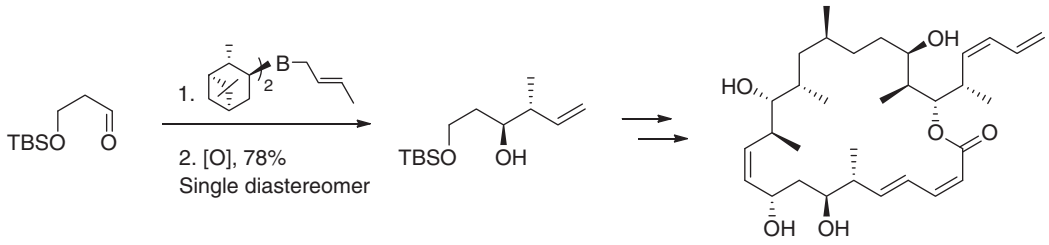


(219)

The similar use of allylborating reagents can be seen in the syntheses of balanol[369]; goniothalamin, hexadecanolide, massoia lactone, and parasorbic acid[370]; umuravumbolide[371]; and anamarine[372]; as well as in the partial synthesis of gambierol.[373]

2.01.12.2 (–)-Dictyostatin

The ability to produce any of the four desired stereoisomers of the β-hydroxymethyl fragment for a system was elegantly demonstrated in the total synthesis of (–)-dictyostatin by Ramachandran et al.[374] Eight of the eleven stereogenic centers were established through the careful choice of reagents during four crotylboration reactions (equation 220). This synthesis opened another route to this incredibly potent microtubule-stabilizing agent.

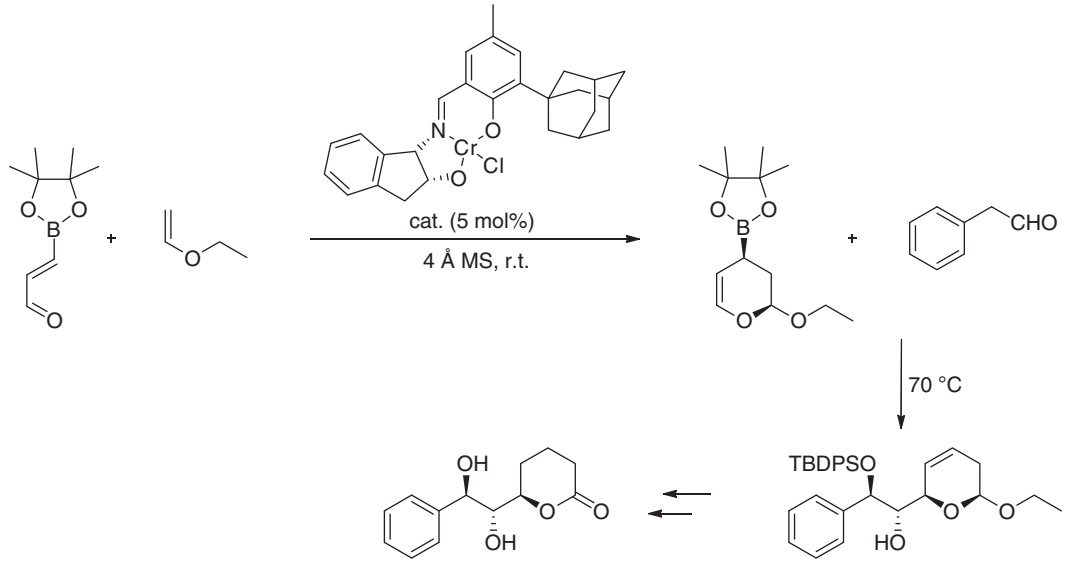


(220)

Crotylboration has been used in dozens of other notable partial and total syntheses, such as calyculin C,[375] cryptophycin-24,[376] the oxaspirolactone core,[377] and the cryptophycins.[378] Dimethylallylboration has also been used in working towards the total synthesis of the core of the epothilones.[379]

2.01.12.3 (+)-Goniodiol

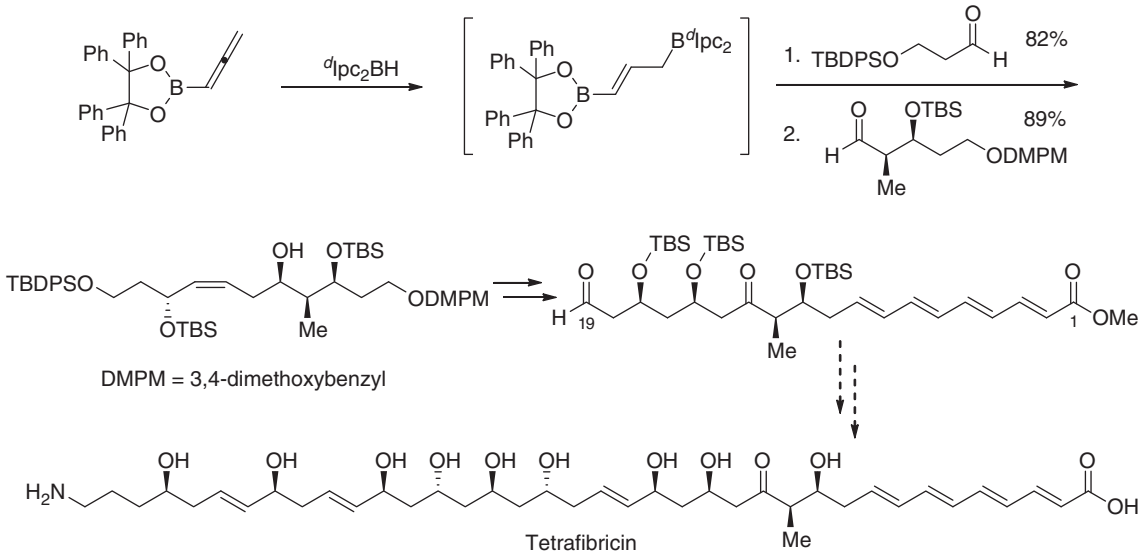
Carreaux and coworkers used the one-pot Diels–Alder reaction/allylboration reaction strategy as a synthetic route to access (+)-goniodiol in very reasonable seven steps and 15% overall yield.[380] This molecule is one of the active ingredients in *Goniothalamus*, a plant whose extracts have been shown to be useful in the treatment of edema and rheumatism (equation 221). Furthermore, the molecule has shown moderate levels of toxicity to the human lung carcinoma cell line A-549. This same Diels–Alder/allylboration methodology has also been applied in the total synthesis of palmerolide A[381] and (+)-iso-*exo*-brevicomin.[382]



(221)

2.01.12.4 C1–C19 Subunit of Tetrafibricin

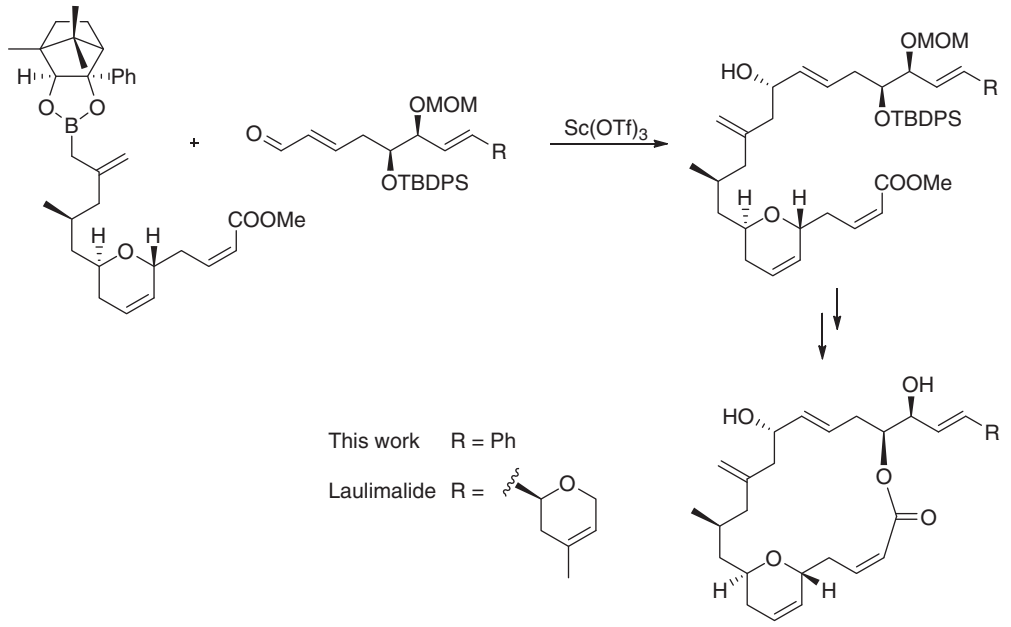
Tetrafibricin is a poloxygenated molecule that has the potential to be used as a means of providing therapeutic treatment to patients of thrombotic diseases. Roush and coworkers synthesized the C1–C19 portion of this molecule utilizing a double borylation procedure with absolute stereocontrol on one of the two borons.[383] The incorporation of three complex molecules through this methodology has demonstrated a remarkable level of convergence, proceeding in excellent yield and with a very good level of diastereoselectivity, namely 16:1 (equation 222). Similar work has also been used in other syntheses such as (–)-teubrevin[160] and (+)-strictifolione.[384]



(222)

2.01.12.5 Laulimalide analogs

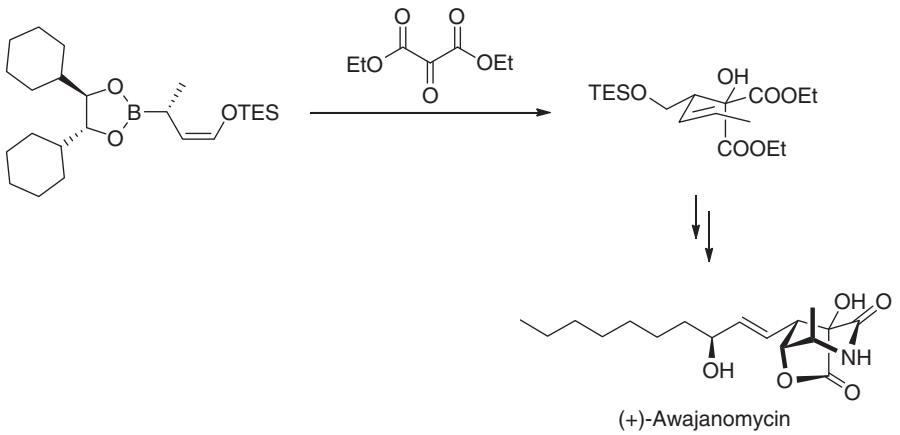
Laulimalide is a highly cytotoxic molecule which exhibits a very high level of potency against several cancer cell lines. Furthermore, it does not suffer the same issues of acquired resistance that plague other notable molecules such as Taxol. As such, much research has gone into the synthesis of it and several different analogs. In one such example, an allylic boronate, which was produced through the palladium-catalyzed cross-coupling of a diborane at the expense of an allylic acetate, was made to couple with a complex aldehyde very late in the synthesis of the des-dihydropyranyl-22-phenyl laulimalide analog.[385] The 'catalyzed' allylboration reaction was accomplished by means of the inclusion of scandium triflate (10 equivalents were used) to promote the allylboration as reported by Hall. This particular reaction occured in excellent yield and with good diastereoselectivity (equation 223). The formed stereogenic center was controlled by means of Hoffman's camphor-derived, 2-phenyl chiral auxilliary. Although the shortest route to ipsenol and ipsdienol was demonstrated with the use of Brown's chiral isoprenylation,[386] the constitutionally isomeric 3-phenyl auxilliary has been used as well by Villiéras and coworkers.[387]



(223)

2.01.12.6 (+)-Awajanomycin

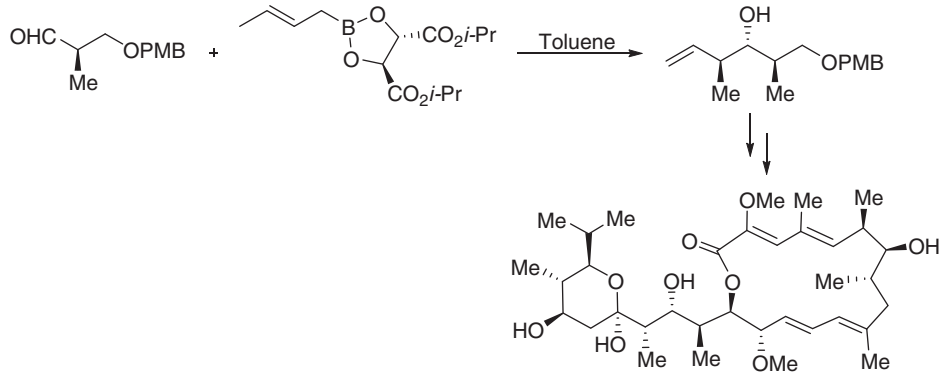
(+)-Awajanomycin is a molecule that has been shown to be cytotoxic toward adenocarcinomic human alveolar basal epithelial cells. Only two total syntheses have been reported to date; the most recent uses a boron-based allylation strategy as the key, chiral-inducing step, and inserts a large portion of the necessary functionality (equation 224). Using the chiral Matteson homologation reaction, the desired polyfunctional allylboronate was produced, and reacted with diethyl mesoxolate under solvent-free conditions for 9 days. The resultant product was formed in 85% yield and 96:4 enantiomeric ratio. Remarkably, the total synthesis of this complex, medium-sized natural product was completed in 10 steps and 22.5% overall yield.[388] The use of the chiral dicyclohexyl boronate in other syntheses is also well-known.[62,389]



(224)

2.01.12.7 (–)-Bafilomycin A

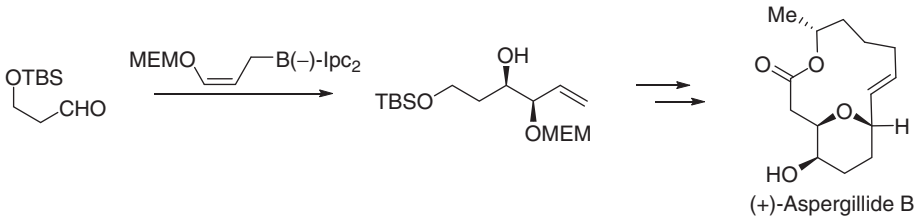
(–)-Bafilomycin A, a member of the macrolide family of hygrolide antibiotics, has been synthesized three times. The latest synthesis, a report by Roush and coworkers,[390] included the use of diisopropyl tartrate as a means to control the absolute stereochemistry during a crotylboration reaction of an α-chiral aldehyde. Despite working in oppposition to the directing effects of the aldehyde itself, the absolute stereochemistry was controlled nicely by the chiral 1,3,2-dioxaborolane derivative, providing the desired diastereoisomer in 78% yield and in an 85:15 ratio with the undesired isomer (equation 225). Roush and coworkers also used this same boronate in working toward the synthesis of superstolide A.[391] The synthesis of (+)-methynolide and (+)-lactacystin also featured this chiral crotylboronate.[392]



(225)

2.01.12.8 (+)-Aspergillide B

(+)-Aspergillide B, a moderately potent molecule that shows promising activity toward the L1210 murine leukemia cell line, has recently been synthesized by Jennings and coworkers.[393] The alkoxyallylboration of 3-(*t*-butyldimethylsilyloxy)propanal, which was performed with absolute stereocontrol by means of Brown's chiral isopinocampheyl ligand, provided the desired diastereomer in 75% yield and greater than 95:5 diastereoselectivity (equation 226).

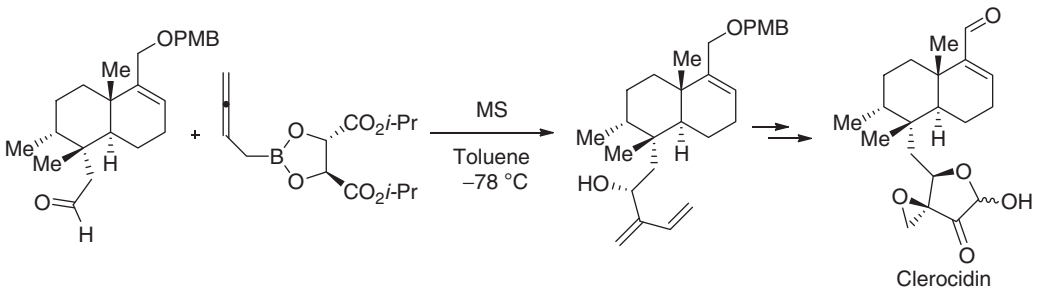


(226)

The use of similar alkoxyallylborations in synthesis is commonly encountered in the literature. For example, the partial syntheses of 8-*epi*-fostriecin,[394] and epothilone A,[395] as well as the azinomycin core[396] have been reported, along with the total syntheses of (+)-goniodiol, (–)-8-epigoniodiol, and (+)-9-deoxygoniopypyrone,[397] and restrictinol.[398] Their use in the synthesis of cyclic oxamides for HIV-1 protease inhibitors has also been detailed.[399]

2.01.12.9 Clerocidin

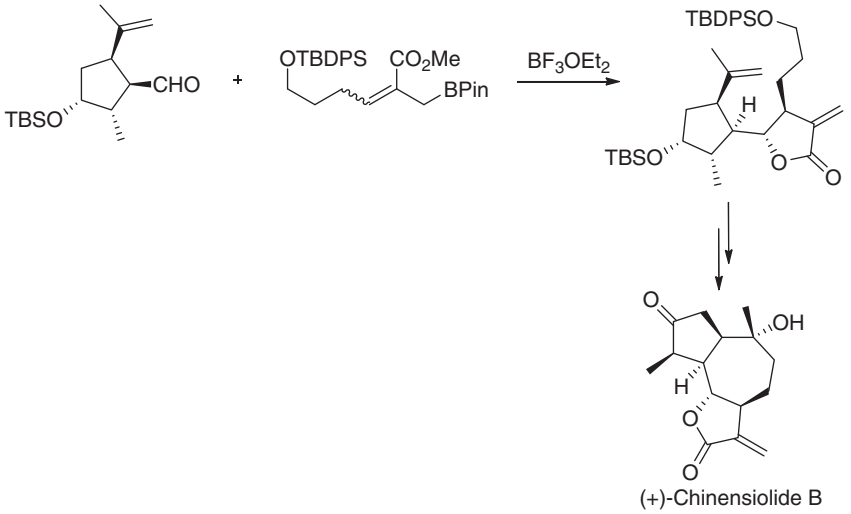
Clerocidin is an antibiotic and antitumor molecule which has attracted attention during the last two decades because of its highly complicated and functionalized structure. The first total synthesis was reported in 1998, in which Theodorakis and coworkers built the necessary butadiene substructure using a chiral, diisopropyl tartrate-derived homoallenyl boronate.[400] The reaction, in which the chirality was being dictated by the boron ligands, proceeded in 83% yield and with a favorable 6:1 ratio of diastereomers (equation 227).



(227)

2.01.12.10 (+)-Chinensiolide B

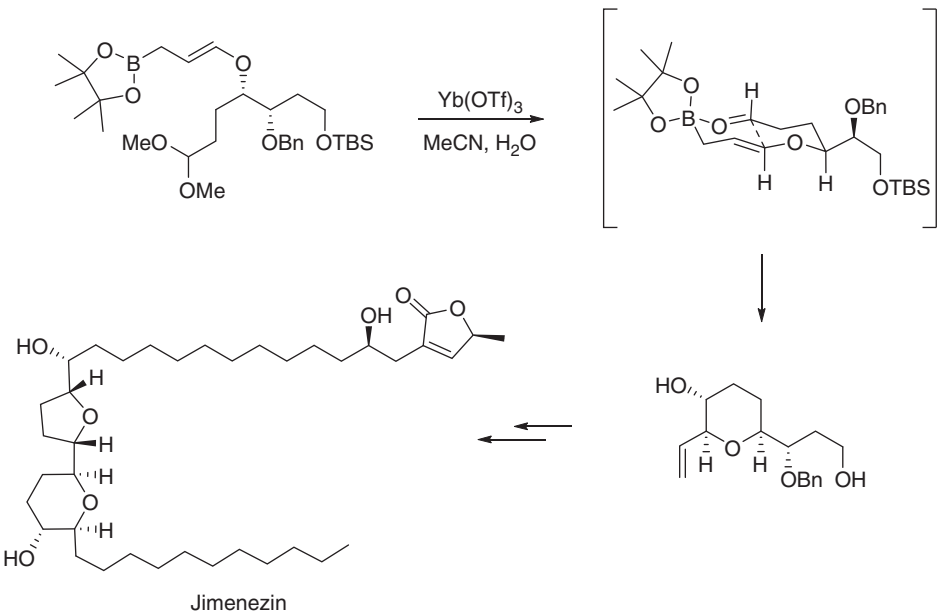
(+)-Chinensiolide B is a member of the ever-growing class of natural products containing an α-methylene-γ-butyrolactone moiety, which is also possibly the pharmacophore that is responsible for its incredibly high level of potency. The molecule, which is highly active against the HepG2 and WI-38 & VA-13 (human primary liver cancer and human lung fibroblast, respectively) cell lines, has a very interesting 5,7,5-tricyclic structure. The first synthesis of any of the members of this family was reported by Hall in 2010, in which the title molecule was completed with an overall yield of 6.7%.[401] A β-methoxycarbonyl-γ-alkoxy substituted allylic boronate was made to react with a pendent aldehyde. A concomittant cyclization to the lactone occured to furnish the second required ring (equation 228).



(228)

2.01.12.11 Jimenezin

Jimenezin is a molecule which has been isolated from a member of the Annonaceau plant. This natural polyketide product is an acetogenin, and has shown to be active against six different human solid tumor cell lines, and in the brine shrimp lethality test. Several syntheses of this molecule have appeared, including a recent one by Hoffmann and Koert, in which an ytterbium-catalyzed intramolecular allylboration was used to create the first tetrahydropyrano ring in a stereoselective manner. The cyclization occured in 79% yield to give a single diastereoisomer (equation 229). The highly selective nature can be attributed to the intramolecularity of the reaction. This particular transformation highlights several of the concepts discussed in this chapter, including the use of a Lewis acid-catalyzed allylboration, a γ-substituted allylborane, and the Matteson homologation that was used to access the starting allylborontate.[402]



(229)

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2.02 Allylsilanes, Allylstannanes, and Related Compounds

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This chapter is a revision of the previous edition chapter by Ian Fleming, Vol. 2, pp 563–593, © 1991, Elsevier Ltd.

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 doi:10.1016/B978-0-08-097742-3.00202-0

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Glossary

Allylsilane A silane molecule bearing an allyl group attached to silicon.

Allylsilation A carbon–carbon bond-forming reaction wherein an allylsilane is added across an aldehyde, ketone, or imine.

Allylstannane A molecule bearing an allyl group attached to tin.

Asymmetric allylsilation Allylsilation wherein a chiral ligand is used to induce chirality in the product.

Corey–Fuchs reaction A reaction for the conversion of an aldehyde into an alkyne.

Homoallylic alcohol Product obtained from allylsilation of an aldehyde or ketone.

Hosomi–Sakurai reaction A Lewis acid-promoted allylation reaction with allylsilanes.

2.02.1 Introduction

This chapter has been constructed so as to include as broad a scope of the chemistry of allylsilanes, allylgermanes, allylstannanes, and allylplumbums as possible. Attempts have been made to introduce those concepts to the reader that will allow for a basic understanding of their chemistry and reactivity.

This chapter begins with an introduction into the relevant physical properties of the four elements, which is necessary for understanding the basic reactivity trends and reaction types observed in their reactions as allyl metals. These reactivities are discussed in the context of their mechanistic considerations, and full consideration is given to the reaction mechanisms and transition states, and in how they are related to the observed products and stereochemistries. Additionally, consideration is given to the relative reactivities of the different species.

As comprehensive knowledge of the synthesis and reactivities of allylic silanes is orders of magnitude larger than that of allylic tins, which is larger still than that of allylgermanes and allylplumbums, this chapter has been written so as to provide the majority of its emphasis on allylsilanes, allylstannanes, allylgermanes, and allylplumbums.

The synthesis of allylsilanes is thoroughly discussed, and is inclusive of both historical and newer methods. The detailed synthetic approaches are usually explained in the context of a particular example, as the authors feel that this allows the reader to more fully understand the practical utility of the chemistry being presented. The structural analogs of allylic groups (such as allenic and propargylic groups) are not treated separately, but are sporadically incorporated into these construction methods.

The reactions of allylic silanes with aldehydes are then discussed, and are broken down into reactions that take place through Type-I and Type-II mechanisms, and then by taking into account the relative stereochemical differences between the inter- and intramolecular versions, and also as to whether or not absolute stereocontrol is taking place. Thereafter, those annulation reactions that can occur during the addition to aldehydes are discussed. Ketones are covered next, again differentiating between the control of absolute stereochemistry or lack thereof. Ketone annulation reactions are then covered.

The reaction of oxycarbenium ions, which are merely a disguised form of highly activated aldehydes and ketones, is next covered, again by the consideration of the inter- and intramolecular versions of the reaction, and by consideration of the absolute stereochemistry.

Afterward, imines are discussed, first with consideration of unactivated, simple free imines and Schiff bases, followed by separation into classes which offer some levels of activation, e.g., iminium ions, acyl imines, etc.

Thereafter, α,β-unsaturated systems are discussed, paying careful attention to the differences in the various annulation modes, and also by contrasting between annulation and allylation processes.

Other systems which are capable of being allylated are then covered, beginning first with carbonyl derivatives such as esters or acyl silanes, then continuing on to other π-systems such as alkenes. All remaining reaction types are then discussed.

Moving down the periodic table, allylic germanium, tin, and then lead compounds are discussed in turn. However, due to space constraints, a complete coverage of these three elements has not been attempted. Instead, their reactions are covered by offering a comparison/contrast to those of allylic silanes. This approach is made possible by the strong similarities in their modes of reactivity with comparable functionalities. Brief overviews of the preparation of these compounds are added in these sections.

In lieu of a subsection specifically devoted to the use of these allylating agents in various syntheses, a few select examples of such work have been included, which employ some of the principle concepts of the chemical reactivities displayed by these species.

There does exist prior reviews on this topic. Nonetheless, every possible effort has been made to be as fully comprehensive with regard to both referencing and coverage, even if it overlaps with previous reviews. It is simply not possible to cover all of the developments of this large area in a chapter such as this; any omissions were not the intent of the authors.

2.02.1.1 Background/History

Historically, Sommer and coworkers were the first group to divulge the reactions of allylic silanes with a variety of electrophiles, including mineral acids, diatomic halogens, and protic acids. This report came in 1948,[1] and was followed by a few reports approximately 20 years later that demonstrated their reactions with chlorosulfonates.[2] Shortly thereafter in 1976, Hosomi and Sakurai divulged that, under strongly Lewis-acidic conditions, aldehydes and ketones could be sufficiently activated to allow for an allylic transfer to take place.[3] This has since been expanded to a variety of electrophiles, including ketones, imines, alkenes, and alkynes. During the course of these investigations, it was also observed by Hosomi and Sakurai that pentavalent allylic silicates could undergo allylation of aldehydes without the need for external Lewis acid catalysis, proceeding instead through a Type-I mechanism.[4] Due to their overwhelmingly large contributions to such processes, these allylation reactions are now referred to as the Hosomi–Sakurai reactions. Many complete and partial reviews on allylsilanes and related topics have appeared over the years.[5] The interested reader should also peruse these reviews for further insight and coverage of these topics.

2.02.2 Overview of Allylsilanes, -Germanes, -Stannanes, and -Plumbums

2.02.2.1 Pertinent Elemental Properties

The Group-IV elements are similar in both their structures and reactivities. Below carbon, however, silicon and the other heavier elements are quite capable of forming expanded valencies, readily taking on pentacoordinate, hexacoordinate, and even larger bonding schemes.[6] The tetravalent compounds take on sp^3 hybridization, similar to carbon. However, the heavier elements can take on additional bonds by expanding their valencies (Figure 1). For this to take place, a dehybridization to sp^2 is necessary, where the d-orbitals play little role except in the slight polarization of the resultant unhybridized p-orbital. It should be emphasized that a rehybridization to sp^3d does not take place, as this would be energetically too demanding.[7]

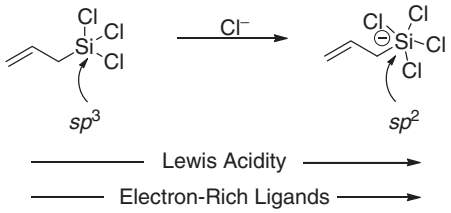


Figure 1 The relationship between Lewis acidity and hypervalent bonding in silicon.

The bonding motif produced through this rehybridization can best be described as three-centered-four electron bonds. For this type of bonding to readily take place, the presence of fairly electronegative ligands is necessary. The expanded valency results in a greater net electronic presence around the metal atom. A mutually increasing repulsion of the ligands necessarily occurs, thereby increasing the metal–ligand bond lengths. The consequence of this geometrical reorganization is actually an increase in the electron density of the ligands, and a net increase in the Lewis acidity of the metal center. It is perhaps not surprising then that the increased Lewis acidity of the metal assures a ready accommodation of a sixth ligand such as a carbonyl.

Silicon, germanium, tin, and lead are all less electronegative than carbon, which dictates a carbanionic character on the ligand for bonds made between these elements and carbon. It is this inherent quality that gives allylsilanes, -germanes, -stannanes, and -plumbums their reactivity.

2.02.2.2 Toxicity of Group-IV Elements

Further down the periodic table in Group-IV, the elements generally increase in their toxicity. Precaution against exposure to all of these compounds should be practiced as part of good chemical hygiene.

Silicon has virtually no known toxicity, except for in extreme cases involving the inhalation of large amounts of silicon-containing substances (such as in silicosis).

Exposure to the relatively nontoxic element germanium has little adversity on human health. However, chronic exposure (such as in dietary supplements) can result in problems such as kidney dysfunction, anemia, and neuropathy.[8a] In certain cases, however, some germanium compounds have been shown to exhibit significantly higher toxicities.[8b] Fortunately, these cases seem to be rare.

Tin-based compounds show a marked increase in their levels of toxicity.[9] Metallic tin does not possess any significant levels of toxicity, nor do its simple salts (due to its incredibly low absorption rate). However, tin hydride compounds (radical-forming species) and organotin compounds are generally quite toxic. Usually, an increase in the number of carbon–tin bonds results in an increased level of toxicity for the compound. For purposes of comparison, tributyltin compounds are of comparable toxicities to humans as hydrogen cyanide gas. The physiological effects of such tin compounds have been shown to appear mostly in the central nervous system and liver. Acute effects of exposure to these compounds are mostly lachrymatory and sternutatory in nature.

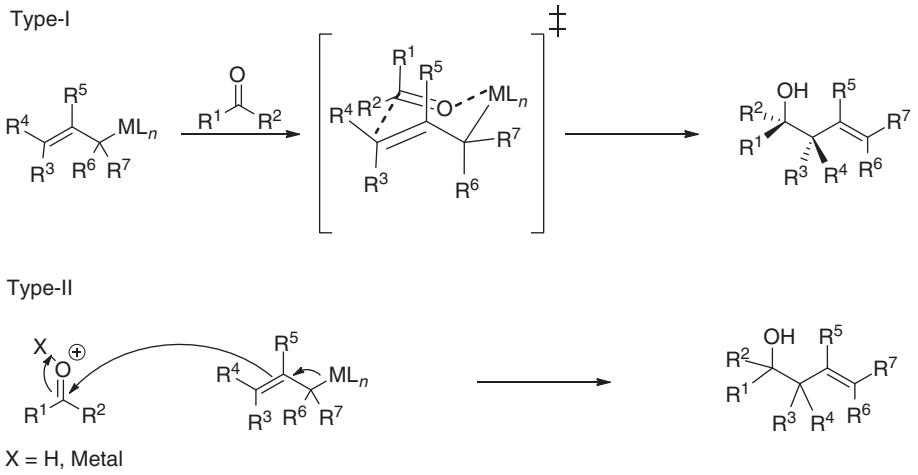
Lead-based compounds are highly toxic to humans.[10] Similar to tin, lead can collect in the central nervous system, but has also been shown to affect virtually every organ and body system. The results of exposure to lead can vary, but nephropathy, malaise, hypertension, kidney failure, infertility, miscarriages, and death can take place. Permanent cognition loss has also been demonstrated, as has anemia. Unfortunately, lead is readily absorbed into the body through all three major routes: digestion, respiration, and tactile contact. Generally speaking, organolead compounds exhibit higher toxicities than do lead salts. All exposure to lead should be avoided as much as possible.

Likely due to a combination of concerns of toxicity and commercial/worldwide availability, the utility of allylic silanes has been investigated far more than those of germanium, tin, or lead. Of the latter three elements, the higher availability of tin has likely resulted in it being the most studied.

2.02.2.3 Mechanisms

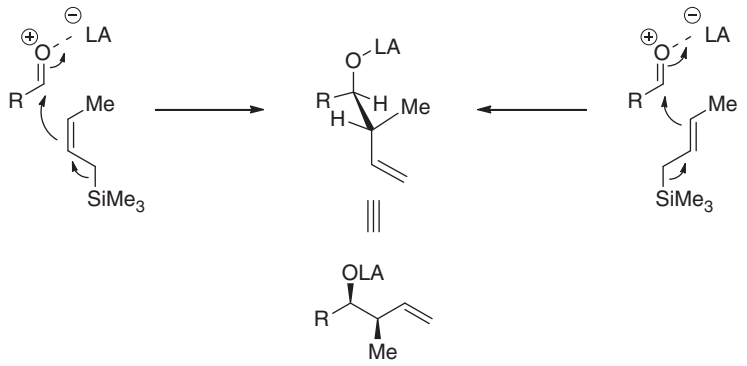
Unlike allylboron compounds (*see* Chapter 2.01),[11]allylic silanes, germanes, stannanes, and plumbums generally do not react with electrophiles in an allylation manner without the presence of Lewis acids. Just as with boron, there exist three distinct mechanisms by

which allylation reactions can occur (Scheme 1).[11] In Type-I processes, a coordination to the metal by the electrophile serves to activate both the metal's allylic group toward allylation and the carbonyl group's reactivity toward electrophiles. A closed, six-membered transition state (Zimmerman–Traxler model) has been used to describe these reactions, and usually accounts quite well for the observed *syn*- and *anti*-stereochemistries.[11] A general rule of such systems is that a *Z*-allylic system will furnish a *syn*-relationship, and that an *E*-geometry provides an *anti*-arrangement. In Type-II processes, there is no internal coordination. Instead, an external activation occurs usually through chelation of the electrophile to either a Brønsted–Lowry or Lewis acid, thereby increasing the electrophilicity of the carbonyl without affecting the properties of the allylmetal system. Without the dual activation seen in Type-I processes, and also due to entropic considerations, Type-II processes are generally slower than Type-I processes.



Scheme 1 Two mechanistic pathways followed during allylsilation reactions.

In the case of Type-II processes, the relative stereochemistry formed is almost exclusively *syn* in nature. This is due to the additional freedom allotted for acyclic processes (Scheme 2). The nucleophile can attack the electrophile, and, in both cases, be positioned so that the closest group of the alkene will be positioned in a nearly antiperiplanar arrangement to the largest substituent, thereby minimizing steric repulsions.

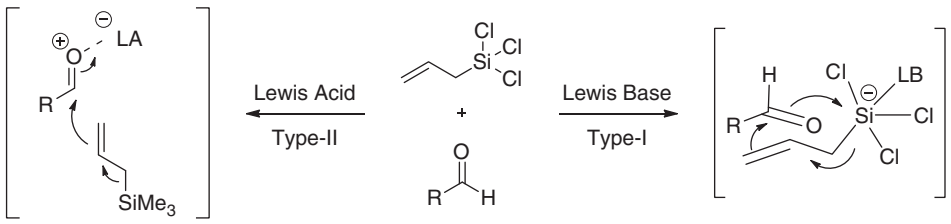


Scheme 2 Transition state rationale for stereochemical outcomes of γ-substituted allylsilation reactions.

Generally, most allylsilations are believed to proceed through an antiperiplanar transition state, akin to that shown in Scheme 2. However, a few anomalous reports have appeared in the literature, which, under case-specific circumstances, have implicated the preference for the existence of *syn*-clinal transition states. In one particular case, Denmark and coworkers demonstrated that in an intramolecular variant of the Hosomi–Sakurai reaction, a *syn*-product was preferentially obtained, and which partially depended on the choice of the Lewis acid catalyst.[11a,b] The formed stereochemistry could only be explained through the invocation of a *syn*-clinal transition state. In another example, Mikami and coworkers showed that the allylsilation of α-benzyloxy-substituted aldeydes resulted in the unexpected formation of the *anti*-adducts.[11c] In that particular case, it was postulated that a chelation effect of the benzyloxy substituent was responsible for this unexpected stereochemistry. In these highly unusual cases, the exact origins of these atypical reaction pathways are not always clear; an enigmatic variety of stereoelectronic or steric factors are likely responsible.

It is obvious in the case of Type-I processes that there is a net transfer of the metal species onto the electrophile on completion of the pericyclic rearrangement. The same net transfer takes place for Type-II processes. It is many times not possible (or even desired) to capture this alkoxymetal species, as it is usually hydrolyzed during the workup stage of a reaction. Almost invariably then, the result of these reactions is the formation of an O–H or an N–H instead of an O–Si or on N–Si bond. An important exception is seen in the case of the reaction with alkenes and alkynes, whereby the formed C–M(etal) bond is usually stable and isolated or used in further chemical manipulations. Unfortunately, due to the fact that most strong Lewis acids that are used in the catalysis of these reactions, and that most of these Lewis acids possess moderately silylphilic ligands (such as halides) which are necessary to impart this high Lewis acidity, the interference of these ligands with this seemingly simple outcome can be problematic. In many cases, rather than obtaining an O–Si functionality, the bond is cleaved in favor of the formation of the more thermodynamically favored Si–X bond. Consequently, Lewis acid promoters in these reactions, while functioning as catalysts, are many times consumed in the reaction, and so amounts greater than catalytic quantities are almost inevitably required to fully promote these reactions.[12]

Most of the allylation reactions using Group-IV elements can take place through either a Type-I or Type-II mechanism. Even the highly Lewis-acidic allyltrifluorosilanes are not capable of directly affecting a Type-I process. As such, all allylation reactions take place with the addition of external acid catalysis, and proceed entirely through a Type-II process. Few exceptions to this exist, such as tetracyanoethylene and chlorosulfonyl isocyanate, which are highly activated electrophiles; these are covered in the appropriate Section 2.02.3.7.6. As discussed in Section 2.02.2.1, the enhancement in Lewis acidity attained by reversion to an sp^2 hybridization (on attainment of a pentavalent bonding scheme) is actually sufficient to allow for chelation from electrophiles into the metal center. This activation, just as it does with normal Type-I processes, activates both the allylic group and the electrophile, thereby allowing the reaction to proceed in a cyclic manner. As such, allylic silanes, when possessing strongly electron-withdrawing substituents, can undergo Lewis base-catalyzed allylation processes, by changing the reaction from a Type-II to a Type-I pathway (Scheme 3). (Although the same method of activation for the other Group-IV metals could theoretically take place,[13] there have been no such reports.) In both cases, allylic inversion, i.e., an S_E2' reaction takes place, almost invariably giving electrophilic attack at the γ-position.



Scheme 3 Mechanistic divergence during allylsilation by changing activation method.

In the case of Type-I processes, a concerted, pericyclic mechanism takes place. However, Type-II processes do not directly undergo allylation and desilylation in one step. Instead, the addition of the olefin, which is generally believed to be slightly more electron rich than a normal alkene,[14] adds onto the electrophilic species, thereby generating a new carbon–carbon bond and a β-silylcarbocation. This carbocation is unusually stabilized, however, by elements such as silicon, germanium, tin, and lead. In general, this effect is known as the β-silicon effect, and is the result of hyperconjugation of the carbon–silicon bond with the unhybridized p-orbital of the carbocation (Figure 2). The stabilization relative to the equivalent carbon–carbon bond stabilizing hyperconjugation is approximately 30 kcal mol^{-1}.[5c,15] A similar effect exists for α-anion stabilization, which is what allows for the facile deprotonation adjacent to silanes (see Section 2.02.3.1.11). There may be a small amount of additional stabilization from the formation of a siliranium ion (a three-membered C–C–Si ring containing a delocalized positive charge, akin to those of bromonium ions found in halogenation reactions). Whether or not such additional stabilization exists is case dependent, and when it does occur, it is usually accompanied by silyl shifts, wherein the silicon moiety entirely migrates from its current carbon to that of the carbocation. These are known as 1,2-silyl-Wagner–Meerwein shifts, and occur readily in most cases when such a shift results in an even more stabilized carbocation. Similar β-effects are known to exist with germanium, tin, and lead. In general, the magnitude of these effects increases down the group.[16]

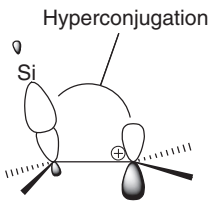
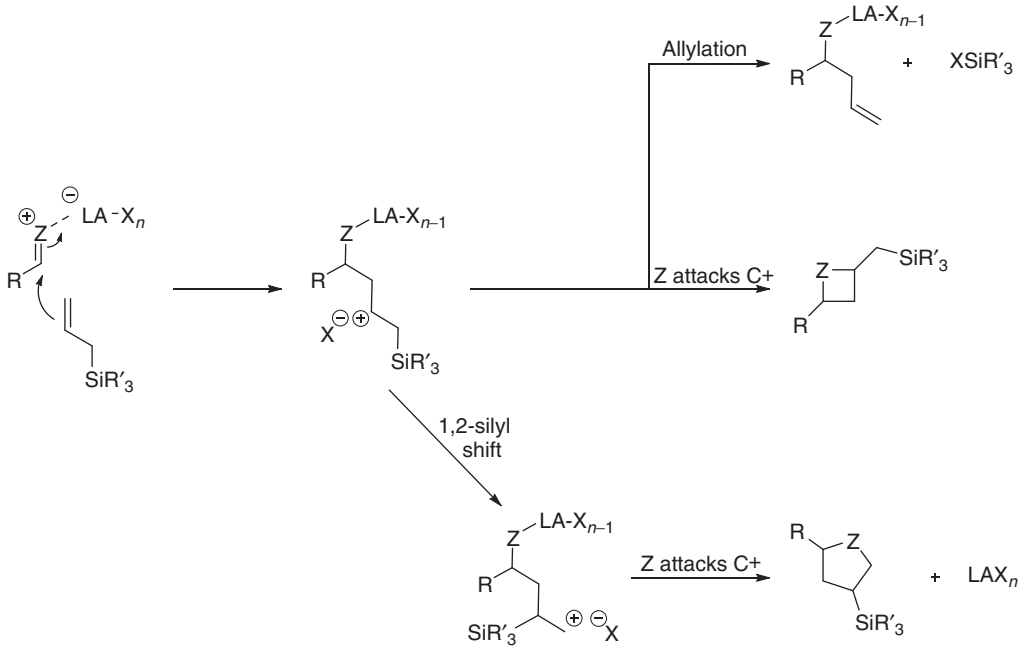


Figure 2 Hyperconjugation and the β-effect of silicon.

The consequence of this shift becomes most apparent in annulation reactions. Specifically, intramolecular capture of these carbocations, both before and after any possible silyl shifts has taken place, has been observed. A more detailed mechanism for these reactions is given in Scheme 4. On initial attack, the β-stabilized carbocation can either undergo allylation, or the carbocation can be captured intramolecularly. Alternatively, silyl migration can take place, followed by intramolecular annulation. As the attack of the Lewis acid's ligand onto silane takes place during the allylation pathway, it can be expected that more sterically encumbered silicon groups would be less prone to undergo reaction by way of allylation, and more strongly favor annulation pathways. In general, this holds true, as bulky silicon ligands such as isopropyl groups tend to encourage annulation reactions instead of allylations. This is further discussed in the following Sections 2.02.3.2.5–2.02.3.2.7, 2.02.3.3.3, 2.02.3.3.4, 2.02.3.6.1, 2.02.3.6.2, and 2.02.5.7.



Scheme 4 Mechanism detailing the formation of the annulation and Hosomi–Sakurai products.

2.02.2.4 Relative Allylation Rates

In simple allylation cases, allyltrimethylsilane is the most commonly used allylating agent, as it is commercially available, cheap, and atom-economical. In Type-I pathways, electron-withdrawing substitutents are necessary for providing the means to produce hypervalent siliconates. For Type-II pathways, however, electron-withdrawing substituents expectedly decrease the rate of allylation reactions by inductively removing electron density from the allylsilane, thereby decreasing nucleophilicity.[17] For example, *p*-methoxyphenyl groups attached to the silane increase reactivity, whereas *p*-nitrophenyl groups decrease the reactivity. Aryl groups are, in general, electron withdrawing.[18] Hydrogen, which is slightly more electronegative than silicon, is considered an electron-withdrawing group (EWG).[19] Increasing the chain length of alkyl groups slightly increases the reactivity, possibly as a result of conformational effects or inductive capabilities. The addition of groups that stabilize the intermediate carbocation drastically enhances the reaction rate, which is evidence of the initial step (carbocation formation) being the rate-limiting one. The same general reactivity patterns have been observed for germanium and tin.[20] Allyllic lead compounds' structural and substitution effects on nucleophilicity have not been quantified, but it is expected that they would behave similarly. The nucleophilicity of Group-IV allyl metals generally increases down the group from silicon to tin. From this trend, it is perhaps reasonable to expect that allylic plumbums would be the most nucleophilic of all of the groups.

2.02.2.5 Stability of Group-IV Allyl Compounds

Organosilanes and their Group-IV relatives exhibit remarkable stabilities. In general, the reactivity of the carbon–metal bonds increases quite drastically down the group. Nonetheless, they typically remain stable enough to handle in the laboratory without much in the way of special precaution. Thermally speaking, allylsilanes are incredibly stable, and can be heated to between 350 and 500 °C before decomposition begins to occur, mostly through a 1,3-silyl migration.[21] Thermal stability decreases down the group, corresponding to a decrease in bond strength. Similarly, photochemical migrations of silicon can occur, although ambient laboratory light typically does not affect them.[22] Generally speaking, they are also stable to oxygen and moisture; excessive

exposure should be avoided nonetheless. Chemically, carbon–silicon bonds are relatively inert toward a very wide range of synthetic chemical transformations, such as reductions, most oxidations, hydrogenation, mild acidification and basification, treatment with Lewis acids, and radical progenitors. Although certain chemical manipulations such as radical reactions and oxidations can affect organosilanes, the careful choice of reagents and conditions can usually allow them to survive a wide array of transformations and manipulations, including column chromatography. Allylgermanes are also generally stable to chromatography. Unfortunately, too few reports on their use have appeared in the literature to allow for a full detailing of their thermal and chemical stabilities. However, it can be expected that they possess chemical and thermal stabilities which are intermediate to those of allylic silanes and stannanes. Similarly, too little is known about allyllead compounds. It is expected, however, that they would be far more reactive than even allylic stannanes. The latter allylic stannanes, much like most carbon–tin bonds, are moderately stable species. They are able to be carried through syntheses, so long as the conditions chosen for each chemical step are not particularly harsh. Many oxidations, reductions, protections, deprotections, and simple chemical manipulations have been reported to occur without disturbing the allylic stannane moiety. They are more sensitive to acidic conditions than are the corresponding silanes, however.[23] As such, they are only moderately stable to chromatographic conditions – so long as such chromatographies are performed quickly and they do not contain any labile ligands, then stability is usually maintained. Nonetheless, minute amounts of decomposition are usually unavoidable. β-Hydroxy (and alkoxy) stannane compounds are generally not stable to silica gel conditions, however, as they readily undergo dehydr(alk)oxystannylation.[24]

2.02.2.6 1,3-Sigmatropic Shifts

In general, allylsilicanes do not undergo appreciable 1,3-silatropic shifts at room temperature. As allylic silanes are of such high thermal stability and lack high levels of Lewis acidity, they are generally incapable of such shifts.[25] In the absence of solvent, very high temperatures are required to affect them, but in solvents the threshold temperature is much lower, usually taking place approximately at 275 °C.[26] When they do occur, such 1,3-silatropic shifts usually take place with retention of configuration at the silicon atom.

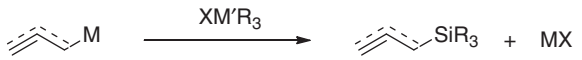
The 1,3-sigmatropic shifts of allylic germanes and plumbums have not been experimentally studied. However, Takahashi and Kira have performed a significant number of calculations on the matter.[27] Their results strongly indicate that the facility of such migration drastically increases down the group. Thus, there should be an intermediate level of stability for allylic germanes to allylic silanes and stannanes, and very little 1,3-sigmatropic stability for allylic plumbums. As it is well known that allylic stannanes can undergo 1,3-stannatropic shifts, and that not many of the produced allylic stannanes are autotropically stable, as such, it appears as though their calculations are in good agreement with the limited amount of reported experimental data. The 1,3-stannatropic stability of allylic stannanes is frequently reported as being solvent polaritydependent, with polar solvents facilitating rearrangement and nonpolar solvents hindering it. The photochemical 1,3-stannylic rearrangement of allylic stannanes is also known.[28]

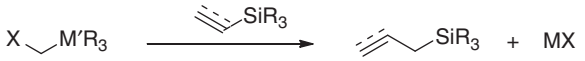
2.02.3 Allylsilanes

2.02.3.1 Preparation of Allylsilanes and Derivatives

2.02.3.1.1 Reactions with alkali/alkaline earth metal systems

The buildup of an allylsilane is commonly performed through either a ligand exchange reaction, in which an allylic anion is reacted with a metal containing a leaving group such as an alkoxide or a chloride, or through the substitution at the methyl group adjacent to a silyl functionality (equation 1). Such reactions usually take place with a countercation identity of lithium, potassium, or else a magnesium halide. Usually, the functionality of this approach is limited only in the formation of the precursor anion. In most cases, a simple mono- or disubstituted allylic system is used, so the inherently low acidity requires the use of very strong bases, such as alkyllithiums or the Schlosser-modified *n*-butyllithium base.

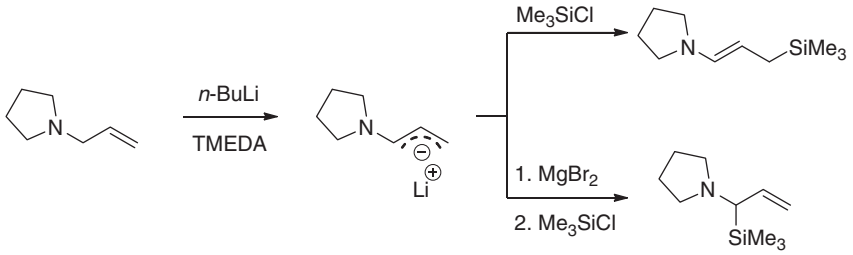




M = Li, Na, K, etc.
M′ = Si, Ge, Sn, Pb
X = Cl, etc.

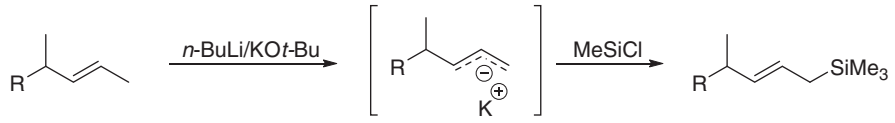
(1)

In one example, the superbase combination of *n*-butyllithium/*N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) was used to deprotonate *N*-allylpyrrolidine.[29] It was found that the direct quenching with trimethylsilyl chloride furnished the γ-pyrrolidin-1-ylallylsilane, whereas salt metathesis to the magnesium salt followed by quenching allowed for the production of the α-substituted product (equation 2).



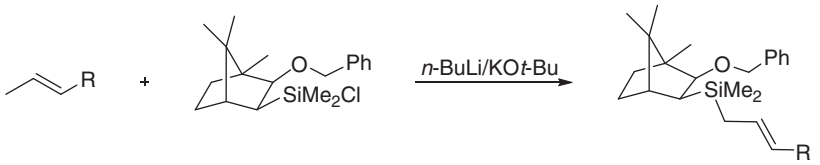
(2)

In a similar manner, the deprotonation of a simple allylic group can be performed.[30] For example, the Schlosser-modified base can be used to deprotonate the allylic positions of alkenes. The reaction with trimethylsilyl chloride gives the terminally substituted allylsilane (equation 3). Similar work has been performed on several occasions.[31]



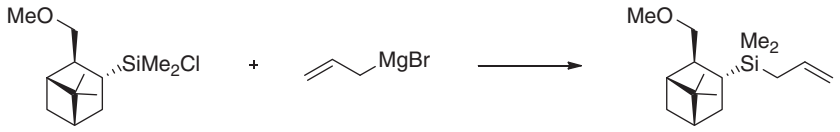
(3)

Chiral allylsilanes can be produced in an analogous manner (equation 4). The camphor-derived β-benzyloxysilyl chloride can be treated with the same allylic anion to provide the optically active allylsilane in very good yield.[32]



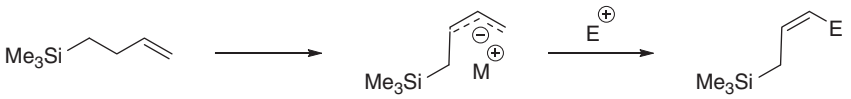
(4)

This type of reaction is not exclusively limited to alkali metal-derived allylic anions. For example, allylic Grignard reagents can be made to react in an analogous manner,[33] resulting in the same basic exchange process (equation 5). As the commercial availability of allylmagnesium halide salts makes this a particularly attractive transformation, it has become a common method of producing such allylsilane systems.[34]



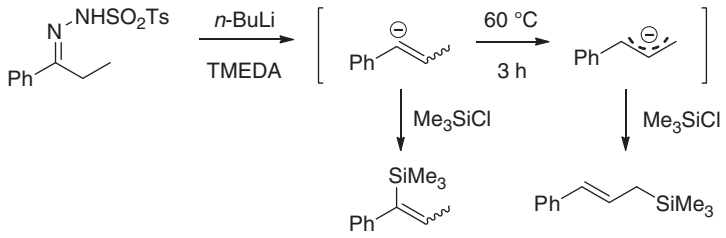
(5)

A homoallylic silane can be converted into an allylic one through such a deprotonation–quenching process.[35] For example, the deprotonation of the allylic system, followed by quenching with any appropriate electrophile such as an acyl, alkyl, or aldehydic group, can give rise to the desired allylsilane (equation 6).



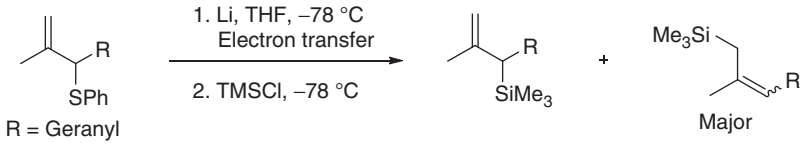
(6)

In an interesting transformation which proceeds in the same manner as a Shapiro reaction, a tosylhydrazide, on treatment with multiple equivalents of *n*-butyllithium in TMEDA can give rise to a vinylic anion (equation 7). While directly quenching this anion with a silyl chloride would generate a vinylic silane, gently heating the anion to 60 °C for 3 h affords a rearrangement to an allylic anion. Subsequent reaction then provides the expected allylsilane.[36] A similar route has been used in the production of 1,3-disilanes.[29,34e,37]



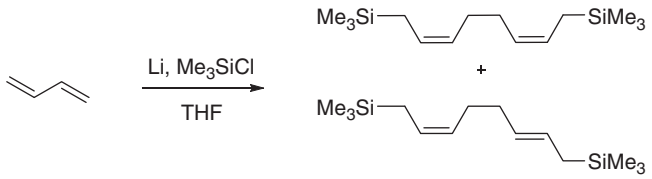
(7)

In a similar manner, deprotonation of alpha to allylic thioethers can be performed.[37] For example, a geranyl-derived allylic thioether has been shown to undergo a displacement of the phenylthiolate functionality on undergoing a $2e^-$ reduction with metallic lithium in an appropriate electron transfer solvent. Quenching of the system with trimethylsilyl chloride results in the formation of the expected constitutional mixture of allylic isomers, with the terminal silane being the predominant one (equation 8). Another method for the *in situ* production of an allyllithium specie is via the exchange of *n*-butyllithium with more readily available allylstannanes.[34f]



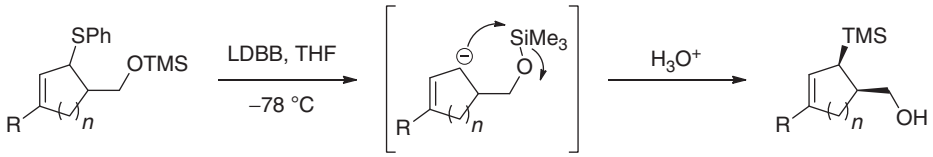
(8)

In a similar vein, metallic lithium, in conjunction with trimethylsilyl chloride and 1,3-butadiene, can undergo a reductive dimerization reaction, giving rise to the *Z,Z*- and *Z,E*-1,8-bis(trimethylsilyl)-2,6-octadienes (BISTRO) as a 1:1 mixture.[38] This unique reaction, which has been championed by Santelli and coworkers, provides access to the synthetically useful bisallylating agents shown (equation 9).



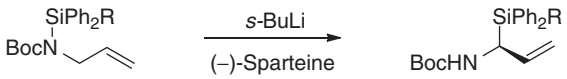
(9)

One synthetically useful but uncommonly utilized reaction is the retro-Brook rearrangement. Kuwajima and coworkers have developed a route to allylsilanes from allylic sulfides with a pendant silyloxy group. On treatment with lithium di-*t*-butylbiphenylide, the allylic thioether decomposes into an allylic anion (equation 10). If treated with an electrophile, the latter will be incorporated into the allylic position. However, in the absence of such a group, the silicon will migrate from the oxygen to the carbon, thereby generating an alkoxide, which is protonated on hydrolytic workup.[39] Additionally, a similar retro-Brook rearrangement has been developed by Linderman and coworkers, in which an α-silyloxystannane, on treatment with *n*-butyllithium, produces an incipient α-silyloxylithium species, which then undergoes a 1,2-retro-Brook reaction.[34f]



(10)

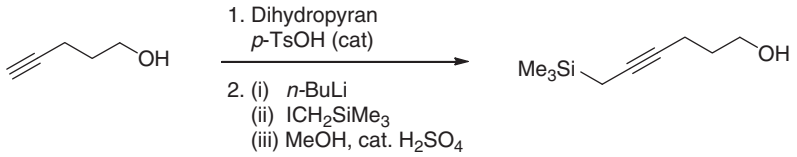
A 1,2-aza-Brook process has been used to generate allylsilanes (among other structures), beginning with readily produced *N*-silyl–*N*-alkyl compounds (equation 11). For example, highly enantioenriched α-aminosilanes, including allylic ones, can be produced through deprotonation, followed by N→C migration.[40] The incorporation of (−)-sparteine allowed for a stereospecific deprotonation, ultimately providing chiral aminosilanes in very good yields and enantioselectivies.



(11)

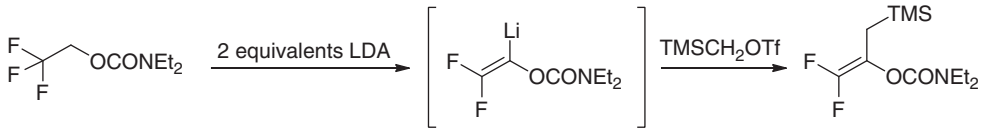
The exchange of silicon ligands is not the sole method of producing allylic silanes through such metal systems. Quite commonly, the nucleophilic displacement of a halogen from the readily produced (and commercially available) halomethyltrimethylsilanes with a vinylic or alkynylic anion is performed, resulting in the desired allylic functionality. For example, the displacement of an iodide from (iodomethyl)trimethylsilane by a monoalkylated acetylene derivative has been described by Tietze

and coworkers (equation 12).[41] A similar displacement of the bromide analog has been described with an alkyne derived from Garner's aldehyde.[42]



(12)

As a final example, 2,2,2-trifluoroethanol carbamate derivatives, on treatment with 2 equivalents of lithium diisopropylamide (LDA),[43] yield a difluorovinylic anion, which, on treatment with appropriate electrophiles such as the trifluoromethylsulfonatomethyltrimethylsilane analog, furnished the allylic silane in excellent yield (equation 13).

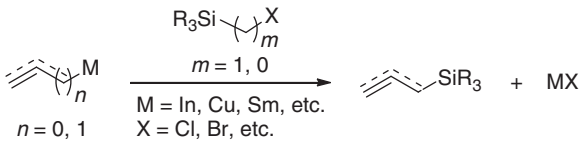


(13)

Another route to produce allylsilanes is in the trapping of enolates, wherein the alkene's presence necessitates the existence of an allylsilane moiety.[44] Such enolates are formed through the Michael addition of a trimethylsilyl anion to an α,β-unsaturated group. The 1,6-addition mode appears to take precedence over the 1,4-mode under such conditions when applicable.

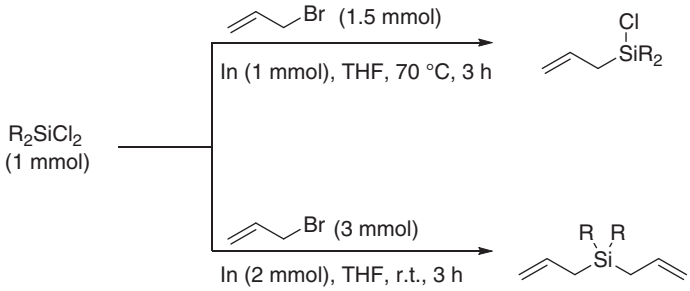
2.02.3.1.2 Reactions with other metal systems

In a manner quite similar to that of Section 2.02.3.1.1, metals other than those appearing in the S-block of the periodic table can be used as a means to produce allylsilanes and derivatives (equation 14). In general, this manner of production is milder than that of the alkali/alkaline earth counterpart, but remains less developed.



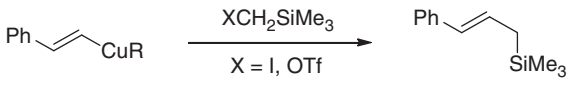
(14)

In one such case, *in situ*-generated allylindium species have been shown to react under stoichiometric control with chlorosilanes.[45] In those cases wherein multiple chloro groups were present on the silicon center, a simple variance of the equivalencies would allow for a controlled exchange of any given number of them, thereby allowing the production of mono-, di-, etc., allylsilanes in excellent yields (equation 15). Allenylsilanes were also produced in this manner. Impressively, silicon–hydrogen bonds were fully tolerated. This reactivity is an extension of an earlier methodology by the same group, in which allylsamariums underwent analogous reactions.[46]



(15)

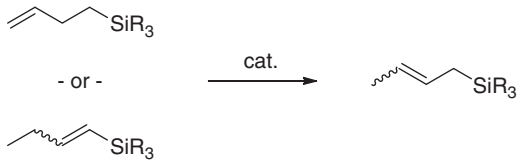
Vinylic cuprates have also been shown to be very effective at displacing appropriate leaving groups situated at the allylic, propargylic, and benzylic positions of various groups.[47] When that group – identical to those substitutions discussed in Section 2.02.3.1.1 – is a halogen or triflate, then such substitution becomes a route for the production of allylic silanes in good yields (equation 16).



(16)

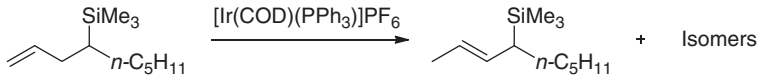
2.02.3.1.3 Olefin isomerization

There are only a handful of reports which have detailed the synthesis of allylic silanes from either vinylic or longer chain alkenes (equation 17). In general, these isomerizations are transition metal-catalyzed, proceed in very good-to-near-quantitative yield, and are highly tolerant of different functional groups.



(17)

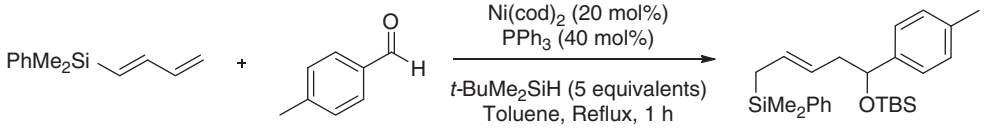
The first example of a catalyzed olefin migration which produced an allylic silane was reported by Matsuda and coworkers.[48] They detailed their thorough investigation on the subject, and demonstrated that, whereas rhodium, ruthenium, and iridium could all function adequately in this transformation, the latter was the most efficient (equation 18), and that its use could allow for the isomerization of a series of structural classes of alkenes.



(18)

Since this seminal report, iridium has been reported by others as successfully catalyzing analogous isomerizations.[49] Cobalt[50] and palladium[51] have also been shown to be efficacious.

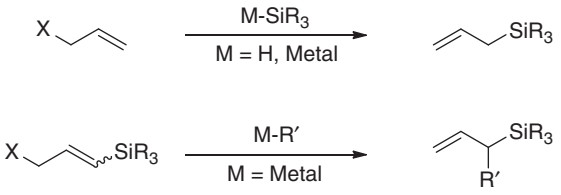
More recently, a report of an isomerization was published by Mori and coworkers.[52] They detailed that the use of *in situ*-generated [bis(triphenylphosphine)di(cyclooctadiene)nickel(0)] catalyst could affect the isomerization of silylbuta-1,3-dienes to allylic silanes. More formally, a nickel(II)-hydride catalyst was being formed, which would undergo hydronickelation, followed by allylic rearrangement to give the terminal η3-nickel(II) complex. Complexation of an aldehyde, followed by migratory insertion and reductive elimination, ultimately furnished the product of what is formally a reduction process (equation 19).



(19)

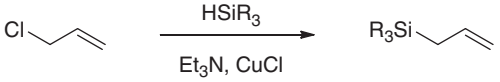
2.02.3.1.4 Displacement of allylic groups

One of the two most commonly used methods to prepare allylic silanes involves the displacement of an allylic leaving group (equation 20). Such reactions can take place in one of two fashions: either a displacement which results in the nucleophile becoming attached to the same location as where the nucleofuge was attached (S_N2), or attacking in a manner which results in allylic rearrangement (S_N2'). Although both regioisomers can be produced in a given reaction, it is usually true that the careful choice of appropriate conditions can furnish only one major product.



(20)

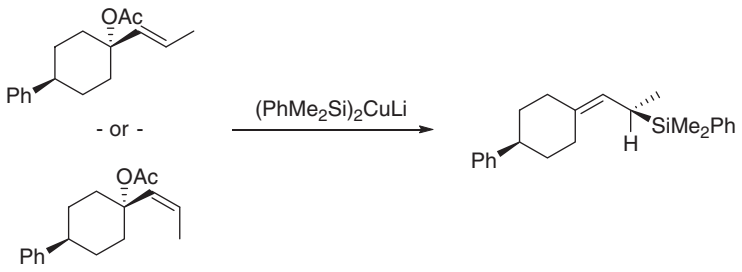
An early method for the production of allylic silanes, which is not currently used with great frequency, is the *in situ* deprotonation–displacement reaction, wherein a silane serves as a masked anion.[53] This reaction can be catalyzed by different metal salts, but copper(I) chloride has proved optimal (equation 21). This reaction has since been used by several different groups, but has received far less attention recently, as newer methods to synthesize allylsilanes have become more commonplace.[54]



(21)

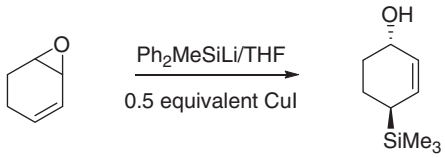
Similar to the earlier example of allylsilane preparation through the reaction of a vinylcuprate with an (activated methyl) trimethylsilane, so too can the opposing approach function.[55] In fact, silylcuprates react with appropriate leaving groups such as acetates quite well, and can do so stereoconvergently. For example, Fleming and coworkers have demonstrated that both the

Z- and *E*-isomers react in a stereoconvergent manner, giving the same allylsilane derivative (equation 22). They have since extended this methodology to include carbamates, sulfonates, and benzoates.[56] Interestingly, the S_N2' reaction of said silylcuprates with benzoates proceeds in an antiperiplanar fashion, but in a *syn*-periplanar manner with carbamates. As such, either stereoisomer can be produced from a common allylic alcohol.[56b] These methodologies can also be used to produce allenylsilanes from propargylic functionalities.[55,57,58]



(22)

This methodology has been used in many other cases, and can lead to either an allylic rearrangement[42,58] or a direct displacement.[59] Phosphates can serve as leaving groups for this reaction,[60] as can silanols.[61] The latter allylic system reacts in a manner which exclusively gives substitution at the least-hindered side, whereas the former system (phosphates) depends on the metal. Use of a silylcuprate gives only an S_N2' displacement, whereas the silyllithium gives mostly a direct displacement, regardless of the steric bulk. The reaction of silyllithiums with allylic phenylthiolates also proceeds via an S_N2' pathway.[62] Allylic epoxides can also be opened through a similar allylic inversion reaction, giving rise to 1-silyl-4-hydroxybut-2-enyl systems (equation 23).[63] In the same report, the analogous reaction of allylic chlorides was reported. In both cases, the silylcuprate was generated *in situ* by the reaction of a copper(I) salt with a silyllithium. A very detailed exploration of the limits of this type of chemistry was performed by Kleijn and Vermeer.[64] They detailed the proclivity of a great number of groups to serve as nucleofuges in this reaction, including epoxides, mesylates, sulfinates, and sulfonates, and demonstrated that a wide range of functionalities could be produced, including allylic, 1-alkylidenylallylic, 3-alkylidenylicallylic, allenic, and propargylic silanes.



(23)

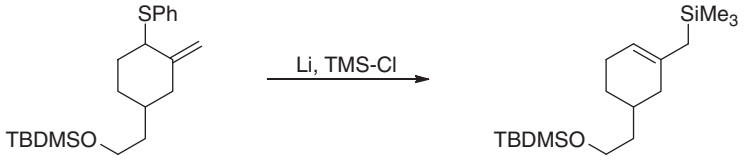
Silylcuprates can be generated for use in other ways. For example, the activation of a borasilane (with base coordination to form the borate complex) can allow for the *in situ* formation of the silyl anion, which generates a silylcuprate.[65] This silylcuprate undergoes reaction with an allylic chloride in a mostly S_N2' manner to give allylic silanes in near-perfect regioselectivity and excellent yields (equation 24). Similarly, disilanes have been reported to serve as adequate silyl anion precursors, capable of displacing both carbonates[66] and halides.[67] Palladium catalysts can also serve to activate such disilanes sufficiently, allowing them to act as nucleophiles, readily reacting with allylic carbonates[68] and trifluoroacetates.[69] In an analogous manner, silylstannanes are capable of being added directly to propargylic chlorides, thereby producing allenylic silanes under conditions of palladium–pincer complex catalysis.[70]

(24)

Vinylic silanes have many times been converted into allylic ones at the expense of an allylic leaving group. Allylic phosphates, carbamates, and oxycuprates have been shown to undergo displacement with the aid of alkylzincates,[71] alkylcuprates,[72] and alkyllithiums. The formally reductive version of this reaction, wherein the nucleophilic specie is a hydride, has also been reported.[73] A palladium-catalyzed addition of the aromatic group of a boronic acid to a vinylic silane with a pendant benzoate group has been demonstrated to occur with the allylic rearrangement taking place at the expense of the benzoate. A chirality transfer takes place with this vinylic to allylic silane transformation.[74]

In an another example, lithium metal was used to produce a silyl anion *in situ*, which then underwent an S_N2' reaction with an allylic thioether, releasing a phenylthiolate anion (equation 25). The release of the phenylthiolate anion is the driving force for these reactions, in which the formal substitution of a silicon atom for a sulfur group occurs. The diminished basicity of a thiolate makes it a superior leaving group to an alkoxide.[75] Similarly, dithioacetals and ketals react under these conditions to produce either 1,3- or 1,1-disilylpropenyl functionalities, in which either one or both of the silyl groups is allylic in nature.[76]

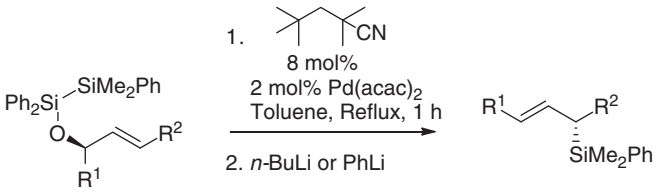
Silylmanganates have also been shown to be sufficiently nucleophilic to effectively displace both allylic ethers and thioethers, proceeding in generally high yields and with the nearly exclusive formation of the less-hindered silane.[77] The sterically demanding allylic supersilanes [tris(trimethylsilyl)silanes] have also been produced in this manner: through a displacement of a pre-existing allylic halide using either the sodium or potassium silanyl salts.[78] Through a sampling of the possible variations, the potassium salts, in conjunction with the chloride leaving groups, were found to be the most effective.



(25)

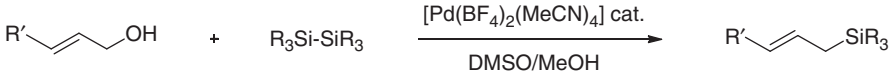
In a very unusual example of a fluoride ion-promoted reaction, 3,3,3-trifluoropropenes have been shown to react with disilanes to form 1,1-difluoro-3-silylprop-1-enes.[79] By reacting initially with the disilane, the attack of the fluoride generates a silicon–fluoride bond, and releases a silyl anion. This anion adds in an S_N2' process, producing the allylsilane, and regenerating a fluoride anion, which further reacts with another molecule of disilane, continuing the chain process. The same net process could be achieved with the use of the lithium salt of the silane.

One very nice method of producing allylic silanes has been developed by Ito and coworkers, wherein a palladium(*tert*-alkyl isocyanide) has been shown to catalyze a rearrangement of 1-(*Si*-(silyl)silyloxy)prop-2-ene into the corresponding allylic silanes (equation 26). This rearrangement, which proceeds with a complete transfer of stereochemical information from the readily produced allylic silanol, is believed to proceed through an oxidative addition reaction of palladium into the disilane bond, followed by a sigmatropic rearrangement, wherein diphenylsilanone is produced as a by-product. As the reaction proceeds and the silanone builds up in concentration, the competitive reaction occurs, wherein the silanone inserts into the incipiently formed 1,2-siloxetane, generating a 1,3-disilyl-2,4-dioxane. The reaction of the latter with an organolithium species in a one-pot process converts the siloxane into the desired product. Thus, in a one-pot, two-step procedure, allylic alcohols are converted into allylic silanes, with a concomitant allylic rearrangement.[80] The same group has since expanded on this methodology, converting it into a polymer-supported technique, and have further used it in the synthesis of large ring systems and polycyclic moieties.[81]



(26)

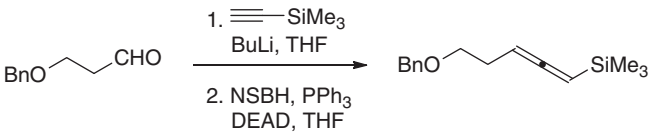
The use of palladium–pincer complexes as a means to directly substitute an allylic alcohol by a silyl functionality has been developed by Szabó and coworkers (equation 27). This is an especially impressive means of producing an allylic silane, as it is quite tolerant of a wide range of functionalities, occurs under mild conditions, and proceeds in very good yields.[82] The formation of the silanol by-product is the thermodynamic driving force for this reaction.



(27)

The use of catalytic palladium to displace allylic chlorides with an incipiently formed silane (from a disilane) has also been performed.[83] This has been subsequently extended to acylic and benzoate leaving groups.[84] An extension of this work to the production of 2-carbonylallylic silanes has also been reported.[85] Palladium has also been used to displace the allylic acetates of homoallylic silanes which possess a vicinal relationship between the silane and leaving group.[86] The addition causes an allylic shift to occur, providing the expected allylic silanes in generally very good yields. A wide range of nucleophiles, including the cyclopentadienyl anion, malonates, enolates, silanes, and boronic acids, were shown to be tolerated.

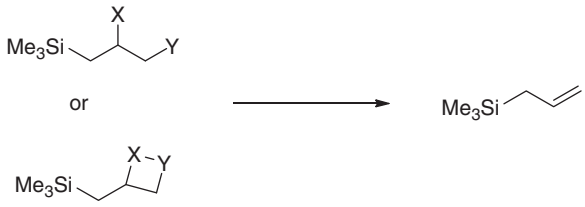
In a final example of an allylic silane synthesis via an allylic displacement pathway, the authors consider a reaction reported by Mori and coworkers, in which a propargylic alcohol bearing a silane at the alkynic terminus was treated with *o*-nitrobenzenesulfonylhydrazide under Mitsunobu-like conditions.[87] The reaction proceeded to obtain the alcohol-displaced sulfonylhydrazide, wherein the sufonamidic nitrogen is the one which performs the displacement (equation 28). Allowing the reaction to stir for some time at ambient conditions allowed for the intramolecular addition of a hydride to the propargylic system. The addition causes an allylic rearrangement, resulting in the substitution of a hydride for a triphenylphosphine oxide leaving group.



(28)

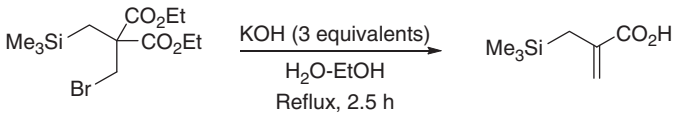
2.02.3.1.5 Elimination reactions

The other most frequently used method for the production of allylic silanes is that of an elimination pathway. Most of these reactions take place in one of two manners: wherein two vicinal groups (equation 29, X and Y), which are not secondarily tethered, are removed in a β-elimination manner, giving rise to the expected allylsilane, or wherein the two groups are tethered to each other, and eliminate as such. To further clarify, the first group would be analogous to a base-promoted 1,2-dehydrohalogenation, and the second by the expulsion of phosphine oxide from a phosphetane intermediate.



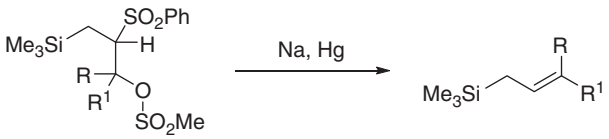
(29)

As an exemplification of the first group, the following example is considered (equation 30). The starting silane, which is readily prepared by a malonic ester synthesis, can be refluxed in alkaline ethanol–water mixture.[88] Two equivalents of the requisite potassium hydroxide are used in a saponification step – the production of the malonic acid derivative – and the third is needed for affecting β-elimination of hydrogen bromide. Under the elevated conditions of reflux, a decarboxylation reaction also takes place, necessarily before the elimination of hydrogen bromide. Similar eliminations of methanesulfonates have been reported.[89] In some cases, allylsilanes have been formed accidentally, such as through the E2′ elimination reaction of carbonates,[90] or the simple E2 elimination of triflates.[91] The direct elimination of an alcohol with trifluoroacetic acid to give a β-alkylidenylallylic silane has also been reported.[92]



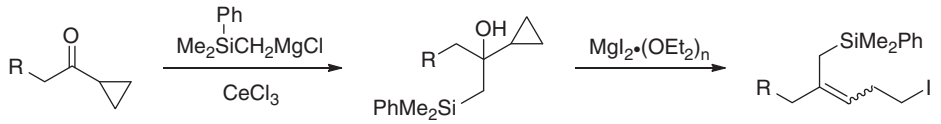
(30)

In many cases, such an elimination can be made through the E1cB mechanism. For example, the use of a sodium–mercury amalgam can generate a carbanion from a sulfone. This highly reactive specie, if present vicinal to a leaving group of an appropriate strength, can degrade through a β-elimination pathway (equation 31). Such a pathway can be used to generate a wide array of allylic silanes. In one example, the aldol reaction of α-lithiosulfones with carbonyls, followed by sulfonate formation, allows for the formation of such a system. Hsiao and Shechter have demonstrated that these systems can undergo the expected elimination with said amalgam, and the result is the formation of allylic silanes in near-quantitative yields.[93] Analogously, the reaction can proceed with methanesulfonyl leaving groups, giving rise to highly conjugated systems.[94] The reduction of β-chloroacetoxy groups with SmI_2 has also been shown to furnish allylic silanes in good-to-excellent yields. The reaction likely proceeds through the formation of a Sm(III) species followed by sigmatropic elimination, or through the formation of a latent carbanion, which decomposes to the alkene product.[95]



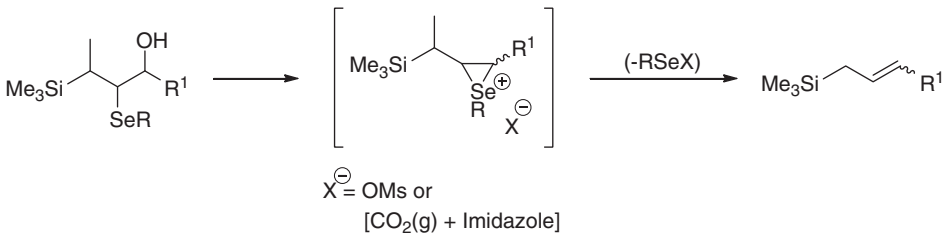
(31)

A very nice approach to difunctionalized allylsilanes was developed by Li and Yang, in which α-cyclopropyl-β-silyl alcohols, which are produced from the reaction of cyclopropylic ketones with (trialkylsilyl)methylmagnesium chloride and cerium trichloride, undergo a cyclopropyl ring-opening homo-E2′ reaction with the iodide anion.[96] The product allylsilanes contain a homoallylic iodide functionality, which provides the opportunity to further functionalize as necessary (equation 32).



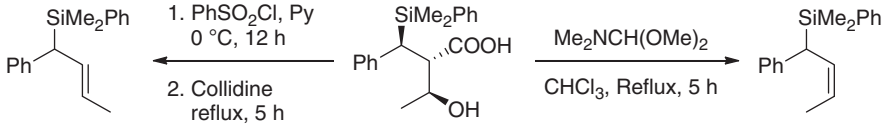
(32)

Somewhere in between the two distinct classes of elimination reactions lies the production of allylsilanes as reported by Sarkar et al.[97] Their approach involves the Krief–Reich elimination of β-silyl-β'-hydroxyselenides (equation 33). The reaction of β-silylaldehydes to form Mukaiyama enolates, followed by the reaction with phenylselenium bromide was shown to furnish β-silyl-α-alkselenoxyaldehydes. The reaction with a variety of Grignard reagents provided a variety of structurally unique secondary alcohols. The formation of either derivative (mesylates or carbonyl imidazole adducts, both of which spontaneously undergo elimination, at 25 and 115 °C, respectively) furnished the desired allylic silanes in very good yields. In addition, in between the two elimination classes are the reports of a Ramberg–Bäcklund elimination of α-arylsulfonato-α-alkyl α'-(β'-silyl)ethyl sulfones,[98] and the Grieco elimination of 3-hydroxylpropylsilanes with *o*-nitrophenylselenenium cyanide and tri-*n*-butylphosphine, followed by treatment with hydrogen peroxide.[99]



(33)

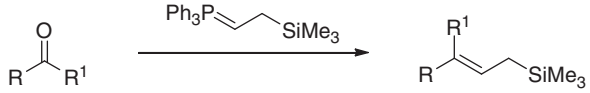
The second class of elimination reactions involves the elimination of a group as a result of the degradation of a cyclic system. These eliminations typically take place with the expulsion of a very good leaving group possessing a strong bond, such as in the formation of a silanol or a phosphine oxide. In one such method developed by Fleming et al.,[100] the treatment of an appropriately functionalized carboxylic acid with phenylsulfonyl chloride, followed by β-lactone formation and elimination, was shown to provide *E*-allylic silanes, whereas the treatment of that same carboxylic acid with the dehydrating agent dimethyl *N*,*N*-dimethylorthoamidate, followed by the same decarboxylative elimination, furnished *Z*-allylic silanes (equation 34).



(34)

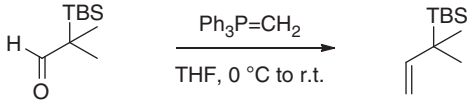
One of the most commonly used methods for the synthesis of allylic silanes is the Wittig reaction. There are four distinct Wittig-type reactions which have been utilized in the synthesis of such silanes. The first two are the classical Wittig, wherein the aldehyde and silicon groups are tethered before the Wittig reaction, and those wherein the silicon is instead attached to the Wittig reagent. The third class is the Corey–Fuchs reaction, which is capable of producing either geminally dibrominated allylic silanes or terminal or internal alkynes. The final method is the collection of those variations based on the Horner–Wadsworth–Emmons Wittig variants, wherein phosphate derivatives are used as the leaving groups.

The first example of a Wittig reaction being used to produce an allylic silane was reported by Seyferth et al. (equation 35). The reaction of the (2-(trimethylsilyl)ethylidenyl)triphenylphosphorane ylide reagent (which is now referred to as the Seyferth–Fleming phosphorane) with a variety of aldehydes and ketones was shown to proceed in fair-to-good yields. Just as is to be expected based on the nonsilyl Wittig reaction, the formation of the highly stable phosphine oxide linkage is the driving force for this reaction, and the product alkene tends to be the *cis* one.[101] Most typically, the necessary Wittig reagent is produced by first deprotonating the Wittig phosphonium halide salt to form the ylid, which is then reacted with a species akin to (iodomethyl) trimethylsilane. An additional deprotonation re-forms the ylid, which is then reacted with an electrophilic partner. Most commonly, aldehydes serve as the electrophiles in this reaction.[102] Similar to the nonsilyl Wittig reaction, aldehydes which are involved in a lactol–aldehyde equilibrium can be made to react in this manner.[103] Only a few examples of the silyl-Wittig reaction of ketones have appeared in the literature, but the results indicate that the reaction is quite feasible, typically offering more than satisfactory conversions.[104]



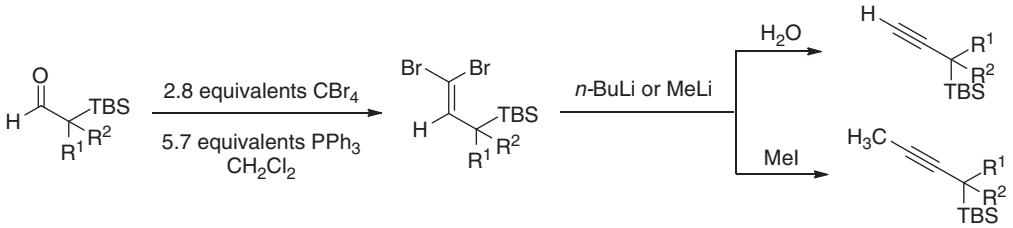
(35)

As mentioned previously, Wittig reactions in which the silicon functionality is attached to the electrophile are known (equation 36). These reactions are quite rarely reported, perhaps because of the comparative ease of preparation of silyl-containing ylides. The α-silylaldehydes which have been reported to date for the purpose of undergoing a Wittig reaction are typically prepared by converting from a simpler aldehyde, usually by means of either the *t*-butylimine[105] or hydrazone[106] functionality. Comparable yields and geometrical stereoselectivities are typically comparable to the previous type of Wittig reaction.



(36)

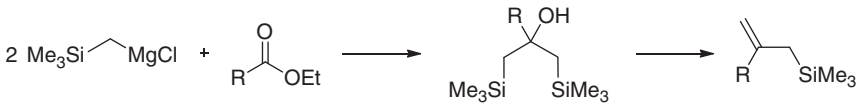
The Corey–Fuchs reaction has been shown to successfully convert these same α-silylaldehydes to either dibromoallylic or propargylic silanes.[107] This reaction, which takes place on reacting the aldehyde with a premixed solution of triphenylphosphine and carbon tetrabromide in dichloromethane, can be stopped at the dibromide stage if so desired. (The coupling of halogen-containing allylic silanes is discussed in Section 2.02.3.1.11.) If necessary, the exposure of the dibromide to strongly basic conditions results in the elimination of hydrogen bromide, followed by the formation of an acetylenic anion, which can further react with electrophiles (equation 37).



(37)

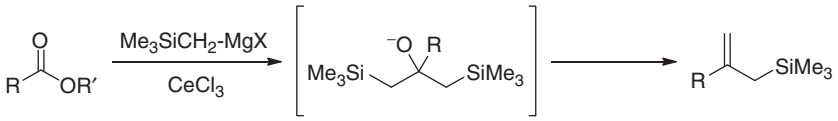
The remaining class of Wittig-style reactions is those of the Horner–Wadsworth–Emmons type. The deprotonation of a trialkyl phosphonoacetate, followed by quenching with a silylalkylating agent (such as (iodomethyl)trimethylsilane) can furnish trialkyl 2-(1-silylalk-1-yl)phosphonoacetates.[108] Further deprotonation and reaction in the normal Horner–Wadsworth–Emmons manner results in the expected elimination of the phosphate group, and directly forms 2-(alkoxycarbonyl)allylic silanes in yields which are generally slightly lower than or comparable to those obtained during the classical Wittig reaction.

Due to the ready availability of (activated methyl)trimethylsilanes and derivatives, and their known ability to form the corresponding Grignard reagent with little difficulty, a methodology which has found widespread use in the synthesis of allylic silanes, and which was initially reported by Petrov et al.,[109] was further developed by Fleming and Pearce.[110] The reaction proceeds through an initial attack of an ester, then undergoes collapse in an α-elimination manner to form the silylmethyl ketone. Subsequent attack of this ketone by a second equivalent of the Grignard reagent produces a 1,3-bis(trimethylsilyl)methylcarbinol functionality, which, although difficult to accomplish, may be isolated if necessary (equation 38). More frequently, the inherent instability of the β-hydroxysilane is taken advantage of, and an elimination of trimethylsilanol is allowed to take place under either basic or acidic conditions. The resulting product is a β-substituted allylic silane. Since its popularization by Fleming and coworkers, this method has become a mainstay of allylsilane synthesis, and has been used for the incorporation of trifluoromethyl groups into molecules,[111] with highly functionalized and acid-sensitive saccharides,[112] and in polymer chemistry.[113] As expected, the natural extension of this work to lactones has been performed, and the reaction proceeds with little difficulty.[114]



(38)

Despite the enormous utility of this reaction, it has very restrictive limitations, in that the yields are generally not much higher than 50% for simple esters or acid chlorides, and the reaction fails almost entirely for those possessing any α-substitution. A report by Anderson and Fuchs,[115] along with one published in the same year by Narayanan and Bunnelle,[116] respectively, demonstrated that the addition of cerium(III) chloride greatly enhanced the yields of such reactions using acid chlorides and carboxylic esters, the latter now being produced nearly quantitatively (equation 39). The reaction has since been expanded even further, and can tolerate a wide range of functional groups, including alkenes, thio-, silyl-, and carbon-based ethers, alcohols (which necessitates the use of an additional equivalent of the Grignard reagent), acetals, dithioacetals, halides, and amines, and functions equally well with lactones.[117]



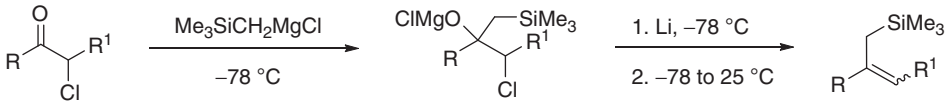
(39)

There are several other examples of the use of the Peterson elimination providing for the formation of allylic silanes. For example, Soderquist and Santiago demonstrated a method for the two-step conversion of vinylic silanes into allylic ones.[118] The epoxidation of a vinylsilane with *m*-chloroperoxybenzoic acid, followed by the reaction of the higher-order cuprate lithium (cyanobis(trimethylsilyl)methylcopper(I)) provided 3-hydroxy-1,2-disilylpropane functionalities. Taking advantage of the findings of Hudrlik and Peterson,[119] the reaction thereof with either a base or a Lewis acid allowed for the synthesis of either the *Z*- or *E*-allylic silanes in very good-to-excellent yields.

It was demonstrated by Kuroda and coworkers that, beginning with ethyl 2,3-bis(trimethylsilyl)propanoate, the aldol reaction with carbonyl compounds could, on Peterson-style elimination reaction, furnish *β*-silylmethyl-*α*,*β*-unsaturated esters in moderate yields.[120]

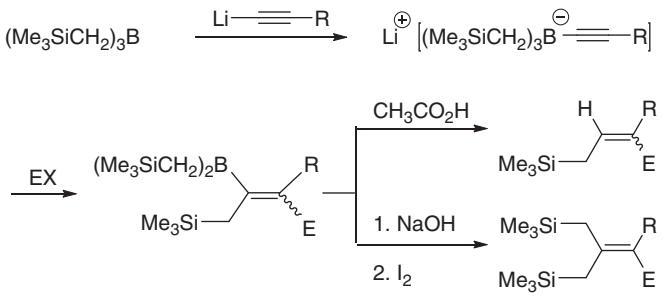
Liu and Wang reported[57] that on the successful hydroboration of 1,2-bis(trimethylsilyl)buta-2,3-diene with 9-BBN, the allylboration reaction of either aldehydes or ketones could provide a vicinal silyl-boryloxy functionality. Just as with the previous example, the careful choice of either an acidic or basic workup of the boronite could provide either the *E*- or *Z*-allylic silane.

Although the synthetic utility of the (trimethylsilyl)methylmagnesium halide protocol – be it in conjunction with the use of cerium(III) chloride or not – is evident in the reaction with esters and acid chlorides, the application of this procedure to aldehydes and ketones is not possible, as the prior reaction requires the presence of a leaving group directly attached to the carbonyl functionality. This problem has since been overcome, however, through a very interesting transformation.[121] It has been shown that the reaction of a single equivalent of the same Grignard reagent with an *α*-chlorocarbonyl compound, which expectedly generates the alkoxymagnesium chloride salt as shown (equation 40), on reaction with metallic lithium, undergoes reduction to form an incipient anion with subsequent *β*-elimination. Both aldehydes (R=H) and ketones provide the desired allylic silane in reasonable yields.



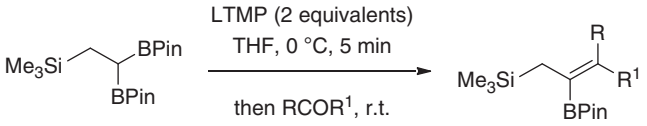
(40)

A small group of reports have appeared in the literature which has detailed the production of allylic silanes by way of a borate complex; some of them are given in detail here. In the case of this first example (equation 41), the reaction of tris(trimethylsilyl) methylborane with a lithium acetylide salt gives, expectedly, the ate complex. Subsequent reaction with an appropriate electrophile allows for a (trimethylsilyl)methyl migration onto the alkyne, whereas the latter attacks the electrophile.[122] Most likely, this mechanism proceeds by the formation of a 3-(electrophile)cycloprop-1-en-1-ylonium cation, followed by ligand migration. The pendant boron functionality can be removed through any of the normal means, such as hydrolytic, protiolytic, methanolic iodine, or oxidative workup.



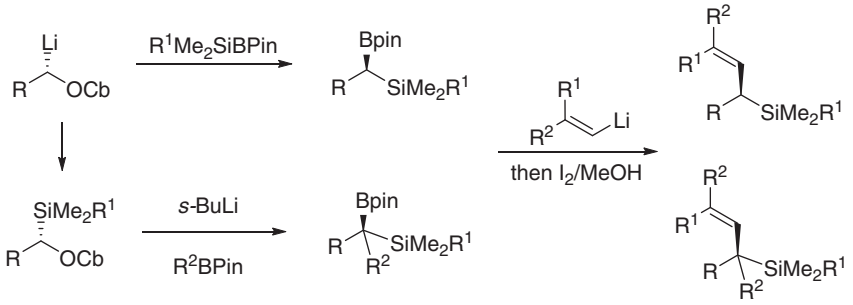
(41)

In one very unusual example, a geminal 2,2-diborylethylsilane can be deprotonated using the nonnucleophilic base lithium 2,2,6,6-tetramethylpiperidide (equation 42). After alpha deprotonation to the boronates, a reaction with carbonyls has been described, wherein the carbanion attacks the carbonyl carbon, and then collapses onto the boronate – akin to the mechanism of the Wittig reaction. The elimination of a borate anion then provided the desired allylic silanes, still bearing a vinylic boronate functionality.[123] As described in the accompanying 'Allylborons' chapter,[11] this vinylic boronate may be further functionalized to produce more complicated systems through reactions such as homologation or cross-coupling.



(42)

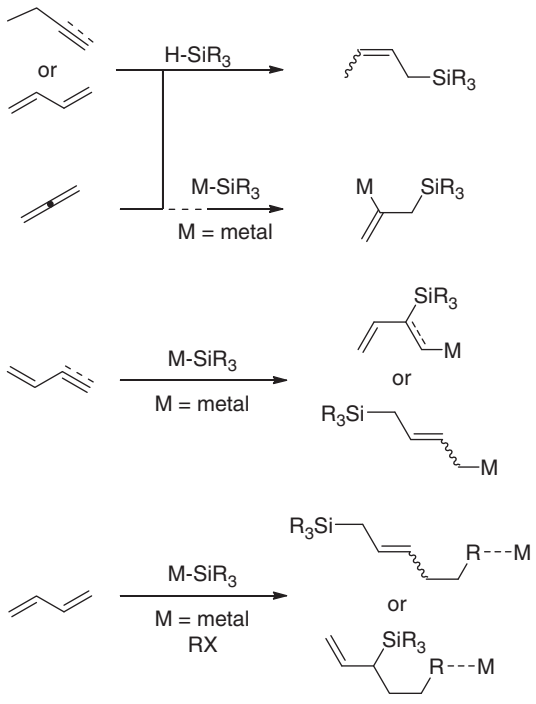
One particularly attractive method for the synthesis of both tertiary and quaternary allylic silanes has been developed by Aggarwal et al.[124] The attack of chiral-lithiated carbamates onto silaboranes produces the expected ate complex. A stereoselective migration–displacement of the silicon ligand then occurs, wherein the carbamate is expelled, providing access to enantioenriched α,α-silaboranes. A subsequent reaction with a vinylic metal species reforms an ate complex, which, on methanolic iodine workup (as in equation 41), results in the formation of the expected allylic silanes (equation 43). If instead, the original chiral-lithiated carbamate is quenched with a silyl chloride to directly form the α-silylcarbamate, then the hydrogen (which is alpha to both the carbamate and silyl groups) can be deprotonated with a superbase. Quenching of this anion with a boronate results in the ate species, which again undergoes ligand migration. In this case, the alkyl group of the boronate migrates and displaces the carbamate, again being stereoselective during the displacement. Repeating the final sequence of vinylation followed by methanolic iodine, quaternary allylic silanes can be produced in very good yields. Simple, aliphatic allylic silanes had been prepared previously by a similar route of ate formation and methanolic iodine workup.[125]



(43)

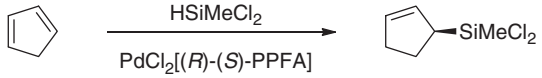
2.02.3.1.6 Reaction of X–Si bonds with π-systems

The reactions of X–Si (X = H, B, C, Si, Sn, or other metals) with various π-systems have been detailed on many occasions, and can provide a variety of products, including allylic silanes (equation 44). These reactions do not occur on their own volition, but require catalytic assistance, either in the form of metal catalysis, or covalent activation.[126] There are a variety of manners in which groups may add to the various π-systems, and the specific explanations for the formation of the resulting regio- and chemoselectivities are not always clear.[127] However, those methods which are available for allylic silane synthesis are presented here with an explanation as to the formed product when applicable.



(44)

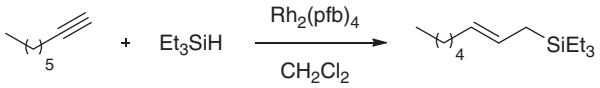
The reaction of a silane (H–Si) functionality with 1,3-butadienes has been championed almost entirely by Hayashi et al.[128] They have demonstrated that the addition of H–Si, which occurs most readily under conditions of palladium catalysis, proceeds in a 1,4-fashion, giving allylic silanes in generally very good yields. The evidence for the 1,4-addition is based on deuterium labeling studies and regioisomeric distributions.[128e–f] As additional evidence for 1,4-addition, allenes are produced via the hydrosilylation of 1,3-enynes.[128] Quite impressively, these reactions can be run with as little as 0.01 mol% catalyst. Additionally, they have been successful at developing an asymmetric version of this reaction, which is mild enough to tolerate even highly labile chlorosilane functionalities (equation 45). Chromiumhexacarbonyl has also been shown to be an effective catalyst for the hydrosilylation of simple 1,3-butadienes under photolytic conditions.[129] Titanium has also been reported to be a successful catalyst for the 1,4-hydrosilylation of dienes.[130]



(45)

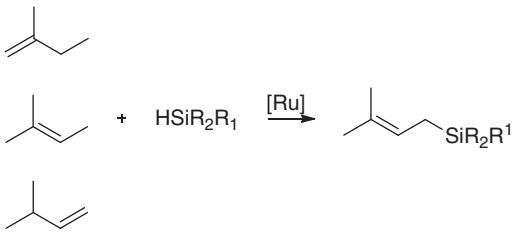
In place of a 1,3-butadiene, the 2,1-hydrosilylation of allenes can theoretically lead to an allylic silane. To the best of the authors' knowledge, only a single report of such a reaction exists. In it, Petrov and Mironov[131] demonstrated that the simplest possible allene, 1,2-propadiene, could be hydrosilylated with triethylsilane under conditions of palladium catalysis. The other reports of the attempted hydrosilylation of allenes have instead demonstrated the formation of vinylsilanes.[132]

The 2,1-hydrosilylation of terminal alkynes, which initially provides terminal vinylic silanes, has been shown on one occasion to provide allylic silanes by means of a Rh-catalyzed isomerization, the latter occurring *in situ* (equation 46). This reaction, which also functioned (but less efficiently) with platinum catalysis, could furnish simple aliphatic allylic silanes in reasonable yields, and was tolerant of the presence of organic ethers.[133]



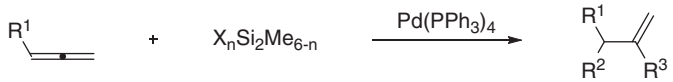
(46)

There are also a few reports of an oxidative hydrosilylation, wherein the reaction of silanes with simple alkenes provided what are initially saturated silanes. However, by increasing the concentration of the catalyst, an increase in the amount of dehydrogenation could be observed. After optimization, reasonable levels of allylic silanes could be directly produced from either a pure or an isomeric mixture of starting materials (equation 47). Quite interestingly, this reaction did not produce hydrogen gas, and did not proceed at all in the presence of phosphine ligands.[134] One other report had appeared a few years prior, in which the use of Wilkinson's catalyst was shown to affect a similar transformation.[135]



(47)

Whereas the hydrosilylation of allenes has not yet become a well-developed reaction, the disilylation of allenes has been described.[136] Using a palladium catalyst, Watanabe et al. performed a disilylation of allenes. Perhaps surprisingly, the disilylation took place at the more sterically hindered end of the allene, providing a range of silane products containing labile chloro- and methoxysilyl functionalities (equation 48).



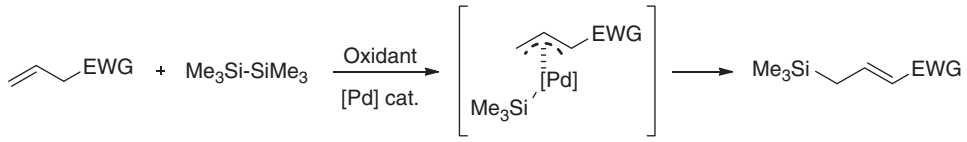
a; R = H
b; R = Me

a; *n* = 0
b; X = Cl; *n* = 3
c; X = OMe, *n* = 3

a; R^1 = H, R^2 = R^3 = $SiMeCl_2$
b; R^1 = H, R^2 = R^3 = $SiMe(OMe)_2$
c; R^1 = Me, R^2 = R^3 = $SiMeCl_2$

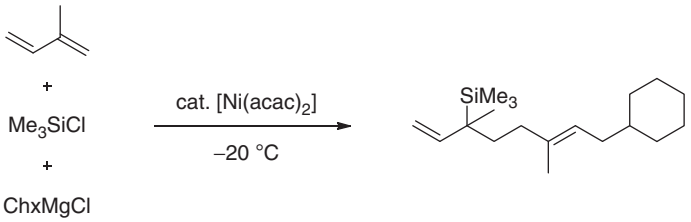
(48)

Szabó and coworkers have described an oxidative reaction of disilanes with allylic groups (equation 49). This reaction, which is catalyzed by palladium, formally describes the activation of an allylic carbon–hydrogen bond, at the expense of an added oxidant such as an iodine(III) reagent.[137] Impressively, only the linear system was produced in each case, which may be indicative of a neighboring group's coordination acting as a directing factor, or that the formation of the thermodynamic product is the preferred pathway.



(49)

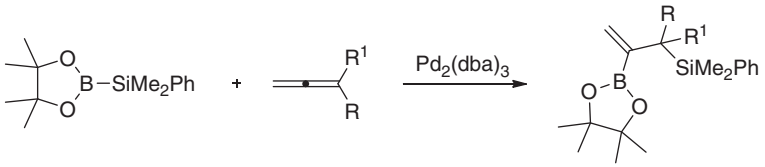
A very interesting reaction, akin to the formation of BISTRO (Section 2.02.3.1.1, equation 9), has been developed by Kambe and coworkers.[138] The use of catalytic nickel(II) can affect the dimerization of 1,3-butadienes, while incorporating silyl and Grignard functionalities simultaneously (equation 50). Nickel(0), which is produced *in situ*, chelates with, then oxidatively adds onto one of the butadienes, producing a nickelocyclopentene, then is chelated to an additional butadiene, undergoing carbonickelation of that diene, producing a diallylnickel(II) species. The reaction with a Grignard reagent dissociates one of the allyl complexes. Allylation of the chlorosilane then follows, allowing for the reformation of the earlier-broken allylcomplex. Reductive elimination provides the observed allylic silanes in generally excellent yields. In most cases, only a single isomer was formed.



(50)

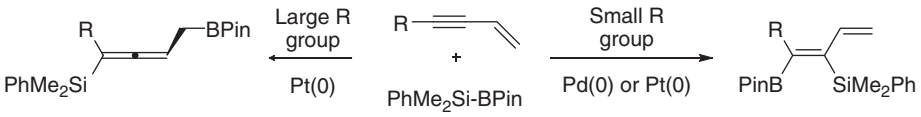
Similarly, palladium has been shown to allow for a multicomponent reaction of allenes, acid chlorides, and disilanes. In what is believed to take place via an oxidative addition of palladium onto the acid chloride, followed by acylpalladation of the allene, then a subsequent ligand exchange with the disilane and reductive elimination, a γ,γ-disubstituted-β-carbonylallylic silane can be produced in good yields and with high functional group tolerance.[139] An intramolecular version of this reaction has also been published, but utilizing a 1,3-butadienyl functionality in lieu of an allene.[140] In general, these reactions proceeded in very high yield.

The first example of the 1,2-addition of silaboranes to allenes was reported by Tanaka and coworkers.[141] They demonstrated that palladium dibenzylideneacetone complexes, in some cases with the addition of a small amount of phosphine ligand, could effectively catalyze the fascinating silaboration reaction of allenes at 80 °C (equation 51). This reaction most likely occurs through the oxidative addition of palladium into the boron–silicon bond, followed by chelation and silylpalladation of the allene in a Markovnikov fashion. Reductive elimination would then furnish the observed 2-boronatoallylic silanes. A few years later, Suginome et al. published a version of this reaction which was asymmetric.[142] Utilizing chiral diol ligands on the boron center, a high level of diastereoinduction could be obtained. The best results obtained were from the isopinocampheyl-derived diol. They later published a version of the same reaction which was reagent controlled and catalytic.[143] Using chiral phosphine ligands tailored to the particular reaction, extremely high enantiomeric ratios and isolated yields were readily obtained, while keeping the reaction temperature at subambient levels.



(51)

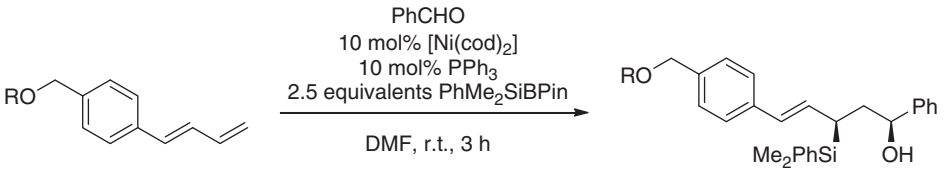
Lüken and Moberg extended the idea of silaboration to 1,3-enynes. They were successful in obtaining two different types of allylic silanes, depending on the conditions chosen, and the steric requirements of the system (equation 52). In general, larger substitutions on the alkynyl portion of the molecule favored the formation of allenylic silanes, whereas smaller groups favored the formation of 1-alkylidenylallylic silanes.[144]



(52)

In one interesting example, in conditions which might initially be predicted to furnish a silaborylated product, the nickel(0)-catalyzed reaction of a 1,3-butadiene with a silaborane instead furnished allylic silanes with an extra carbinolic center, so long as an appropriate aldehyde was added to the reaction flask.[145] The reaction likely proceeded through an oxidative addition of nickel into the silicon–boron bond, which then formed a chelate to the terminal alkene of the diene. Silylnickelation followed by chelation and migratory insertion are expected, followed by a terminal reductive elimination (equation 53). A wide variety of

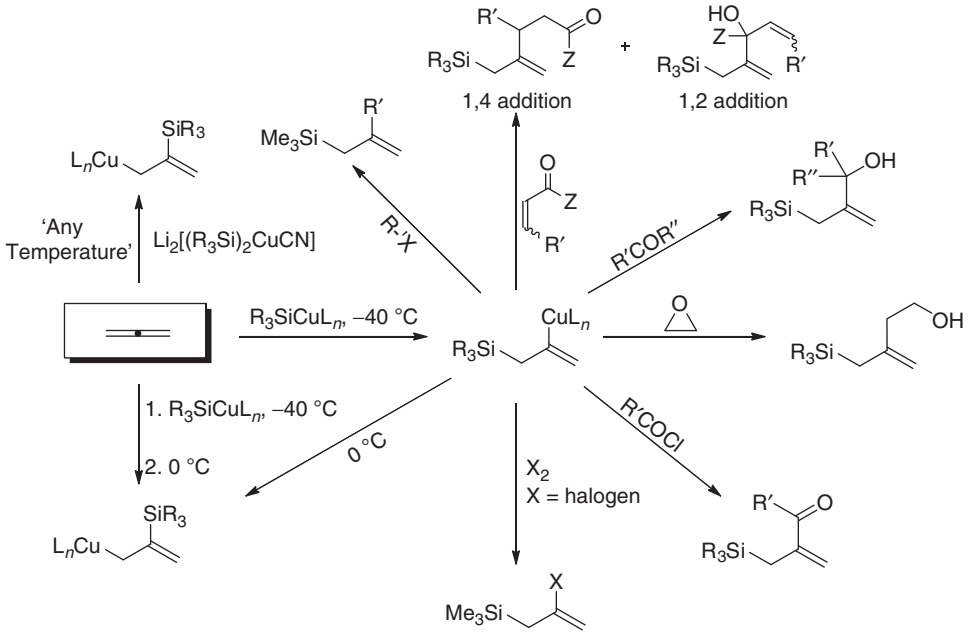
structurally unique aldehydes and 1,3-butadienes were tolerated in this reaction, which occurred in generally very good yields. Additionally, the use of chiral phosphine ligands was shown to provide excellent levels of enantioinduction, with the best results coming from a 1-1'-bi-2-naphthol (BINOL)-derived phosphoroamidite ligand.



(53)

As can be seen from the previous examples, the attempted silaborations of different π-systems can provide a variety of results, many times unpredictably so, just by slightly tweaking the structural features of any one of the reaction's components. One case published by Gerdin and Moberg highlights this idea quite strongly. In an attempted nickel(0)-catalyzed silaboration of an aliphatic 1,3-butadienyl system, they instead observed two products: a vinylic boronate and an allylic silane. As both products possessed the 1,3-butadienyl system, and had no additional incorporation of silicon or boron into each other, it was necessarily true that one species had been reduced and the other oxidized. Without having added any external reactant to allow such a transfer to occur, it was logically concluded that a formal hydride transfer must have occurred from one species to the other. This likely took place as a result of a competitive dehydronickelation step, in lieu of the expected reductive elimination, which would have furnished the silaboration product.[146]

One of the most versatile methods for producing a wide variety of β-substituted allylic silanes has been developed by Fleming et al.[147] The reaction of silylcuprates with allenes occurs in a 1,2-fashion, and can so provide either an allylic silane and vinylic cuprate functionality, or an allylic cuprate and vinylic silane structure (equation 54). Beginning with an allene (inside of the box in equation 54), it has been shown that the reaction with higher order silylcuprates proceeds to give a 2,1-silylcupration of allenes, nearly independent of the temperature of the reaction. Contrarily, the reaction of a lower order silylcuprate at −40 °C proceeds entirely in a 1,2-fashion. The thus-formed allylic silanes possess a vinylic cuprate moiety which can be reacted as such; some of the reactions thereof are discussed in Sections 2.02.3.1.2 and 2.02.3.1.6. These species are not thermodynamically stable, as they can undergo a retro 1,2-addition followed by a 2,1-addition to furnish the same product as would have been formed by a higher order cuprate addition. However, they are quite stable if maintained at a lower temperature, and can react with a wide variety of electrophiles, including small ring systems such as epoxides, or with electrophiles such as acid halides, aldehydes, ketones, esters, α,β-unsaturated carbonyls, and halogens, to furnish β-functionalized allylic silanes in excellent overall yields.

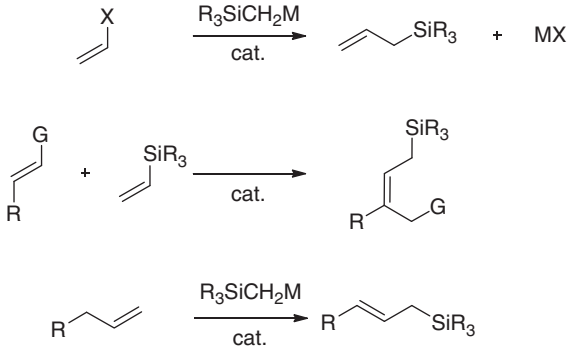


(54)

Further work on these systems has also been performed by Bäckvall and coworkers. They have shown that these vinylic cuprate species are also able to undergo S_N2' reactions with appropriate electrophiles such as allylic phosphonates. The resulting 1,4-dienes necessarily possess an allylic silane functionality.[148] Further effort to expand on the work of Fleming and coworkers has also been performed by Pulido et al. They have demonstrated that the reaction of the vinylic cuprate intermediates with α,β-unsaturated cyano compounds, in the presence of Grignard reagents and boron trifluoride leads to the formation of 1-alkyl-4-(silylmethyl) pent-4-en-1-one species.[149]

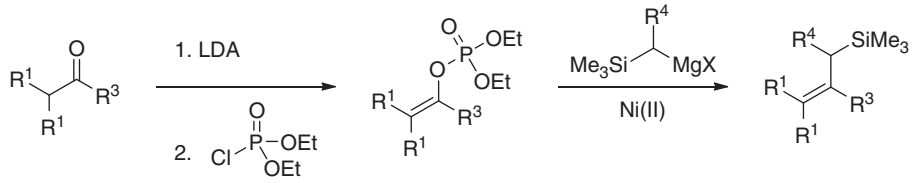
2.02.3.1.7 Coupling reactions

One of the comparatively newer methods for the synthesis of allylic silanes is in the field of coupling (equation 55). Using a coupling approach as a means to form allylic silanes offers several distinct advantages, in that the reactions are synthetically convergent, and that the conditions are typically quite mild (thereby allowing for the inclusion of a wide range of sensitive functionalities to survive the transformation), and that they are catalytic. Such coupling reactions take place through a transition metal-catalyzed process, using mostly nickel, palladium, copper, zirconium, or ruthenium as catalysts. The use of a coupling procedure necessitates that the formation of the allylic silane takes place through the formal substitution of a leaving group on one of the two coupling fragments and a metal from the second. The new bond is produced at the expense of these two groups. Typical leaving groups for these reactions include phosphates, halides, carboxylates, alkoxides, silanols, acetates, carbamates, trifluoromethylsulfonates, and thioalkoxides. Those metals which are sacrificed most commonly include magnesium and aluminum. In a few cases, carbon–hydrogen bond activation can take place. Couplings which take place with a rearrangement are also known. (For further discussion on the production of allylic silanes through cross-coupling processes, see Section 2.02.3.1.11.)



(55)

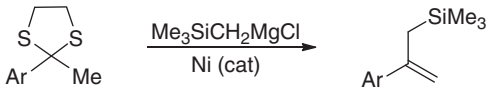
A very early report by Kumada and coworkers detailed the cross-coupling reaction of enolic phosphates with Grignard reagents of (halomethyl)trimethylsilane derivatives (equation 56). This reaction is one of the silyl variants of the reaction commonly called the Kumada–Corriu–Tamao coupling.[150] The production of allylic silanes, which generally proceeds in very good yields for all substrates, occurs first through the deprotonation of ketones with LDA, followed by the quenching with diethyl phosphorochloridate to form the enolic phosphates. The coupling of these enolic phosphates under conditions of nickel catalysis occurs at the expense of both the phosphate and the magnesium halide portion of the starting silane. Thus, the allylic silane bond is formed at the expense of the formation of a diethyl phosphato magnesium halide salt, whose formation serves as the thermodynamic driving force of the reaction.



(56)

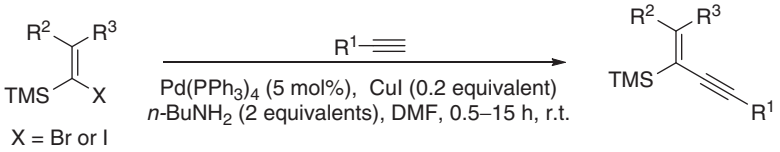
Shortly after the seminal publication by Kumada and coworkers, Negishi et al. reported their findings that this reaction could also function under conditions of palladium catalysis; it is this metal which has now became the more frequently used one in this reaction.[151] This particular transformation has grown immensely in use,[152] and has been expanded to include the use of bromides,[153] iodides,[154] carboxylates,[155] acetates,[156] alkoxides,[157] and carbamates.[158] Kumada and coworkers have also developed this into an asymmetric method for the synthesis of allylic silanes,[159] and have further expanded it to the production of propargylic silanes.[159b,160] Saulnier and coworkers have developed an aluminum variant of the Kumada–Tamao–Corriu coupling procedure, in which aluminum may serve as a surrogate for magnesium.[161] The reaction uses palladium catalysis to couple silylmethyl aluminates with enolic triflates, and was successful in demonstrating the chemoselective reaction of triflates in the presence of bromides.

One very useful version of the same reaction was developed by Ni and Luh, in which dithioacetals and ketals, which are readily produced from simple carbonyl compounds, could undergo a reaction with various Grignard reagents under conditions of nickel (II) catalysis.[162] By introducing (halomethyl)trimethylsilyl Grignard reagents, the elimination of the dithioacetal or ketal moiety could be achieved, producing an allylic silane in good-to-very good yields. The net result of this reaction is the conversion of an enolizable carbonyl compound into one which possesses an alkene between the former carbonyl site and the alpha position, and the transformation of the carbonyl functionality into a (trimethylsilyl)methyl group (equation 57).



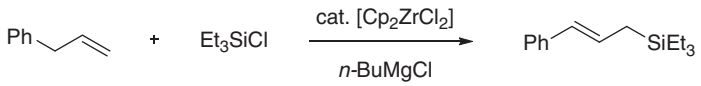
(57)

Sonogashira coupling has also been used as a means to produce allylic-type silanes.[163] Specifically, 1-alkylidenylpropargylic silanes were prepared by means of a palladium-catalyzed cross-coupling of acetylenic cuprates and vinylic bromides or iodides (equation 58). So long as the latter bears a silyl group geminal to the sacrificial leaving group, then such a reaction should occur, thereby producing the desired silanes. Indeed, under the conditions of *n*-butylamine and cuprous iodide in dimethylformamide, the product silanes were produced in very good-to-excellent yields, and were mild enough to allow for the incorporation of even highly reactive functionalities such as acyclic acetals and unprotected alcohols.



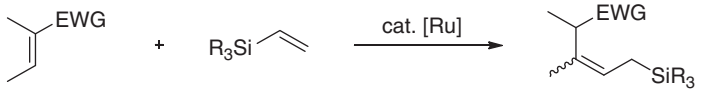
(58)

In a remarkable development which was first reported by Kambe and coworkers, the use of a catalytic amount of zirconium(II), which was formed *in situ* from a zirconium(IV) source, was shown to be capable of catalyzing the reaction between chlorosilanes and allylic carbon–hydrogen bonds, as a means of furnishing allylic silanes in very good yields (equation 59). The reaction is believed to proceed through the formation of a zirconium(II) species, which undergoes oxidative addition into the silicon–chloride bond, followed by salt metathesis with the Grignard reagent. The resultant species, (*n*-butyl)bis(cyclopentadienyl)(trialkylsilyl)zirconium(IV), becomes complexed to the alkene, and undergoes silylzirconation. Dehydrozirconation to form the most stable alkene (usually a styryl group) then takes place, followed by reductive elimination of butane gas to restore the zirconium(II) species.[164] Deuterium labeling was used to provide the evidence for the mechanistic rationale.



(59)

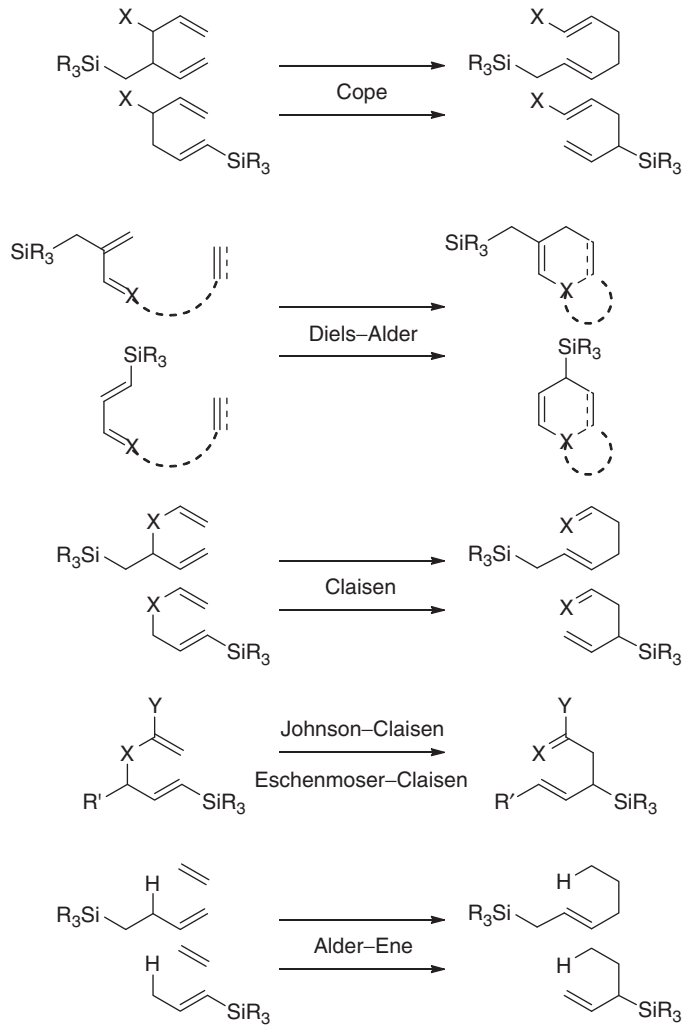
In a very unusual rearrangement reported by Darses and coworkers,[165] ruthenium(II) species have been shown to effectively catalyze a reaction between vinylic silanes and α,β-unsaturated EWGs (such as esters and amides) (equation 60). It is believed that an *in situ*-formed ruthenium(0) species undergoes oxidative addition into the β-carbon–hydrogen bond, followed by a 1,2-hydroruthenation of the vinylic silane. Subsequent reductive elimination would then regenerate the catalyst for further reaction.



(60)

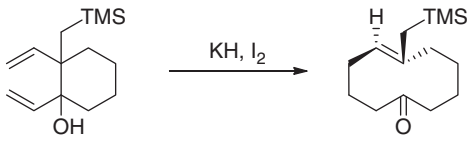
2.02.3.1.8 Sigmatropic reactions

The sigmatropic reactions (equation 61) of silicon-containing organic compounds are well studied, and many variations have been described to date in the literature. Due to the relatively high stability of carbon–silicon bonds, and especially their elevated thermal tolerance, most carbon–silicon bonds can survive sigmatropic reactions with little difficulty. The installation of appropriately placed silyl groups on carbon backbones can allow for the production of allylic silanes in this manner.



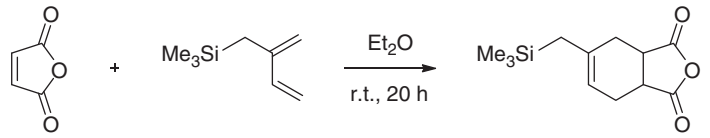
(61)

The Cope reaction is a well-known [3,3]-sigmatropic rearrangement of allylic homoallylic allyl ethers into 1-substituted-hexa-1,5-dienes. When the substitution at the 1-position is a hydroxy (or deprotonated hydroxy) group, then the resulting enol (or enolate) rearranges into a carbonyl compound. The production of allylic silanes by this method has been reported. For example, the synthesis of 10-membered cyclic ketones through this method is made incredibly facile by way of deprotonation (equation 62), and occurs in near-quantitative yield at room temperature within 4 h.[166] Anionic oxy-Cope reactions have also been used to produce acyclic allylic silanes in this manner.[167]



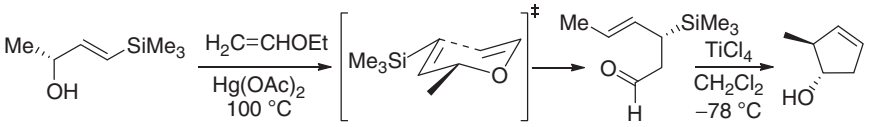
(62)

The [4,2]-sigmatropic reaction of a 1,3-butadienes with a dienophile – the Diels–Alder reaction – is arguably the most famous of all sigmatropic processes, and has been used on countless occasions to produce cyclohexenyl moieties, and also heterocyclic ring systems in the hetero-Diels–Alder variant. Just as with the Cope reaction, the Diels–Alder reaction has been used on several occasions to furnish allylic silanes, and generally does so in good yields. In one case, the thermal reaction of maleic anhydride and 2-(trimethylsilylmethyl)buta-1,3-diene provided the expected Diels–Alder adduct in quantitative yield at room temperature (equation 63), without disturbing the allylic silane functionality.[168] Such Diels–Alder reactions with alkynes serving as the dienophile have also been reported.[168,169] A Lewis acid-catalyzed version of these Diels–Alder reactions has also been developed, and allows the reaction to proceed at subambient conditions and in only a few minutes.[170] The direct incorporation of a silicon atom into the cyclohexene ring system – a tetrahydrosiline – can also be formed via a Diels–Alder reaction. The requisite silenes can be produced through a Peterson elimination of a starting β-hydroxyl-α-(bis(trimethylsilyl)phenylsilane).[171]



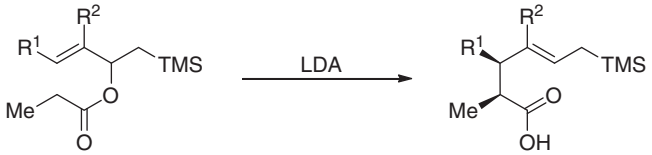
(63)

The Claisen reaction of vinylic allylic ethers is a [3,3]-sigmatropic rearrangement which forms γ,δ-unsaturated carbonyl compounds. The ready availability of chiral allylic alcohols makes this an especially attractive approach to such allylsilane syntheses. The formation of the vinylic ether can many times be the most difficult step of such a reaction, and so is sometimes carried out along with the Claisen rearrangement in a one-pot process.[11c] For example, mercuric acetate has been used in combination with ethyl vinyl ether and the starting chiral allylic alcohol. The chirality of the starting alcohol was completely transferred in this process, providing enantiopure allylsilane in nearly quantitative conversion (equation 64). Another report, in which a diallylic ether was isomerized by an iridium(I) catalyst, demonstrated that, after the isomerization, a Claisen rearrangement could take place in a one-pot process, thereby providing the desired allylic silanes in excellent yields.[172] It was also noted that the incorporation of a geminal substitution (such as in a cyclic system) increased the conversion efficiency – likely a result of the Thorpe–Ingold effect.



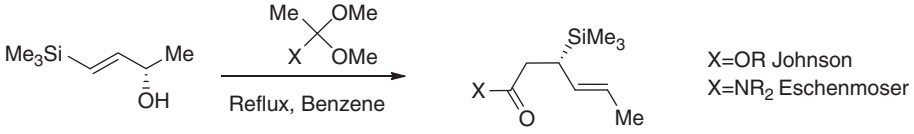
(64)

A popular variation of the Claisen reaction is the Ireland–Claisen rearrangement, wherein the vinylic ether is replaced by an ester enolate, and the reaction is allowed to proceed to furnish a carboxylic acid. This variation of the Claisen reaction is the far more popular route to allylic silanes within the synthetic community, perhaps because of the comparably facile production of the requisite ester starting materials and increased stability of the resultant carboxylic acid (as compared to the aldehydic functionality obtained in classical Claisen rearrangements). In a simple example, the use of LDA was chosen for its ability to control the stereochemistry of the enolate (equation 65).[173] The facile cyclization is usually completed at ambient or even lower temperatures in these reactions. This reaction has been used with great frequency throughout the literature,[39a,b,174,175] and several useful variations have been developed. For example, a Reformatsky–Ireland–Claisen rearrangement has been developed by Akiba and coworkers, in which metallic zinc is reacted with α-bromoesters, to give the zinc enolates, which undergo facile rearrangement.[176]



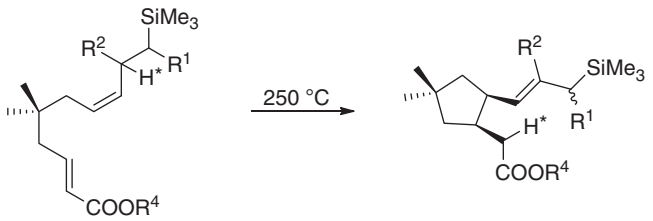
(65)

The Johnson[177] and Eschenmoser[178] Claisen rearrangements (equation 66) have both been reported as successfully furnishing allylic silanes in excellent yields. Unlike the Ireland–Claisen rearrangement, which is anionic in nature, both the Johnson and Eschenmoser–Claisen rearrangements are cationic in nature, reacting an allylic alcohol with trialkyl orthoformates and dialkyl orthoamides, respectively. In both cases, a pair of α-eliminations take place, furnishing oxycarbenium and iminium ions, respectively, followed by deprotonation at the adjacent position. The resulting 1-alkoxyenol ethers and 1-alkoxyenamines undergo very rapid [3,3]-sigmatropic rearrangement, providing the expected products.



(66)

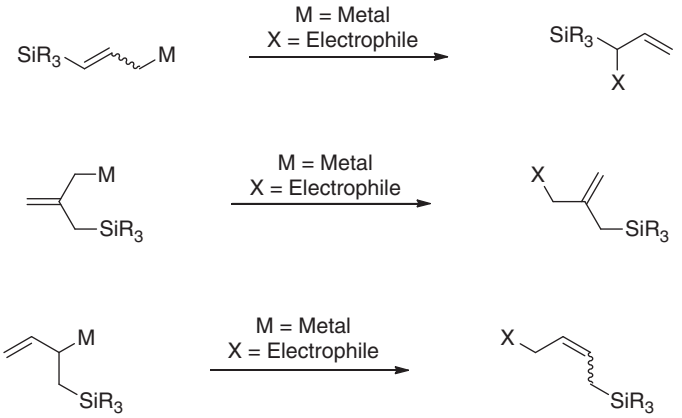
The Alder–ene reaction is another type of sigmatropic variation, specifically, a [1,5]-one, whose net result is that an allylic hydrogen atom undergoes a thermally induced rearrangement to add across a pendant olefin. This olefin adds across the alkene of the allylic system, which has shifted to replace the missing valency left by the hydrogen atom. The disrotatory nature of the reaction necessarily forces a *syn*-relationship for the two groups attached to the newly formed carbon–carbon bond. As an example, Sarkar et al.[179] reported that homoallylic silanes, could be converted into allylic ones through an Alder–ene reaction with the concomitant formation of a cyclopentanyl moiety (equation 67; migrating hydrogen is indicated with an asterisk). The elevated temperatures necessary to successfully affect an Alder–ene reaction are incompatible enough with a variety of sensitive functional groups, thereby making this a fairly unattractive synthetic route in the production of these synthons. There is a lone report of a cobalt(II)-catalyzed reaction of homoallylic silanes with alkynes which – by way of catalysis – undergoes a structural rearrangement equivalent to an Alder–ene reaction, furnishing allylic silanes in good yields and exclusively *E*-selectivities.[180]



(67)

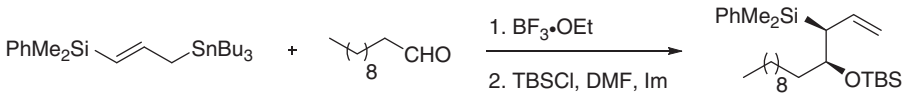
2.02.3.1.9 Allylmetalation processes

Many different types of bismetal reagents have been made and characterized to date. Such reagents can many times be designed and synthesized in such a way that, on rearranging through a predetermined allylation reaction, the resultant alkene is allylic with respect to the second metal (equation 68). This has been performed with silicon as the second metal many times, using a metallic element such as tin or a metalloid like boron as the first metal. As discussed earlier, it is possible to control the allylation reaction of bismetallation reactions when two or more are potentially competitive. Such chemospecificity depends on the relative rates of such allylmetallation reactions. Such relative rates are not important in the first and third general reactions shown in equation 68, as the starting materials are vinylic and homoallylic silanes, respectively, but rather in the case of the second pathway, wherein the starting material is allylic with respect to both the silane and the second metal. The reactions of this middle type are discussed in Section 2.02.3.1.11, wherein allylsilanes are converted into more complicated forms. In general, the formation of allylic silanes via allylmetalation processes takes place with the sacrificant being either a tin or boron functionality. There are only a few examples in which tin has been used as the sacrificial metal, and a multitude of those involving boron.



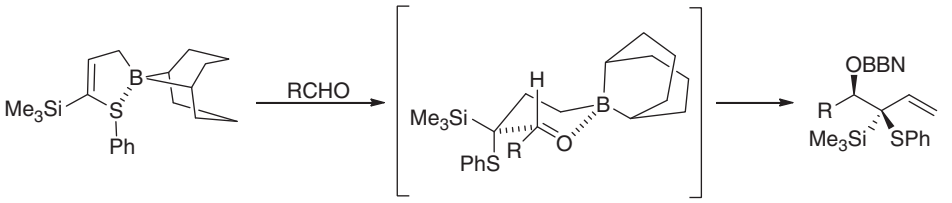
(68)

In one example of an allylstannation by Roush and coworkers,[181] a silylated allyltributylstannane was reacted with undecanal in the presence of catalytic boron trifluoride to furnish the *β*-silylalcohol. Protection of the secondary alcohol with a *t*-butyldimethylsilyl group provided the allylic silane shown (equation 69). The resultant allylic silane is nicely positioned for further derivatization, such as through allylsilation or through a cycloaddition process. Such allylstannylation routes to allylic silanes have been reported elsewhere,[182] especially in the context of total syntheses (*vide infra*).



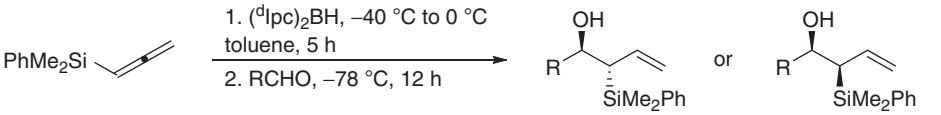
(69)

Similarly, the allylboration of electrophiles has been shown to lead to allylic silanes, and generally does so in better yields than those obtained from their allylstannylation counterpart reactions. The formation of these allylboron species has been thoroughly discussed in the accompanying chapter.[11] It is quite common to prepare the necessary allylic borane *in situ* through a hydroboration reaction, then to perform the allylboration step in a one-pot sequence. For example, Pearson et al. described the formation of an allylic borane in this manner, which, likely due to the rapid 1,3-boratropic shifts of allylic boranes, formed the thermodynamically favored *Z*-chelate (equation 70). The reaction with aldehydic electrophiles furnished the expected allylic silanes, which could be eliminated to form either the *Z*- or *E*-butadienyl system, depending on the conditions chosen for the subsequent Peterson elimination.[183] Most frequently, when such allylboration reactions are used to form allylic silanes, they are performed in the context of a total synthesis[184] (much like their stannanylic counterparts), or are used in the production of allylic silane synthons.[185]



(70)

It is also possible to produce enantioenriched allylic silanes through a route in which the chirality is induced during the allylmetallation step. For example, the inclusion of chiral ligands, including chiral diols or alkyl group such as enantiopure isopinocampheyl ones, can affect high levels of enantioinduction. Chen and Roush have reported one such case,[186] wherein allenylic silanes were hydroborated. Such hydroborations typically occur in a 2,1-fashion, in which the hydrogen adds to the central carbon atom, and the boron onto the terminal position. On allylboration, allylic silanes are produced in a >12:1 diastereomeric ratio (*Z*-allylborane gives *syn* and *E*- furnishes *anti*), and with enantiomeric ratios of approximately 93:7 (equation 71).



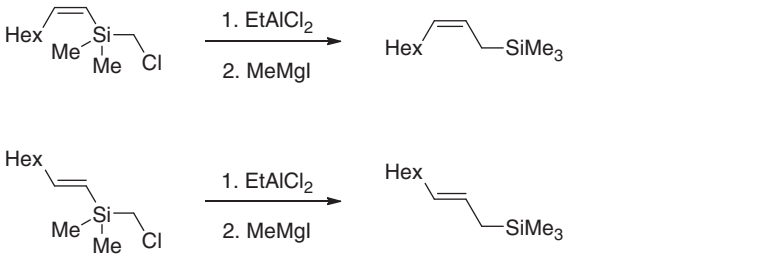
(71)

2.02.3.1.10 Other synthetic means

There have been many reported methods of producing allylic silanes and derivatives through means that cannot be readily classified into the previous categories. These types, which are not frequently used throughout the literature, are included herein for purposes of completeness and variety.

There have been several cases wherein vinylic silanes are directly converted into allylic ones. One example has already been discussed in Section 2.02.3.1.5; of the remaining two types, the conversion of unsaturated EWGs is the more frequently seen method.

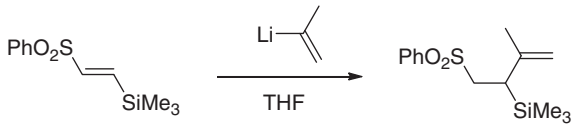
Hudrlik et al., while systematically investigating the migration reactions of α-substituted organosilicon compounds under Lewis-acidic conditions, observed that vinylic silanes could indeed be converted into the desired allylic ones, and that, in so doing, the displaced chloride would migrate onto the silicon atom (equation 72). The latter functionality was reacted with a Grignard to formulate the trimethylsilyl group reported.[187] Unfortunately, these rearrangements were severely limited in their scope, and would not function with methyl, alkynyl, or furyl-substituted silanes.



(72)

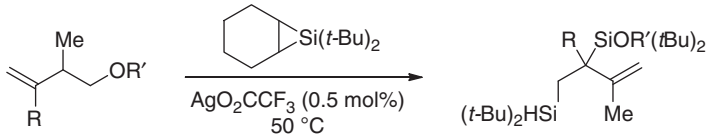
In a few cases, electrochemical processes have been used as a means to produce allylic silanes. For example, the reaction of benzylic and allylic halides with trimethylsilyl chloride, wherein a potential is applied across the reaction medium with an appropriate anode/cathode combination, can furnish allylic silanes.[188a] In a similar manner, allylic difluorochloromethyl groups can be silylated under such conditions.[188b] In general, such electrochemical syntheses of allylic silanes do not proceed well, and give unpredictable results and poor yields.[188]

The conjugate addition of groups onto Michael acceptors such as sulfones and ketones has been thoroughly described in the literature. The resulting species can possess an allylic silane moiety in one of several different constitutional manners as a result of this process. For example, Fujita and coworkers described the addition of a vinylic species to a sulfone Michael acceptor (equation 73). The resulting species is necessarily an allylic silane, and can be used as such.[189] A similar work has appeared, wherein α,β-unsaturated ketones serve as the Michael acceptors.[190] Additionally, the trapping of the enolate which results from the initial conjugate addition directly results in the formation of an allylic silane, which can be further derivatized as desired.[191] Both of these systems have been further developed into asymmetric reactions.



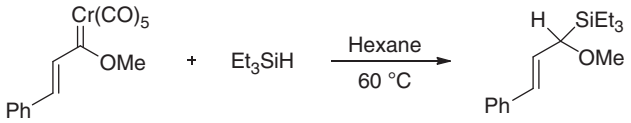
(73)

A fairly young area of research in the literature is the use of silylenes to produce allylic silanes. Silylenes, which are the silicon analog of carbenes, can be readily produced in a variety of ways, including from the decomposition of silacyclopropanes under certain conditions.[192] Quite interestingly, these highly reactive species have been shown to undergo addition to homoallylic etheric carbon–oxygen bonds, rearranging to give an allylic silane, which occurs along with what is a net addition to the homoallylic carbon–hydrogen bond by a second silylene (equation 74).[193] Although the use of silylenes remains a slightly unpredictable method for the preparation of various synthons, it appears as though this is a readily reproducible reaction, and is so likely to find much future synthetic utility. It has also been shown that two silylenes can insert contiguously into the same bond type, furnishing an allylic silane which is fitted with a Si-(hydroxysilyl) group (a hydroxy-substituted disilane).[194]



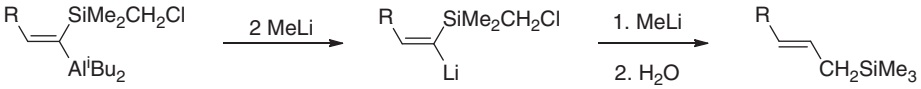
(74)

More classical carbene chemistry can also be used to furnish allylic silanes. Instead of silylene insertion into carbon–atom bonds, the approach is the reverse: the insertion of a carbene into a silicon–(other atom) bond. In general, the necessary allylic carbenes are produced in one of several different means, such as in the reductive desulfurization of dithioacetals or ketals with titanium,[195] or in the diazo activation by rhodium(II) species.[196] Platinum, palladium, molybdenum, tungsten, and chromium have also been shown to be active species for such reactions[197]; chromium was found to be optimum, and was shown to offer reasonable yields of allylic silanes (equation 75).



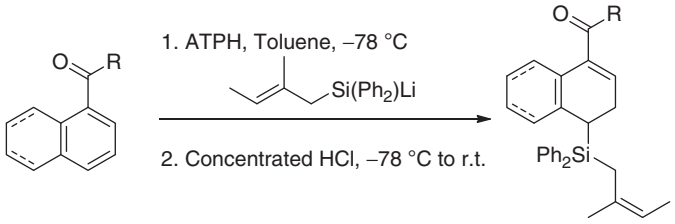
(75)

In one very unusual and not-understood reaction which was reported by Utimoto and coworkers, the reaction of a silylated vinylic aluminate with an excess of methyllithium (equation 76) resulted in the formation of a vinylic lithium species, which, on further reaction with methyllithium, rearranges to give *E*-allylic silanes in good yields.[198]



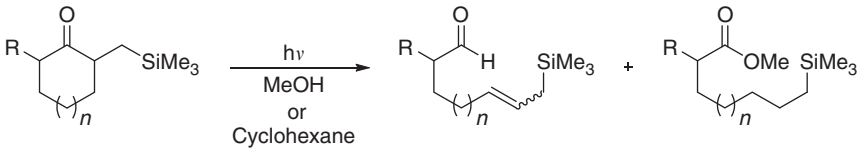
(76)

Yet another approach was reported by Fleming and coworkers, in which Lewis acids catalyzed the conjugate addition of silylic anions onto aromatic carbonyl compounds.[199] The very bulky Lewis acid, tris(2,6-diphenyl)phenyoxyaluminum(III) (ATPH), was used for both the promotion of the reaction, and in sterically shielding the carbonyl moiety, so that any 1,2-addition was significantly retarded. The resulting species are either allylic or benzylic, depending on the nature of the aromatic system being used (equation 77).



(77)

There has been one report of a light-induced reaction of α-(silylmethyl)cyclic ketones, in which alpha cleavage took place to furnish a diradical species.[200] When the reaction was performed in protic solvents such as methanol, solvolysis took place, providing the methyl ester of an aliphatic silane. However, in the absence of protic solvents, an elimination pathway was preferred, wherein a formal intramolecular carbon–hydrogen activation took place, necessitating the formation of an aldehyde-terminated allylic silane (equation 78).

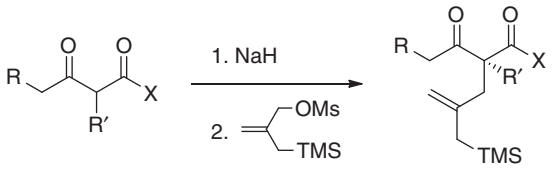


(78)

2.02.3.1.11 Derivatization of simple allylsilanes

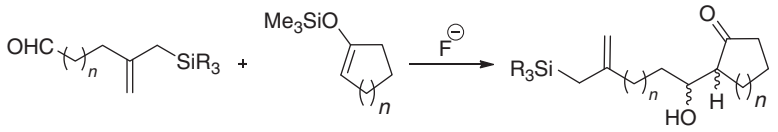
As discussed earlier, allylic silanes are very stable species both thermally and chemically, but will react under certain harsher conditions. Due to this stability, the allylic silane functionality can be readily carried through to other, more complicated species possessing the same group. Thus, the synthesis of complicated allylic silanes via the derivatization of simpler ones is presented here. The starting allylic silanes in the following schemes are mostly available through the means already discussed in Sections 2.02.3.1.1–2.02.3.1.10. The derivatizations shown here attempt to show methods which have not yet been discussed in Sections 2.02.3.1.1–2.02.3.1.10, and which allow for the synthesis of complicated allylic silane synthons.

Allylic silanes, when bearing pendant alkyl groups fitted with appropriate leaving groups, are very stable to conditions of nucleophilic substitution. For example, malonate derivatives – including esters and amides – can be readily deprotonated and subsequently reacted with 2-(methanesulfonyloxymethyl)allyltrimethylsilane (equation 79).[201] Such reactions generally occcur with very good yields, and, depending on the steric bulk at the leaving group and allylic sites, can undergo either a direct displacement through an S_N2 pathway, or an allylic displacement one (S_N2'). As is typical for such displacement reactions, very good leaving groups such as mesylates, bromides,[202] iodides,[203] or trichloroacetimidates[204] are generally used. Propargylic silanes have also been reacted in this manner.[203b,204] The use of metal catalysts (such as nickel or palladium) to assist in such substitutions (Tsuji–Trost conditions) has also been performed.[205]



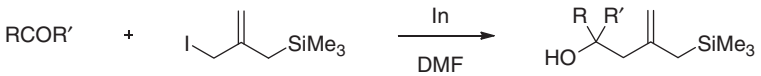
(79)

Substitutions, wherein the nucleofuge is not a simple leaving group, but rather a π-bond such as a carbonyl, have also been reported. For example, the use of allylic and homoallylic aldehydes and oxycarbenium ions (which are generated *in situ* from acetals and ketals) as leaving groups, furnishing alcohols and ethers, respectively, has been reported by Lee et al.[206] The Mukaiyama aldol reaction of silyl enol ethers with the said species has also been reported to proceed in good yields (equation 80).



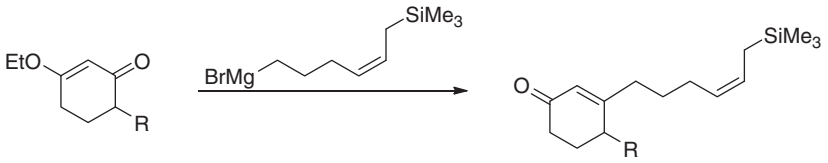
(80)

Beginning with the same basic β-(functionalized-alkyl)allylic silanes, wherein the functionality is a leaving group, the Umpolung inversion, by producing the sesquihalide indium species *in situ*, has also been performed.[207] By simply reacting a mixture of an electrophile such as an aldehyde or ketone, along with the allylic-functionalized silane and indium powder in *N*,*N*-dimethylformamide at room temperature, very good conversions into the desired δ-hydroxyallylic silanes can be achieved within a single hour (equation 81).



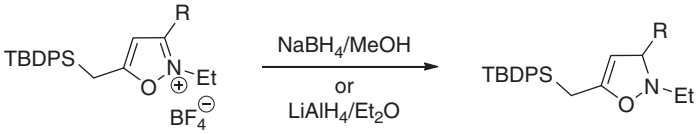
(81)

Similarly, Grignard reagents can be produced from allylic and propargylic silanes which bear a pendant alkyl halide moiety. Such reagents are stable, and have been used on several occasions to add to vinylogous ester compounds (equation 82), thereby furnishing β-(silylalkyl)-α,β-unsaturated ketones in reasonable yields.[208] However, there appears to be some capricious character to these attempted reactions, as the results are not always reproducible.[209]



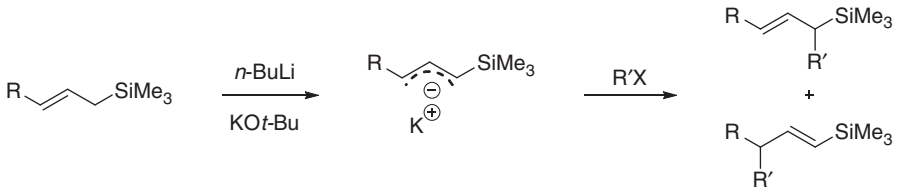
(82)

Benzylic silanes can be reduced down to allylic silanes, depending on the nature of the ring system. For example, González-Nogal and Calle have demonstrated that azolium salts, on reduction with an appropriate hydride donor, can furnish a series of allylic silanes, wherein the olefin is internal to a heterocycle (equation 83). The generality of this reaction with regard to allylic silanes was not probed, as the authors' intention was more focused on the variability of the heterocyclic functionality.[210]



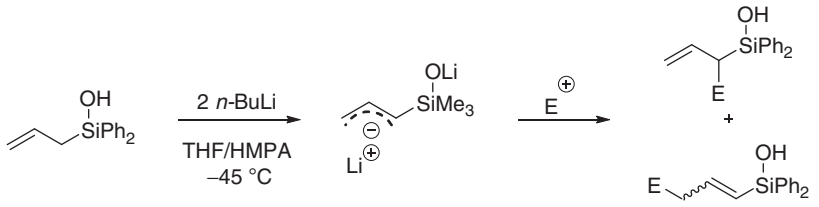
(83)

Just as with the earlier-described chemistries, wherein allylic silanes could be produced by the reaction of allylic anions with silicon groups, so too may allylic silanes be deprotonated and further functionalized (equation 84). This deprotonation is more facile than initially expected, due to the silicon α-effect. For example, Taddei and coworkers demonstrated that the use of the Schlosser-modified *n*-butyllithium base to deprotonate allylic silanes can provide, on reaction with electrophiles, functionalized allylic silanes in reasonable yields.[211] Indeed, the reactions with many electrophiles have been described, including ketones,[212] aldehydes,[213] epoxides,[213a,214] alkyl halides,[213b] and silyl chlorides.[215] Generally, the site of alkylation is controlled by the steric bulk of the allylic anion. However, γ-alkylation (relative to the silane) results in the formation of a vinylic silane system, which is not of interest for the purposes of the authors.



(84)

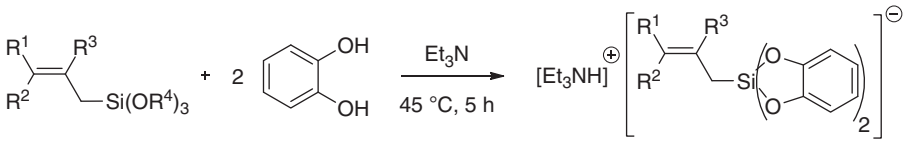
As allylic silanes are not particularly strong proton acids, the use of a very strong base is required for these deprotonations. Almost certainly, the most commonly used superbase is *n*-butyllithium, which also suffers from a high degree of nucleophilicity. In the case of silanes bearing labile ligands such as alkoxides or halides, the use of *n*-butyllithium in an attempted deprotonation–functionalization sequence is generally not possible, as an association–dissociation ligand exchange pathway will proceed, furnishing the butylated silane. Oshima and coworkers[216] demonstrated that the use of the silanol compound, in place of such labile groups, can function without issue in such pathways. The requirement, however, is for the addition of a second equivalent of base. Such dianions usually react at the allylic position exclusively (equation 85).



(85)

In general, the ligand exchange on silicon is a facile process, so long as the group that is being replaced has a high enough pK_b. Most commonly, the reaction involves the exchange of a chloride or an alkoxide substituent, for the conjugate base of a weaker acid. Seeing such group exchanges when beginning with an allylic silane are rare, as the act of building the said group is usually the end result of such synthetic efforts. Nonetheless, alkoxides[217] and chlorides[218] have been shown to undergo facile exchange in such systems.

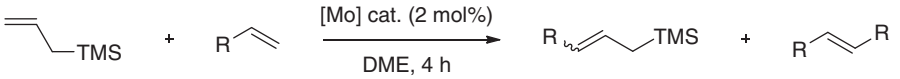
In a similar vein, when silicon has ligands of high electronegativity such as alkoxides or halides attached to it, it readily undergoes reactions to form hypervalent complexes, such as those shown in equation 86, wherein the addition of two equivalents of catechol add onto the silicon center, expelling those labile ligands in place, thereby forming a siliconate complex.[218] These reactions are highly interesting, as they usually occur in nearly quantitative yield, and provide pentacoordinate allylic siliconates which, although formally bearing a negative charge at the silicon center, are actually of a higher Lewis acidity at the metal center than the simpler tetravalent silane.[219] This Lewis acidity is extremely important, as it allows access into the Type-I cyclization Hosomi–Sakurai reactions discussed earlier.



(86)

The use of sodium hydride has been reported to catalytically evolve hydrogen from the reaction that occurs between alcohols and silanes, and, in so doing, catalytically build up silyloxy functionality.[220] Additionally, the use of Piers and coworkers' tris (pentafluorophenyl)borane methodology[221] for the production of allylic silanes has been reported to function in excellent yields.[222]

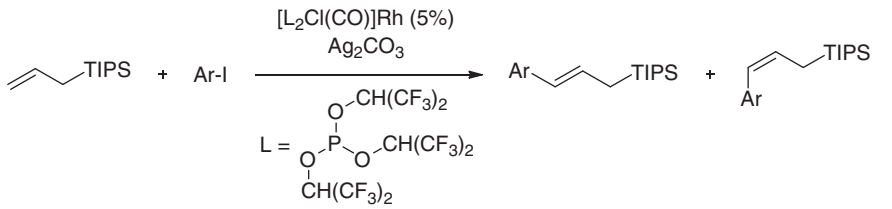
Allylic silanes may be derivatized by functionalization through a cross-metathesis pathway. For example, Crowe et al.[223] have demonstrated that Schrock's molybdenum-based catalyst can be used to metathesize allylic silanes with a wide variety of olefinic partners, proceeding in generally good yields and with mostly *E*-selectivity (equation 87).



(87)

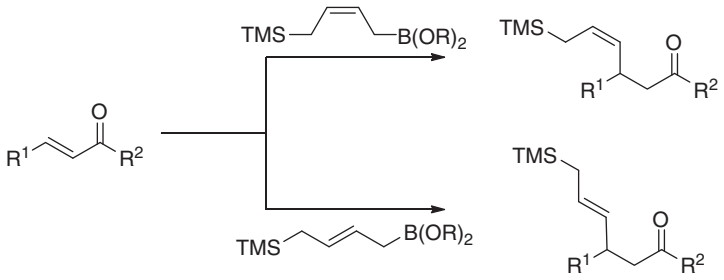
The majority of the metathesis reactions of allylic silanes thus far reported make use of ruthenium catalysts, however. Ring-opening metathesis to furnish allylic silanes has been described,[224] as has ring-closing metathesis,[117a,225] including the use of enantioenriched substrates.[40] The cross-metathesis with ruthenium catalysis of both symmetric[226] and asymmetric substrates[71] has been reported on several occasions.

Transition metals can also be used for many other functionalizations of allylic silanes. For example, the direct vinylic carbon–hydrogen activation of allylic silanes with rhodium(I) complexes has been described by Omachi and Itami.[227] The reaction, which proceeds only slowly and at higher temperatures, furnished reasonable yields of mostly the *E*-allylic silane, along with minor amounts of the vinylic and *Z*-allylic silane (equation 88).



(88)

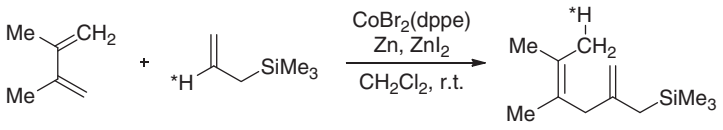
The use of rhodium as a catalyst for conjugate additions of boronate esters of allylic silanes has also been reported.[228] For example, both *E*- and *Z*-allylic silanes react with Michael acceptors such as enones to furnish allylic silanes have been functionalized at the γ-position (equation 89). Such reactions occur in good yields and with the complete retention of the olefin's geometry.



(89)

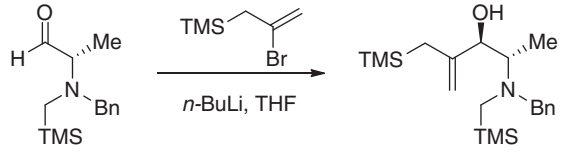
Olsson and Szabó have combined the previous two concepts into one.[229] By first using an iridium catalyst for C–H bond activation, and then performing a palladium-catalyzed Suzuki–Miyaura cross-coupling, the formation of *E*-allylic, γ-substituted silanes (starting from allyltrimethylsilane) has been achieved. The two-step procedure furnished these allylic silanes in very reasonable yields. Suzuki coupling has also been used to convert vinyl triflate-containing allylic silanes into more complicated ones.[191]

A very interesting functionalization of allylic silanes was reported by Hilt and coworkers, wherein a combination of cobalt and zinc catalysis was found to be capable of performing what amounts to a 1,4-hydrovinylation of 1,3-butadienyl systems in near-quantitative yield.[230] In this difficult-to-envision reaction, the secondary vinylic hydrogen is formally transferred onto the butadiene system, which undergoes a π-bond transfer, forming a tetrasubstituted alkene. This olefin shift causes the remaining π-bond to add onto the site of the earlier hydrogen removal (equation 90).



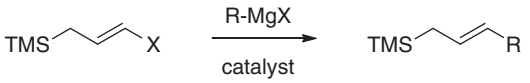
(90)

The reaction of vinyllithiums derived from allylic silanes is stable, and can be reacted with a variety of electrophiles.[231] For example, aldehydes can serve to alkylate, and thereby functionalize the β-position of the said allylic silanes (equation 91).



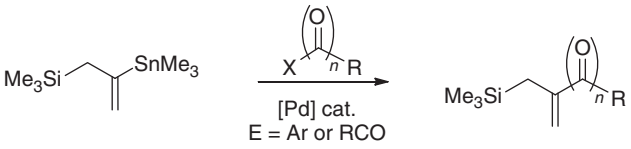
(91)

Although the active vinylic lithium from the above reaction is generated through a lithium–halogen exchange reaction, most vinylic halides on allylic silanes are not reacted as such. Far more common is the cross-coupling reaction of such halides and related leaving groups. For example, the Kharasch cross-coupling reaction of vinylic halide-containing allylic silanes with various Grignard reagents was investigated by Okamoto and coworkers.[232] They demonstrated that the use of iron, cobalt, palladium, or nickel as a catalyst choice could affect such a coupling reaction. The use of nickel was found to be superior, offering very high isolated yields with short conversion times at even subambient temperatures (equation 92).



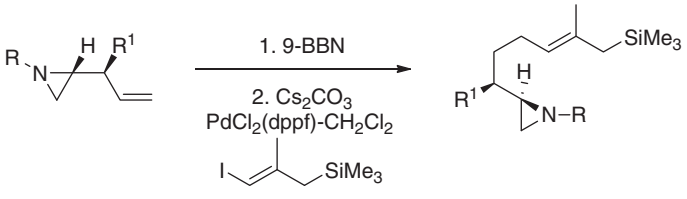
(92)

Stille cross-coupling has also been used to further functionalize allylic silanes which are fitted with stannane functionalities. For example, Kang et al. have demonstrated that allylic silanes have no stability issues when subjected to palladium-catalyzed cross-coupling with a variety of electrophiles such as benzylic chlorides (equation 93, $n=1$, X=Cl) and aromatic halides ($n=0$).[233] The resulting allylic silanes are generally produced in very good yields, and can tolerate a wide range of functionalities with little difficulty. Stille coupling has also been used to attach alkynes to 2-iodoallylic silanes, starting from the alkynylstannane.[234]



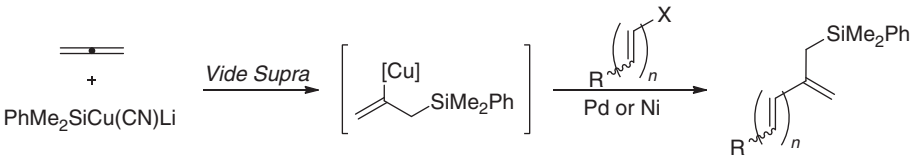
(93)

Similarly, Suzuki–Miyaura cross-coupling has been used as a means to further derivatize allylic silanes. Bergmeier and coworkers provided an example of a palladium-catalyzed cross-coupling of a vinylic iodide with a primary borane (equation 94). The reaction, which proceeded with satisfactory yield, demonstrated the remarkably mild conditions of such cross-coupling reactions, and furnished the necessary *E*-allylic silane with a pendant aziridine functionality.[235]



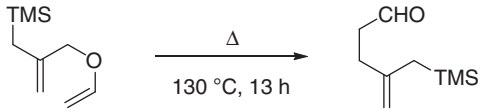
(94)

A magnesium-free Normant coupling reaction was recently reported by Pulido et al.[236] In that work, they demonstrated that those allylic silanes with a vinylic cuprate group (developed by Fleming and coworkers) could be successfully coupled to vinylic or aromatic bromides or iodides through the use of either palladium or nickel-catalyzed cross-coupling (equation 95). The desired allylic silanes, which could be highly functionalized, were obtained in generally very good-to-excellent yields. The use of Kumada–Corriu–Tamao coupling to further derivatize allylic silanes has also been reported.[237]



(95)

Sigmatropic reactions have also been used to convert simple allylic silanes into more complicated ones. For example, the Claisen reaction of an allylic vinylic ether which contained an allylic silane was converted into the expected aldehyde, and, in which, that produced group was not attacked through a thermal Hosomi–Sakurai reaction (equation 96). The fact that even at 130 °C the formed aldehyde is not allylated intramolecularly is a testament to the need for electrophilic activation through one of the means discussed in Sections 2.02.2.1 and 2.02.2.3.[238] The Diels–Alder reaction, wherein an allylic silane is converted into a different allylic silane, has also been reported.[239]



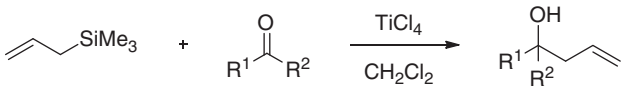
(96)

2.02.3.2 Allylation of Aldehydes

2.02.3.2.1 Tetravalent silicon – without absolute stereocontrol

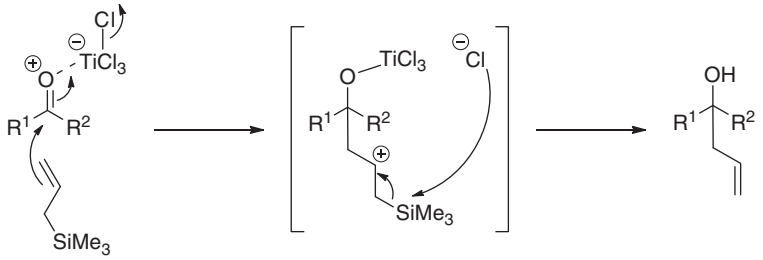
As discussed in Section 2.02.2.3, the reaction of allylic silanes with aldehydes can occur through either a Type-I or a Type-II process, providing homoallylic alcohols which can be further derivatized. The reaction of tetravalent silicon, where one of the ligands is the allyl or allyl derivative, and the other three are strong electronegative groups such as fluorides, chlorides, or alkoxides, can undergo activation through the formation of a penta- and then hexacoordinate silane, which then proceeds through a Type-II process. The activation process can occur from the reaction with strongly coordinating solvents, by reaction with highly nucleophilic species such as fluoride ions, or by reaction with polyvalent ligands. In the absence of such activation, all tetravalent silanes, regardless of the ligands' identities, require an external additive to catalyze such allylation reactions.

The first report of the allylation of carbonyl compounds was published by Hosomi and Sakurai in 1976.[3] They reported that titanium tetrachloride could effectively catalyze the reaction of allylic silanes and carbonyl compounds, providing, on workup, generally excellent yields of the homoallylic alcohol products (equation 97).



(97)

This first example of an intermolecular allylsilane reaction occurred without any level of absolute stereocontrol, and is believed to occur through the formation of a carbonyl–titanium chelate complex, which is attacked externally by the allylic silane, forming a β-silylcarbocation (**Scheme 5**). Nucleophilic attack onto the silane results in a net elimination process, furnishing the allylic silane.

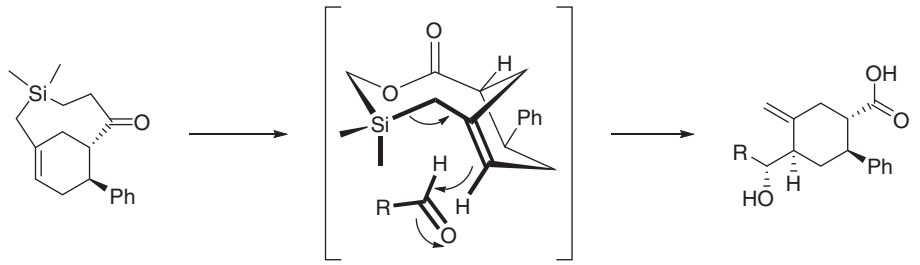


Scheme 5 $TiCl_4$-mediated allylsilation of a carbonylic electrophile.

Since the seminal report, allylsilation has expanded greatly in its utility, and has been developed to include an enormous variety of functionalities. For example, the stereoselective incorporation of deuterium atoms adjacent to the resulting carbinols has been performed with this methodology.[240] In other cases, aldehydes can be allylated, and the resulting hydroxy group can be replaced with halogens[241] or cyclopropanyl groups *in situ*.[242] Many different types of ring systems have been produced through this route (usually in tandem with another type of chemistry), such as tetrahydro-2*H*-pyrans,[34c,243] α-methylene-γ-butyrolactones,[88] 1,6-dioxecanes,[244] 9-oxabicyclo[3.3.1]nona-2,6-dienes,[245] 1*H*-isochromenes,[246] and spirooxindoles.[140] Titanium

tetrachloride was the Lewis acid of choice for the original Hosomi–Sakurai reaction, and has been used as such many times since.[88,153a,b,247] Since that time, a large variety of Lewis acid catalysts have been shown capable of successfully promoting this reaction, including tin(IV) chloride,[247a] boron trihalides,[88,240,241] alkylaluminum and aluminum halide complexes,[34c,236,243a] indium(III) chloride,[248] including one report with the use of trimethylsilyl chloride as an additive,[249] bismuth(III) trifluoromethanesulfonate,[243b] scandium(III) trifluoromethanesulfonate,[250] ytterbium(III) trifluoromethanesulfonate,[251] niobium (V) chloride,[242] ionic salts, such as lithium tetrafluoroborate,[252] trimethylsilylonium trifluoromethanesulfonate,[244,253] platinum (II) and palladium(II) salts,[245,246] and mesoporous aluminosilicates.[254] Additionally, Brønsted–Lowry acids have also been reported to promote such reactions,[140,243c,255] which is significant, considering the relative ease of protiodesilylation.

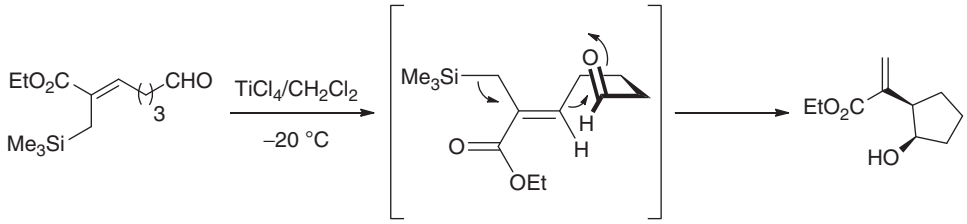
Intermolecular reactions, wherein chiral centers are already present on the molecule, proceed with the directing effects of the stereogenic center acting on the allylsilation, and can thereby dictate the relative stereochemistry of the newly formed stereogenic center. For example, Shea and coworkers have reported on the intermolecular reaction of a bicyclic allylic silane with various aldehydes, which proceeds to give only a single diastereomer in each case. The reaction, which likely proceeds through a pathway similar to the one shown in equation 98, necessitates a geometry in which the aldehyde is outside of the [5.3.1]-bicyclic system, and in which there exists minimal repulsion between the aldehyde and the bicyclic structure. The cleavage of the silylmethyloxy ligand was performed in the same pot, resulting in readily purifiable carboxylic acids in good-to-very good yields.[256] There are a variety of reports dealing with similar allylsilation reactions occurring without absolute stereocontrol, but occurring with relative stereocontrol stemming from a present stereogenic center.[257]



(98)

Such stereocenters will always have some effect on the reaction, and induce some amount of asymmetry in the newly formed center, so long as the pre-existing stereogenic center is not significantly removed from the site of bond formation. Such stereocontrol can come from the silane functionality,[225,258] or from the aldehyde.[230]

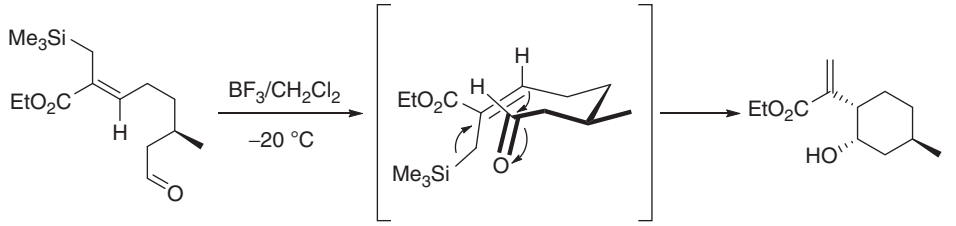
Just as intermolecular reactions can be performed between allylic silanes and aldehydes, so too can be intramolecular ones. Such reactions, which necessitate the formation of ring systems, are usually dictated by the sterics of these very ring systems themselves. For example, Nishitani and Yamakawa have shown that certain systems, when possessing an attached ester group, can undergo allylsilation to furnish the expected cyclic alcohols, which can be closed into the ester functionality to provide fused bicyclic lactones. In the case of the example shown in equation 99, the two hydrogens must both be oriented downward, thereby positioning the two substituent groups in a manner which again minimizes steric repulsions while leading into the transition state.[89a] Ideally, any imaginable ring size could be produced in this manner, but practice has shown that four-,[259] five-,[89a,b,260] and six-membered[89a,b,259] rings are best suited to such transformations. In those cases in which the attacking allylic group is positioned as a ligand on the silicon, as opposed to being a portion of the tether, a silicon–oxygen-based heterocycle (a siloxane) is produced.[261]



(99)

In the preceding example, the relative stereochemistry is formed as a result of the minimization of the steric repulsion between all of the groups in the system. However, sometimes tangential groups can allow for the energetics associated with the sterics in more remote regions of the molecule to interfere with what is normally controlled by the area of interest. The incorporation of additional, pre-set stereocenters in the ring system being formed can help to minimize such remote effects. Such intramolecular allylsilation reactions of aldehydes, wherein there is a pre-existing stereogenic center, are moderately common in the literature. The consideration made in these cases is one of double diastereoselectivity; will the remote effects agree with steric interactions proximal to the reacting portion of the molecule or not? A similar example to the one shown above can be used to illustrate this effect.[262] By incorporating a methyl into the backbone of the system, there becomes additional incentive for the Zimmerman–Traxler model transition state cyclohexane ring to become more tightly locked, as the additional substituent attempts to maintain a pseudoequatorial position throughout the reaction (equation 100). The first example of this type of reaction was used by Sarkar

and Anderson to furnish bicyclic compounds.[263] Such intramolecular allylations have also been used in many syntheses. For example, Yamakawa and coworkers used this strategy in the total synthesis of diplophyllin.[264]



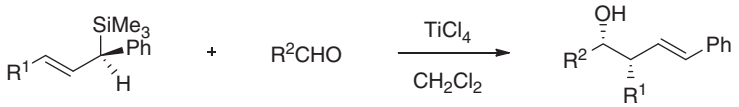
(100)

Just as before, many different ring sizes have been constructed this way, including five-,[265] six-,[11a,204,215,265,266] and seven-membered[265] rings. Bicyclic ring systems have also been constructed in this manner,[11a] as have siloxanes.[220]

2.02.3.2.2 Tetravalent silicon – with absolute stereocontrol

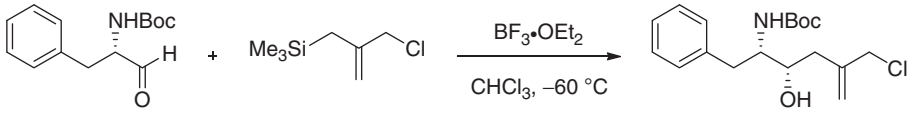
The relative stereochemistry of allylsilation reactions was discussed in Section 2.02.3.2.1. The absolute stereocontrol of these reactions is possible, and can be controlled through four possible routes: absolute stereocontrol induced by (1) the allylic silane; (2) the aldehyde; (3)(a) both the aldehyde and silane, and (b) an intramolecular reaction of a chiral substrate; and (4) a chiral Lewis acid–ligand pair.

The use of an allylic silane to induce chirality during bond formation has been reported on several occasions, and has been quite successful. Usually, there is little absolute loss of stereochemical information, as the chirality is transferred through the first step, and there is no opportunity for racemization thereafter. For example, Kumada and coworkers[267] demonstrated that allylic silanes reacted with simple aliphatic aldehydes in mostly very good yields, and with a complete maintenance of enantioenrichment (equation 101). In nearly all cases, the stereoselectivity was almost entirely *syn*, as is to be expected for these reactions (*vide supra*). Other reports have also demonstrated a complete transfer of chirality from the silane to the product homoallylic alcohol.[11c,30,31c,33,74,81a,185d,268] The synthetic utility of such an approach has been demonstrated in various total syntheses, such as in that of methyl-L-callipeltose by Huang and Panek.[269]



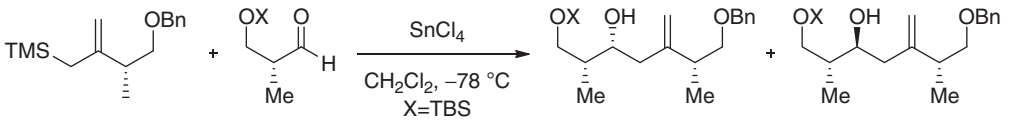
(101)

Until more recent asymmetric allylsilane technologies emerged, it had historically been easier to access chiral aldehydes than it had been for chiral allylic silanes. As expected then, there are many more reports of the use of achiral allylsilanes in the allylation of chiral aldehydes than vice versa. In one example, D'Aniello and Taddei demonstrated that the reaction of the chiral, phenylalanine-derived α-aminoaldehyde shown in equation 102 with a simple β-chloromethylallyltrimethylsilane could proceed to give the expected product in very good yield and with nearly complete *syn*-diastereoselectivity.[270] The transfer of chirality with this approach was again quantitative, as there exists no real opportunity for racemization at the pre-existing stereogenic carbon atom. There are many similar examples of the addition of fully symmetric allylsilanes being added to chiral aldehydes available in the literature.[271] The utility of such chiral aldehyde strategies is pronounced, as such allylations have been used in many syntheses. For example, Panek and coworkers used this strategy in the total synthesis of mycotrienol and mycotrienin I.[272]



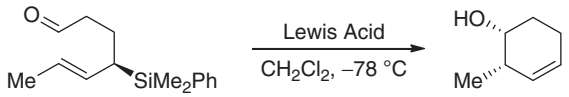
(102)

The interaction of a chiral aldehyde and a chiral allylsilane can result in either a destructive (mismatched) or constructive (matched) effect on the stereochemistry of the final product. As long as there is no opportunity for racemization of the individual substituents, the final product will necessarily maintain the chirality of both of the reactants, and the diastereoselectivity may be altered depending on the state of matching. As an example of this, a report by Dias and Giacomini is considered, in which they detailed the effects of interacting the two pieces in this manner. The reaction, which is shown in equation 103, provided a 75:25 mixture of the *syn*:*anti* isomers (matched), whereas the same reaction with the enantiomeric aldehyde gave a 48:52 mixture of the *syn*- and *anti*-isomers (mismatched).[273] There has been other work related to this type of mixed system which has demonstrated similar tendencies toward matching and mismatching.[117d,274]



(103)

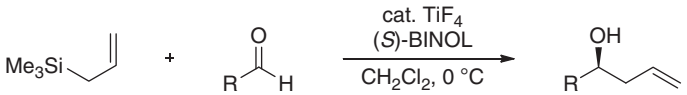
Similarly, intramolecular reactions of chiral substrates will dictate both the diastereo- and enantioselectivity of the reaction. For example, any of the four possible stereoisomers could be formed from the reaction shown in equation 104, but only one major stereoisomer was formed, in a ratio near 9:1 in favor of the *syn*-product of the indicated enantiomer.[81b] The obtained isomer's preferential formation is readily explained through the invocation of a cyclic transition state akin to those in the previous few examples.



(104)

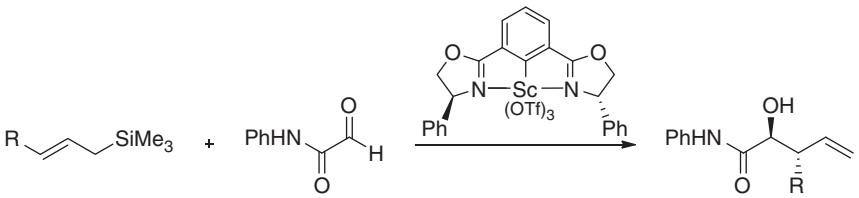
As the final method of producing enantioenriched homoallylic alcohols through the reaction of aldehydes with allylic silanes, the Lewis acid-mediated approach is arguably the most economical, as it usually does not necessitate the use of a stoichiometric amount of chiral compound, but rather is catalytic with respect to both the activator and the chiral moiety. Most frequently, the use of Lewis acids with a chiral ligand is responsible for the observed enantioinduction in these reactions.

There have been only a few reports of the use of such chiral Lewis acid–ligand combinations to control the absolute stereochemistry of these reactions. One of the earliest reports was published by Carreira and coworkers, wherein they described the use of the seldom-used titanium tetrafluoride-(*S*)-BINOL complex as a means to promote the reaction of allyltrimethylsilane with a variety of aldehydes (equation 105). The yields ranged from good to excellent, and the enantiomeric ratios were obtained between 92:8 and 95:5.[275]



(105)

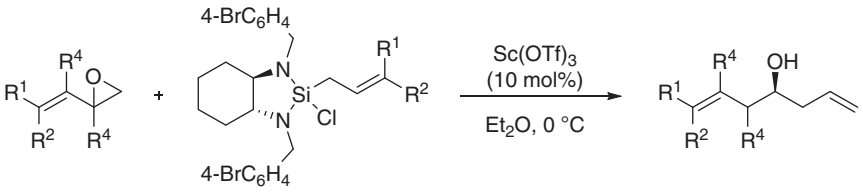
Evans et al. have reported that the use of scandium(III) trifluoromethanesulfonate, when allowed to form a complex with chiral pyridyl-bis(oxazoline), could also provide very high levels of stereoinduction, with enantiomeric ratios ranging from 95:5 to 99:1, without compromising the yields of the reaction (equation 106). Unfortunately, this system was designed for functionality on the activated aldehydic portion of glyoxamides, and is not entirely generalized. This necessitates further synthetic manipulation to transform the resulting α-hydroxyamides into relevant chemical building blocks.[276]



(106)

The use of chiral, tartrato-boronate ligands was the first reported catalytic system found to be efficacious for this type of transformation, but was not demonstrated to have a wide scope with respect to the reaction's aldehyde.[277] The use of palladium (II) complexes, in combination with certain phosphine ligands, could also produce high levels of enantioinduction in the reaction of chiral vinylboronate-containing allylic silanes and aldehydes, so long as a matched system was used.[142]

One very interesting case reported by Lautens and coworkers achieved absolute stereocontrol through chiral induction with cyclohexyldiamino-based ligands on the silicon (equation 107). They began with a variety of epoxides which underwent Meinwald reaction to furnish aldehydes which served as the actual electrophiles. It was found that scandium triflate could effectively catalyze this reaction, providing good yields and excellent levels of enantiomeric excess.[278]

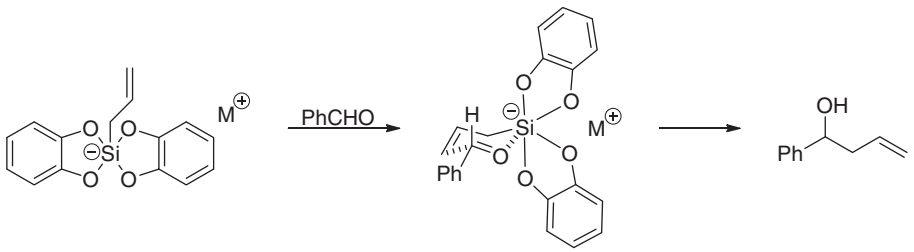


(107)

2.02.3.2.3 Hypervalent silicon – without absolute stereocontrol

As discussed in Section 2.02.2.1, silicon, when in possession of highly electronegative ligands, has an elevated partial positive charge, rendering it capable of Lewis acidity. Although this acidity is not high enough to readily affect allylsilation through either a Type-I or Type-II process, it is sufficient to increase the electrophilicity to the point that silicon will readily accept an additional ligand, producing a pentavalent species. Interestingly, this increase in valency is accompanied by a substantial increase in partial positive character, rendering the silicon center Lewis acidic enough to be capable of successfully affecting a Type-I process, wherein chelation from an electrophilic partner such as an aldehyde is highly favorable. Most typically, the additional ligand found on the silicon centers are fluorides, which come as a result of the addition of additives such as tetrabutylammonium fluoride (TBAF) or alkali/alkaline earth fluorides.

Similar to the ability of fluoride ion in catalyzing this reaction, other pentavalent siliconate species have been found to be capable of similar reactions. Most especially, allylic silanes, when reacted with 2 equivalents of bidentate ligands such as catechol in the presence of amine bases, provide pentacoordinate allyl silicates which readily undergo allylsilation of aldehydes.[4b] For example, Sakurai and coworkers have demonstrated that salts of allyldicatecholatosiliconates readily react with aldehydes to furnish the expected homoallylic alcohols (equation 108). This occurs entirely without assistance from the countercation. As the mechanism of this reaction is now changed into a Type-II process, wherein a six-membered, Zimmerman–Traxler argument is now used to describe the transition state of the process, it can be expected that generally better diastereomeric ratios will be obtained with these processes.

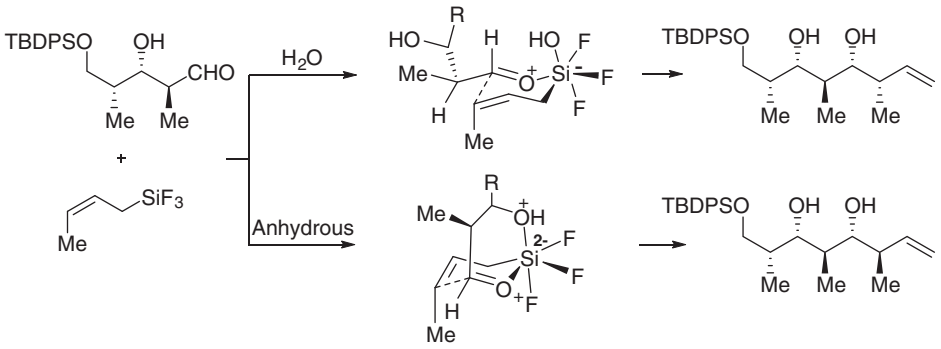


(108)

This procedure has now been generalized, and several aspects of these systems are now well understood.[218a,279] For example, such allyl silicates, unlike their allylboron relatives, do not react with nitro- or cyano-compounds under typical laboratory conditions.[280] It has also been demonstrated that the reactions can be promoted with a variety of ligands, including fluorides, alkoxides, and certain polar, aprotic solvents.[281] It has been further demonstrated that the more electron-withdrawing the ligands which are attached to the silicon, the more reactive the allylating agent, with allyldiaryloxysiliconates being completely inert.[282]

This method has been used as a means to incorporate several synthetically interesting and pharmacologically important functionalities into molecules, such as α,α-difluorocarbinols[43] and trifluoromethyl groups.[79]

A consequence of the Type-I transition state for the hypervalent allyl silicates is the fact that there is now a stringent relationship between the starting material's geometry and the resulting product's diastereoisomerism. Just as with other metals/metalloids such as boron, which do proceed through a Type-I process, an *E*-stereochemistry will furnish the *anti*-isomer, whereas the *Z*-olefin will give the *syn*-product. This maintenance of stereochemistry is especially important for these hypervalent silicon processes, but it can be interrupted if needs be. For example, the use of *Z*-crotyltrifluorosilane, on interaction with a β-hydroxyaldehyde, allows for the formation of the chelate complex, which undergoes the same basic reaction.[283] The chelation of the additional alcohol, however, was shown to force the fabrication of an *anti*-product. By simply adding a small amount of water to block the internal chelation, the bicyclic transition state could not be attained, and the normal pathway leading to the *syn*-product occurred (equation 109).



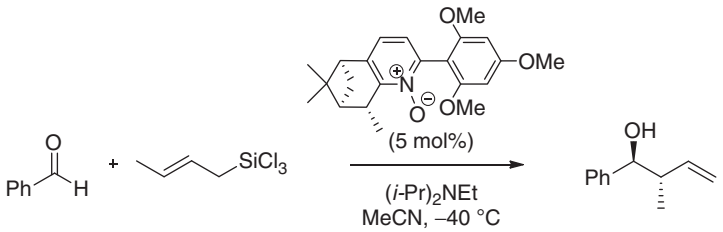
(109)

Ever since the initial report by Kobayashi detailing that polar, aprotic solvents could form the hypervalent allyl silicates through chelation, there have been investigations of different potential ligands based on such chelates as *N*,*N*-dimethylformamide, hexamethylphosphoramide, and *N*-oxido compounds. For example, Bergbreiter and Ortiz-Acosta have reported on the use of

polymer-supported pyridyl *N*-oxides as recyclable catalysts that can catalyze these reactions in nearly quantitative yields and with almost full recyclability (determined by several reaction-recovery iterations).[284]

2.02.3.2.4 Hypervalent silicon – with absolute stereocontrol

As expected, the extension of this methodology to include asymmetric allylations has been developed. *N*-oxides have proved to be highly effective at affecting this reaction in a chiral manner. For example, one report of an asymmetric, pinane-derived pyridyl *N*-oxide-derived bidentate compound has been shown to offer nearly quantitative yields and excellent enantiomeric ratios when promoting the reaction of stereodefined trichlorocrotylsilanes with aldehydes (equation 110).[285]

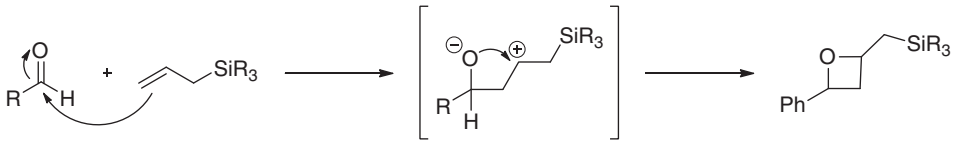


(110)

Other reports with *N*-oxides, including those derived from dipyridyl *N*,*N*′-dioxides, have had only limited success, generally offering either excellent isolated yields or enantiomeric ratios, but rarely both.[286] Chiral diols, such as those derived from BINOL and tartrates have been used, but have also not had spectacular success,[215,287] as is the case for bis(oxazoline)-based ligands.[288] Chiral silanes have also been shown to function without difficulty in this reaction, and do offer a complete transfer of chirality to the final products.[289]

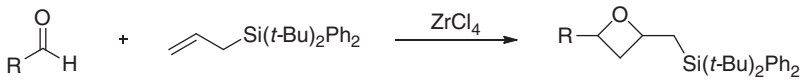
2.02.3.2.5 Net [2+2] annulation

In general, net [2+2] annulation reactions (equation 111) occur most readily from the reaction between α,β-unsaturated carbonyl compounds and allylic silanes, so a more complete discussion of them is given in Section 2.02.3.6.1. Furthermore, for those times in which such annulation reactions can occur, 1,2-sila-Wagner–Meerwein shift is usually the preferred route, which end up resulting in a net [2+3] annulation in place of the [2+2] route. To the best of the authors' knowledge, there is only a single report of a [2+2] annulation reaction with aldehydes. It should be pointed out to the reader that silanes with labile ligands generally cannot be used for these reactions, because in the absence of a nucleophilic species that affects the silyl elimination (to formally furnish the Hosomi–Sakurai product), the alkoxide ion that has resulted from the allylation step is capable of displacing one of these ligands. As such, only silicon moieties with four carbon-based ligands are used in these reactions, thereby necessitating the use of the Lewis acid-promoted allylation pathway. This generally precludes the possibility of using hypervalent siliconate species in this reaction.



(111)

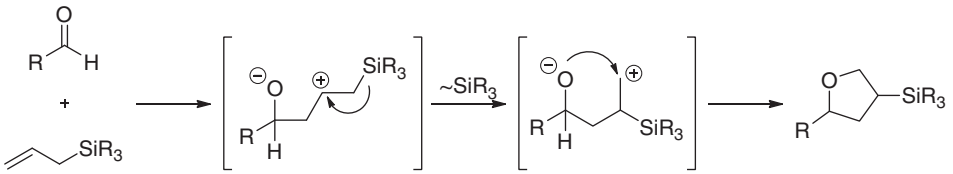
In one report (see Section 2.02.3.2.6 *vide infra*), it was showed that stoichiometric amounts of zirconium tetrachloride could successfully affect the desired [2+2] annulation reaction.[290c] They also demonstrated that the use of the bulky di-*t*-butylphenylsilane group optimized the annulation pathway, and that the reaction could proceed at subambient temperatures (equation 112). Unfortunately, in no cases were both the isolated yields and diastereomeric ratios especially high. The net result of this reaction is the thermal equivalent of a Paterno–Büchi reaction, wherein 2,4-disubstituted oxetanes are produced from an activated alkene and an aldehyde.



(112)

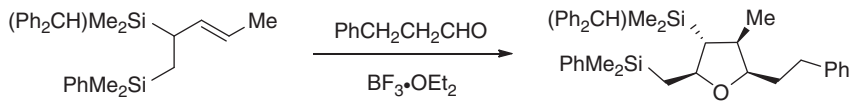
2.02.3.2.6 Net [2+3] annulation

In adding to aldehydes, allylic silanes can readily undergo a 1,2-sila-Wagner–Meerwein shift, followed by an annulation reaction in place of elimination (equation 113). Although this type of reaction is far more common than the [2+2] annulation reaction discussed in Section 2.02.3.2.5, it is still less common than those observed with α,β-unsaturated systems.



(113)

In one example, Peng and Woerpel demonstrated that an allylic silane, on reaction with hydrocinnamaldehyde, could furnish the [2+3] annulation product in nearly quantitative yield through the catalytic promotion of boron trifluoride (equation 114).[72] The alkylsilanes which result from these reactions are usually quite stable, and can be carried for some time through a synthesis.[181,184a] Usually, they are oxidatively removed under Kumada–Fleming–Tamao oxidation conditions (*vide infra*). Reactions of this type using enantioenriched allylic silanes have also been performed with arabinose derivatives, although the products were initially misidentified as the [2+2] annulation products.[290] One very interesting report came from Angle and Choi, in which an α-hydroxyaldehyde, which was O-protected with a labile triethylsilyl group, when subjected to [2+3] annulation conditions, could result in carbocation capture by the silyloxy group, after the initial 1,2-sila-Wagner–Meerwein rearrangement.[291] Other oxidations have also been developed as modifications of these procedures.[292]



(114)

2.02.3.2.7 Net [2+4] annulation

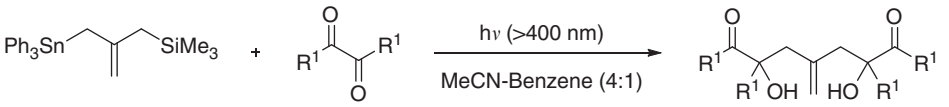
Quite similar to that which is discussed in the immediately preceding section, Angle et al. have shown that the use of β-hydroxyaldehydes, when O-protected with the labile triethylsilyl group, can again effectively capture the post-1,2-silyl-Wagner–Meerwein-formed carbocation/siliranium ion, resulting in what is a net [2+4] annulation reaction, wherein a 4-hydroxy-2-(silylmethyl)tetrahydro-2*H*-pyran is produced.[293] Unfortunately, there has been little further development with this reaction, possibly due to the fact that the products are produced in variable yields (14–62%).

2.02.3.3 Allylation of Ketones

2.02.3.3.1 Without absolute stereocontrol

By comparison with aldehydes, there have been far fewer reports detailing the allylsilation of ketones. Generally, in accord with the known reactivity differences of aldehydes and ketones, the reactions of the latter with allylic silanes tend to be slower and lower yielding than their aldehydic counterparts. All of the models and rules that apply in determining the stereochemical outcome of the addition to aldehydes can also be applied to ketonic carbonyl compounds.

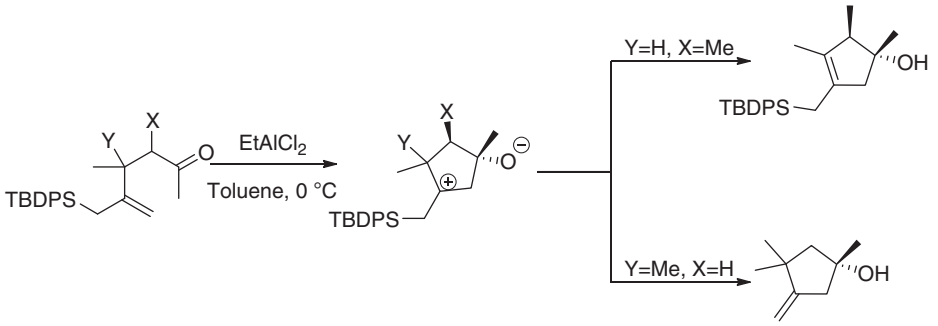
Unlike the addition to aldehydes, the addition to ketones has also been studied under conditions of photocatalysis, proceeding through a radical mechanism. For example, bisallylating reagents, wherein the two metals are silicon and tin,[294] can undergo a bisallylation with highly activated diketones to furnish the bisallylated products in varying yields (equation 115).



(115)

Aside from this photochemical route, there are few differences between the reactions of allylic silanes with ketones and those with aldehydes. For example, Lewis acids such as titanium tetrachloride are still used.[295] One major difference is seen in the reactions of hypervalent silicon-derived allylic groups: they generally react with ketones quite sluggishly or not at all, except for those ones which can perform a pendant chelation to silicon (e.g., α- or β-hydroxyketones), thereby forming an octahedral environment around it,[296] or with highly activated ketones such as 1,2-diones.[297]

Similarly, the intramolecular allylsilation of ketones has been performed; expectedly, it is an easier process than intermolecular ones. One especially interesting case was reported by Pulido and coworkers, in which the allylation of a ketone took place intramolecularly to form a cyclopentanol moiety.[298] With the given rearrangement, there was little thermodynamic incentive for a sila-Wagner–Meerwein rearrangement to take place, so no silatropic shift was observed. However, when a vicinal hydrogen was present, elimination took place to furnish a new allylic silane functionality (equation 116, top pathway); in the absence of such a hydrogen, no elimination was possible, so a more typical S_E2' reaction took place, furnishing the *exo*-methylidenylcyclopentanol observed (equation 116, bottom pathway). It should be noted that an alternative reaction mechanism could account for the product formed from the pathway. Specifically, an Alder–ene pathway would furnish the observed product directly, and would explain why no elimination of the hydrogens that would have been beta to both the alcohol and carbocation took place. Such a distinction is important, as the Alder–ene reactions of allylic silanes have been documented in a number of cases (*vide infra*).



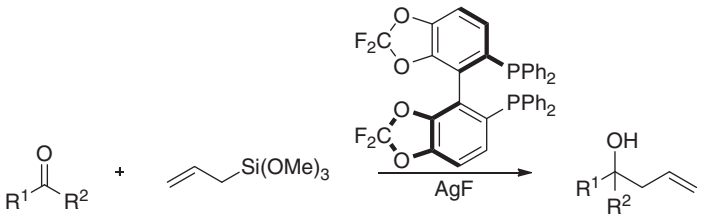
(116)

The reactions of allylic silanes with simple ketones have been reported on a number of occasions, in each case only readily occurring with intramolecular examples. Cyclobutanols have been produced in this manner,[228] as have a variety of spiro- and fused bicyclic compounds.[166,206a,299]

2.02.3.3.2 Absolute stereocontrol

There have been very few reports of the asymmetric allylation of ketones with allylic silanes. Just as with other asymmetric additions, the use of a chiral electrophile has been attempted. For example, the use of pyruvates with chiral ester groups can provide modest levels of enantioenrichment, when the addition is catalyzed with titanium tetrachloride.[300] There has also been some advancement in the use of β-hydroxyketones for the asymmetric allylsilation reaction. The use of chiral 1,2-diaminocyclohexane-based ligands on the silicon has been shown to allow for the achievement of good levels of stereoinduction. Unfortunately, such reactions are incredibly limited in their scope.[296]

Quite recently, Yamamoto and coworkers have reported on the use of a silver(I) fluoride-promoted reaction of allylic trimethoxysilanes with a wide variety of ketones.[301] The use of chiral tetrafluorinated 2,2'-bis(diphenylphosphino)-1,1'-biphenyl derivative was shown to provide superb levels of enantiomeric excess and generally excellent yields (equation 117). However, the evidence collected thus far is indicative of the *in situ* formation of an allylic argentate species. If this is indeed the case, then there would still remain no highly general asymmetric allylsilation reaction of ketones.



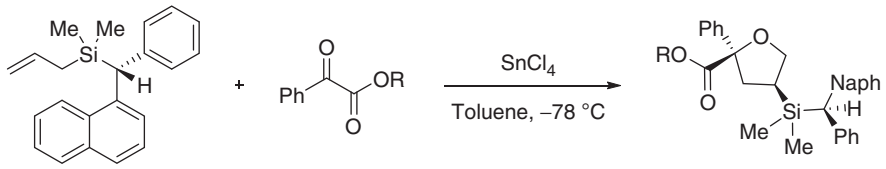
(117)

2.02.3.3.3 Net [2+2] annulation

To the best of the authors' knowledge, there is only a single report which described the use of ketones for the formation of oxetanes from allylic silanes. Akiyama and Kirino, when investigating the course of [2+3] annulation reactions,[302] discovered that allyl-*t*-butyldiphenylsilanes, under conditions of titanium tetrachloride catalysis, underwent a very smooth [2+2] annulation reaction with α-ketoesters. Unfortunately, little generality of the reaction was presented, but it nonetheless demonstrated that the annulation of ketones could indeed occur.

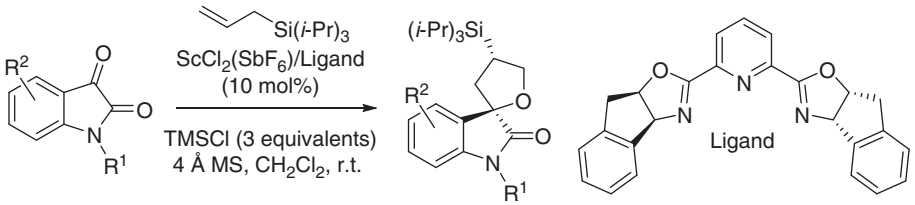
2.02.3.3.4 Net [2+3] annulation

Again, the lower reactivity of ketones has resulted in far fewer reports of [2+3] annulation reactions being published than has been for aldehydes. Akiyama et al. have provided much of what is known about this particular subject matter. They have published a series of papers which detailed the use of tin tetrachloride serving as an effective catalyst for [2+3] annulation reactions of α-ketoesters. These strongly activated ketones are transformed in excellent yields and diastereoselectivities. It was shown, in agreement with that which was discussed in Section 2.02.2.3, that an increase in the steric bulk of the silane resulted in a suppression of the elimination pathway, and an increase in the proportion of reaction that occurred through the [2+3] annulation route.[303] Since then, an asymmetric version of this reaction has been published, wherein the chirality is transferred from the starting silane (equation 118). There was no degradation of the absolute stereochemistry in the reaction.[304] Similarly, Micalizio and Roush have taken advantage of chiral allylic silanes in their partial synthesis of pectenotoxin II.[305] In a different but very interesting case, Peng and Woerpel utilized a kinetic resolution as a means of controlling the relative stereochemistry of a [2+3] annulation reaction during the course of the total synthesis of citreoviral and its 5-*epimer*.[306]



(118)

Much more recently, it was reported by Franz and coworkers that complex salts produced *in situ* from the interaction of scandium(III) chloride, silver(I) trifluoromethylsulfonate, and trimethylsilyl chloride, on chelation of certain pyridyl-derived PyBox ligands, can induce nearly flawless levels of enantiopurity into the reaction to produce the [2+3] annulation products of allyltriisopropylsilane and isatin derivatives (equation 119). The products, which were mostly obtained as a single enantiomer, were produced in good-to-very good yields. Again, this reaction is limited to the use of isatin derivatives only.[307]

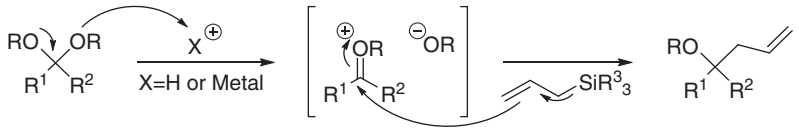


(119)

2.02.3.4 Allylation of Oxycarbenium Ions

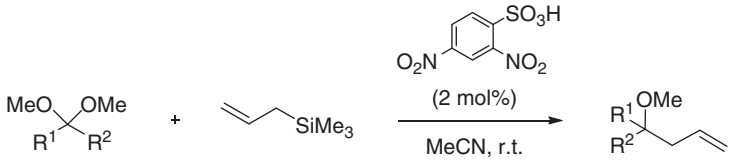
2.02.3.4.1 Intermolecular – without absolute stereocontrol

The reactions of a wide variety of oxycarbenium ions with allylic silanes have been described to date in the literature. In general, the reaction occurs through the Brønsted–Lowry or Lewis acid-assisted decomposition of an acetal or ketal group to form an alkylated carbonyl compound (equation 120). It is this compound that is actually attacked by the allylic silane in a Type-I process. The acid additive is used only to produce the oxycarbenium ion, which is already an activated species; it does not further interact with it during the allylation stage.



(120)

There have been many examples of Brønsted–Lowry acid catalysts serving to promote these reactions. Stereochemically, they can generally be treated as aldehydes, providing the *syn*-products, regardless of the stereochemistry (if present) in the allylic silane. In one example, Kampen and List demonstrated that 2,4-dinitrophenylsulfonic acid could effectively catalyze the reaction of simple allylic silanes with a wide variety of aliphatic and aromatic acetals and ketals (equation 121). A wide range of functionalities could be tolerated, including ethers, nitriles, and esters. The reactions generally proceeded in very high yields, and were completed within a few hours at room temperature.[308] Similarly, other acids have been used for these types of reactions,[309] including trifluoromethanesulfonic acid,[310] disulfonimides,[311] and trifluoromethanesulfonium tetrakis(trifluoromethylsulfonato) boronate.[312]



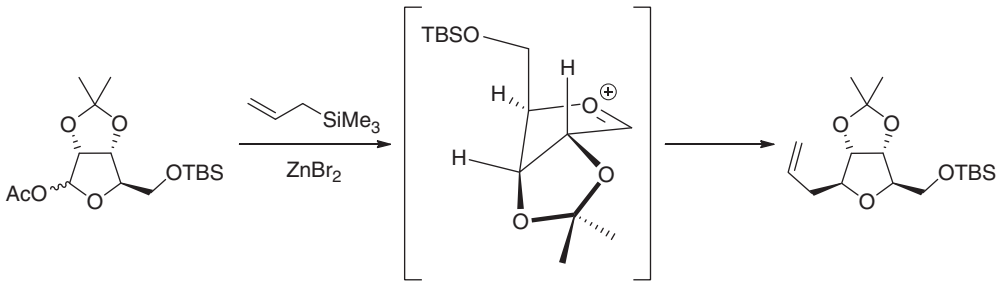
(121)

Lewis acids have become especially prominent in use for affecting this conversion. Probably due to the wide variety of properties and chemoselectivities that can exist with transition metal catalysts, there has been a far greater amount of research into their use than into that of protic acid catalysis. At this point, a very wide range of catalysts have proved effective, including titanium (IV) chloride,[313] boron trifluoride,[194,313g,h,314] tin(IV) halides,[314g,h,315] aluminum trichloride,[313g] indium(III) salts,[316] scandium (III) trifluoromethanesulfonate,[313g,317] trimethylsilyl halides and trifluoromethanesulfonates,[313a,318] and some less common ones, including rhenium complexes,[319] silica-alumina,[320] and cuprous bromide under microwave conditions.[321] They have been used in many simple additions, and also in more complicated ones, such as in the reaction of 1,2,4-trioxolanes (an acetal or ketal)[315a] and in the reaction of 1,3-catecholate acetals and ketals to perform diallylations.[313e] Silacyclohexenes have been successfully used in this reaction,[314b] as have allylic disilanes.[194]

Squaric acid esters, which are readily alkylated on the carbonyl oxygens, thereby forming oxycarbenium ions, can react with allylic silanes in reasonable yields.[322] Similarly, vinylic esters can also be alkylated, and undergo ready allylation.[323] The reaction with oxycarbenium ions formed from orthoacetates has also been reported.[324]

2.02.3.4.2 Intermolecular – with absolute stereocontrol

Surprisingly, the intermolecular reaction of oxycarbenium ions with allylic silanes occurring in an asymmetric fashion has been scarcely reported. The only reports which have been published all obtain chirality through the use of chiral substrates, from which are generated the oxycarbenium ions of interest. In one case, Wilcox and Otoski reported that ribose-derived 2-acyloxytetrahydrofurans could readily undergo allylation at the anomeric position with the use of catalytic zinc bromide (equation 122). The use of other, stronger Lewis acids such as boron trifluoride was incompatible with the sensitive acetonide and silyloxy functional groups, resulting in the degradation of the starting materials.[325] The stereochemical outcome is readily understood when considering that the fused bicyclic compound is nearly locked into a conformation that prevents an *endo* attack onto the oxycarbenium ion, thereby necessitating the formed 2,5-*cis* stereochemical relationship.

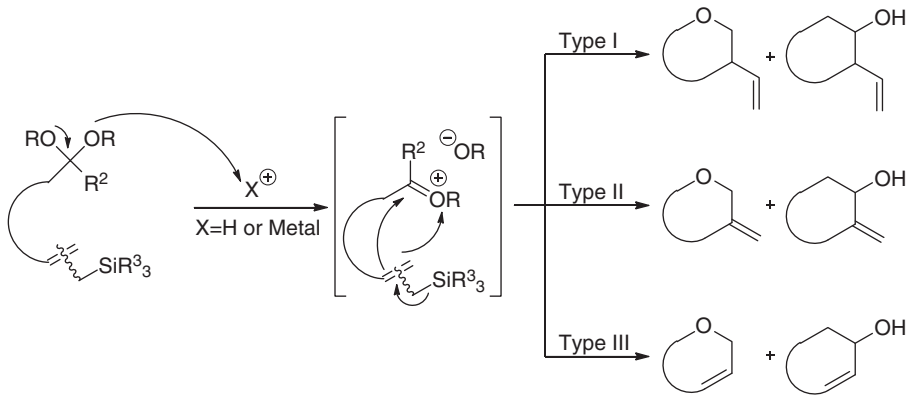


(122)

Other sugars have also been used as a means to control the absolute stereochemistry in such allylation reactions.[112a,326] Additionally, the use of an enantiopure silanol, in conjunction with Lewis acid catalysis, has been shown to generate mixed alkoxy silyloxy ketals *in situ*, generate oxycarbenium ions in turn that can be successfully allylated.[327]

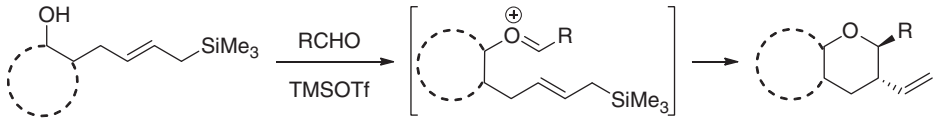
2.02.3.4.3 Intramolecular – without absolute stereocontrol

The intramolecular reaction of allylic silanes with oxycarbenium ions is, due to entropic reasons, a more facile reaction than those that are performed intermolecularly, but are less well studied. The reactions shown in equation 123, when the silicon is replaced with a hydrogen atom, are known as intramolecular Prins reactions, and can proceed in any of the three fashions shown. The cyclic ethers are obtained in the case of attack when the oxycarbenium ion is part of the ring (*endo* attack), and the alcohols are obtained when the oxycarbenium is outside of the ring (*exo* attack). When the silicon atom is present, however, these reactions, which are many times referred to as intramolecular silyl-Prins reactions in the literature, occur far more rapidly due to the increase in nucleophilicity of the alkene as discussed in Section 2.02.2.3. They are simply Hosomi–Sakurai reactions of alkylated carbonyls. The methods of generation of these carbonyls are the same as for the intermolecular compounds.



(123)

Most commonly, the ring systems that are produced through these means are either furan or pyran derivatives. For example, Kjellgren and Szabó have reported on the production of a series of monocyclic and fused, bicyclic tetrahydro-2*H*-pyran derivatives through a Type-I Prins process (equation 124). Utilizing trimethylsilyl trifluoromethanesulfonate as a Lewis acid, the alcohol reacts with the aldehyde to produce the hemiacetal. This hemiacetal can react further to produce either a full acetal functionality, which decomposes under catalytic conditions to form an oxycarbenium ion, or can decompose directly (from the hemiacetal form) into the same. Allylsilation then provides the tetrahydropyrans in good yields.[328] The 2,3-*trans* relative stereochemistry is produced as a result of Zimmerman–Traxler-type transition state, wherein the lowest energy conformation places the two groups in the pseudoequatorial positions.



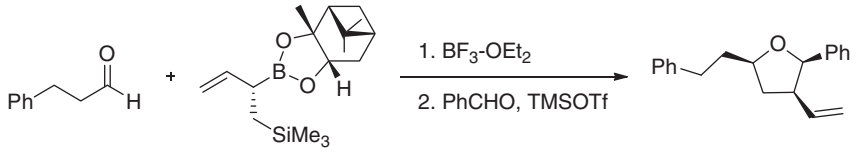
(124)

There are countless reports in the literature of such cyclization reactions. They have been used to produce a wide variety of ring types and sizes, and have incorporated heteroatomic functionalities as well. For example, tetrahydro-2*H*-pyrans,[329] dihydro-2*H*-pyrans,[195b] tetrahydrofurans,[81c,330] piperidines (from iminium species),[331] and spirocyclic compounds[332] have been reported on many occasions.

2.02.3.4.4 Intramolecular – with absolute stereocontrol

Such cyclization processes can also be made to occur with a complete control of the stereochemistry. As oxycarbeniums are not Lewis basic, and therefore are nonchelating species, they cannot generally coordinate into a Lewis acid, thereby preventing chiral induction through such means. Those few reports which have appeared are believed to occur through other mechanistic variants, such as back-chelation into the oxycarbenium ion, which effectively blocks one side of the cation.[333] As a consequence, nearly all reports of chiral control in these cyclizations have detailed the use a conferred chirality, starting with a chiral allylsilane, or with additional chiral centers proximal to the oxycarbenium ion.

In one such example, Sivasubramaniam and Hall detailed the use of a chiral double metallating reagent to affect the allylboration of an aldehyde, thereby providing a chiral homoallylic alcohol.[334] Subsequent treatment with an aldehyde and Lewis acid then produced an oxycarbenium ion *in situ*, which reacted via a Type-I Prins process, furnishing the 5-(3,5)-tetrahydropyran product in good overall yield, and excellent all-*cis* stereochemistry in 91% total enantiomeric excess (equation 125).



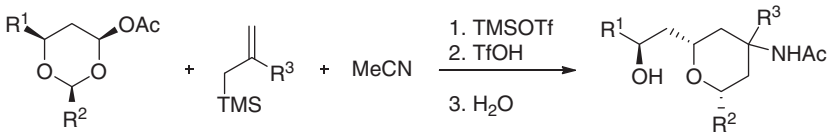
(125)

Ito and coworkers have described the use of chiral allylsilanes (derived from chiral allylic alcohols by the methodology discussed in Section 2.02.3.1.4) as a means to produce chiral oxepanes through a Type-I process (a 7-(3,5)-Prins methodology) through the trimethylsilyl trifluoromethanesulfonate-catalyzed methodology of the reaction of an alcohol with an aldehyde. The resulting oxepanes are produced in very good yields and with nearly complete stereoconservation.[335] The use of sugars to obtain chirality control has also been performed.[336] Such a strategy of the intramolecular allylation reaction of oxycarbenium ions with absolute stereocontrol was demonstrated nicely in the total synthesis of leucascandrolide A by Kopecky and Rychnovsky,[117b] and by Ley and Kouklovsky in a partial synthesis of rapamycin.[337]

2.02.3.4.5 Noteworthy allylation reactions of oxycarbenium ions

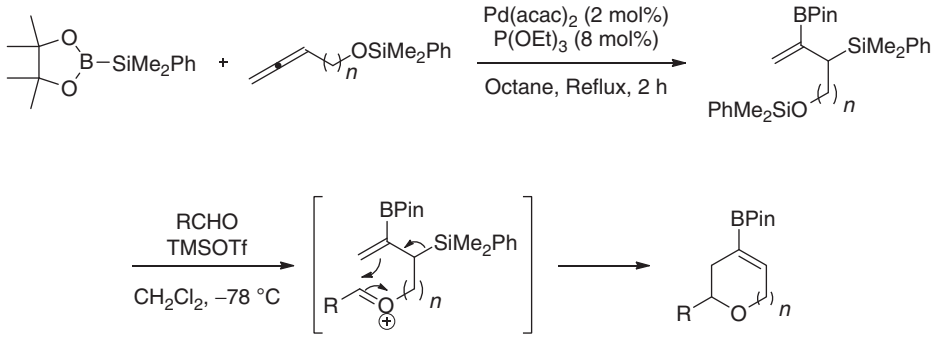
There have been several different reactions involving oxycarbenium ion allylsilations that are especially interesting and therefore deserve special mention. These reactions typically involve unusual rearrangements or cascades, or offer access to unusual or highly functionalized moieties.

Epstein and Rovis published an unusual allylsilation reaction of a bisacetal. This reaction proceeded under trimethylsilyl trifluoromethanesulfonate catalysis.[338] The more reactive *exo*-acetal reacted first, providing an oxycarbenium ion which was allylated in a normal Hosomi–Sakurai manner. A second oxycarbenium ion was then produced, which underwent a formal 6-(1,5)-Prins reaction, generating a carbocation. The carbocation is then captured by an acetonitrile additive, which is hydrolyzed *in situ* to an amide (a Ritter reaction). The multistep cascade is formally a [Hosomi–Sakurai]-[6-(1,5)-Prins]-Ritter reaction cascade. The final products were produced in excellent yields and with nearly perfect 2,6-*cis* diastereomeric ratios (equation 126).



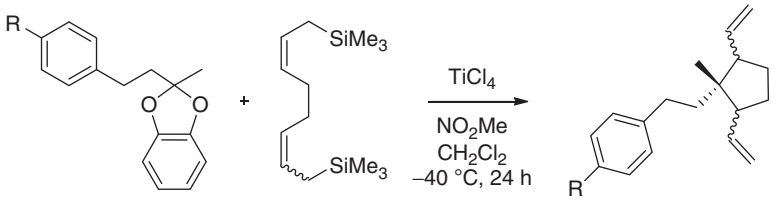
(126)

Suginome et al. reported a Lewis acid-promoted allylsilation reaction of acetals with allylsilanes that carried a vinylboronate functionality as part of the olefin (equation 127). The oxycarbenium ion generated was cyclized by attack of the allylsilane functionality, resulting in the final vinylboronate species.[339] This olefin could also be used in a 6-(1,5)-Prins reaction, wherein the carbocation was captured in a Friedel–Crafts manner. The products of these reactions were obtained in very high yields and without any olefin stereoscrambling.



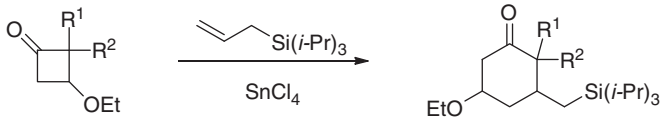
(127)

Santelli and coworkers have developed their BISTRO molecule, and have applied it in the allylsilation of acetals and ketals. They have shown that cyclic acetals and ketals, when reacting under conditions of titanium tetrachloride catalysis, can be made to give diallylated cyclopentane products.[340] For example, dialkyl ketals can provide some highly functionalized cyclopentane functionalities possessing a quaternary stereocenter (equation 128). Unfortunately, the control of both the relative and absolute stereochemistry remains difficult; currently, the 2,5-divinyl groups are obtained in a mostly *trans*-relationship.



(128)

Matsuo et al. reported a very interesting reaction of cyclobutanone derivatives. Using tin tetrachloride, chelation by the ketone drastically increases the reactivity of the ring system. Donation of a lone pair from the etheric oxygen opens the ring, resulting in an oxycarbenium ion, bearing a positive charge on the said oxygen. Allylation of the oxycarbenium ion, followed by attack of the enolate onto the incipient carbocation, results in an expanded cyclohexanone ring system (equation 129). These reactions generally proceeded in excellent yields, and furnished roughly 3:1 diastereomeric ratios.[341]



(129)

2.02.3.5 Allylation of Imines

2.02.3.5.1 N–*H* and N–*C* imines

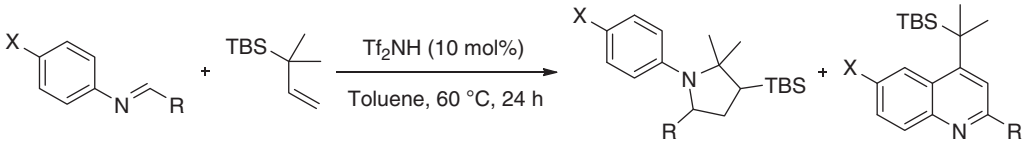
The allylsilation of imines is well known, and can proceed in a variety of different manners. Due to the enhanced nucleophilicity of nitrogen as compared to oxygen, the resulting aza anion is more willing to undergo further reactions. As a result, cyclization processes ([*n*+*m*] annulation reactions) are more commonly observed in comparison with allylation reactions than they are for carbonyl-based substrates. Just as with their carbonyl-based counterparts, larger silyl groups encourage annulation reactions, whereas smaller silyl groups promote Hosomi–Sakurai allylations.

Simple free imines and carbon-based imines (Schiff bases) react with allylsilanes under Lewis acid catalysis. Brønsted–Lowry acids are infrequently used for these reactions, as both the imines and (especially the) resultant amines are basic, and the use of these catalysts would result in their consumption and therefore a decrease in catalytic activity. Additionally, the generally lower reactivity of imines by comparison with that of carbonyls has resulted in a decrease in the number of reports of successful imine allylations.

There have been several reports on the use of different catalysts for imine allylsilation. For example, Fernandes and Yamamoto described the asymmetric allylation of imines with a tetraallylsilane system, which was promoted by a TBAF/methanol system.[342] Chiral formamides,[343] carbohydrates,[344] and asymmetric allylpalladium species[345] have been used to control the absolute stereochemical outcome of these reactions. Leighton and coworkers have also reported a convergent approach to such allylation, which integrates a cross-metathesis reaction as a means to produce complicated allylsilanes directly before their use in imine allylation.[346]

As the annulation reactions of these imines are facile, a number of reports have appeared describing their occurrence. In a rare case of a protic acid-catalyzed reaction, triflic imide was shown to effectively catalyze the allylation of *N*-aryl imines in generally good yields (equation 130). The main product of this reaction was the desired pyrrolidine, but small amounts of the quinoline

were also obtained. The latter resulted from the Friedel–Crafts alkylation after the allylation, followed by oxidation.[105] The [2+4] annulation reaction of *N*-aryl imines has also been described as a means to furnish tetrahydroquinolines.[347]

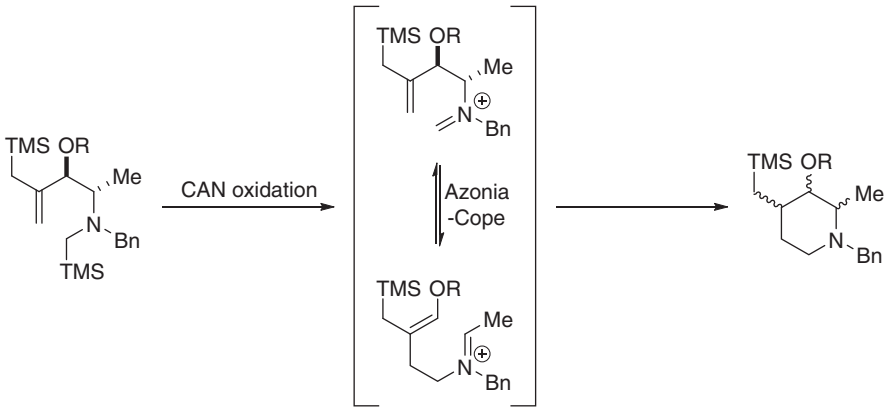


(130)

2.02.3.5.2 Iminium ions

For the allylation of iminium ions, the requisite ions are usually produced *in situ* from the collapse of an aminal functionality. Quite frequently, the Mannich-type reaction of amines with formaldehyde under conditions of protic acids can give rise to iminium ions, which can be captured with allylic silanes with relative ease.[348] Other methods of generation include the direct decomposition of hemiaminals under acidic conditions, usually by reduction of amides or aromatic groups.[349] Thioaminals can also be decomposed to furnish iminium ions,[350] as can be α-haloamines.[351] Perchlorite iminium salts have also been used for this reaction.[352] The formation of an iminium ion by forced acylation has also been shown to serve as a means to sufficiently activate an imine for allylation.[353] They have also been generated through the direct oxidation of pyrrolidines.[354] The use of such allylation reactions of iminium ions in the context of total syntheses has been described on several occasions.[355]

One very unusual reaction involved the formation of an iminium ion through the oxidation of an α-silyl amine with a cerium (IV) oxidant (equation 131). On interaction with cerium(IV), the α-aminosilylmethylene unit is oxidized directly to an iminium ion. A pendant allylic silane was then able to capture the iminium ion, resulting in a reasonable yield of product. Unfortunately, a competitive azonia-Cope rearrangement was found to be competitive with the desired oxidative Mannich-type reaction, so stereochemical information was not well retained through the cyclization process.[231]

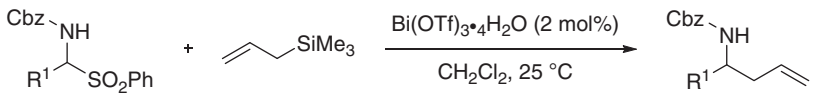


(131)

2.02.3.5.3 N–C(O)–X imines

The activation of imines through *N*-substitution is a means to greatly enhance the utility of the allylsilation thereof. For instance, the *N*-acylation of imines serves to activate the imine not only through the inductive and mesomeric effects but also by allowing the imine to serve as a formal Michael acceptor.

In one example, Ollevier and Li demonstrated that the use of a catalytic amount of bismuth(III) trifluoromethanesulfonate tetrahydrate could affect the formation of an imine from an α-amino phenylsulfone precursor.[356] The resulting species could undergo rapid reaction with allyltrimethylsilane, providing generally very good yields of the expected homoallylic amines (equation 132). The presence of the urethane group, which was responsible for the ready allylation of the molecule, has been used on several other occasions to facilitate similar allylations.[357] Carbamates have also been used with some frequency.[357a,c]

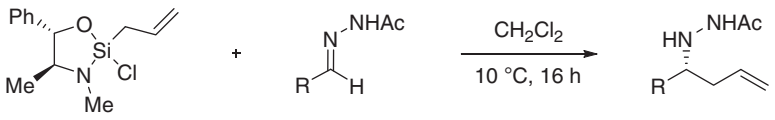


(132)

2.02.3.5.4 N–N imines

The use of hydrazone derivatives as allylsilane recipients has been reported on only a few occasions. Their use has been mostly limited to asymmetric reactions, wherein either a chiral silane or a chiral hydrazone derivative is used to induce asymmetry in the reaction (equation 133). For example, Leighton and coworkers have described the use of silanes with a chiral 1,2-aminol backbone

that serve as allylating reagents of hydrazone derivatives. The yields are generally very good, and the induced enantiomeric ratios are mostly high as well. There is no need for any Lewis acid, as a coordination to the silane by the hydrazonamide group is anticipated, thereby furnishing a pentavalent siliconate.[358]

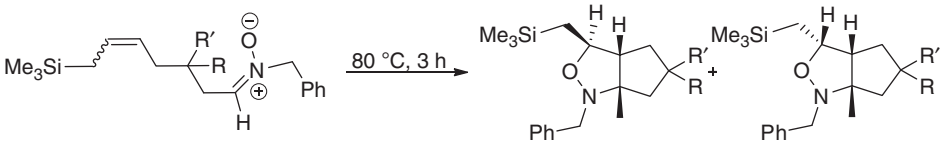


(133)

In aqueous media, zinc(II) fluoride is capable of acting as an efficient Lewis acid for the dual activation of α-alkoxycarbonylhydrazones. The reaction is believed to proceed through both the chelative activation action of zinc and with the fluoride ion activation of the allylic silane.[359] Still another report has been published, wherein dual activation is claimed through the combination of indium(III) trifluoromethanesulfonate Lewis acid activation and fluoride ion activation of tetraallylsilane.[360] It is postulated that the slightly enhanced polarizing effects of the allyl groups render the silicon Lewis acidic enough to accept an incoming fluoride ion. However, it is unclear that such an activation is actually taking place, as no apparent reaction between the fluoride ion and tetraallylsilane was reported by the authors based on NMR studies, and that the more highly Lewis-acidic silanes, such as those with alkoxides and chlorides for ligands, were not active in providing the desired allylation products.

2.02.3.5.5 N–*O* imines

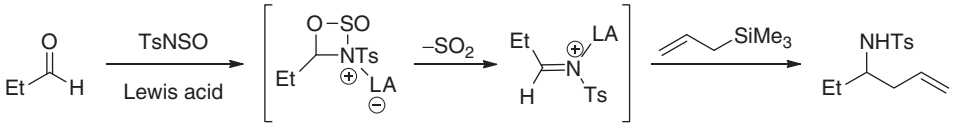
Nitrones have also been shown to be capable of being allylated by allylic silanes. Due to their strong propensity to act as 1,3-dipolar groups, they tend to undergo very rapid annulation in place of allylation. Unusual about them, however, is that, in addition to a formal allylation–annulation pathway, they might also undergo a direct [2+3] dipolar addition. In fact, [2+3] annulation reactions, wherein the silicon moiety migrates, are never observed for these reactions. Instead, 1,3-dipolar addition takes place more rapidly than does the allylation–annulation pathway. As such, isoxazolidines are the products formed from these reactions. For example, very good yields of such dipolar additions have been achieved by Arnold and Mohr (equation 134) and others.[103a,361] Dipolar additions to allylic silanes have also been described with analogous triazo compounds.[362]



(134)

2.02.3.5.6 N–*S* imines

There are almost no examples of the allylation of sulfonimides and their derivatives. One example published by Weinreb and coworkers[363] demonstrated that the use of a Lewis acid such as iron(III) chloride, in combination with allyltrimethylsilane, could furnish the allylated *N*-toluenesulfonamides in excellent yields (equation 135). Another example was published by Nair et al., in which a competition between allylation and Diels–Alder reactions was described.[364]



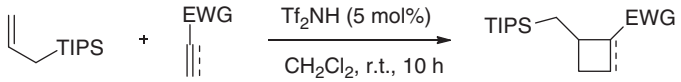
(135)

2.02.3.6 Allylation of α,β-Unsaturated Systems

2.02.3.6.1 Net [2+2] annulation

Historically, the first actual report of a [2+2] annulation reaction of allylic silanes was made by Santelli and coworkers, wherein they demonstrated that the titanium enolates formed by allylation of an α,β-unsaturated ketone partially cyclized, thereby resulting in a small amount of a cyclobutane derivative.[365] This was later challenged, but then proved accurate, as highly detailed studies demonstrated that the [2+2] annulation product is the kinetic one, and that, if conducted at higher temperature, the reaction would produce the thermodynamically preferred [2+3] annulation product.[366] In both cases, the use of sterically hindered ligands on the silane was necessary to ensure a high ratio of annulation product(s) to Hosomi–Sakurai product.

The addition of an allylic silane onto any α,β-unsaturated EWG (such as esters, nitriles, ketones, and aldehydes) can furnish ring systems such as cyclobutane or cyclobutene derivatives (equation 136). These reactions are almost invariably carried out by Lewis acid catalysis, again likely due to issues of protiodesilylation of the allylic silane. In one report by Ihara and coworkers, the use of triflic imide serving as a protic acid was reported in which a variety of substrates were shown to function adequately in this reaction.[367]



(136)

Since the initial report by Jellal and Santelli,[368] this methodology has been well developed, and has been shown to function with other Michael acceptors such as *α,β*-unsaturated amides[369] and quinones,[370] and has been shown to be dependent on a variety of factors such as remote steric effects[369] and the choice of Lewis acid.[371] Additionally, it has been demonstrated that the proper choice of starting materials and conditions can allow access to spirocyclic compounds,[372] fused [2.2.0]-bicyclic systems,[373] and fused bicyclic compounds containing *exo*-silylmethylidenylic groups.[368]

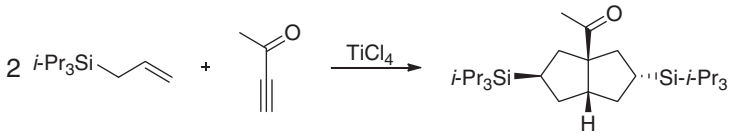
2.02.3.6.2 Net [2+3] annulation

As mentioned above, the [2+3] annulation pathway is that which forms the thermodynamic product of these reactions. By conductance at a slightly higher temperature than for those of the [2+2] annulation reactions, it is ensured that there be sufficient thermal energy to allow for the necessary 1,2-sila-Wagner–Meerwein rearrangement to proceed.

The stereochemical outcome of these annulation reactions has also been well studied, and it has been generally shown that the EWG tends to become oriented *trans* to the silicon group.[374] The explanation for this is simple: since the enolate needs to attack *anti* to the siliranium's C–Si bond(s) to access the antibonding orbitals, a backside attack is necessary. This necessarily places the silicon *anti* to the incoming enolate nucleophile, and 'pushes' the former downward on bond formation.

The same holds true for the formation of fused bicyclic compounds, of which there are a multitude of reports.[375] Although other controlling factors such as additional strain or steric requirements could potentially offset this propensity to form the *trans*-compound, it does not appear to happen readily. For example, even stereochemically rigid fused bicyclic compounds can react to form fused tricycles without violating this generality.[376]

There is one example, however, in which a one-pot process reported by Knölker and Graf violated this generality.[377] Although the first addition readily occurred to obtain the expected *trans*-relationship, the steric bulk of the first silyl substituent was so great that the second could not also be forced into a *trans*-relationship with the EWG. As such, the major diastereomer isolated possessed a *trans*-relationship between the two silyl groups (equation 137).



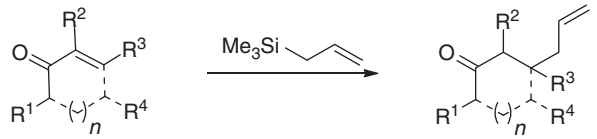
(137)

In cases wherein a bicyclic compound is being formed and the unsaturated moiety is *exo* to the ring, a spirocyclic compound is produced. In such cases, the *trans*-relationship between the EWG and the silyl substituent is still maintained.[378] The same holds true for intramolecular variants of this reaction.[379]

In some cases, O-alkylation can take place instead of the C-alkylation that is normally observed in these reactions. So, in the case of a five-membered ring, tetrahydrofurans would be obtained in place of cyclopentanes. The prospect of trapping the incipient carbocations with an oxygen is quite a difficult one, as the chelation by the oxygen to a Lewis acid usually prevents it from occurring. In the case of certain aromatic compounds, the driving force of aromatization can force such an O-alkylation. For example, the allylation of quinones can provide such an opportunity.[380] The use of amides, wherein *N*-alkylation occurs, has also been reported to occur readily on the attempted allylation of triazolinediones.[381]

2.02.3.6.3 Net Hosomi–Sakurai reaction

As a decrease in the steric requirements of the allylic silane's silicon portion typically allows for allylation reactions to occur instead of annulation reactions, most allylation reactions occur with the use of allyltrimethylsilane as the chosen allylating source. The use of many of the same Lewis acids, such as titanium(IV) chloride[382] or indium(III) chloride,[383] is typical. For example, the latter, which is believed to be the active agent produced by the reaction of indium metal and trimethylsilyl chloride, has been shown to facilitate such Hosomi–Sakurai reactions (equation 138).



(138)

Many different functional groups' Michael acceptor capabilities have been utilized for this transformation. For example, *α,β*-unsaturated nitro compounds undergo rapid allylation under Lewis acid catalysis,[384] as do malonate derivatives[385] and quinones.[386] The latter have also been produced *in situ* and reacted in a one-pot process under oxidative conditions.[387] Asymmetric versions of these reactions have also been reported.[388] *α,β*-Unsaturated acyl silanes have also been used as a masked carboxylic

acid functionality in such reactions.[389] This has been demonstrated through the allylation of functionalized steroidal systems such as in the synthesis of gonatetraenes by Santelli and coworkers.[390]

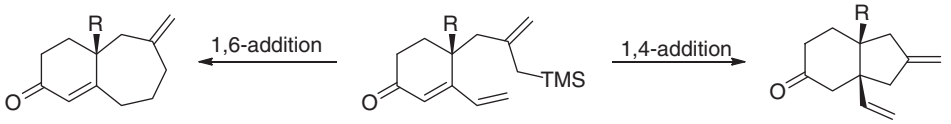
In those cases wherein the allylic silane system is tethered to the Michael system, a new ring system is necessarily formed. Usually, such ring systems are produced in higher yield than are the intermolecular variants.[173,391] Similarly, the intramolecular conjugative allylation of *endo*-α,β-unsaturated Michael acceptors results in the formation of a *cis*-fused bicyclic system, so long as the ring system being produced is of a favored size.[102d,392] There are no reports of the production of macrocycles in this manner. In certain cases, competitive 1,2-addition can dominate the given product distribution. A large amount of research effort has been put forth to address this issue, and it has been demonstrated that the use of different Lewis acids or promoters (such as fluoride ion) can result in drastic changes to the reaction outcome, both in terms of stereo- and regio(chemo) selectivity.[238,393]

The Nazarov cyclization of α-silylmethyldivinylic systems has been shown to be greatly accelerated by the presence of appropriately placed silanes. Instead of the normal cyclopent-2-en-1-one, however, α-methylenic ketones are generally produced, as a result of the more rapid elimination of the silicon functionality.[108a] The normal cyclopentenone-producing pathway of the Nazarov cyclization can also be trapped by allylic silanes in a similar way by an intermolecular variant.[394] A domino Hosomi–Sakurai–Schmidt reaction of cyclic enones to furnish lactams has also been reported.[395]

The modes of addition of reactions such as these cyclizations, or more generally, these conjugate allylations, normally take place through the Hosomi–Sakurai pathway of addition–elimination, but they can undergo a radical mechanism, so long as appropriate conditions for initiation are chosen.[396]

2.02.3.6.4 Addition to $\alpha,\beta,\gamma\delta$-systems

When an α,β-unsaturated system has a vinylic substitution at the β-position, a new mode of homologous conjugate addition, a 1,6-version, becomes possible. The exact mode of addition depends on the exact conditions and the choice of promoting agent, but typically a 1,6-addition is preferred.[203b,397] In one example, Majetich and coworkers have shown that Lewis acid catalysis favors a 1,6-addition pathway, whereas fluoride ion promotion favors a 1,4-addition (equation 139).[398] The utility of these 1,6-addition reactions has been demonstrated in their facile production of seven-membered ring systems, such as in the synthesis of *epi*-Widdrol.[399]

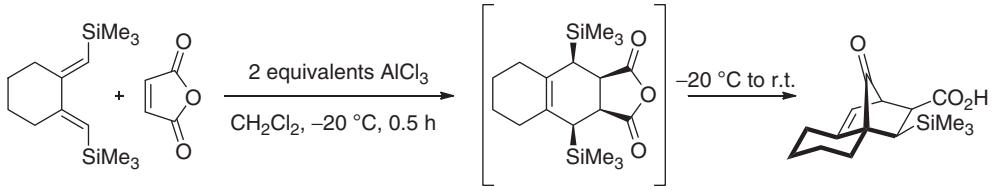


(139)

2.02.3.7 Allylation of Other Carbonyl Systems

2.02.3.7.1 Esters

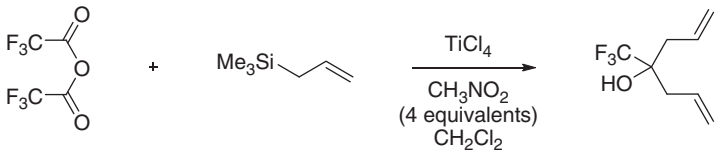
In general, esters are not highly reactive toward allylic silanes, except under very unusual circumstances, such as with very strong Lewis acids.[102b,400] In one reported case, a divinylic disilane was reacted in a Diels–Alder fashion, leading to an allylic disilane functionality. Under the harsh conditions of the reaction (catalysis by aluminum trichloride), the strong Lewis acid was also successful in promoting the intramolecular allylation reaction of the anhydride, thereby furnishing a carboxylic acid on workup (equation 140). Interestingly, the reaction did not proceed beyond the Diels–Alder stage without the added equivalent of Lewis acid. It should also be noted that, unexpectedly, the *exo*-product was obtained in this reaction.[170]



(140)

2.02.3.7.2 Anhydrides

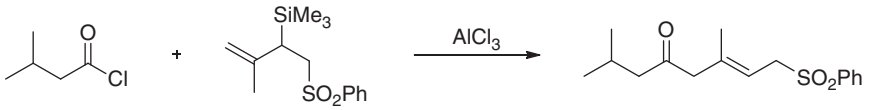
Just like esters, anhydrides are typically unreactive substrates for Hosomi–Sakurai reactions. When they do react, the reaction occurs beyond the intermediate ketone stage, arriving finally at the quaternary alcohol. For example, Santelli and coworkers[401] have shown that allyltrimethylsilane, on reaction with trifluoroacetic anhydride, provides 4-(trifluoromethyl)hepta-1,6-dien-4-ol in very good yield (equation 141). More reactive alkyl tellurinyl anhydrides can also react with allylic silanes under conditions of Lewis acid catalysis.[402]



(141)

2.02.3.7.3 Acid halides

In significant contrast, the allylation of acid chlorides with allylic silanes has been well studied. Typically, the reaction is promoted by strong Lewis acids such as aluminum(III)[128b] or titanium(IV) chloride.[76] In one such example, Fujita and coworkers[189] described the allylation of an acid chloride with a sulfone-containing allylic silane to furnish a ketone in high yield (equation 142). The allylation of acid chlorides was demonstrated in the total synthesis of heritonin by Silveira et al.[403]

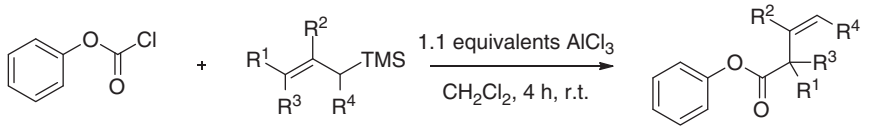


(142)

Intramolecular versions of this reaction have also been reported as a means to produce a variety of ring sizes.[108c,404] Additionally, the allylation of an unsaturated acyl chloride–iron complex has been reported as occurring in excellent yields.[405]

2.02.3.7.4 Chloroformates

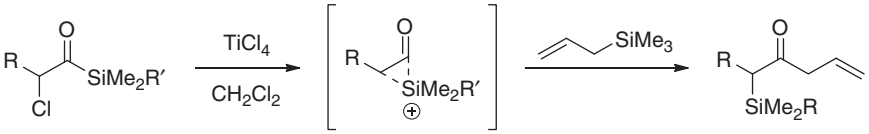
If the reaction of acid chlorides with allylic silanes is more facile than those of esters, then it is plausible that this is the result of the high Lewis basicity of the chloride atom, making possible the formation of an incipient acylium ion. It stands to reason then that chloroformates could also function as allyl group acceptors in a Hosomi–Sakurai process, so long as the chosen Lewis acid is not strong enough to result in the complete ionization of the acid chloride. Olah et al. have reported that aluminum(III) chloride can successfully promote the desired reaction in excellent yields (equation 143). Unfortunately, as alkyl chloroformates are completely ionized in the presence of strong Lewis acids, the use of aryl chloroformates is a must for this reaction, so the scope is somewhat limited.[406]



(143)

2.02.3.7.5 Acyl silanes

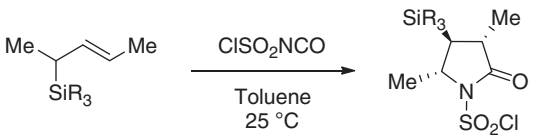
The use of titanium(IV) chloride as a means to affect the partial ionization of α-chloroacylsilanes has been reported by Horiuchi et al.[407] If considered to be truly ionized, then the resultant species is isoelectronic with respect to other β-silylic carbocations, and is therefore prone to undergo a 1,2-sila-Wagner–Meerwein shift to produce a more stable carbocation, should one exist. These acylsilanes do indeed undergo this rearrangement, as the product of the silyl shift is stabilized both by the β-effect of silicon and by the mesomeric effect of the carbonyl. It is this carbocation/siliranium/acylium ion that can be captured by an added allylic silane (equation 144).



(144)

2.02.3.7.6 Isocyanates

Isocyanates have been reported to react with allylic silanes, and do so to furnish chlorosulfonamide anions, which then undergo 1,2-sila-Wagner–Meerwein rearrangement.[408] This carbocation is then trapped by the sulfonamide, furnishing pyrrolidin-2-ones in excellent overall yield and diastereoselectivity (equation 145). The preferred relative stereochemistry for these products is the *trans*–*trans* one.[191,408]



(145)

2.02.3.8 Allylation of C=X Bonds (X=S, Se, etc.)

2.02.3.8.1 Thiocarbonyl compounds

The allylation of thiocarbonyl compounds has not been reported with great frequency. Twenty years ago, Degl'Innocenti and coworkers reported in one publication the results of their attempts at allylsilation of thioketones.[409] Interestingly, they showed that allylsilation occurs in a thiophilic manner, providing only the S-allylated products. Additionally, the reaction occurred not through the expected S_E2' reaction, but rather through a bond formation at the site of the silicon–carbon bond, which may be indicative of an S_E1 reaction mechanism. The evidences for this are in the fact that the reaction was promoted with fluoride ion, and that group substitution proved that an S_E2' reaction was not taking place.

2.02.3.8.2 Thionium ions

The bond polarization in favor of a sulfur atom in a carbon–sulfur double bond can be used as a means to ensure that C-allylation will take place, and not S-allylation. Thionium ions, which can be readily produced through the Lewis acid-catalyzed decomposition of dithioacetals and ketals[410] and α-halosulfides,[411] react exclusively at the thionyl's carbon atom, thereby producing homoallylic thioethers in generally very good yields.

An alternative approach to the allylation of thionium ion alkylation was reported by Westerlund, in which hydride abstraction with trityl tetrafluoroborate from 1,3-dithianes provided 1,3-dithienium tetrafluoroborate salts, which are thioester equivalents of thionium ions. Allylation thereof with a variety of allylic silanes proceeds in very good yields.[412]

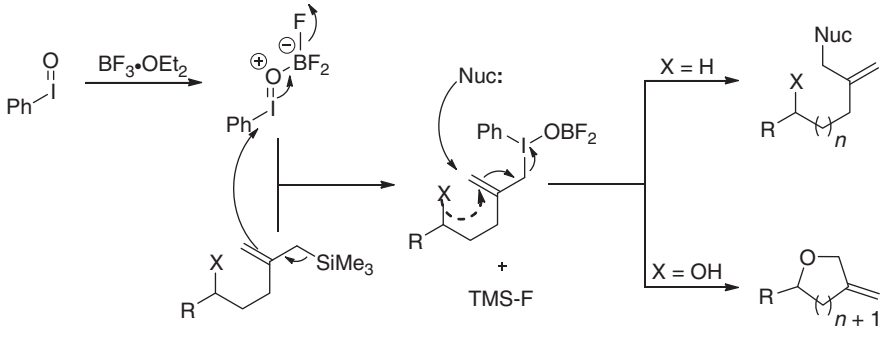
2.02.3.8.3 Selonium ions

Selonium ions ($C=Se^+$-R groups) are a highly underexplored class of ions that are seldom used in classical organic chemistry. It is perhaps not surprising then that very little work on their allylation has appeared in the literature. A report by Hermans and Hevesi described how diselenoacetals and ketals, by way of Lewis acid catalysis, are made to react to produce selonium ions. These can then be allylated in a manner analogous to oxycarbenium and thionium ions.[413] As selenols are moderately acidic[414] (pK_a values near 5) they are good-enough nucleofuges to be directly replaced with an allyl group, especially under conditions of Lewis acid catalysis. Indeed, overallylation is one problem that was reported, as was the formation of a small amount of alkyl silyl selenide by-product. Another report by Silveira et al. described the similar reaction of triselenoformates to form allylated diselenoacetals.[415]

2.02.3.9 Allylation of Other π-Systems

2.02.3.9.1 Iodosyl/iodine(III) compounds

Allylsilanes are believed to react with iodosyl compounds in the presence of strong Lewis acids such as boron trifluoride to produce a trivalent iodide species (equation 146). The olefin thus formed is then part of an allylic iodide system, and therefore has undergone an Umpolung inversion, as it is now in possession of a very powerful leaving group, iodobenzene. In the case of an internal nucleophile such as an alcohol, allylic displacement readily takes place to afford a cyclized product.[114] In the absence of an internal nucleophile, one added (nucleophile) can react to provide the displacement product.[416] The trivalent iodine species are such good leaving groups that even unactivated benzene can react in a Friedel–Crafts manner.[417] Additionally, iodosylbenzene has been shown to directly oxidize allylic silanes (again under boron trifluoride catalysis), replacing the carbon–silicon bond with a carbon–oxygen double bond. This furnishes enals directly from allylic silanes.[418] Other iodine(III) compounds have been shown to function as reducing agents, thereby facilitating certain substitutions such as a trifluoromethyl group in place of the silicon portion of allylic silanes.[419]



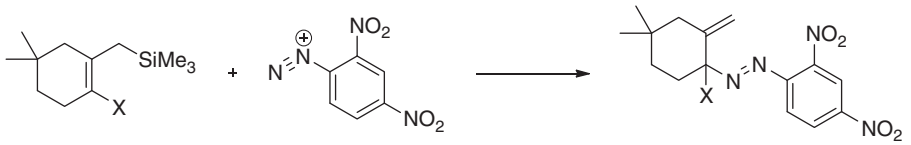
(146)

2.02.3.9.2 Alkylidenes

Titanium alkylidenes, which are believed to be produced from the reaction of titanocene(II)-derivatives with thioacetals and thioketals,[182b] react with allylic silanes through a metathesis reaction, and can furnish functionalized *E*- and *Z*-substituted allylic silanes in good yields. Thus, alkylidenes do react in a [2+2] manner with allylic silane species. Further evidence of this reactivity is seen in the successful metathesis with ruthenium[225] and molybdenum[223] species.

2.02.3.9.3 Diazonium salts

Diazonium tetrafluoroborate salts, which are famous for their reaction with a variety of nucleophiles in such transformations as the Sandmeyer reaction, have been shown to react with allylic silanes in good yields to furnish allylic azo compounds without the need for catalysis (equation 147, X≠H). The initially formed allylic azo products, which were produced by the normal S_E2' route, would undergo a 1,3-tautomerization to form hydrazone derivatives on warming to room temperature, so long as there was an allylic hydrogen adjacent to the diazo group (X=H).[420]



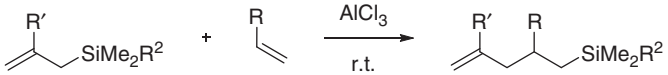
(147)

2.02.3.9.4 Formal carbocation systems

Along the vein of addition to positively charged species, allylic silanes have been shown to add into formal carbocations without the need for any external catalysis. This is expected, as it is an increase in carbocationic character that makes the thus-far discussed species reactive toward allylic silanes. As an example, both tropylium[421] and diarylmethanium cations[422] have been shown to react with allylic silanes. In the latter case, a complete study was performed as a means to assess the relative nucleophilicities of a variety of allylic silanes and silyl enolates.

2.02.3.9.5 Alkenes

Under the conditions of very strong Lewis acids such as aluminum trichloride, alkenes can coordinate to the Lewis acid, rendering the olefin highly electrophilic. Under these conditions, the former can react with certain other molecules which possess limited functionalities (limited due to the strongly Lewis-acidic conditions). Allylic silanes are one of these types of molecules, as they can undergo allylsilation of the alkene. The addition takes place in a Markovnikov manner: the silane adds onto the terminal position, and the allyl group adds to the more highly substituted position of the alkene (equation 148).[423] The substitution onto cyclic alkenes takes place in a *trans*-fashion. Allylic inversion is typically observed for this transformation.

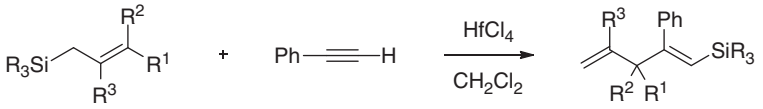


(148)

Cycloaddition products are readily observed during these reactions, especially in those cases wherein buta-1,3-dienes or diallylic silanes are used as substrates.[424] When the intramolecular allylsilation reactions of these conjugated systems are carried out with lithium tetrachloropalladate catalysis, chloride incorporation takes place as a result of the oxidative conditions.[425] Other activators, such as montmorillonite, superacids, and certain heavy metals can catalyze this reaction as well.[152a,426] Logistically, great care must be practiced when adding the allylic silanes into these systems, as they too are olefinic, and are capable of undergoing autoallylsilation.

2.02.3.9.6 Alkynes

Very similar to the reactions of alkenes, alkynes also react with allylic silanes, again providing *trans*-substitution and Markovnikov regioselectivity. For example, Yamamoto and coworkers reported on the hafnium(IV) chloride-catalyzed addition of allylic silanes to a variety of alkynes, demonstrating that even excellent yields with this reaction can be attained, and that further reaction of the produced alkenes can be readily avoided (equation 149).[427] They have further extended this reaction to an intramolecular version.[428]



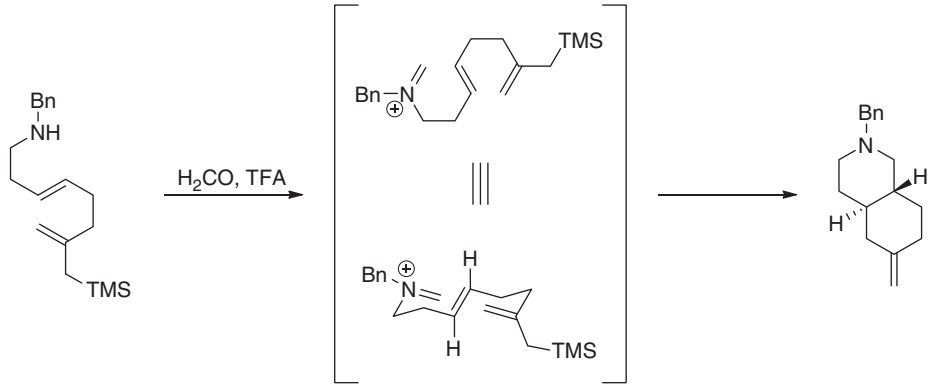
(149)

Versions of this allylsilation reaction of alkynes have also been catalyzed by montmorillonite,[429] aluminum complexes,[430] indium,[431] gallium,[432] and a variety of transition metals.[433]

2.02.3.9.7 Other systems

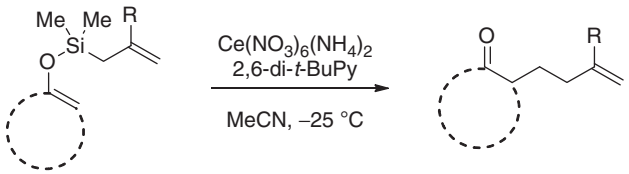
There are two additional types of allylic silane additions onto π-systems that warrant mention. First, cascade reactions, wherein the allylic silane adds onto a species that is being activated through its own reaction with a different species, thereby undergoing the formation of a carbocation. Whether the allylic silane adds at the point when a carbocation is entirely or incipiently formed is likely dependent on the system. No matter the case, multiple rings can be produced in these cascade reactions. For example, Grieco and Fobare have shown that homoallylic amines, when allowed to react under Mannich conditions, furnish an iminium ion that

undergoes a 6-(1,5)-Prins reaction with an alkene. The incipient carbocation is then captured by an allylic trimethylsilyl group to provide a *trans*-fused bicyclic compound (equation 150). The stereochemistry is readily explained through a Zimmerman–Traxler argument.[434] Other polycyclic systems such as steroidal backbones have been produced in this manner.[154a,435] This has also served as an approach in the total syntheses of albicanyl acetate and isodrimenin by Armstrong et al.[436]



(150)

In several cases, electron-rich olefins such as vinyl ethers and silyl enol ethers can be allylated under oxidative conditions. For example, silyl enol ethers, wherein the silicon moiety possesses an allylic residue, can undergo oxidation with cerric ammonium nitrate at the electron-rich enol ether (equation 151). Intramolecular allylation quickly ensues, providing α-allylated carbonyl compounds in good yields.[437] Vanadium[438] and manganese[439] reagents have also been used to affect this transformation. Anodic methods have also been reported with some frequency.[440]



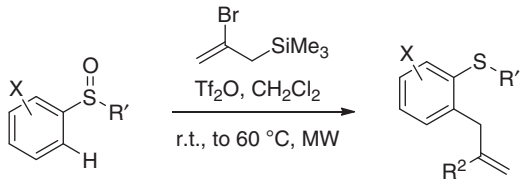
(151)

The Umpolung-like reaction of allylic silanes with sulfur dioxide and electron-rich dienes has been described by Vogel and coworkers. On completion of the reaction, the sulfur dioxide group is then removed under protiolysis conditions to furnish a molecule that would result from a net hydrosilylation reaction of one of the alkenes. Dimerization is also possible through this process.[441]

2.02.3.10 Other Reactions of Allylic Silanes

Allylic silanes have been shown to react with selenium chlorides at the expense of a sacrificial tin(II) chloride functionality.[54a,b,442] The resulting allylic selenides have synthetic utility that is not covered here. Similarly, they have been shown to react with phosphorus–chloride bonds.[443]

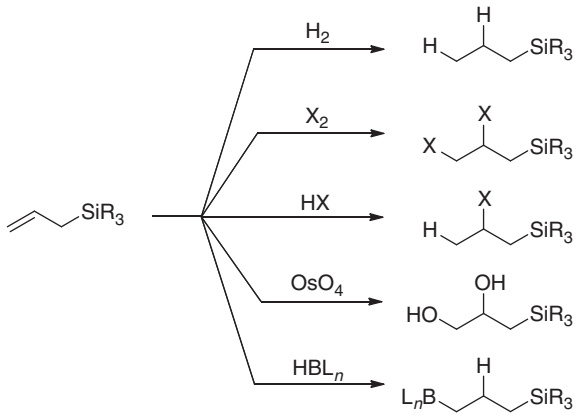
In a report by Procter and coworkers, the reaction of trifluoromethylsulfonylated sulfoxides with allylic silanes was described. The net result is a reduction of the sulfoxide to a thioether, and occurs with concomitant *ortho*-carbon–hydrogen bond allylation (equation 152). It is believed that the reaction undergoes a direct S_E2' displacement at the sulfur, thereby forming the sulfonium trifluoromethanesulfonate salt. Friedel–Crafts alkylation would then take place in an S_N2' fashion, furnishing *ortho*-allylated arenium ion. Deprotonation would then restore the aromaticity. An alternative mechanism, wherein a tetravalent sulfur(IV) intermediate is present, is unlikely, as the evidence that the successful trapping of the siliranium ion with a nucleophilic aromatic group (thiazoline) was shown to provide a species that did not possess a tetravalent sulfur(IV) species.[444]



(152)

The photochemical reaction between allylic silanes and both aromatic nitriles and imides has been thoroughly described by several groups.[445] These reactions lead to a wide variety of complex structures, including a number of fused polycyclic compounds, many possessing different levels of unsaturation, and, in certain cases, to unexpected elimination products and rearrangements.

A variety of simpler reactions can be performed on allylsilane species, mostly resulting in little in the way of unexpected reactivity (equation 153). For example, hydrogenation of allylic silanes[224] and analogs is facile, and they can be readily hydrogenated all the way down to the alkylsilanes. In the case of propargylic silanes, partial hydrogenation to the alkene, such as with Lindlar's catalyst, is readily performed and in a stereoselective manner.[1,42,203b,208a]



(153)

The reaction of molecular halogens with allylic silanes has been described on several occasions, but many times with apparently conflicting results. In some cases, vicinal dibromination[1] is said to take place; in others, γ-bromination, followed by elimination occurred to furnish allylic bromides (a formal oxidation reaction). In still other cases, tribromides are formed, presumably through a combination of these processes. Careful study has demonstrated that the mechanism and product identity appear to be dependent on the chosen solvent, and that both ionic and free-radical pathways can take place.[446] Pseudohalogens can also be added onto allylic silanes with little difficulty.[447]

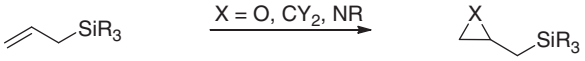
The reaction of allylic silanes with hydrogen halides takes place through a protonation mechanism to provide a β-silyl stabilized carbocation. In general, nonnucleophilic counterions are not capable of adding to the carbocation, and protiodesilylation becomes the major pathway; the same holds true in the presence of water. However, in the case of highly nucleophilic halide counterions, carbocation capture can take place, providing the net Markovnikov addition product.[1]

The osmylation of allylic silanes has been demonstrated by Fleming et al. as a means to provide 2,3-dihydroxypropylsilane moieties. In general, the reaction proceeds in good yields and *syn* to the silane. A potential pitfall of these reactions is the strong potential for Peterson elimination, as a 2,1-hydroxysilane functionality is present.[448]

Fleming and Lawrence have investigated the hydroboration of allylic silane residues. What they have found is what is to be expected: barring any large steric hindrances on the γ-olefinic carbon, hydroboration occurs in an anti-Markovnikov fashion to provide the expected terminal hydroxy compound.[449] The β-effect of silicon is expected to increase the partial positive character of the internal olefinic carbon, thereby increasing regioselectivity. One drawback is that, during the oxidation stage of a hydroboration, care must be exercised to avoid oxidation of the carbon–silicon bond.

The aminohydroxylation of allylic silanes has also been investigated briefly,[450] as have been nitrosylation[451] and nitration.[452]

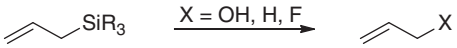
Similarly, Fleming et al. have described the epoxidation of allylic silanes with *m*-chloroperoxybenzoic acid (equation 154, X=O). The reactions are straightforward, but the product epoxysilanes undergo ready elimination on treatment with fluoride ion, or with certain acids or bases.[448]



(154)

Proceeding with the same *anti*-stereochemistry (to the silane) as epoxidation, the cyclopropanation of allylic silanes has been reported. Both Simmons-Smith and Yamamoto cyclopropanation conditions have proved effective. The latter has generally offered near-quantitative yields.[448] The reaction of dihalomethyl carbenes with allylic silanes has also been described, and proceeds in virtually quantitative yields to furnish dihalocyclopropanylsilanes. Just like their nonsilyl counterparts, dihalocyclopropanylic silanes can undergo thermal ring opening. When these cyclopropyl groups contain two silylmethyl groups and additional substitution, such ring opening is even more facile.[453] Azetidination has also been performed on allylic silanes, usually through the reaction with nitrenes. The resulting products are not always stable, and can undergo rapid desilylative elimination to provide allylic amine products.[454]

Highly electrophilic fluorines, such as those found in Selectfluor®, undergo rapid reaction with allylic silanes in an S_E2' manner, thereby furnishing allylic fluoride compounds (equation 155, X=F).[58,226a,455] The reactions are generally very rapid and occur in very good yields. Unfortunately, these conversions generally do not occur with a high level of stereoselectivity at the site of fluorination, even in the presence of internal directing effects. Some amount of externally induced stereocontrol has been attempted, but only moderate levels of success have been demonstrated.[456]

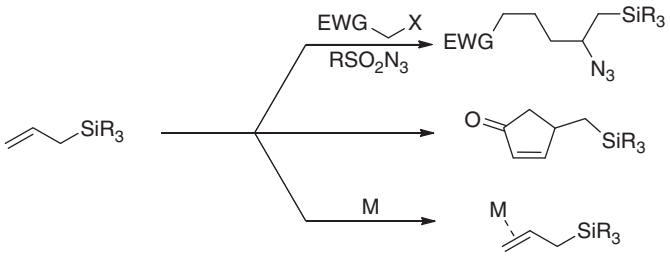


(155)

Protiodesilylation of allylic silanes is a reaction which generally occurs with allylic rearrangement to furnish an olefin (equation 155, X=H).[457] In general, acids whose counterions are not nucleophilic are used to affect this transformation, as nucleophilic species may be captured by the intermediate carbocation. Intramolecular acids and nucleophiles can be tolerated, however, and sometimes can even direct the protonation stereoselectively.[458] In certain cases, nucleophiles can intramolecularly trap the carbocation, allowing for the formation of a variety of heterocyclic ring systems.[459] Trifluoroacetic acid, acetic acid, dilute hydrochloric or sulfuric acid, *p*-toluenesulfonic acid, methanolic hydrochloric acid, etc., are among the most common choices. Generally speaking, the more stable the formed carbocation, the less difficult is the protiodesilylation. Another method used for protiodesilylation relies on nucleophilic catalysis. Species such as fluoride ions and *t*-butoxide ions have been shown to affect these types of eliminations.[460] Interestingly, the Zaitsev olefin is usually the predominantly formed product, which may be indicative of a thermodynamic distribution controlling the reaction pathway.

The direct oxidation of a carbon–silicon bond most generally occurs by one of two reactions. The reaction of a carbon–silicon bond with fluoboric acid (HBF_4) and an oxidant (usually *m*-chloroperoxy benzoic acid) is known as the Fleming oxidation. Similarly, the reaction of the same bond with potassium bifluoride (KHF_2) and an oxidant (usually hydrogen peroxide) also provides an alcohol, and is known as the Tamao oxidation. Both oxidations proceed with stereoretention at the carbon atom during conversion.[461] Unfortunately, larger groups around the silicon atom tend to slow the rates of these oxidations, which is highly disadvantageous in the annulation reactions discussed in Sections 2.02.3.2.5–2.02.3.2.7, 2.02.3.3.3, 2.02.3.3.4, 2.02.3.6.1, and 2.02.3.6.2, as the larger silyl groups are what promote them. In general, the Fleming oxidation is the choice conversion for trialkylallylic silanes, whereas the Tamao oxidation is the preferred option for those silanes bearing more electronegative ligands. Generally speaking, more electron-withdrawing ligands also greatly facilitate these oxidation reactions.

Carboazidation of allylic silanes has also been reported, and proceeds in a radical fashion with the azide group ultimately being located at the internal olefin position, and with the carbon at the terminus (equation 156).[182a,213a] The reactions have been reported to occur in reasonable yields, and with good *syn*-stereocontrol being observed between the azide and silyl groups (when applicable).

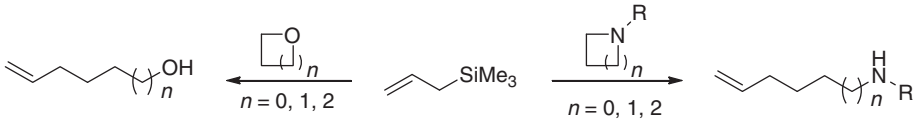


(156)

Allylic silanes bearing pendant alkynes have also been shown to effectively participate in the formation of cyclopentenone derivatives in very good yields (equation 156, middle pathway). As is typical for such Pauson–Khand-style reactions, dicobalt octacarbonyl is the catalyst of choice.[462]

Due to their electron-rich nature, allylic silanes are good π-donors, and react readily with a variety of metals. In certain cases, only the η^2-complex is obtained, whereas in other cases a desilylation reaction takes place to provide η^3-complexes, which can be useful in cross-coupling or other rearrangements.[463]

Allylsilanes have been shown to react with oxiranes, oxetanes, tetrahydrofurans, aziridines, and azetidines (equation 157). Lewis acid catalysis is required in all cases.



(157)

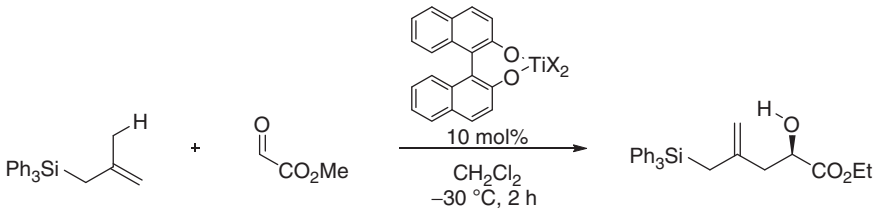
In the case of oxiranes, only a few examples are known[89c,464]; they are sometimes coupled with other processes such as lactonization. Mixtures of regiochemistries are common. Plaguing these reactions is the fact that Mienwald rearrangements are a common alternative that can take place. This type of addition has been used in the total synthesis of (+)-Brefeldin by Takano and coworkers.[465]

Oxetane has also been shown to function moderately well, although substituted oxetanes have not been fully studied.[466] One report of the reaction of an allylic silane with 2-methoxy-2-silyloxyoxetane, which was catalyzed by various Lewis acids, most likely reacts through the oxycarbenium ion, and so is not likely a true oxetane ring-opening reaction.[467] There is also one report of a 3,4-benzo-bridged furan ring-opening with allylic silanes under conditions of either gold or platinum catalysis, wherein both oxygen–carbon bonds are allylated.[468]

Considering that aziridines are generally less reactive than epoxides, it is perhaps surprising that their ring-opening reactions with allylic silanes proceed as well as they do. In general, intramolecular versions of these reactions occur in very good yields to give the allylation product cleanly.[102a] Likewise, intermolecular reactions occur in good yields.[469] Interestingly, the same group reported a certain amount of pyrrolidine formation, which is certainly the result of the trapping of the carbocation with the amide anion. Although both examples used identical conditions, the former ran the reaction for 9 h, and the latter for only an hour. Since fluoride ion can convert the silylmethylpyrrolidines into the Hosomi–Sakurai products, it is likely that the pyrrolidine was formed in both cases, but then reverted entirely to the allylation product due to the extended reaction time. This pyrrolidine formation has been used as a means to produce both fused[470] and bridged[235,471] bicyclic compounds. In each case, the [2+3] annulation products observed occur by amide attack onto the carbocation before 1,2-sila-Wagner–Meerwein migration. As a result of these reports, it has become apparent that the enhanced nucleophilicity of the amide is high enough to undergo a competitive ring-closing reaction with a greater precedence than silyl migration.

Azetidine rings can also be opened by their reaction with allylic silanes under Lewis acid conditions.[472] Generally speaking, the ring closure to produce piperidines is not observed in most cases (nor is silyl migration–azepane formation). Instead, allylation takes place cleanly and in reasonable yields with a variety of substrates. The reactions reported in this area have been chemospecific, undergoing alyllation at the more highly stabilized of the two possible 'carbocation' positions of the azetidine.

Depending on the choice of conditions, especially the Lewis acid, the hetero-Alder–ene reaction of allylic silanes with various electrophiles can take place preferentially to the allylation (and derivative) pathways. Generally speaking, the reaction is catalyzed by coordination of the electrophile to the Lewis acid, thereby activating the carbonyl to attack. For example, Mikami and Matsukawa have reported the asymmetric, titanium(IV)-catalyzed ene reaction of allylic silanes and glyoxylates (equation 158).[473] The reasons for the ene-pathway being the preferred one in certain cases as opposed to the normal Hosomi–Sakurai pathway are not clear, and are often completely unexpected.[474] The hetero-Alder–ene reaction of allylic silanes with iminium ions has also been reported,[475] as has been an uncatalyzed variant with tetracyanoethylene.[476] Both Lewis acid-catalyzed and thermal Alder–ene reactions of α,β-unsaturated systems with allylic silanes have been reported in the context of either partial or total syntheses.[477]



(158)

2.02.4 Allylgermanes

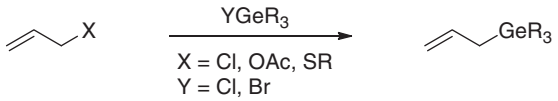
Comparatively speaking, there are very few reports in the literature for allylgermanes that describe their use and preparation. Only the basic ideas behind this class of molecules are given here.

2.02.4.1 Preparation of Allylgermanes and Derivatives

Those allylgermanes which have been prepared to date have been so constructed through means quite similar to those of allylsilanes. There are not as many reports, however, and so many of the methods used in the synthesis of allylsilanes have not been explored with germanium.

2.02.4.1.1 Displacement of allylic groups or exchange at the metal center

The majority of allylic germanes have been produced through the displacement of either an allylic group or one at the metal (equation 159). Only a few reviews on the subject matter of organogermanes which make special consideration for allylgermanes have appeared.[478]



(159)

It has been shown that the reaction of allylic Grignards and allylic alkali metal systems with germanium halides results in a net ligand exchange, thereby forming allylic germanes and metal salt by-products.[114,479] In general, this reaction proceeds in very good yields to give the desired products. The inverse of this process, wherein a germanide anion reacts with an allylic group, is also known, but has seen only limited use. This is probably due to the great difficulty in obtaining the actual ion. The superbase combination of *N*,*N*,*N*′,*N*′-tetramethylenediamine/*t*-butyllithium is needed for obtaining the anion in quantitative yield.[479c] The anion has been shown to react with typical leaving groups such as acetates, halides, and arylic sulfides, although regiochemical

control remains a serious issue, as both S_N2 and S_N2' products are obtained from these reactions.[479c] Another route detailed the approach of a similar leaving group (arylic sulfides) in a radical desulfurizative germylation.[480] This was shown to produce allenyl germanes from propargylic starting materials.

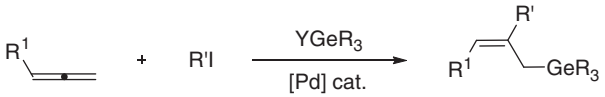
The problem of regioselectivity observed with germanide anion additions has been addressed by Takeda and coworkers. They have shown that lithium bis(trialkylgermanyl)cuprates, which are formed from the reaction of cuprous iodide and germanide anions, regioselectively add in a controlled manner, providing consistently predictable products in excellent yields.[479c,481]

Palladium-catalyzed cross-coupling has been used as a means to catalyze allylic substitution reactions. For example, both the Kabalka[482] and Nakano groups have developed the palladium-catalyzed germylation reaction of allylic chlorides that employ the use of digermane complexes as a germanium source. There is evidence that, unlike many other types of similar substitutions, these reactions proceed first through the formation of (allyl)chloropalladium(II) species, which then undergo transmetallation followed by reductive elimination. Unfortunately, these reactions were very slow and required elevated temperatures and increased reaction times, and an increase in electron density around the germanium centers.[483] It was later shown that the reactions could proceed even at room temperature and far more rapidly if a chloride substituent was used as a ligand on the germanium. The reactions generally have been shown to provide mostly *E*-olefins.[484] Mixed main-group metals have also been used for this reaction. For example, germanium–tin[485] and germanium–silicon[486] compounds also furnish the allylic germanes as the exclusive and major products, respectively. It is unclear as to why the germanium products are formed in such high proportion to allylstannes or allylsilanes, although it is likely a question of the very high affinity that silicon and tin exhibit for halides.

Normally, dimetal reagents such as these are used for attempting allylic couplings for Group-IV metals, because in the more atom-economical substitution using metal–hydrogen compounds, reduction of the allylic groups is observed in place of a substitution pathway.[487] There is one report that is an exception to this, wherein a tri(2-furyl)germane was shown to undergo substitution direction onto allylic leaving groups. For reasons unknown, however, only the furyl ligand was tolerated. No other germanium species functioned, and this could not be applied to other Group-IV metals.[488]

2.02.4.1.2 Reaction of X–Ge bonds with π-systems

The only other method that has become at least moderately well developed as a means of production of allylgermanes has been in the elementogermylation of π-systems. For example, Cheng and coworkers have developed the carbogermylation reaction of allenes (equation 160).[489] Beginning with arylic iodides, palladium is believed to oxidatively add into the said bond, then undergo chelation and carbopalladation onto the allene scaffolding. Transmetallation with the same germanyl-stannanes from above is thought to then provide the allylic germanes. The hydrogermylation of dienes has also been reported.[490]



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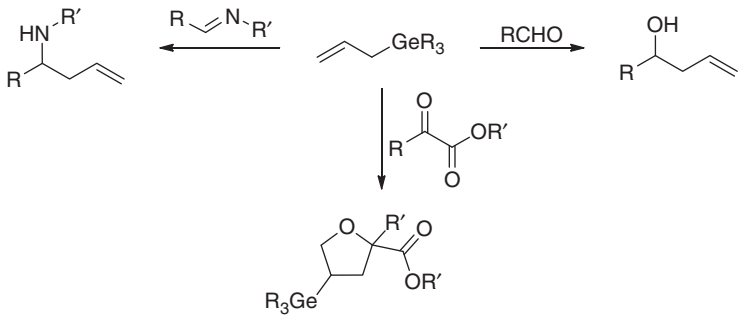
2.02.4.1.3 Other synthetic means

There are a handful of additional reports that have addressed the synthesis of allylic germanes, but that have since seen little use. For example, chiral germyl halides have been used to generate chiral germanes from germyl-nickel reagents and allylic Grignards in the presence of nickelic chloride.[491] Germylene species (germanium analogs of carbenes) have been shown to add to allylic halide compounds in varying yields.[492] Allylic alcohol salts, on reaction with silylgermanes, can also furnish allylic germanes in varying yields.[493] The use of germanium(II) iodide in the formation of allylic germanes has been investigated. Oxidative addition to allylic halides was shown to proceed rapidly and in excellent yields, to provide allylgermanium products without purification.[494] Allylic germanes can also be produced by allylation with other, more reactive main group allyl metals. For example, allylstannanes react with germanium halides to produce nearly quantitative yields of allylgermanes.[495]

2.02.4.2 Reaction with Electrophiles

Allylgermanes react with electrophiles in much the same way that silicon does (equation 161). For example, the simple allylation reaction has been described, and generally occurs with comparable or slightly faster kinetics, but in lower yields than the equivalent reactions with silicon.[479d,481,494] For cases of α,β-unsaturated systems, 1,2-addition generally takes precedence, and occurs with allylic transposition via an S_E2' rearrangement. Just as with silicon, a *syn* preference is observed in the absence of outside influences. Quite interestingly, the use of a propargylic germane resulted in a propargylation of the aldehyde, and not the allenylation.[494] The reaction with ketone substrates has only been scarcely reported, but both allylation[494] and [2+3] annulation reactions[496] have been published. Interestingly, the former annulation pathway appears to require tin(IV) chloride, as other common Lewis acids were not successful in promoting the annulation reaction. Additionally, bulky ligands around the germanium were required to affect this transformation, just as is true for silicon-based annulations.



(161)

Oxycarbenium ions have also been demonstrated to be readily captured by allylic germanes.[497] As expected, the formed products are etheric in nature. Imines have also been electrophiles that have been briefly studied as allylgermane partners in this reaction, and can be both allylated or annulated. For example, Akiyama et al. have shown that allyltriethylgermanes add to such electrophiles under the catalysis of boron trifluoride to provide homoallylic amines in very good yields.[347b] When they utilized the bulkier allyltriisopropylgermane, then the [2+3] annulation product was formed through a Friedel–Crafts pathway before a 1,2-germanyl-Wagner–Meerwein rearrangement.[498] Imines produced *in situ* have also been used in this process.[499] Diazodicarboxylates have been shown to react with allylic germanes. Mixtures of allylation and annulation products were consistently formed.[500]

Just as with allylic silanes, cyano and nitro groups appear to remain relatively inert toward allylic germanes, but much more work needs to be performed in order to further assess this generality. To the best of the authors' knowledge, there is only a single report of the reaction of allylic germanes with cyano compounds. The photochemical reaction proceeded to furnish a mixture of allylated and polycyclic products.[445b]

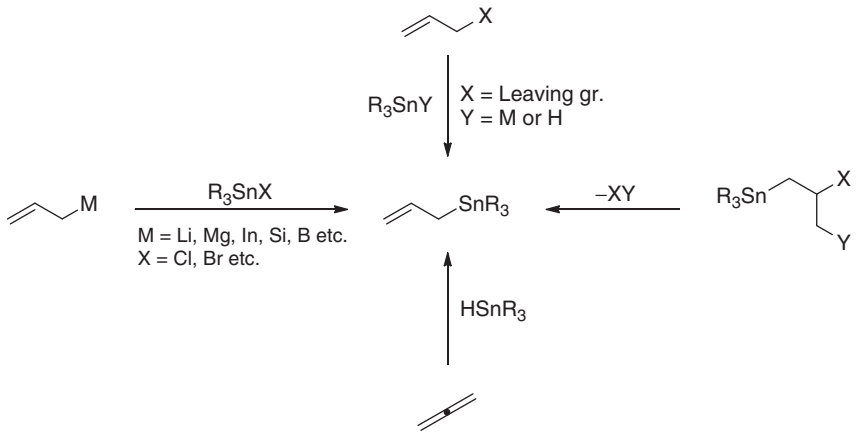
Allylic germanes have been reported to react with a few other chemical species as well, but these reports are sporadic at best. For example, they have been reported to react with tin halide complexes to furnish allylic tin reagents that are used directly, thereby undergoing a net allylation reaction at the α-position of the allyl germane.[479d,481] They have also been reported to react with certain thallium(III) compounds.[501] Their reactions with iodine(III) reagents have also been published on several occasions. Internal nucleophilic cyclization can occur,[114] as can intermolecular nucleophilic displacements[416] and/or allylic oxidations.[418]

2.02.5 Allylstannanes

2.02.5.1 Preparation of Allylstannanes and Derivatives

2.02.5.1.1 Substitution, elimination, allylic displacement, and hydrostannylation

Although there are a far greater number of reports on the synthesis of allylic silanes than for the related stannanes, the methods are quite similar in most cases, and similar outcomes are usually observed. As such, this area has been covered with only a minimum amount of explanation, offering instead facts and examples.



(162)

In much the same way as has been done for silanes and germanes, the reaction of allylic systems of alkali and alkaline earth metals with tin compounds containing labile ligands results in a net exchange reaction, thereby forming a simple salt and an allylic stannane (equation 162). For example, Hoppe has used this as a means to prepare chiral allylic stannanes from chiral allylic carbamates.[502] Other allylic systems such as enolates have been used in this preparation method.[503] Sonochemical conditions have also been reported.[504] The addition of vinylic metal systems to 1-stannylacylonium ions also results in the formation of allylic stannanes.[505] The reaction of halomethylstannanes with vinylic nucleophiles has also been reported.[47] Dianionic metal

systems have been shown to react with chlorostannanes to form the stannalyted product, by reacting at the site of the more reactive anion.[506]

Other metal systems can also be used to furnish allylic stannanes. For example, the reaction of allylic silanes[503d] and indiums[507] with chlorostannanes provides very good yields of the expected products. Allylzinc species, which are formed *in situ* under Barbier conditions (from the reaction of zinc metal and allylic bromides), also react to furnish allylic stannanes.[508] Allenic titaniums have been shown to react to furnish propargylic stannanes.[509] There is also an isolated report that details a ligand exchange of triallylborane with alkynylic tins to provide allylic stannanes.[510] Likewise, different allylic stannanes can undergo exchange processes, resulting in the net formation of a new allylic tin functionality.[511]

There are only a few examples of elimination processes being used to furnish allylic stannanes. In a report by Jephcote and Thomas, a Grieco elimination was chosen as an approach to these compounds. By converting (γ-hydroxyalkyl)stannanes into (γ-hydroxyalkyl)selenides, hydrogen peroxide-promoted elimination resulted in the desired allylic stannanes in reasonable yields and selectivities.[512] Analogous to their approach to allylic silanes, Fleming and Rowley showed that γ-hydroxy-β-alkoxycarbonyl stannanes could be converted into either geometric isomer, depending on the choice of decarboxylative elimination conditions.[513]

The direct substitution of allylic groups by tin anions has been performed on numerous occasions, and generally proceeds in good-to-very good yields. For example, Wuest and coworkers demonstrated that two substitutions could take place in a one-pot process, resulting in a bimetallic system.[514] Other such reports have surfaced,[515] and sodium and copper stannates have also been demonstrated to undergo effective substitution reactions.[516] The conversion from allylic alcohols to allylic stannanes by way of a halide intermediate (formed through an Appel reaction) has also been described.[517] Other common leaving groups are also readily displaced, including acetates (under palladium assistance),[518] mesylates,[519] and alkylselenides.[520] Palladium–pincer complexes have also been detailed as being capable of displacing allylic leaving groups with tin substituents, the latter being derived from bimetallic sources.[70,521] The net regioselectivity of these displacement reactions depends on each of the cases, but steric factors are usually the major players in determining the location.

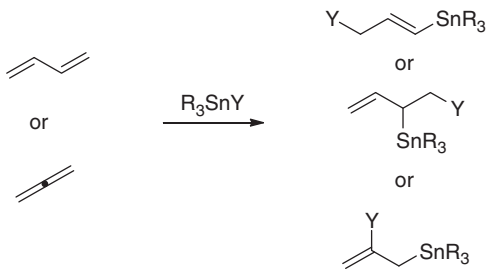
As tin–hydrogen bonds are very weak, homolytic cleavage to form stannyl radicals is facile. This reactivity has been used in the displacement of allylic groups such as thioalkoxides[522] and sulfones.[523] In an effort to obtain a greater level of regioselectivity in such allylic displacements, Ueno et al. developed a new system, wherein allylic alcohols are deprotonated, reacted with carbon disulfide, S-methylated, and finally reacted under substitutive radical conditions. The final, stannylated product ultimately replaces the hydroxyl group directly with a stannane.[524]

Alkynylic stannanes containing propargylic leaving groups have also been reacted in an allylic displacement manner, thereby providing allenylic stannanes.[525]

The hydrostannylation of allenes has also been reported as a means to obtain allylic stannanes. The palladium-catalyzed process only occurs in a 2,1-manner, providing good yields of allylic stannanes in mostly a *Z*-configuration.[526] Subsequent reports have claimed that both the *E*- and *Z*-isomers can be produced, depending on the conditions.[527] Molybdenum has also been shown to affect the hydrostannylation of allenes.[528]

2.02.5.1.2 Reaction of X–Sn bonds with π-systems (X≠H)

The elementostannylation of a variety of π-systems has been studied as a means to produce allylic stannanes (equation 163). For example, Tanaka and coworkers have shown that the 1,4-borastannylation of 1,3-butadienes takes place in excellent yields to provide a *Z*-relationship between the boramethyl and stannylmethyl substituents.[529] The produced reagents are particularly useful, as they readily undergo allylboration without the need for an added Lewis acid, as allylborations are faster (through self-promotion via chelative activation) than allylstannylations.



(163)

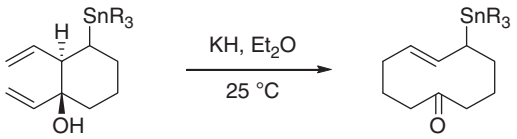
In the presence of a reactive alkyl or acyl halide, palladium can catalyze the 2,1-carbostannylation of allenes when distannanes serve as the tin source. The reaction likely proceeds through the oxidative addition of palladium into the carbon–halogen bond, followed by 2,1-carbopalladation of the allene. Transmetallation followed by reductive elimination would then provide the observed products.[139,530] Acylstannanes can be butadienylated with a nickel catalyst, which gives the same net result as the previous transformation, but in a more atom-economical method.[531]

The stannylcupration of allenes behaves in a manner quite similar to silylcupration, in that either the vinylic or allylic stannane can be obtained, depending on the choice of temperature and order of the cuprate.[532] The marked versatility of this approach is seen in the host of compounds that can be introduced as functionalities at the β-position of the allylic stannane (see equation 54, *vide supra*).

The silylstannylation of allenes and 1,3-butadienes[533] has also been partially studied. In the case of the former, palladium(0)–phosphine ligand complexes have been reported on several occasions,[526,534] but the exclusion of phosphine ligands gives markedly better results, with nearly perfect *E*-geometrical isomerism and excellent yields being observed.[535]

2.02.5.1.3 Sigmatropic reactions and conjugate addition

Sigmatropic reactions that form allylic stannanes are scarce, possibly due to the higher level of instability of allylic stannanes when compared to their silane counterparts. However, one report detailed an anionic oxy-Cope reaction of *E*-cyclodec-5-en-1-ones that produced an allylic stannane (equation 164). The stannane likely remained intact as a result of the mild conditions associated with the anionic oxy-Cope[536] reaction. Allylic stannanes can also be produced through a retroallylstannylation of homoallylic alkoxystannanes.[537] This reaction, which is simply the reverse of the reaction of an allylic stannane with a carbonyl compound, has very limited practical use, as the allylation reaction is the reaction of interest in classical organic chemistry.



(164)

The conjugate addition reaction of stannyl anions to Michael acceptor systems furnishes enolates or enol ethers which are allylic stannanes by structure.[536,538] However, their reactivity patterns are, expectedly, different than normal allylic stannanes, as they react as nucleophiles at the position beta to the stannane, and not gamma to it.

Allylstannanes have also been produced through the reaction of dimetalation reagents such as those containing a 1,5-stannylborane functionality. In this case, allylboration can furnish allylic stannanes in very good yields, and with very high levels of relative and absolute stereocontrol.[185d] This approach has been used in the total synthesis of (−)-Basiliskamide A by Chen and Roush.[539]

2.02.5.1.4 Other synthetic means

A few other synthetic methods have been employed in the effort to produce allylic stannanes. In one such report, it was shown that certain stannylenes can undergo addition into allylic bonds, thereby forming allylic tin(IV) species.[540] 2-Stannylethylidenylphosphoranes can react with aldehydes in a Wittig reaction to form allylic stannanes, but the yields tend to vary considerably.[208a,541] Metal alkylidene bonds such as those between carbon and tungsten or carbon and chromium have been shown to react well with tin–hydrogen bonds, undergoing a formal insertion reaction to furnish allylic stannanes. The reactions generally proceeded in very good yields and gave predictable products.[542] The 1,2-addition of anionic stannane salts to α,β-unsaturated aldehydes furnishes α-hydroxyallylic stannanes. Oxidation and enantioselective reduction was used as a means to obtain these nearly enantiopure compounds.[543]

In a report by Schrock et al., it was shown that vinylic stannanes, in the presence of ethylene gas, could undergo a formal homologation reaction, furnishing allylic stannanes. This unprecedented and unexpected reaction – whose mechanism is not clear – has not yet been completely generalized.[544]

2.02.5.1.5 Derivatization of simpler allylstannanes

There are a few stand-out cases in which allylic stannanes have been derivatized into more complicated ones. The examples included here are only for purposes of broadening the synthetic approaches to these stannane structures.

The Diels–Alder reaction of 2-vinylallylic stannanes has been reported by Hosomi et al. Only one example was given by the authors, wherein an alkyne was chosen as the dieneophile. The reaction completed within 15 h in refluxing dichloromethane, to furnish a nearly quantitative yield of the stannylmethyl-substituted 1,4-cyclohexadiene that possessed the allylic stannane functionality.[168]

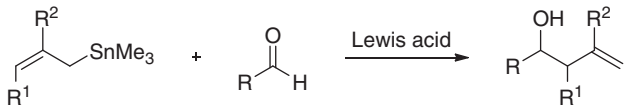
Due to the carbon–tin bond being weaker than the carbon–silicon bond, the former is usually much more reactive, and, due to the ease of homolytic cleavage, it can also undergo radical formation far more readily than do allylic silanes. However, as the two do have different bond strengths, it stands to reason that the allylic silanes could be cleaved photochemoselectively, if the correct frequency light was used. Kang et al. found that Vycor-filtered light (>220 nm) could be used to accomplish this, and that the photochemoselective reaction of the allylic silanes via a radical mechanism in acceptable yields could be performed.[54d]

Allylic stannanes can also undergo cross-metathesis with appropriate partners to obtain more complicated structures.[545]

2.02.5.2 Allylation of Aldehydes

As the reactions of electrophiles with allylic stannanes are very similar to those reactions with allylic silanes, they are not covered here in an in-depth manner, simply for purposes of avoiding repetition. In general, however, allylic stannanes are similar to silanes: they generally follow Type-II mechanisms and usually proceed with the same manner of stereocontrol (equation 165).[11b,546] In contrast to allylic silanes, the reaction of allylic stannanes with some electrophiles can be induced to occur through thermal means, due to their higher reactivity,[547] but high temperatures are still required, the only exceptions being those cases in

which tin cations (which are partly formed due to solvation) undergo allylation.[548] Additionally, allylic stannanes generally do not favor annulation processes, likely due to the greater ease of elimination. There has been some debate over the exact mechanism of Lewis acid involvement.[549] The effects of substitution on the nucleophilicity of allylic stannanes have also been studied.[550]



(165)

This transformation, due to Keck's large contribution toward the general development of symmetric and asymmetric versions of this reaction, is known as the Keck allylation reaction.[551]

The first reported reaction of an allylic stannane with a carbon-based electrophile was given by Hosomi et al.[552] Similar to their reaction of allylic silanes, they showed that certain Lewis acids could effectively activate carbonyl-based electrophiles toward allylstannation. Since this time, both intra-[553] and intermolecular versions of the Keck reaction have been developed, and its scope with aldehydes expanded.

In general, the higher sensitivity of allylic stannanes (by comparison with allylic silanes) toward protic acids has tended to detract from the latter's use as catalysts for Keck reactions. As such, the focus has been on Lewis acids, and a wide variety thereof has been explored and used as alternatives. For example, just as with the Hosomi–Sakurai allylation reaction, titanium-,[554] tin-,[555] and boron-based[240,554b,556] Lewis acids have been used with good success. Again, the exact role of the Lewis acids in the Keck reaction is not always clear.[557] Generally speaking, the yields for these reactions are excellent, with slightly lower yields being observed for aliphatic or hindered substrates.

Several other Lewis acids have also proved successful in this regard, which is interesting considering that they are not notorious for their Lewis acidity in these types of reactions. The list of these perhaps conspicuously used metals includes palladium,[558] magnesium,[559] indium,[560] zirconium,[561] lanthanum,[562] zinc,[563] ytterbium,[564] bismuth (under microwave conditions),[565] niobium,[566] and silicon (which occurs without transmetallation).[567] Bisstannyl reagents, wherein the Lewis acidity is innate to the reagent itself, has also been shown to affect allylation.[568] Room-temperature ionic liquids can also catalyze allylation with tetraallyltin, using all four allyl groups in an atom-economical and comparatively environmentally friendly version of the Keck allylation.[569] The use of high pressures can also promote allylstannylation, possibly by way of a Type-I pathway.[570] It has been found that allylic tris(perfluoroalkyl)stannanes can undergo allylation, and offer an advantage of a different means of purification.[571] Tetra-*n*-butylamminium fluoride has also been shown to affect allylation.[572] Protic acid promotion of the Keck reaction is quite rare, but is possible, as protonolysis of allylic stannanes can sometimes be a kinetically slow process.[573]

The combination of the Keck reaction with other synthetic transformations in a cascade process has also been described on more than one occasion. For example, Taylor and coworkers described the oxidation–allylation–oxidation reaction sequence of primary alcohols under a variety of conditions and with a number of different allylating agents, including allylic stannanes.[574] Schmalz and coworkers published their findings that halogenated benzaldehyde derivatives, on reaction with allylic stannanes under palladium catalysis, could undergo a one-pot allylation–Heck coupling reaction.[575]

Two very nice examples of the use of the Keck allylation reaction have been published by Martin and Thomas in the synthesis of some members of the Epothilone family[576] and by Crimmins et al. in the synthesis of (−)-Laulimalide.[577]

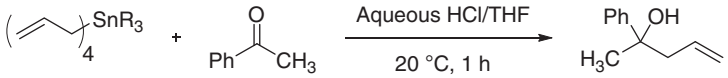
Absolute stereocontrol in the Keck allylation of aldehydes has become well advanced, and a wide variety of methods have been chosen for study in this area. The classical choice of enantiomeric control coming from the use of chiral aldehydes has been performed on a wide variety of occasions,[578] as has been the use of chiral allylic stannanes.[579]

The use of a chiral ligand–Lewis acid pair has seen some very good preliminary results in inducing chirality. Many of the most commonly used chiral ligands have been met with good levels of success, including 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP)-[580] and BINOL-derivatives,[581] Salen,[582] Pybox,[583] and a few boron-based ligands,[584] among others.[585] Generally speaking, the best results have come from the BINOL- and BINAP-based ligands.

2.02.5.3 Allylation of Ketones

The development of the allylation of ketones with allylic stannanes has proceeded well, and a number of advances have been made. Among the findings for these reactions is that, unlike the allylation of aldehydic electrophiles, the allylation of ketones with allylic stannanes is readily reversible, and can run into legitimately debilitating equilibrium issues that can prevent reaction completion.[586] Aside from this particular difference, the reaction is similar to the allylation of aldehydes, in that mostly Lewis acids such as boron-,[587] magnesium-,[294] lead-,[588] and indium[560a,589] have been used in the context of simple and/or stereoselective allylations. A few reports have appeared which are intramolecular in nature,[587a] including ones which take different stereochemical pathways that depend on the chosen Lewis acid catalyst.[518b] Some effort has also been given to the development of enantiocontrolled versions of this Keck allylation reaction.[589] One interesting example published by Noyori and coworkers involved the transmetallation to form allylic lithiums, which then underwent allylation reactions *in situ*.[525]

The thermal allylation of ketones with allylic stannanes has been reported to occur without catalytic assistance, occurring over a time period of several days if conducted at ambient temperature.[590] Additionally, the protic acid-catalyzed reaction of allylic stannanes has been reported (equation 166),[591] and likely occurs through attack onto adventitiously activated carbonyls, or even hydrogen-bonded ones.[592]



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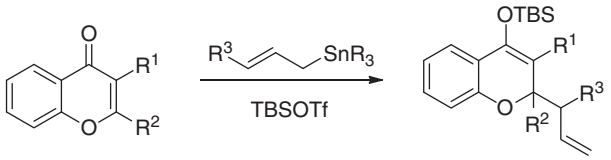
The aqueous-phase allylation reaction of ketones using allylic stannyl chlorides has also been reported. The high reactivity of the chlorine–tin bond is believed to be responsible for the activity of the reaction, as solvation into a tight ion pair could conceivably enhance the Lewis acidity of the tin center sufficiently to allow for a Type-I mechanism to occur.[548d]

2.02.5.4 Allylation of Oxycarbenium Ions

Only a few reports have appeared in the literature which detail the reactions of allylic stannanes with oxycarbenium ions. Generally speaking, the reactions are characterized as being both rapid and high yielding, so long as appropriate conditions are chosen.[548d,593] For example, the reaction of vinylogous esters with allylic stannanes proceeds entirely through allylation at the β-position (equation 167), which is in sharp contrast to the equivalent reaction of allylic silanes which provides both the allylation and annulation products.[323]



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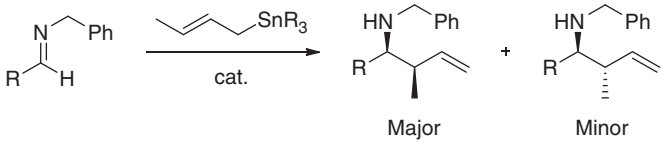
2.02.5.5 Allylation of Imines

The reaction of allylic stannanes with imine-based electrophiles has been investigated on multiple occasions. In general, the reactions proceed quite well and with very good relative stereoselectivities. For example, Keck and Enholm published the reaction of *N*-benzylimines with crotylstannanes (equation 168). They found that the reactions proceed in a mostly *syn*-fashion, providing approximately the same ratio regardless of the metal promoter being used.[594] A variety of Lewis acids have been developed for this reaction, including boron-,[595] magnesium-,[596] indium-,[597] gold-,[598] scandium-,[599] zirconium-,[562,600] and palladium-based[558a,601] catalysts.



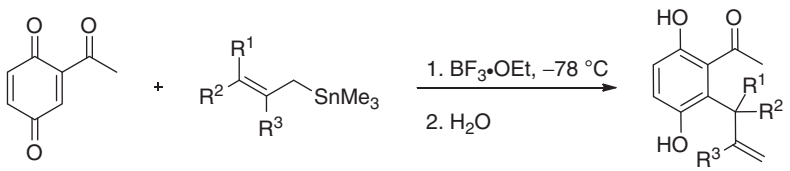
(168)

The imines for this reaction have also been produced *in situ* as a one-pot allylative amination reaction.[602] The use of nitro compounds in place of amines has also been reported. The combination of an *in situ*-performed reduction with the allylative amination can provide excellent yields of a variety of aniline derivatives.[603]

Iminium ions have also been exploited as a means to perform the Keck allylation without the need for Lewis acids in the actual allylation step,[604] although one is still needed for the production of the iminium ions, unless very forcing conditions are used. Hydrazones have also been used in the Keck allylation reaction.[604] A variety of work has been performed in an effort to afford enantioenriched products, but so far only limited success has been met.[605,606]

2.02.5.6 Allylation of Other Carbonyl Systems

The reaction of a variety of Michael acceptor systems with allylic stannanes has been described. The reactions almost invariably occur in a 1,4-addition, and not in a 1,2-manner. The reactivity is generally limited to ketones and aldehydes, as esters are typically unreactive in this regard. For example, Maruyama and coworkers[380a,607] have demonstrated that the reaction of acylquinones, under conditions of boron trifluoride catalysis, undergoes very rapid conjugate addition in high yields (equation 169). They have since developed this methodology into an uncatalyzed version by using more reactive 1,2-naphthone compounds.[608]



(169)

A variety of other metals have appeared, the compounds of which can serve as Lewis acids in this reaction, including, silicon,[609] ytterbium,[385a] zirconium,[610] and zinc.[606a] The more common boron, aluminum, and titanium-based Lewis acids have also appeared.[611] The addition to malonates[385a] and α,β-unsaturated nitro compounds has also been described.[612] A radical pathway has been reported on multiple occasions as a means to perform allylstannylations of α,β-unsaturated carbonyl compounds.[613] Lithium perchlorate has been shown to catalyze the reaction of tetraallyltin with dialkyl diazodicarboxylates.[614]

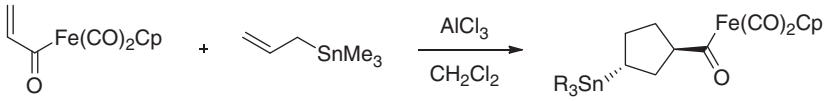
Other singular reports on the allylation of carbonyl derivatives have also appeared. For example, acid chlorides have been shown to react with allylic stannanes in reasonable yields under palladium-catalyzed cross-coupling conditions.[505] There is also a report which details the Keck allylation of α-ketophosphonates with indium catalysis. Very good levels of both isolated yields and enantioinduction could be obtained with the use of chiral *N*,*N*′-dioxide ligands.[615] Aromatic nitriles also react to furnish a variety of products.[445b] Isocyanates have also been shown to react with allylic stannanes and allylic chlorides in a three-component coupling reaction.[616]

2.02.5.7 In Annulation Reactions

In contrast to allylic silanes, there are only a few reported examples of the annulation reactions of allylic stannanes. In what is probably attributable due to its larger atomic size, the enhanced rate of attack at the tin atom by comparison with the silicon results in a faster elimination process. There has not been a clear demonstration of the relationship to the size of the organic ligands on the tin center and the annulation pathway as has been performed for silicon.

In a stand-alone case, the allylation of *o*-quinonediimines has been shown to result, depending on the *N*-substituent, in either an allylation or conjugate addition pathway.[617] For the case of higher nucleophilicites such as those of sulfonimides, attack at the latter takes place, which is then followed by cyclizative capture. In the case of less electrophilic species such as benzoylamides, the initial site of attack is in the Michael-acceptor position.

The use of chromatographically stable acyliron species has been shown by Herndon and coworkers to result in a net [2+3] annulation process.[606] The resulting species are obtained with the same *trans*-stereochemical relationship between the tin and acyliron substituents as are observed in the analogous silicon-based annulation reactions (equation 170). Remarkably, the cyclic stannylated acyliron products are also stable to column chromatography.



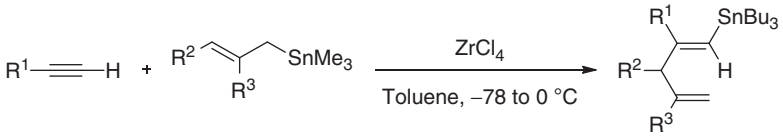
(170)

One report published by Maruyama and Matano demonstrated that under certain cases, the addition of allyltrimethyltin to acylated quinones could provide [2+3] annulation products.[618]

The chiral addition of allylic stannanes to 2-nitrosopyridines was described by Studer and coworkers. By combining a copper(I) catalyst with a chiral diphosphine ligand, excellent levels of enantiomeric excess could be induced in the cyclization reaction, with isolated yields being very good.[619]

2.02.5.8 Allylation of Carbon–Carbon π-Systems

The allylstannylation of entirely organic π-systems has only been explored very recently. Generally speaking, it occurs only at moderate rates at best, normally undergoing *trans*-addition. For example, Yamamoto and coworkers have shown that zirconium tetrachloride can catalyze the allylstannylation of alkynes in mostly *trans*-selectivity and in varying yields (equation 171).[620]



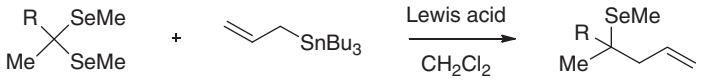
(171)

Although rare, the *cis*-addition to alkynes has been reported to occur through a nickel-catalyzed approach.[621] Intramolecular examples of this reaction have also been reported,[433a,b,622] as have radical versions.[622,623]

The palladium-catalyzed allylstannylation of norbornene has also been reported, and occurs with the expected *exo*-selectivity.[624]

2.02.5.9 Allylation of C=X Bonds (X=S, Se, etc.)

The reaction of allylic stannanes with thionium ions has been briefly described by Saigo et al. The reaction, which is catalyzed by gallium(III) salts, occurs to provide homoallylic thioethers in good-to-very good yields, but with little diastereocontrol.[625] Similarly, the reaction of selonium ions with allylic stannanes has been reported to occur in acceptable yields under conditions of tin(IV) catalysts (equation 172).[413] Telluronium (and selonium) salts have also been shown to react with allylic stannanes in reasonable yields.[626]

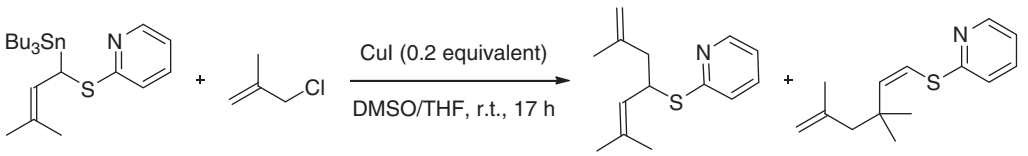


(172)

2.02.5.10 Other Reactions of Allylic Stannanes

Allylic stannanes react with iodine(III) compounds to undergo a formal Umpolung inversion. The resulting species readily react with a variety of nucleophiles such as aromatic and alcoholic species.[416] Such polarity inversion reactions have also been reported with the use of thallium compounds.[501b–e]

A variety of coupling reactions have been performed on allylic stannanes. For example, Takeda et al.[627] showed that copper can be used to catalyze the allylation reaction of allylic chlorides when a 2-mercaptopyridyl group was present for chelation (equation 173). The major product obtained was the vinylic thioether. Similarly, the reaction of allylic stannanes with allylic silanes can be catalyzed by tin.[628]



(173)

The allylic displacement of chlorides in the presence of carbon dioxide results in the formation of allylic esters. Palladium catalysis is necessary for this reaction, which proceeds to give a mixture of four possible products.[629] Similarly, the use of carbon monoxide can furnish ketones.[630] Generally speaking, the palladium-catalyzed cross-coupling of organostannanes with reaction partners is known as the Stille coupling reaction. It has only been applied to allylic stannanes on a few occasions, however. Usually, the leaving groups are carbonyloxy derivatives[631] (such as acetoxy and carbamate groups) or halides.[632] Intramolecular versions have also been reported.[633]

An oxidative coupling with silyl enol ethers has also been reported.[634] In addition, a formal oxidation, the allylation of carbon–hydrogen bonds, has been published.[635] A number of radical couplings have also been reported.[514,522b,636]

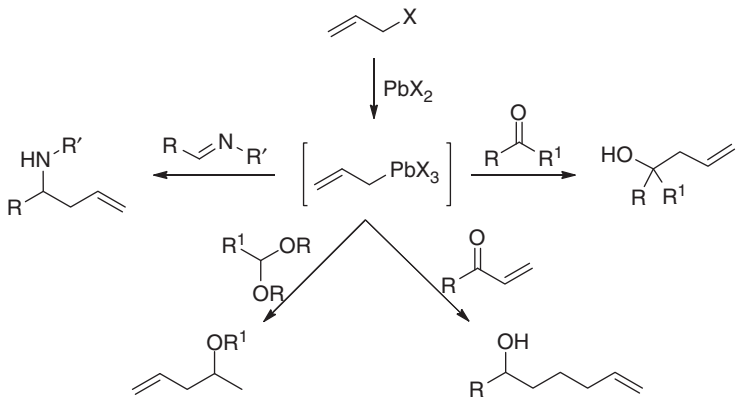
A variety of transmetallation reactions of allylic stannanes are well known. Some of these have already been presented in the course of earlier portions of this chapter. Other main group compounds also react with these compounds.[570b,637] In a related reaction, lithium–tin exchange is a widely used alternative to lithium–halogen exchange. Its use with allylic stannanes has been demonstrated.[638]

Allylic stannanes can be oxidized to allylic alcohols with a variety of reagents.[639] The reactions occur through an S_E2' oxidation pathway, wherein the allylic stannane attacks the oxidizing agent. Allylic stannanes will also undergo attack into a variety of other reagents, including epoxides, which are attacked at the more highly substituted position.[464c,640] The ene reaction of singlet oxygen ($^1O_2$) with allylic stannanes has also been documented, and reacts to form a vinylic stannane with an allylic hydroperoxide functionality.[641] The reaction with buckminsterfullerene has also been documented.[642]

If not carefully controlled, allylstannanes, in the absence of more acid-reactive species, will readily undergo protiodestannylation in the presence of protic media. The kinetics of this reaction have been studied, and it has been found that stronger acids most readily affect this reaction, which is first order in proton concentration.[643] The reaction of allylic stannanes with proton sources can also occur in a substitutionary manner, so long as oxidizing conditions are chosen.[644]

2.02.6 Allylplumbums

There are virtually no reports appearing in the literature detailing the synthesis and use of allylplumbums.[645] In all cases, their synthesis has come in the context of their immediate use. As such, the production and use of these compounds is discussed in tandem.



(174)

Allylic lead reagents are believed to be produced *in situ* from the interaction of freshly activated, metallic lead and allylic halides.[646] The reaction of these *in situ*-produced compounds has been shown to provide a means for the allylation of a variety of electrophiles. The efficiency of this attack is enhanced by the presence of tetrabutylammonium bromide. Due to the high toxicity of lead, and the desire to eliminate its use, Tanaka et al. later expanded this work into a method which is catalytic in lead. By beginning with a lead(II) compound, an oxidative addition into an allylic carbon–halogen is expected to occur, just as is the case with the other Group-IV elements (equation 174). The generated allyllead(IV) species undergoes allylplumbation, generating a lead(IV) salt as a by-product. Simply by adding a stoichiometric amount of sacrificial aluminum metal as a reductant, the lead(II) species is regenerated, and thereby becomes catalytic. They have since managed to expand the scope of this reaction, and have shown that the allyllead reagents undergo controlled reactions with a wide variety of electrophiles, including aldehydes, ketones, oxycarbenium ions, imines, acid chlorides, esters, lactones, anhydrides, and nitriles.[647] The chemoselectivity trends follow those that are expected based on similar allylation chemistries. The addition of allyllead compounds to dialkyl diazodicarboxylates has also been described on one occasion.[613] The use of lead in the synthesis of lactones via an allylation reaction has also been reported.[648]

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2.03 Prins Reactions and Carbonyl, Imine, and Thiocarbonyl Ene Reactions

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This chapter is a revision of the previous edition chapter by Barry B. Snider, Vol. 2, pp 527–561, © 1991, Elsevier Ltd.

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Glossary

Carbonyl ene reaction The thermal or Lewis acid-catalyzed reaction of an aldehyde or ketone with an alkene to give a homoallylic alcohol by either a concerted reaction proceeding through a six-membered ring transition state or a stepwise reaction with intramolecular proton transfer.

Oxonium ene reaction The intermolecular reaction of $R^1C{=}O^+\text{-}R^2$ with an alkene or the cyclization of $R^1C{=}O^+\text{-}R^2$ containing a double bond in the R^2 side chain to give a protonated ether that can occur by a concerted reaction proceeding through a six-membered ring transition state or a stepwise reaction with intramolecular proton transfer.

Prins addition The addition of a carbonyl compound to an alkene, usually catalyzed by a Brønsted acid, to give a carbocation that can lose a proton to give an allylic or homoallylic alcohol or react with a nucleophile.

Prins cyclization The cyclization of an alkoxonium ion $R^1C{=}O^+\text{-}R^2$ containing a double bond in the R^2 side chain to give an oxacycle with a carbocation β to the oxygen, most commonly a 4-tetrahydropyranyl cation, that can react with a nucleophile or lose a proton.

Prins-pinacol reaction In the first step, a β-hydroxy cation is formed by an intermolecular or intramolecular Prins addition or a Prins cyclization to an allylic alcohol. In the pinacol rearrangement step, a 1,2-hydride or alkyl shift converts the β-hydroxy cation to a ketone or aldehyde.

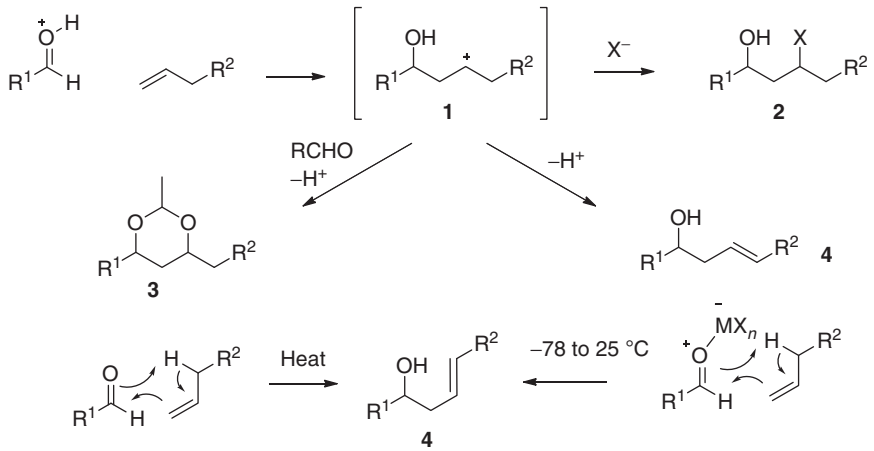
 doi:10.1016/B978-0-08-097742-3.00203-2

2.03.1 Introduction

The Prins and carbonyl ene reactions were reviewed in the first edition of Comprehensive Organic Synthesis more than 20 years ago.[1] This chapter is designed to update, but not replace, the first edition and also covers the analogous addition reactions of C=S and C=N double bonds to alkenes. Early reviews were cited in the first edition.[1] Recent reviews cover Lewis acid-induced additions of carbonyl compounds to alkenes,[2–4] asymmetric ene reactions of electron-deficient carbonyl compounds,[5–8] Prins reactions,[9] carbonyl ene reactions,[10] Prins cyclizations to form cyclic ethers,[11,12] pinacol-terminated Prins reactions,[13,14] and imine ene reactions.[15,16]

Coverage is restricted to the addition of carbonyl and thiocarbonyl compounds and imines to simple alkenes. Additions to enol ethers are more properly considered aldol reactions and are not covered. Similarly, additions to vinylsilanes and allylsilanes (*see* Chapter 2.02) in which the silyl group is lost during the reaction are also not covered because these are more properly considered as organometallic addition reactions. Ene reactions of imines and iminium ions are covered, but the cyclizations of *N*-acyliminium ions, which have been recently reviewed,[17,18] are not covered (*see* Chapter 2.17). The principles of ene and Prins reactions were well developed when the first edition was written in 1991. These principles are covered fully so that this chapter can be understood independently of the first edition, but most of the examples are new to both update the coverage and avoid overlap with the first edition. Some of the covered reactions, including asymmetric ene reactions of electron-deficient carbonyl compounds, Prins cyclizations leading to cyclic ethers, and pinacol-terminated Prins reactions have been developed in the past 20 years and are covered in greater detail.

The addition of aldehydes and ketones to alkenes in the presence of Brønsted acids is usually called the Prins reaction. Addition of the protonated carbonyl compound to the alkene gives a γ-hydroxy carbocation **1**, which reacts with a nucleophile such as chloride, water, or acetate to give **2**, adds to a second molecule of aldehyde to give **3** or loses a proton to give homoallylic alcohol **4** (see **Scheme 1**). Formaldehyde and electron-deficient carbonyl compounds undergo concerted thermal ene reactions with alkenes at temperatures ranging from 100 to 200 °C to give homoallylic alcohols **4** (R^1=H, CCl_3, or CO_2R).[1] A wide variety of carbonyl compounds undergo Lewis acid-catalyzed ene reactions with alkenes to give homoallylic alcohol ene adducts **4** in excellent yield at or below room temperature with high selectivity, although in some cases γ-chloro alcohols are formed as byproducts.[2–4] Recent investigations suggest that at least some of these Lewis acid-catalyzed ene reactions are stepwise, rather than concerted, but that the intermediate bears more resemblance to a π-complex than to the open carbocation intermediate in the Prins reaction.[19–25]

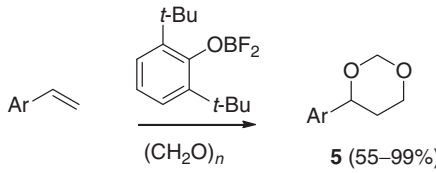


Scheme 1

2.03.2 Intermolecular Ene Reactions

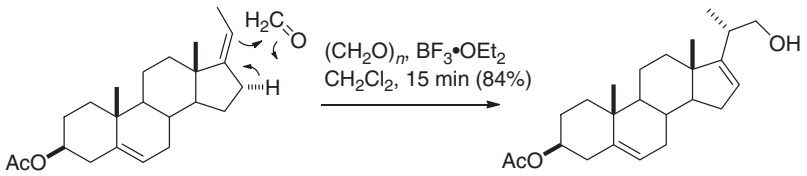
2.03.2.1 Formaldehyde

The reaction of formaldehyde with alkenes is of industrial interest, has been extensively studied, and was fully covered in earlier reviews.[1] Recent examples of its use include the use of the sterically congested Lewis acid 2,6-di-*t*-butylphenoxyboron difluoride as a catalyst for the reaction of styrenes with paraformaldehyde to give 4-aryl-1,3-dioxanes **5** in 55–99% yield (equation 1).[26] Iodine has also been reported to be an effective catalyst for the reactions of styrenes and other alkenes with formaldehyde and other aldehydes to give 4-substituted-1,3-dioxanes.[27a] Similar results have been obtained with cation-exchanged montmorillonite as a Brønsted acid catalyst.[27b]



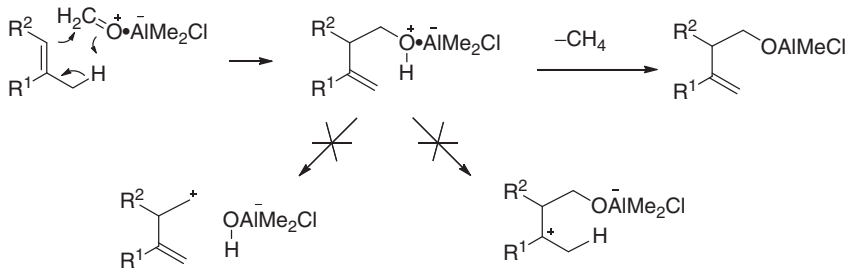
(1)

Formaldehyde undergoes thermal ene reactions with reactive 1,1-disubstituted and trisubstituted alkenes at 180–220 °C.[1] Excellent yields of ene adducts can be obtained from $BF_3{\cdot}Et_2O$- or $SnCl_4$-catalyzed addition of formaldehyde to alkenes that can give a tertiary carbocation. For instance, $BF_3{\cdot}Et_2O$-catalyzed ene reaction of formaldehyde with (*Z*)-5,17(20)-pregnadien-3β-yl acetate occurs exclusively from the less-hindered α-face to give the alcohol ene adduct with the correct stereochemistry at C-20 and functionality suitable for construction of the vitamin D side chain (equation 2).[28] A mixture of $BF_3{\cdot}OEt_2$ and 4 Å molecular sieves (MS) has been reported to efficiently promote the ene reactions of paraformaldehyde with α-methylstyrenes.[29]



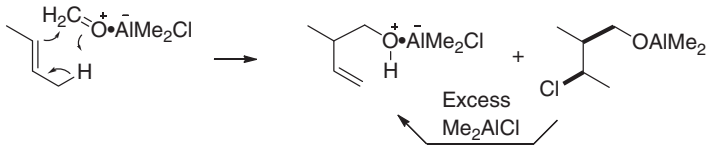
(2)

A problem with Lewis acid-catalyzed ene reactions of aldehydes is that the alcohol–Lewis acid complex produced in the reaction is susceptible to solvolysis and is a strong protic acid capable of protonating the double bond of the ene adduct or alkene starting material. Me_2AlCl in equivalent or greater amounts is a useful catalyst for these reactions.[30] The alcohol-Me_2AlCl complex formed in the reaction decomposes rapidly to give methane and a nonbasic aluminum alkoxide which does not undergo these side reactions (see **Scheme 2**). With this Lewis acid, ene adducts are obtained in good yield from formaldehyde and mono- and 1,2-disubstituted alkenes as well as those that can give a tertiary carbocation. These reactions involve a zwitterionic intermediate or π-complex that selectively undergoes a [1,5]-proton shift to give the ene adduct-Me_2AlCl complex, which loses methane. Because these reactions require a full equivalent of Lewis acid, which is consumed in the reaction, they are more properly referred to as Lewis acid-induced rather than catalyzed reactions.



Scheme 2

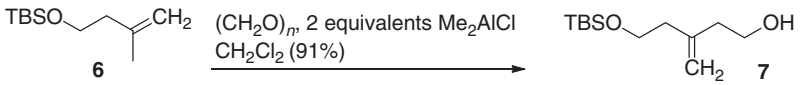
With 1 equivalent of Me_2AlCl, a γ-chloro alcohol is formed as a byproduct when the carbocation is secondary. With 1.5–2 equivalents of Me_2AlCl, γ-chloro alcohols are formed as transient intermediates. Those derived from acyclic alkenes give ene adducts. Those derived from cyclohexene and cyclopentene give complex mixtures of products. The chloro alcohols formed from 1,2-disubstituted alkenes result from the stereospecifically *syn* addition of the hydroxymethyl group and the chloride to the double bond (equation 3).[30]



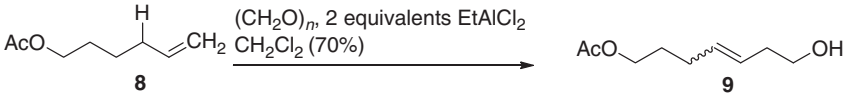
(3)

These Me_2AlCl-induced reactions of formaldehyde are successful because the Lewis acid is a Brønsted base as well as a strong Lewis acid. Unfortunately, the methyl group of Me_2AlCl can also act as a nucleophile. Formaldehyde undergoes Me_2AlCl-induced addition reactions with all simple alkenes and many functional groups are tolerated. In a recent example, TBS ether **6** reacts with paraformaldehyde and two equivalents of Me_2AlCl to give **7** in 91% yield (equation 4).[31] The second equivalent of Me_2AlCl presumably binds to the silyl ether. Other Lewis acids are less effective. However, functionalized alkenes that contain less nucleophilic mono- and 1,2-disubstituted double bonds are not nucleophilic enough to react with the formaldehyde–Me_2AlCl complex.

Reaction of 5-hexen-1-yl acetate (**8**) with formaldehyde and Me_2AlCl gives only ethanol from addition of a methyl group to the aldehyde. Me_2AlCl preferentially complexes to the more basic acetate group rather than formaldehyde. Furthermore, the acetate–Lewis acid complex is electron withdrawing and decreases the nucleophilicity of the double bond relative to that of the methyl group of Me_2AlCl. Therefore, no ene reaction occurs even if a second equivalent of Me_2AlCl is used. Fortunately, use of 2 equivalents of $EtAlCl_2$, a stronger Lewis acid with a less nucleophilic alkyl group, gives **9** as a 3:1 (*E*):(*Z*) mixture in 70% yield (equation 5).[32]

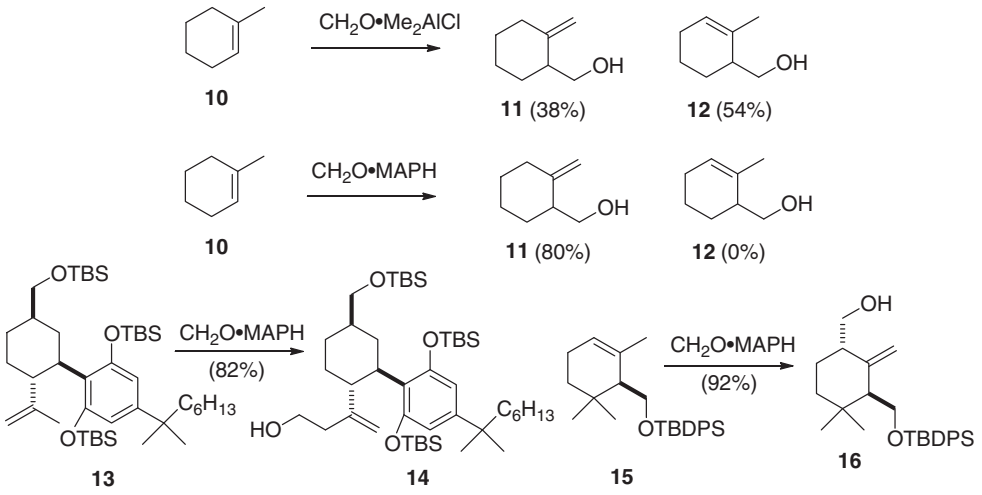


(4)



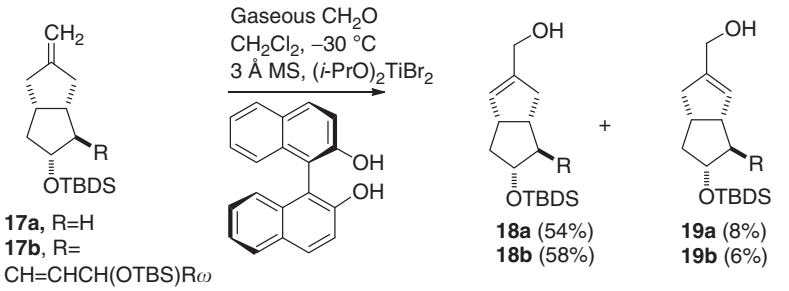
(5)

Yamamoto prepared a stable formaldehyde complex by reacting trioxane with methylaluminum bis(2,6-diphenylphenoxide) (MAPH).[33] The resulting very hindered aluminum formaldehyde complex undergoes ene reactions with 1,1-di- and trisubstituted alkenes to give ene adducts in high yield with very high selectivity for abstraction of a proton from the least hindered allylic carbon. For instance 1-methylcyclohexene (**10**) affords a 41:59 mixture of **11** and **12** in 92% yield with $CH_2O{\cdot}Me_2AlCl$,[30] but gives only **11** in 80% yield with $CH_2O{\cdot}$MAPH (see **Scheme 3**).[33] The latter complex is also compatible with more acid sensitive functional groups. For instance, reaction of **13** with $CH_2O{\cdot}$MAPH affords **14** in 82% yield.[34] Similarly, reaction of **15** with $CH_2O{\cdot}Me_2AlCl$ provides a 4:1 mixture of **16** and the *cis* isomer in only 50% yield, whereas reaction with $CH_2O{\cdot}$MAPH provides only **16** in 92% yield.[35] Formaldehyde encapasulated in zeolites has also been used for ene reactions with 1,1-di- and trisubstituted double bonds.[36] This reagent shows selectivity for the ring double bond of limonene, whereas $CH_2O{\cdot}Me_2AlCl$ and $CH_2O{\cdot}$MAPH are selective for the side chain double bond.



Scheme 3

Asymmetric ene reactions of formaldehyde have been very difficult to achieve because the formaldehyde does not have diastereotopic faces even after complexation to a Lewis acid. The first example was reported by Mikami who found that gaseous formaldehyde undergoes an ene reaction with **17a** catalyzed by BINOL and $(i\text{-PrO})_2TiBr_2$ to give an 88:12 mixture of enantiomers **18a** and **19a** in 61% yield (see equation 6).[37] A similar reaction with **17b** gives a 90:10 mixture of regioisomers **18b** and **19b**, in which the double bond position is controlled primarily by the catalyst stereochemistry. The major isomer **18b** was elaborated to a 3-oxaisocarbacyclin.[37]



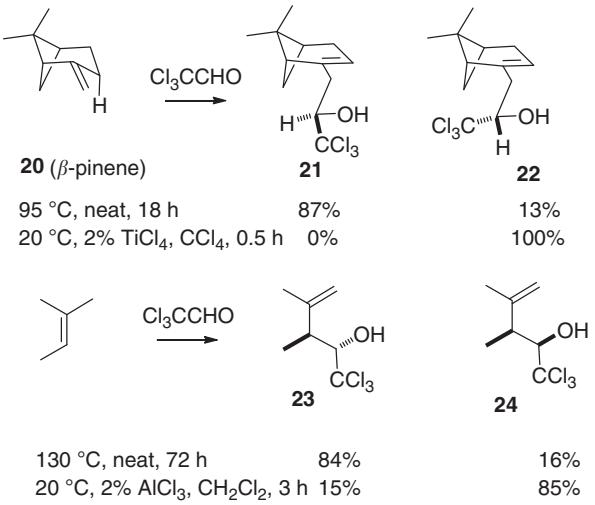
(6)

2.03.2.2 Electron-Deficient Aldehydes

The thermal and Lewis acid-catalyzed reactions of electron-deficient aldehydes such as chloral, fluoral, glyoxylate esters, and phenylglyoxal have been extensively studied. The electron-withdrawing substituent makes these aldehydes much more reactive in both thermal and Lewis acid-catalyzed ene reactions. Ene reactions proceed with a high degree of enantioselectivity with chiral Lewis acid catalysts.

2.03.2.2.1 Chloral

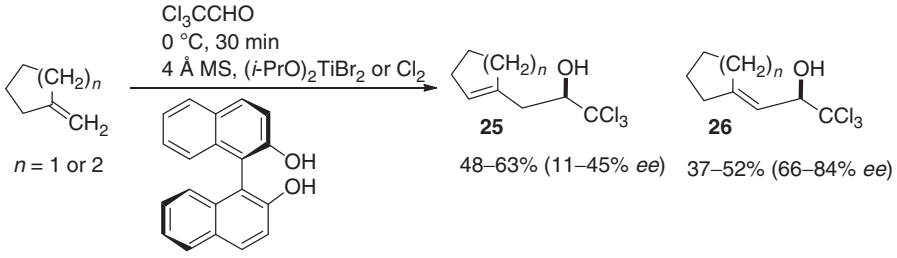
A series of papers by Gill and coworkers extensively explored the ene reactions of chloral.[38] The general trend in reactivity with alkenes is as follows: 1,1-di- > tri- > mono- > *cis*-1,2- > alkynes > *trans*-1,2-disubstituted.[38a] Thermal reactions can be carried out at 90–130 °C with 1,1-di- and trisubstituted alkenes. Lewis acid-catalyzed reactions are best carried out with 2% $AlCl_3$ or $TiCl_4$ in CH_2Cl_2 or CCl_4 for reactive alkenes and 6–20% $AlCl_3$ for less reactive alkenes. *Endo*/*exo* selectivity appears to be determined largely by steric interactions rather than electronic effects. Thermal reaction of *β*-pinene (**20**) with chloral at 95 °C gives an 83:17 mixture of **21** and **22** (see Scheme 4). The major product is formed with the trichloromethyl group *exo* to avoid steric interactions with the one-carbon bridge. A $TiCl_4$-catalyzed reaction of chloral with *β*-pinene (**20**) gives exclusively **22**. The Lewis acid complexes to the lone pair of the carbonyl group *trans* to the trichloromethyl group. Reaction occurs selectively from transition state with the trichloromethyl group *endo* and the $TiCl_4$ *exo*, which minimizes steric interactions of the bulky Lewis acid with *β*-pinene. Reactions with trisubstituted alkenes are more complex since the hydrogen can be transferred from two different sites. Reaction occurs with some preference for transfer of a hydrogen from the alkyl group *anti* to the vinylic hydrogen. The thermal ene reaction of 2-methyl-2-butene with chloral at 130 °C for 72 h gives an 84:16 mixture of diastereomers **23** and **24**. As with *β*-pinene, the stereoselectivity is switched with Lewis acid catalysis. Reaction in CH_2Cl_2 with 2% $AlCl_3$ at 20 °C for 3 h provides a 15:85 mixture of **23** and **24**.



Scheme 4

Yamamoto found that the organoaluminum reagent prepared from Me_3Al and (*R*)-(+)-3,3′-bis(triphenylsilyl)binaphthol catalyzes the ene reaction of chloral and pentafluorobenzaldehyde with 1,1-disubstituted alkenes at −78 °C giving the expected ene adducts in 40–90% yield and 60–90% enantiomeric excess.[39] Use of the sterically hindered binaphthol is necessary; low yields of racemic products are obtained with 3,3′-diphenylbinaphthol.

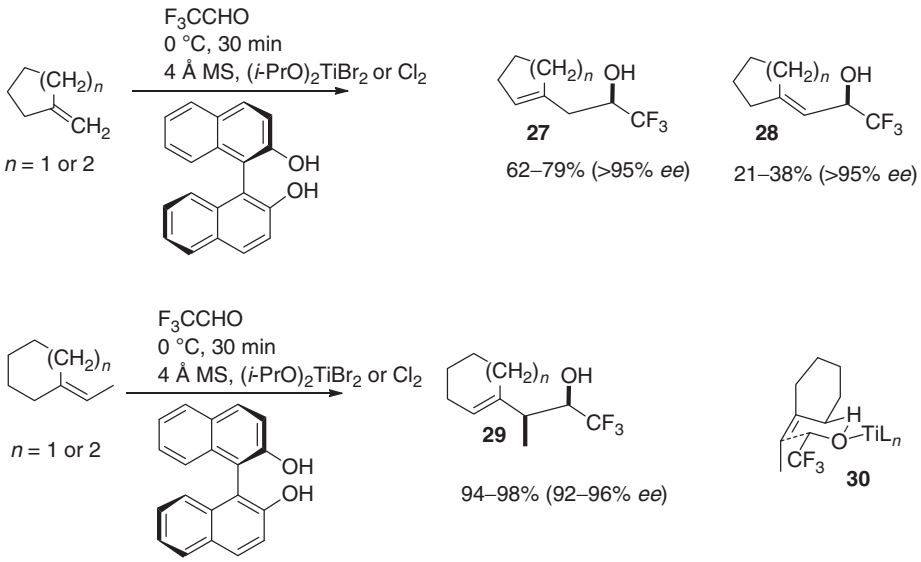
Mikami found that chloral reacts with methylenecyclopentane or methylenecyclohexane with BINOL and $(i\text{-PrO})_2TiBr_2$ or $(i\text{-PrO})_2TiCl_2$ as the catalyst to give mixtures of the homoallylic alcohol ene adduct **25** and the allylic alcohol **26**, which must be formed by a stepwise reaction. Both **25** and **26** are formed with moderate *ee* (see equation 7).[40,41] Faller found that a $(i\text{-PrO})_2TiCl_2$/racemic BINOL catalyst can be poisoned with an inactive enantiopure catalyst, $(i\text{-PrO})_2TiCl_2$/diisopropyl D-tartrate to yield a catalyst that sometimes gives better *ees* than enantiopure BINOL.[42]



(7)

2.03.2.2.2 Fluoral

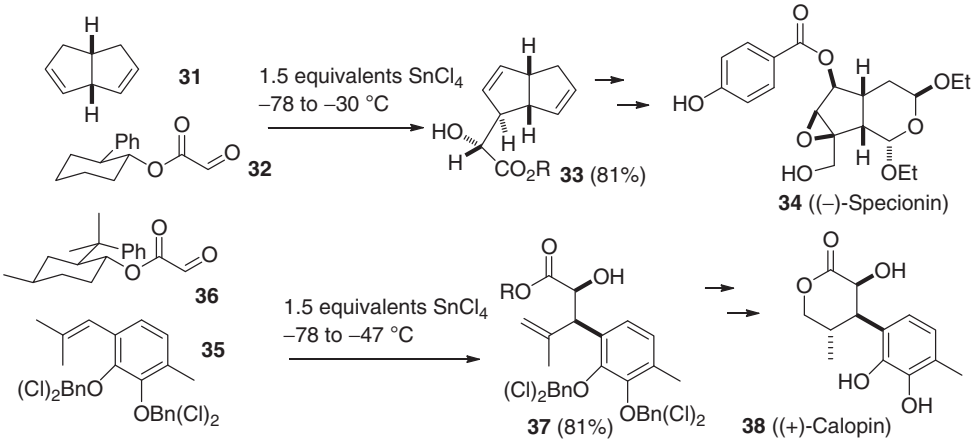
Thermal ene reactions of fluoral are unsuccessful. Mixtures of homoallylic alcohol ene adduct and Prins-type products are obtained from fluoral and mono- and 1,2-substituted alkenes with $FeCl_3$ at 80 °C,[43a,b] or $AlCl_3$ or $MeAlCl_2$ at −78 °C.[43b] Mixtures of ene and Diels–Alder adducts are obtained from fluoral and dienes with $ZnCl_2$ or $Zn(OTf)_2$ catalysts.[43c] Mikami found that the BINOL and $(i\text{-PrO})_2TiBr_2$ or $(i\text{-PrO})_2TiCl_2$ catalyzed ene reactions with fluoral are much more successful than those with chloral.[40,41,44,45] The reaction of fluoral with methylenecyclohexane or methylenecyclopentane affords primarily ene adduct homoallylic alcohol **27** (62–79%) with much less of the allylic alcohol **28** (21–38%) (see Scheme 5). More significantly, both products are formed in >95% *ee*. Similar results are obtained with difluoroacetaldehyde. The analogous reactions of fluoral with trisubstituted alkenes occur with excellent control of absolute and relative stereochemistry. Reaction of ethylidenecyclohexane or ethylidenecycloheptane affords 94–98% of the *syn* alcohol **29** in 92–96% *ee*. The reaction is proposed to proceed through transition state **30**. The diastereoselectivity is similar with 2-methyl-2-butene, but the *ee* drops to 78%.



Scheme 5

2.03.2.2.3 Glyoxylate esters

The previous edition[1] included the determination of *endo*/*exo* stereochemistry of the thermal and $FeCl_3$-catalyzed ene reactions of methyl glyoxylate with various alkenes,[46] and Whitesell's development of asymmetric ene reactions of glyoxylate esters using 8-phenylmenthol and *trans*-2-phenylcyclohexanol as chiral auxiliaries.[47] Applications[48] of the latter reaction in total synthesis include the $SnCl_4$-catalyzed reaction of diene **31** with *trans*-2-phenylcyclohexyl glyoxylate (**32**) to give **33** in 81% yield, which was elaborated to (−)-specionin (**34**) (see Scheme 6).[48b] The ene reaction occurs with only one of two double bonds related by mirror

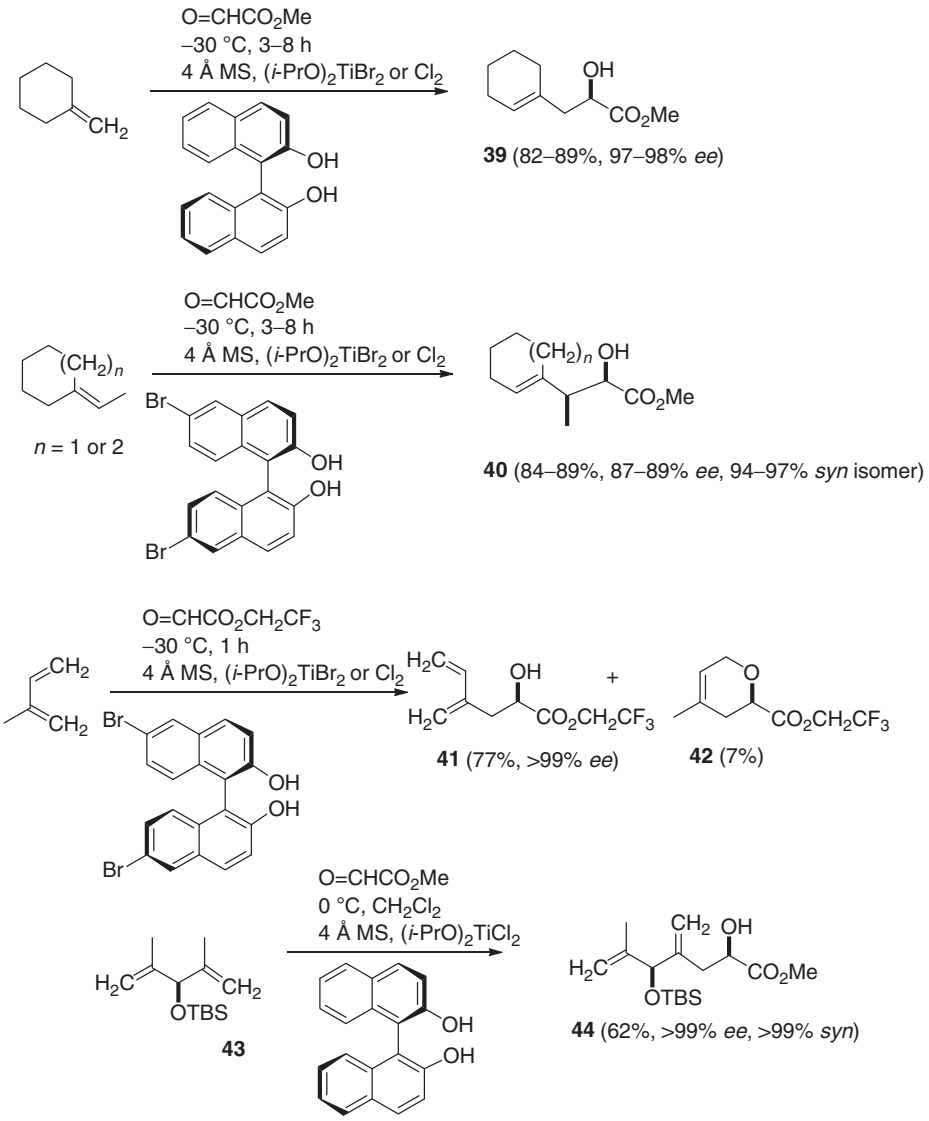


Scheme 6

symmetry and controls the stereochemistry at both centers. Steglich found that the $SnCl_4$-catalyzed reaction of alkene **35** with 8-phenylmenthyl glyoxylate (**36**) affords ene adduct **37** in 81% yield, which was elaborated to (+)-calopin (**38**).[49]

A major advance since the first edition has been the development of asymmetric catalysts for asymmetric glyoxylate ene reactions, which has been recently reviewed.[10,50]

Mikami found that reaction of BINOL with $(i\text{-PrO})_2TiBr_2$ or $(i\text{-PrO})_2TiCl_2$ and 4 Å MS forms a BINOL-Ti dihalide *in situ* that efficiently catalyzes the ene reactions of methyl glyoxylate with methylenecyclohexane at –30 °C to give **39** in 82–89% yield and 97–98% *ee* (see **Scheme 7**).[51] Similar results are obtained with other 1,1-disubstituted alkenes, such as isobutylene, α-methylstyrene, 2-ethyl-1-butene, and methylenecyclopentane.[51] Reaction with methallyltrimethylsilane affords mainly ene adducts rather than Sakurai–Hosomi products resulting from loss of the trimethylsilyl group.[52] These reactions show a remarkable positive nonlinear effect. The optical purity of the product exceeds the optical purity of the BINOL because the catalyst forms an unstable RR dimer that dissociates to the monomer, which catalyzes the reaction and a stable RS dimer that does not catalyze the reaction.[53] BINOL-derived μ-oxo titanium complexes catalyze the ene reactions of methyl glyoxylate with α-methylstyrene in 98.7% *ee* and 88% yield with only 0.2 mol% of catalyst.[54] Catalysts derived from 6-Br-BINOL are also very effective for this reaction.[55]

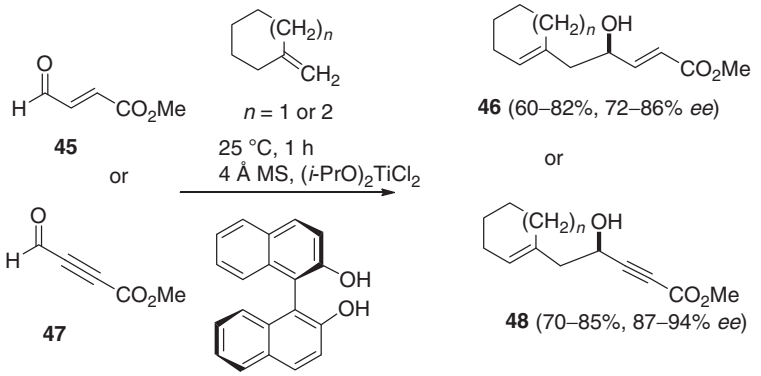


Scheme 7

The reaction of α-methylstyrene and methyl glyoxylate has been used to demonstrate the efficacy of catalysts prepared by self-assembly of several components,[56a] the sodium counter cations in the zeolite molecular sieve have been shown to be important for formation of the active catalyst,[56b] and the effect of flexible biphenols has been explored.[56c] Highly enantioselective catalysts are formed from the pseudoenantiomeric mixture of BINOL, the opposite enantiomer of F_8BINOL and $Ti(O\text{-}i\text{-}Pr)_4$,[56d] catalysts

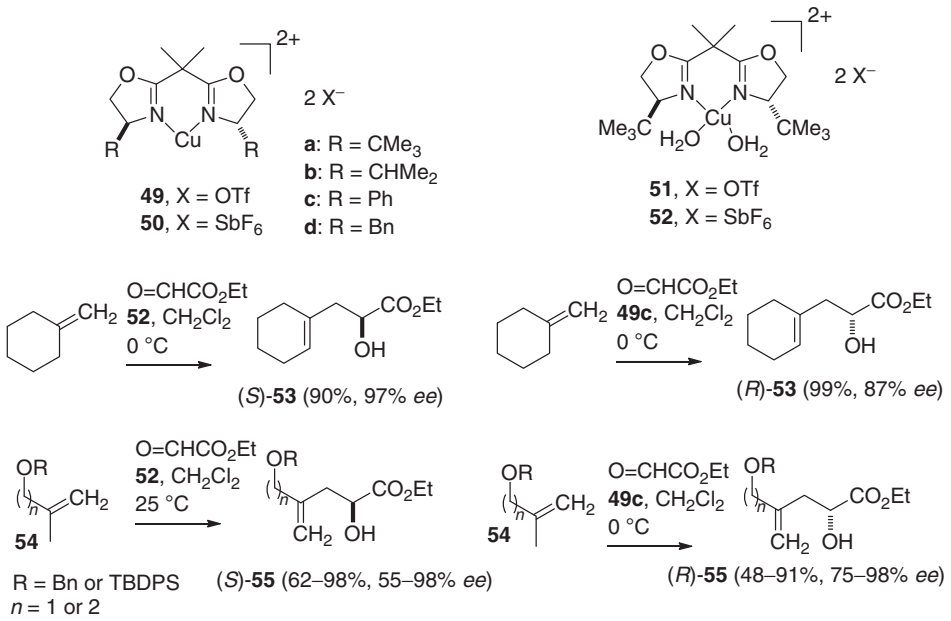
have been prepared from noncross-linked copolymers with pendant BINOL groups,[56e] complexes prepared from 6,6′-I_2- or 6,6′-$(CF_3)_2$-BINOL catalyze ene reactions in high enantiomeric excess and low-catalyst loadings under quasi solvent-free conditions,[56f] Ti-bridged polymers and catalysts derived from highly modified BINOLs are also effective catalysts,[56g,j] and self-supported heterogenous catalysts are also effective.[56k,l] Asymmetric synthesis by enantiomer-selective activation of racemic catalysts has also been described for this reaction.[56m]

Mikami studied the scope and selectivity of asymmetric glyoxylate ene reactions with unsymmetrically substituted alkenes. A 9:1 mixture of *E*- and *Z*-isomers was obtained from 2-ethyl-1-butene.[51] With 2-methyl-1-butene, there is a approximately 3:2 preference for abstraction of a methylene, rather than a methyl, hydrogen. However, with 2,3-dimethyl-1-butene, there is an approximately 85:15 preference for abstraction of a methyl, rather than methine, hydrogen.[51] Using a catalyst derived from 6,6′-dibromo-BINOL in toluene, ethylidenecyclohexane and ethylidenecyclopentane afford *syn* adduct **40** selectively in high yield and 87–89% *ee*.[57] Using this catalyst, trifluoroethyl glyoxylate undergoes an ene reaction with isoprene to give the ipsdienol precursor **41** in 77% yield and >99% *ee*, with only 7% of the hetero Diels–Alder adduct **42**.[58] More **42** is formed with other esters or catalysts. With the chiral alkenes *β*-pinene (**20**) and *α*-fenchene different products are obtained from the matched and mismatched catalyst.[59] The symmetrical bis-allylic silyl ether **43** reacts at only one double bond to give the ene adduct **44** in >99% *ee* and >99% selectivity for the *syn* isomer.[60] The vinylogous and alknylogous glyoxylates **45** and **47** also undergo ene reactions with 1,1-disubstituted alkenes with good control of absolute stereochemistry to give **46** and **48** (see equation 8).[61] Transition state models have been proposed for the ene reactions of glyoxylates and alknylogous glyoxylates.[62]



(8)

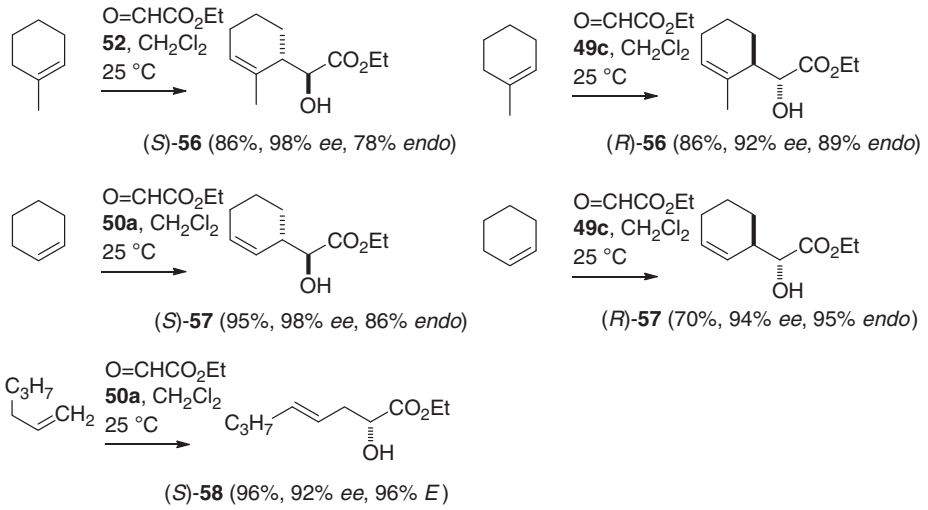
Evans reported a series of bis(oxazoline) (BOX) Cu(II) complexes that are effective catalysts for the reaction of ethyl glyoxylate with 1,1-di-, tri-, and even the much less reactive 1,2-di- and monosubstituted alkenes (see **Scheme 8**).[63] Complex **52** (1 mol%) catalyzes the reaction of methylenecyclohexane and ethyl glyoxylate to give (*S*)-**53** in 97% *ee*. Complex **49c** catalyzes the ene reaction to give (*R*)-**53** even though the substituents on the BOX ligand are *S,S* in both cases. Similar results are obtained with



Scheme 8

isobutylene, α-methylstyrene, and methylenecyclopentane. Allylic and homoallylic ethers **54** give adduct (*S*)-**55** with catalyst **52** and (*R*)-**55** with catalyst **49c**. A proton is transferred exclusively from the methyl group in these reactions. Little regioselectivity is seen in the ene reaction with 2-methyl-1-butene and either catalyst, whereas the reaction with 2,4,4-trimethyl-1-butene gives a mixture with catalyst **52**, but transfers a proton exclusively (98%) from the methyl group with catalyst **49c** to give products analogous to (*R*)-**55**.[63]

The ene reactions with 1-methylcyclohexene proceed in good yield at 25 °C to give ene adducts (*S*)-**56** with 78% selectivity for the *endo* isomer shown with catalyst **52** and (*R*)-**56** with 89% selectivity for the *endo* isomer shown with catalyst **49c** (see Scheme 9). Cyclohexene is less reactive, but similar yields of ene adducts **57** are obtained from cyclohexene with slightly greater selectivity for the *endo* isomers shown using the more reactive and less stable anhydrous catalyst **50a** rather than **52**. The enantioselectivity is also high with cyclopentene and *cis*-2-butene, but the *endo* selectivity is significantly lower, except for the reaction of *cis*-2-butene catalyzed by **49c**. Even 1-hexene forms (*S*)-**58** in 92% *ee* with 10 mol% of catalyst **50a**.[63]



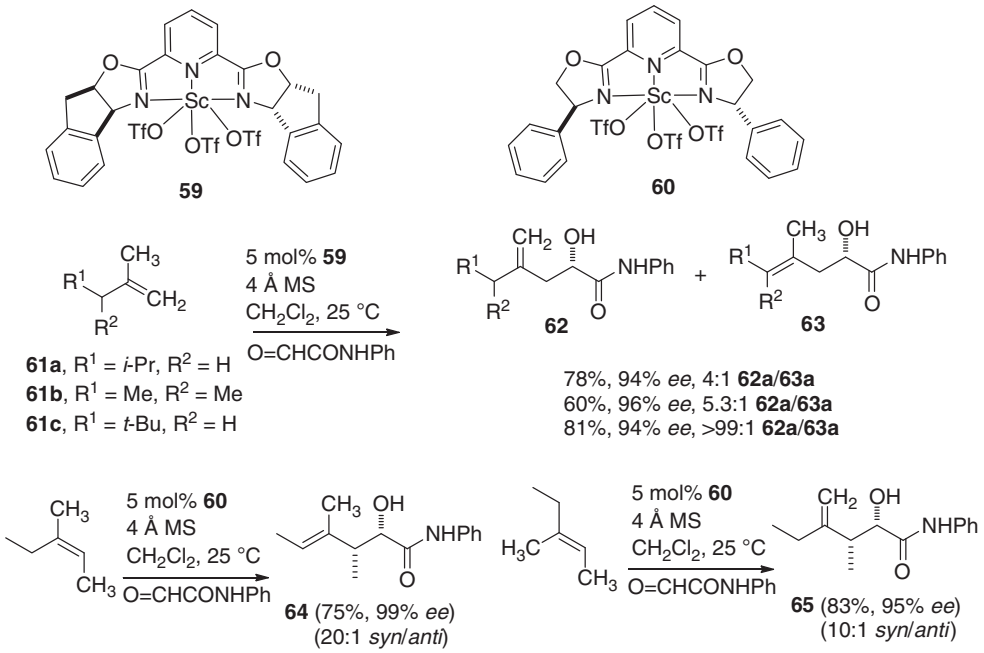
Scheme 9

Calculations suggest that these reactions proceed by a stepwise mechanism.[64] These ene reactions are also catalyzed by lanthanum PyBOX catalysts,[65a] using copper complexes of poly(ethylene glycol) supported BOX ligands,[65b] perfluoroalkyl BOX ligands,[65c,f] heterogenous zeolite supported catalysts,[65d] polystyrene-bound BOX ligands,[65g] nano-sized BOX catalysts,[65h] and electrostatically immobilized BOX catalysts.[65k] BOX ligands in a spiro skeleton have been explored,[65e,i] In(III)-PyBOX ligands have been used successfully for a variety of 1,1-disubstituted alkenes[65j,l] and copper complexes of more highly substituted box ligands are also effective.[65m]

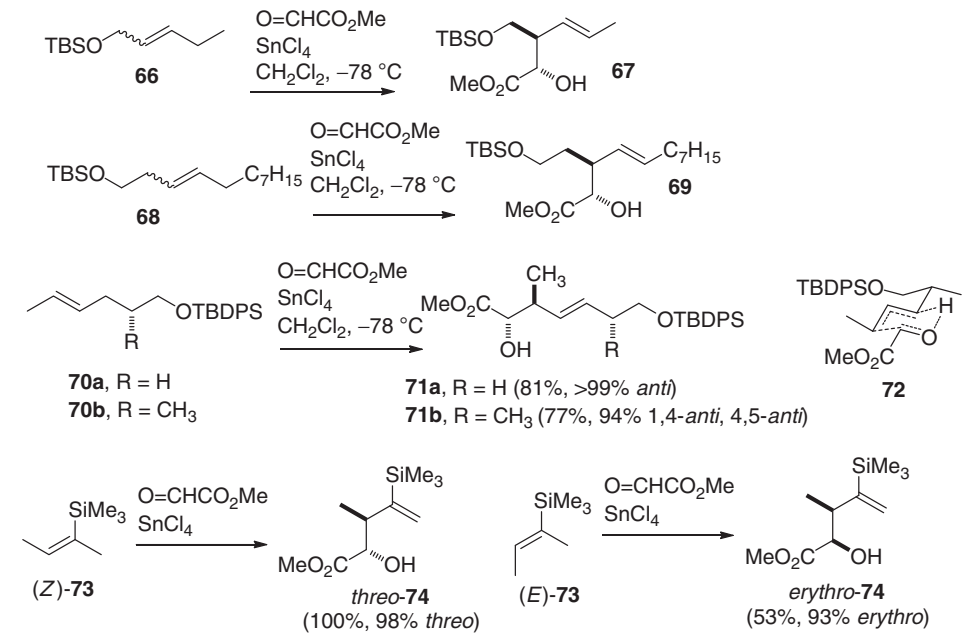
Evans found that scandium PyBOX complexes **59** and **60** catalyze the ene reactions of *N*-phenyl glyoxamide with 1,1-di- and trisubstituted alkenes (see Scheme 10).[66] The *N*-phenyl glyoxamide was used rather than the ester because the products are crystalline and can be purified by recrystallization rather than chromatography. Methylenecyclopentane, methylenecyclohexane, isobutylene, and α-methylstyrene give the ene adducts with catalyst **59** in 73–99% yield and 92–94% *ee*. A proton is abstracted preferentially from the allylic methyl group of **61a-c** to give mixtures of **62a-c** and **63a-c** containing mainly the terminal alkene **62**. Scandium complex **60** catalyzes the reaction with the isomeric 3-methyl-2-pentenes through an *exo* transition state with selective abstraction of a proton from the alkyl group *anti* to the vinylic hydrogen. Products **64** and **65** are formed with very high enantioselectivity, diastereoselectivity, and regioselectivity. It is noteworthy that ene reactions catalyzed by **59** and **60** proceed through an *exo* transition state, whereas those catalyzed by Cu-BOX complexes **49–52** proceed through an *endo* transition state.

Mikami reported that $[Pd(CH_3CN)_2(S)\text{-Tol-BINAP}](SbF_6)_2$ catalyzes the ene reaction of ethyl glyoxylate with 1,1-di- and trisubstituted alkenes at 60 °C in excellent yield and 73–88% *ee*.[67] Related helically chiral palladium complexes also catalyze the enantioselective ene reactions of 1,1-disubstituted alkenes with ethyl glyoxylate.[68] These reactions have also been catalyzed with BIPHEP and other Pt complexes[69] and DPPF-Ni complexes.[70] Jurczak found that (salen)Cr(III) complexes are effective catalysts[71] and Rawal reported that hindered (salen)Co(III) complexes are effective at catalyst loadings as low as 0.1 mol%.[72] This complex also catalyzes the ene reaction of methylenecyclopentane with 2-pyridinecarboxaldehyde, but not other electron-deficient aldehydes suggesting that there is bidentate coordination of the catalyst to the aldehyde.

Glyoxylate ene reactions have been widely used in organic synthesis. Mikami and Nakai examined the $SnCl_4$-catalyzed reaction of methyl glyoxylate with allylic and homoallylic silyl ethers such as **66** and **68** (see Scheme 11).[73] The glyoxylate adds to the end of the double bond closer to the oxygen to give the *anti* products **67** and **69** as the (*E*)-isomer regardless of the stereochemistry of the starting double bond. Alkene **68** was prepared by the $EtAlCl_2$-catalyzed reaction of formaldehyde with 1-undecene[32] and



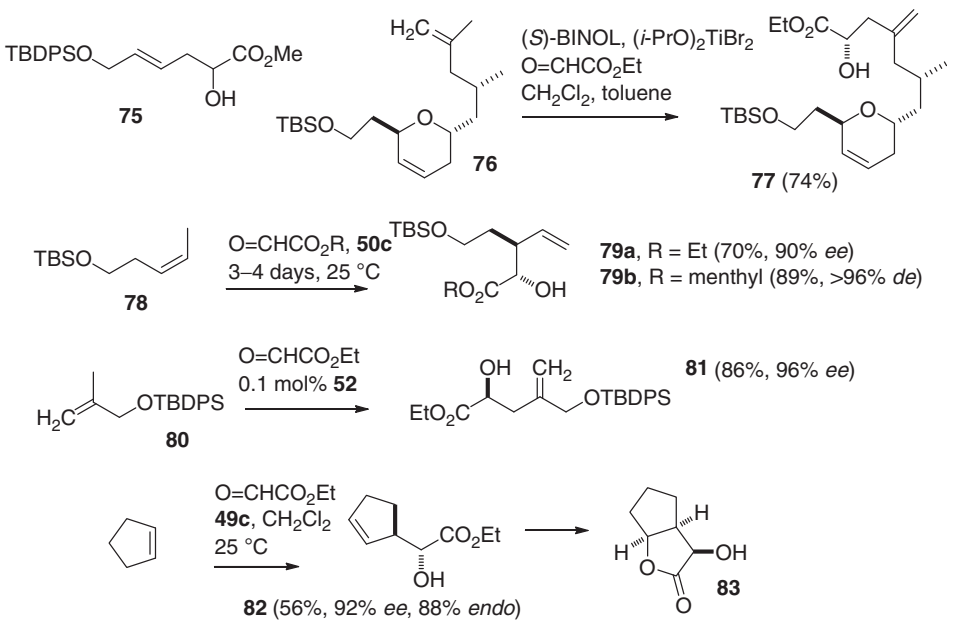
Scheme 10



Scheme 11

silylation. The ene product **69** was elaborated to avenaciolde.[73] The regioselectivity with bishomo silyl ethers **70** is opposite to that with allyl and homoallyl silyl ethers **66** and **68**.[74] The enophile adds to the end of the double bond of **70** away from the silyl ether to give exclusively the *anti* product **71**. Remarkably, the stereochemistry of the methyl group of **70b** controls the stereochemistry of the two newly formed chiral centers of **71b**, suggesting that the ene reaction occurs through transition state **72**. Methyl glyoxylate undergoes stereospecific $SnCl_4$-catalyzed ene reactions with vinylsilanes (*Z*)-**73** and (*E*)-**73** to give predominantly threo- and erythro-**74**, respectively.[75]

The $SnCl_4$-catalyzed reaction of 3-buten-1-yl *tert*-butyldiphenylsilyl ether (TBDPS) affords **75**, which was elaborated to 2-keto-3-deoxy-D-gluconic acid (KDG) (see Scheme 12).[76] The ene reaction of ethyl glyoxylate with **76** catalyzed by (*S*)-BINOL and $(i\text{-PrO})_2TiBr_2$ provides **77** in 74% yield as >95% one stereoisomer that was elaborated to a laulimide intermediate.[77] Reaction of **78**



Scheme 12

with ethyl glyoxylate and $SnCl_4$ at −40 °C yields racemic **79a** in 76% yield.[78] The same reaction catalyzed by Cu-BOX ligand **50c** for 4 d at 25 °C gives **79a** (70% yield, 90% *ee*), which was used for the synthesis of amide-linked RNA. The selectivity was improved by using double asymmetric induction with the appropriate menthyl glyoxylate which gives **79b** in 89% yield and >96% *dr*.[78] The ene adduct prepared from isobutylene and ethyl glyoxylate using catalyst **49c** has been used as an intermediate for amphidinolide B1 synthesis.[79] The same ene adduct prepared using (*R*)-BINOL and $(i\text{-PrO})_2TiCl_2$ as the catalyst has been used as an intermediate in the synthesis of (*S*)-γ-fluoroleucine ethyl ester.[80] These procedures usually require the use of freshly distilled ethyl glyoxylate, which is problematic on a large scale. Use of 5 mol% zinc chloride as an additive allowed the use of polymeric ethyl glyoxylate and the ene adduct was prepared on a 20 g scale.[80] The ene reaction of methallyl TBDPS (**80**) with ethyl glyoxylate and Cu-BOX catalyst **52** affords **81**, which was used as an intermediate in the synthesis of (+)-azaspiracid-1.[81] The ene reaction of cyclopentene with ethyl glyoxylate catalyzed by **49c** affords ene adduct **82**, which was elaborated to the synthetically useful bicyclic hydroxylactone **83**.[82]

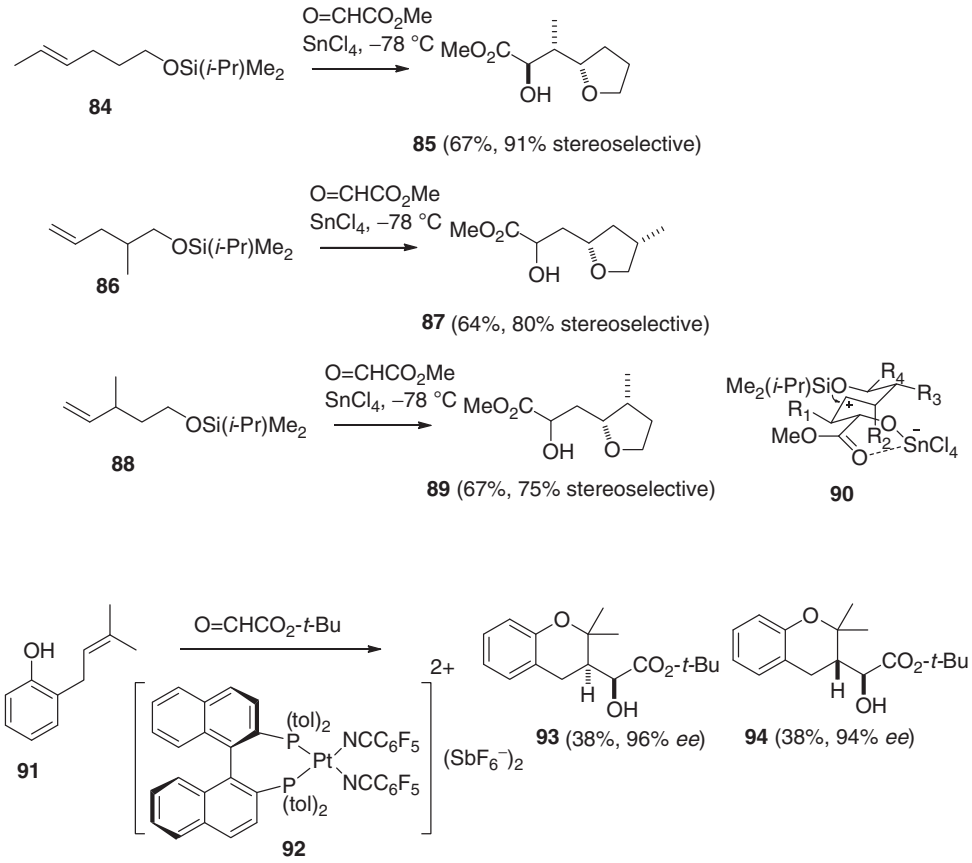
Mikami and Shimizu found that the $SnCl_4$-catalyzed reactions of methyl glyoxylate with a series of bishomoallylic silyl ethers **84**, **86**, and **88** gave tetrahydrofurans **85**, **87**, and **89**, respectively, by a Prins reaction resulting from intramolecular trapping of the intermediate secondary cation by the silyl ether oxygen (see **Scheme 13**).[83] The stereocontrol was >91% with **84**, but lower with **86** and **88** and other examples and appears to be explained by the proposed cationic intermediate **90**. Gagné recently reported a series of asymmetric Prins reactions between allyl phenols and glyoxylate esters catalyzed by (*R*)-[(tolBINAP)Pt$(NCC_6F_5)_2$][SbF_6]$_2$ (**92**) in which the phenol adds to the cation intermediate to give dihydrobenzopyrans and dihydrobenzofurans.[84] For instance, reaction of *t*-butyl glyoxylate with **91** affords a 1:1 mixture of **93** (96% *ee*) and **94** (94% *ee*). Other catalysts afford mainly ene products without phenol participation.

2.03.2.2.4 Phenylglyoxal

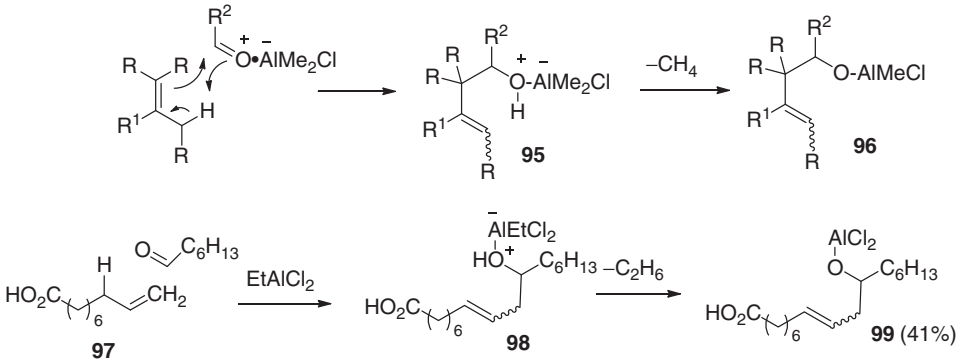
Asymmetric catalysis of the ene reactions of phenylglyoxal and substituted phenylglyoxals with 1,1-disubstituted alkenes has been achieved with optically active β-ketoiminato cationic cobalt(III) complexes (76–94% *ee*),[85] chiral platinum catalysts (84–94% *ee*),[69b] λ-[(BIPHEP)Pt][SbF_6]$_2$ (74–94% *ee*),[86] and chiral *N*,*N*′-dioxide nickel(II) complexes (97–99% *ee*).[87]

2.03.2.3 Aliphatic and Aromatic Aldehydes

Normal aliphatic and aromatic aldehydes, for example, acetaldehyde and benzaldehyde, are much less reactive than formaldehyde and electron-deficient aldehydes in ene and Prins reactions. Prins reactions of these aldehydes leads to even more complex mixtures of products than Prins reactions of formaldehyde, because of the additional stereocenter introduced in the reaction. Thermal ene reactions of these aldehydes cannot be carried out successfully. Lewis acid-catalyzed reactions may be successful, but the products sometimes decompose in the presence of Lewis acids. Snider and coworkers have found that moderate to good yields of adducts can be obtained from Me_2AlCl-induced ene reactions of these aldehydes and 1,1-di-, tri-, and tetra-substituted alkenes (see **Scheme 14**).[30,88] Use of a stoichiometric amount of Me_2AlCl is necessary since the adduct–Me_2AlCl complex **95** loses methane to give **96**, which prevents Brønsted acid-catalyzed isomerization of the ene adduct or starting alkene (**Scheme 2**). $EtAlCl_2$, a stronger Lewis acid than Me_2AlCl, with a less nucleophilic alkyl group, successfully induces the ene reactions of



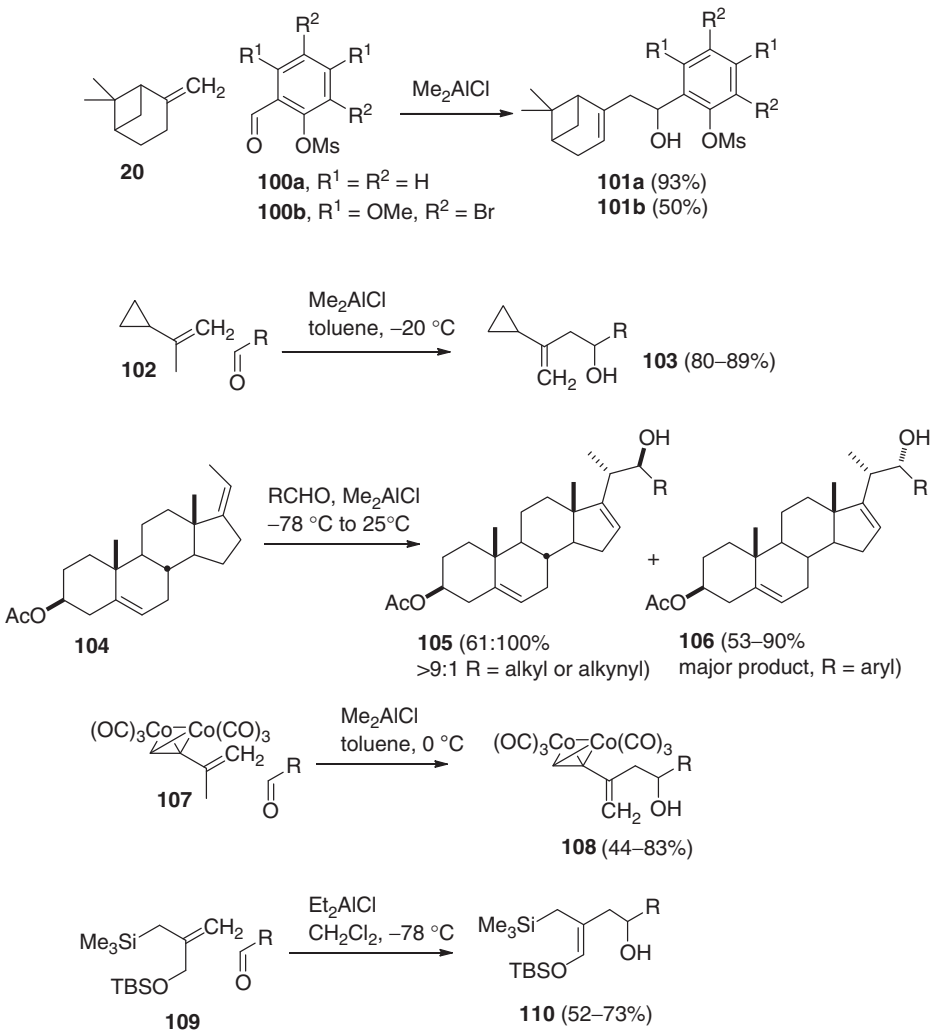
Scheme 13



Scheme 14

aliphatic aldehydes with terminal alkenes. For instance, reaction of 10-undecenoic acid (**97**) with 1 equivalent of heptanal and 2.2 equivalents of $EtAlCl_2$ for a few minutes at 0 °C provides a 41% yield of a 4:1 mixture of the $EtAlCl_2$ complex of ricinelaidic acid (*E*)-(**98**) and ricinoleic acid (*Z*)-(**98**), which loses ethane to give **99**.[32]

Some recent examples of alkylaluminum halide-induced ene reactions are shown below. The Me_2AlCl-induced ene reaction of *β*-pinene (**20**) with 2-mesyloxybenzaldehydes **100a** and **100b** afford the ene adducts **101a** (93%) and **101b** (50%), which were elaborated to the dimethyl ethers of robustadials A and B (see Scheme 15).[89] Isopropenylcyclopropane (**102**) undergoes Me_2AlCl-induced ene reactions with a variety of aromatic and aliphatic aldehydes to give ene adducts **103** in excellent yield.[90] Aldehydes undergo Me_2AlCl-induced ene reactions with steroid **104** to give a mixture of ene adducts **105** and **106**.[91] Stereoisomer **105** is the major product with aliphatic and alkynyl aldehydes, whereas **106** is the major product with aromatic aldehydes. The cobalt complexes of 2-(1-alkynyl)propenes **107** undergo Me_2AlCl-induced ene reactions with a variety of aldehydes giving **108** in 44–83% yield.[92] Allylsilane **109** undergoes Et_2AlCl-induced ene reactions with a variety of aldehydes to give enol ether **110** without involvement of the silyl group.[93] Use of $TiCl_4$ as the catalyst results in a Hosomi–Sakurai reaction with loss of the trimethylsilyl

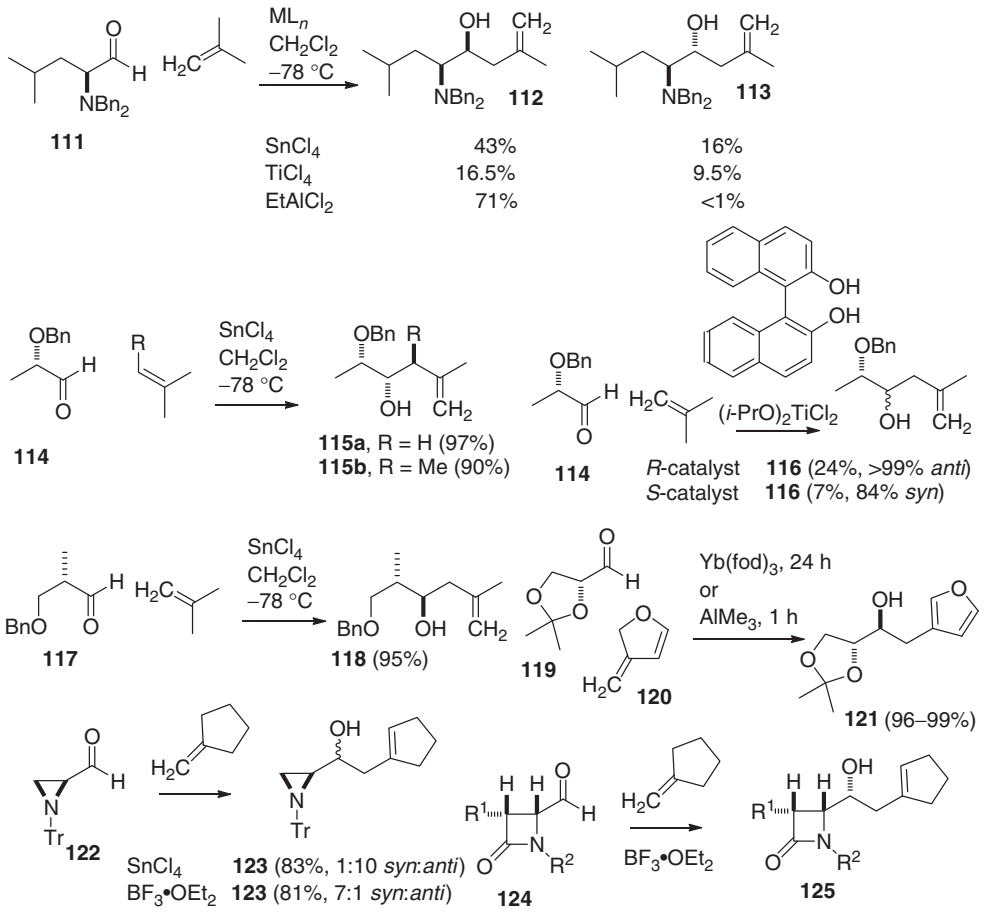


Scheme 15

group. Use of $BF_3{\cdot}OEt_2$ as the catalyst results in the formation of **110**, which reacts further with a second molecule of aldehyde to give a Prins cyclization product.

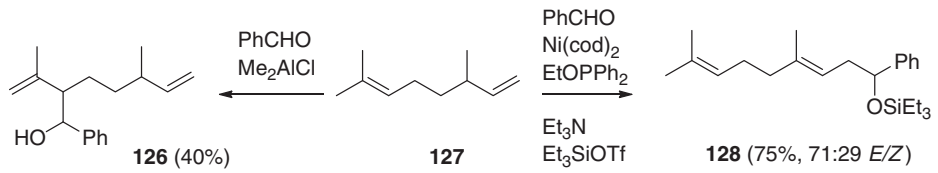
Mikami explored the reaction of α-dibenzylaminoaldehyde **111** with isobutylene and methylenecyclohexane (see Scheme 16).[94] The *syn* product **112** is formed preferentially in the best yield and stereoselectivity with $EtAlCl_2$. α-Benzyloxypropanal (**114**) undergoes a $SnCl_4$-catalyzed ene reaction with isobutylene to give exclusively the *syn* adduct **115a** resulting from chelation-controlled addition to the aldehyde.[95] A similar reaction with 2-methyl-2-butene affords the *syn*, *anti* adduct **115b** exclusively. In both reactions the selectivity and yield is lower with other Lewis acids. The reaction of isobutylene and **114** was also examined with BINOL and $(i\text{-PrO})_2TiCl_2$ as the catalyst. The *R*-catalyst is matched and preferentially gives the *anti* isomer of **116** via a nonchelated complex. The *S*-catalyst is mismatched and gives **116** in lower yield and with less selectivity for the *syn* isomer of **116**.[96] Similar results were obtained with methylenecyclohexane and methylenecyclopentane. $SnCl_4$-catalyzed ene reaction of aldehyde **117** with isobutylene affords exclusively **118** resulting from chelation controlled addition to the aldehyde.[95] The ene reaction of 3-methylene-2,3-dihydrofuran (**120**) with a variety of aldehydes was explored.[97] The best results were obtained with $Yb(fod)_3$ or $AlMe_3$ as in the reaction of isopropylidene glyceraldehyde (**119**) to give **121** in high yield.[97] The complex *trans*-$[Ru(salen)(NO)(H_2O)]^+$ catalyzes the ene reaction of aromatic aldehydes and dimethyl 2-oxomalonate with the reactive 1,1-disubstituted alkenes, methylenecyclohexane, 2-ethyl-1-butene, and β-pinene in 35–88% yield.[98] *N*-Tritylaziridinecarboxaldehyde (**122**) undergoes ene reactions with reactive 1,1-disubsituted alkenes.[99] The *anti* isomer of **123** is formed preferentially with $SnCl_4$ and the *syn* isomer is formed preferentially with $BF_3{\cdot}OEt_2$. 4-Oxoazetidine-2-carboxaldehydes **124** undergo $SnCl_4$ or $BF_3{\cdot}OEt_2$-catalyzed ene reaction with methylenecyclopentane, methylenecyclohexane and α-methylstyrene to give *syn* ene adducts such as **125** in 33–85% yield.[100]

Jamison has developed procedures to give homoallylic alcohol derivatives by the reaction of monosubstituted alkenes with aldehydes, Et_3SiOTf and catalytic $Ni(cod)_2$ and Ph_3P or $EtOPPh_2$ (see equation 9).[101,102] These reactions are mechanistically



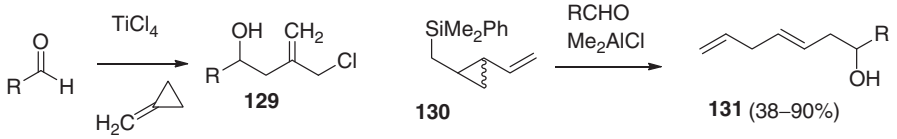
Scheme 16

distinct from Lewis acid-catalyzed ene reactions which occur at the most electron-rich alkene, whereas the Ni-catalyzed reactions occur only with monosubstituted alkenes. This distinction is exemplified by the reaction of **127** with benzaldehyde and Me_2AlCl in CH_2Cl_2 to give **126**, and with benzaldehyde, $Ni(cod)_2$, $EtOPPh_3$, Et_3N, and Et_3SiOTf in toluene to give **128**. A palladium catalyst and the Xantphos ligand in the presence of Et_3B catalyzes the reaction of dienes with aldehydes to give ene-type products, although the reaction is probably not an ene reaction in a mechanistic sense.[103]



(9)

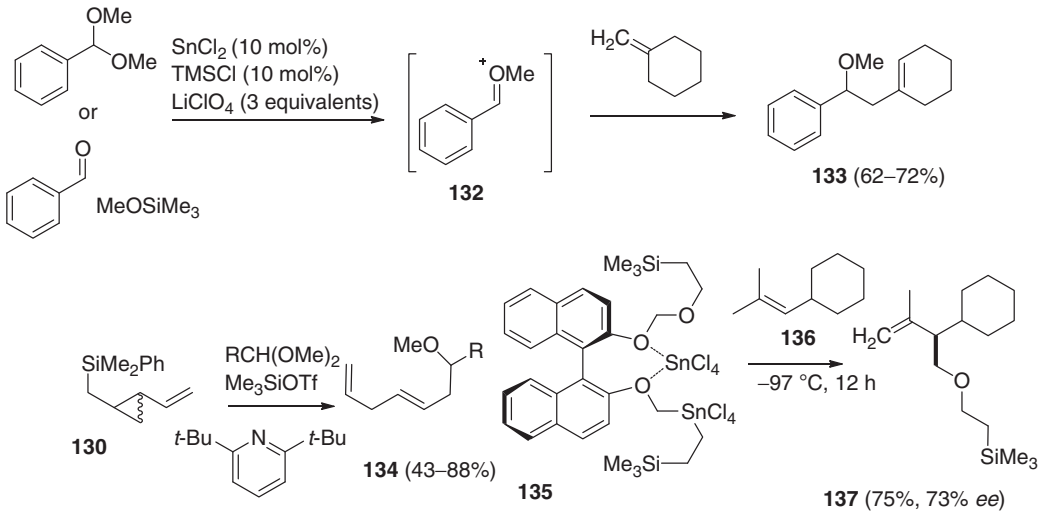
A few recent applications of Prins reactions of aliphatic aldehydes have been reported. In the presence of $TiCl_4$, aliphatic aldehydes add to methylenecyclopropane to give a cyclopropyl cation that opens to an allyl cation which is trapped by chloride to give **129** (see Scheme 17).[104] Me_2AlCl-catalyzed reaction of aliphatic and aromatic aldehydes with vinylcyclopropane **130** gives a cyclopropylcarbinyl cation that opens to a homoallyl cation that loses $PhMe_2Si$ to give dienol **131**.[105]



Scheme 17

2.03.2.4 Acetals

Ene-type products have also been obtained by the Lewis acid-catalyzed addition of acetals to alkenes. Mukaiyama found that treatment of benzaldehyde dimethyl acetal with $SnCl_2$ and TMSCl in the presence of excess $LiClO_4$ generated cation **132** which undergoes an ene reaction with methylenecyclohexane to give **133** (see Scheme 18).[106] Intermediate **132** can also be prepared from benzaldehyde and trimethylsilyl triflate and the same reagents. This reaction is also successful with acetals of aliphatic aldehydes and a variety of 1,1-disubstituted alkenes. Ghosez found that $FeCl_3$ was equally effective as a catalyst, but the reaction is still restricted to 1,1-disubstituted alkenes.[107] Miura found that $PtCl_2$ and AgOTf or $AgSbF_6$ also effectively catalyze this reaction.[108] Acetals and trimethylsilyl triflate react to give the cation analogous to **132** that adds to vinylcyclopropane **130** to give the cyclopropylcarbinyl cation that opens to a homoallyl cation that loses $PhMe_2Si$ to give dienyl ether **134**.[109] Yamamoto found that **135**, prepared by combining $SnCl_4$ and (*R*)-BINOL-$(SEM)_2$, generates $Me_3Si(CH_2)_2OCH_2^+$ in a chiral environment that adds to alkene **136** to give the ene-type adduct **137** in 75% yield and 73% *ee*.[110] Similar results are obtained with other trisubstituted alkenes.



Scheme 18

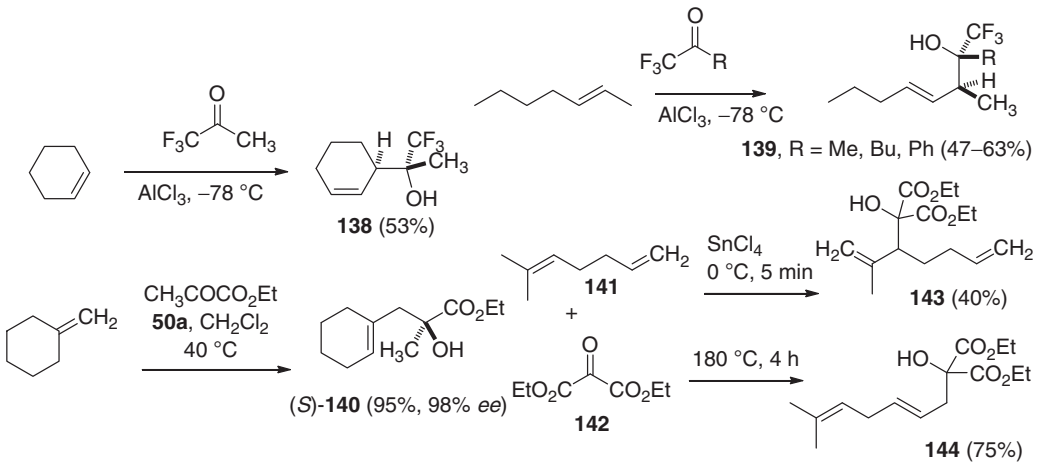
2.03.2.5 Ketones

Ketones are less electrophilic than aldehydes and the ene adducts are tertiary alcohols that are much more acid sensitive than the secondary alcohols produced from aldehydes. Ene adducts can be isolated from the $EtAlCl_2$-catalyzed reactions of cycloalkanones and reactive ene components, that is 1,1-disubstituted alkenes with one end of the double bond sterically accessible and the other end capable of stabilizing a positive charge in an intermediate.[111] The yields are moderate at best (6–55%), but the reaction does provide an extremely simple route to homoallylic tertiary alcohols.

2.03.2.5.1 Electron-deficient ketones

Thermal and Lewis acid-catalyzed ene reactions of electron-deficient ketones proceed in good yield. An adjacent trifluoromethyl group provides sufficient activation as described in the previous edition[1] for hexafluoroacetone, hexafluorocyclobutanone, and trifluoromethyl ketones. Recent studies have demonstrated that the ene reactions of trifluoromethyl alkyl or aryl ketones are regio and stereoselective.[112–113] Cyclohexene undergoes $AlCl_3$-catalyzed reaction with 1,1,1-trifluoracetone at –78 °C to give adduct **138** in 53% yield as a single stereoisomer resulting from the addition of the "larger" CF_3 group *endo* to avoid steric interactions with the ring (see Scheme 19).[112] Similarly, 1,1,1-trifluoroacetone, 1,1,1-trifluoro-2-heptanone, and α,α,α-trifluoroacetophenone undergo $AlCl_3$-catalyzed reaction with *trans*-oct-2-ene at –78 °C to give **139** regio- and stereoselectively. The ketone adds to the double bond carbon with the smaller methyl substituent and the "larger" CF_3 group adds *exo* to avoid steric repulsion.[113]

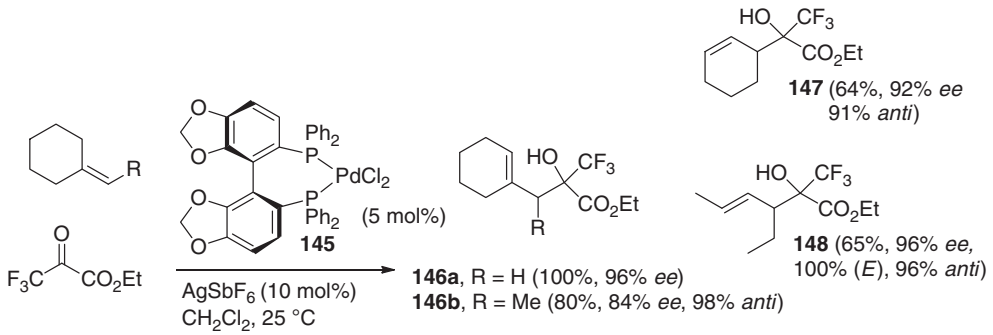
Pyruvate esters have been extensively studied as enophiles.[1] Recently, Evans showed that Cu BOX **50a** catalyzes the ene reaction of methyl pyruvate with the reactive 1,1-disubstituted alkenes methylenecyclopentane, methylenecyclohexane, isobutylene, and α-methylstyrene to give ene adducts such as **140** in 76–95% yield and 98% *ee*.[63c] Ketones with two electron-withdrawing substituents are even more reactive as enophiles. 1,2,3-Indanetrione has been reported to be a super enophile reacting with a wide range of alkenes and alkynes at 70–130 °C to undergo an ene reaction at the central carbon.[114] Thermal and $SnCl_4$-catalyzed ene reactions of diethyl oxomalonate (**142**) have been extensively explored by Salomon.[115] Mono-, 1,1-di-, 1,2-di-, and trisubstituted alkenes afford ene adducts up on heating with 1 equivalent of diethyl oxomalonate at 80–185 °C for 1–340 h. Ene adducts can also be obtained in comparable yield with $SnCl_4$ at 0 °C. $SnCl_4$-catalyzed ene reaction with diene **141** occurs only at the more nucleophilic-trisubstituted double bond to give **143** in 40% yield. Thermal ene reaction with **141** occurs mainly at the less



Scheme 19

hindered terminal double bond to give an 11:1 ratio of **144** and **143** in 75% yield. Recent mechanistic studies suggest that thermal ene reactions of **142** are concerted and that Lewis acid-catalyzed ene reactions of **142** are either concerted or stepwise proceeding through an equilibrating intermediate.[19b,116]

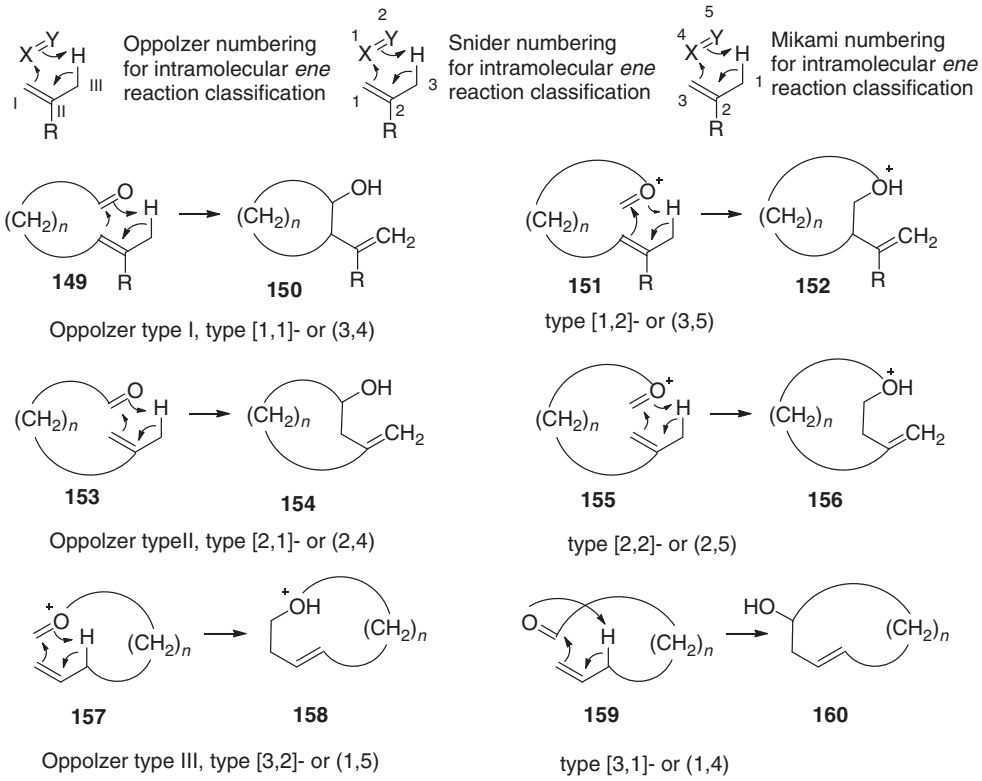
The use of asymmetric Lewis acid catalysts has been extensively explored with very reactive trifluoropyruvate ester enophiles that generate a tertiary alcohol stereocenter in the ene reaction. Mikami prepared a very reactive dicationic SEGPHOS-Pd(II) catalyst by removal of both chlorides from **145** with two equivalents of $AgSbF_6$ (see Scheme 20).[117] This complex catalyzes the ene reactions of ethyl trifluoropyruvate with 1,1-di-, tri-, and even the much less reactive mono- and 1,2-disubstitued alkenes in excellent yield and enantioselectivity, and high (*E*) and *anti* diastereoselectivity. Methylenecyclohexane, ethylidenecyclohexane, cyclohexene, and *trans*-3-hexene afford **146a**, **146b**, **147**, and **148**, respectively in the indicated yields and selectivities.[117] A variety of other catalysts have been developed that are effective with the most reactive 1,1-disubstituted alkenes. These catalysts include copper complexes of C_1-symmetric aminosulfoximines,[118] Pt, Pd, and Ni-BINAP complexes,[119] thioureas,[120] chiral *N*-triflylphosphoramide catalysts,[121] indium(III)-PyBOX complexes,[122] and chiral *N*,*N*′-dioxide magnesium(II) complexes.[123] A dicationic NU-BIPHEP-Pt catalyst[119b] and platinum and palladium complexes of Me_2-CATPHOS[119e] are also effective for the asymmetric ene reactions of ethyl trifluoropyruvate with allylbenzenes. The Lewis acid-catalyzed ene reactions of isopentenyl TBS ether (**6**) with ethyl pyruvate, ethyl trifluoropyruvate, and diethyl oxomalonate have been extensively explored (see equation 4 for the analogous reaction with formaldehyde).[31]



Scheme 20

2.03.3 Intramolecular Ene Reactions

Oppolzer and Snieckus divided intramolecular ene and Prins reactions into three classes depending on the connectivity pattern. These are shown for carbonyl ene reactions in Scheme 21.[124] In type I intramolecular ene reactions, the tether is attached to the proximal end of the double bond of the ene component. Concerted or stepwise ene reaction of **149** occurs to give **150**. These reactions work well for $n=4$ or 3 to form cyclohexanols and cyclopentanols. In Type II intramolecular ene reactions the tether is attached to the distal end of the double bond of the ene component. These reactions work best for $n=4$ or 3, which lead to the



Scheme 21

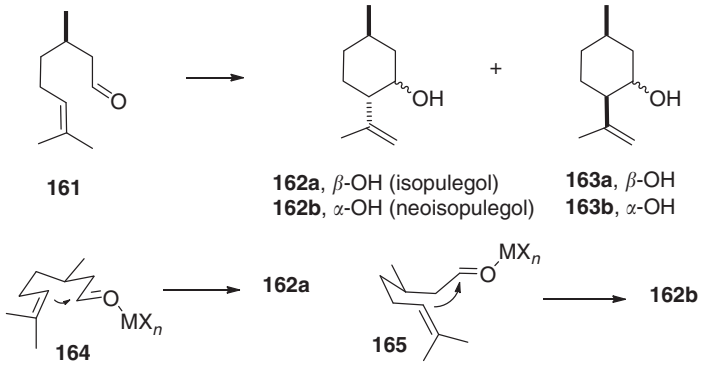
formation of cycloheptanols and cyclohexanols **154** from aldehydes **153**. A cyclopentanol cannot be formed in an ene reaction with $n=2$ because the tether is too short for intramolecular proton transfer. Prins reactions that form cyclopentanols **154** from **153** are covered in the section on Prins reactions. In type III reactions of **157** the tether is attached to the allylic carbon of the ene component. Because of geometric constraints, the other end of the tether must be attached to the oxygen, rather than the carbon, of the carbonyl group. Oxonium ene reactions of **157** that form cyclic ethers **158** are covered in the section on oxonium ene reactions.

There are of course six types of ene reactions because the tether can be attached to three different atoms in the ene component and two different atoms in the enophile component. Snider classified these as [X,Y]-, where the first number refers to the point of attachment on the ene component as used by Oppolzer and the second number is the enophile component.[125] This system is therefore easily correlated to the widely used Oppolzer scheme since the first number corresponds to the Oppolzer classification and has been used in discussion of thiocarbonyl ene reactions. Mikami later classified these as (X′,Y′) numbering the atoms of the ene and enophile 1 to 5 on the basis of the [1,5]-hydrogen shift system as shown in Scheme 21.[126b] This classification has been widely used in oxonium ene reactions. Like Oppolzer type III ene reactions of **157**, the (3,5) and (2,5) ene reactions of **151** and **155** are oxonium ene reactions and are covered in that section. Geometric constraints preclude intramolecular proton transfer in type (1,4) ene reactions of **159** that would lead to 3-cyloalken-1-ols **160**. These products are occasionally formed in Prins reactions and are covered in that section.

2.03.3.1 Type I Reactions

2.03.3.1.1 Formation of cyclohexanols

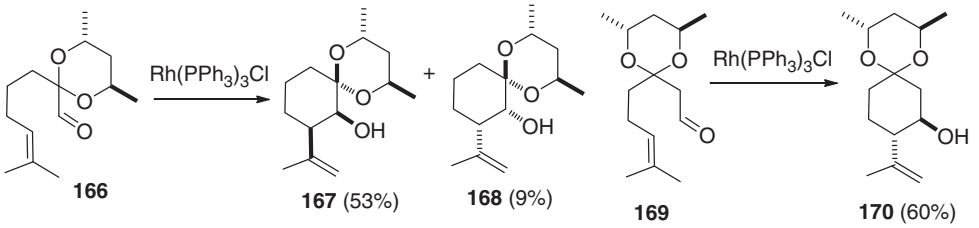
The thermal cyclization of citronellal (**161**) to give mixtures of the four ene adducts **162a** (isopulegol), **162b** (neoisopulegol), **163a**, and **163b** is the prototypical type I ene reaction (see Scheme 22). The cyclization of citronellal to give isopulegol (**162a**) is a step in the industrial synthesis of menthol so this reaction has been extensively optimized and recently reviewed.[127] Thermal cyclization at 180 °C gives a 49:16:4:12 mixture of adducts. Zinc bromide was shown to be an optimal Lewis acid catalyst giving a 95:5 mixture of isopulegol (**162a**) and neoisopulegol (**162b**). However, Sakai found that use of Wilkinson's catalyst ($Rh(PPh_3)_3Cl$) gives a 25:75 mixture of isopulegol (**162a**) and neoisopulegol (**162b**).[128] Other bulky Lewis acids such as $NbCl_5$ give mixtures rich in **162b** and $Bn(Et)_3N^+$ $[Mo(CO)_4ClBr_2]^-$ gives a 25:75 mixture favoring **162b**.[129] Kočovský suggested that with small Lewis acids cyclization occurs preferentially through chair transition state **164** to give **162a**, whereas with large Lewis acids this transition state is disfavored by steric interactions between the Lewis acid and alkene substituents so cyclization occurs through boat transition state **165** to give **162b**.



Scheme 22

Sakai explored the ene reactions of a series of ketals using Wilkinson's catalyst (see Scheme 23).[130] Enal **166** with the acetal attached to carbon 2 of the 6-octenal gives a mixture of *cis* adducts **167** and **168**.[130c] Enal **169** with the acetal attached to carbon 3 gives only the trans adduct **170**.[130a,b] The enal with the acetal attached to carbon 4 gives a mixture of all four adducts.

The use of asymmetric catalysts have been explored relatively little because the stereochemistry is usually controlled by substituents on the tether. Asymmetric catalysis is most useful with achiral enals. Yamamoto has shown that BINOL-Zn catalyzes



Scheme 23

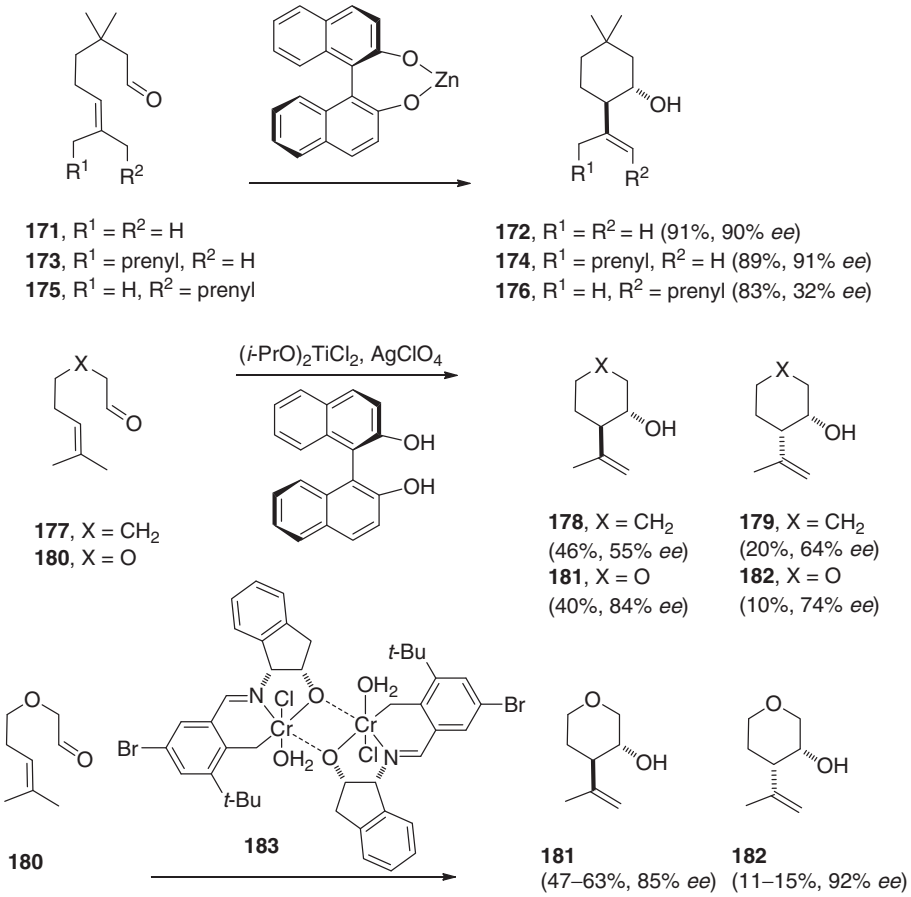
the ene reaction of **171** to give **172** in 91% yield in 90% *ee* (see Scheme 24).[131] BINOL-Zn catalyzes the ene reaction of 7-methyl-6-octenal (**177**), lacking the methyl groups at carbon 3, to provide racemic adduct **178** in only 31% yield. These results indicate that the gem dimethyl group of **171** is necessary for asymmetric induction and that the buttressing effect of the methyl groups facilitates the ene reaction. Yamamoto has also shown that the hydrogen is selectively removed from the trans alkyl group. Ene reaction of **173** gives **174** in 89% yield in 91% *ee*. Similar cyclization of **175** gives **176** in 83% yield but in only 32% *ee*.

Mikami found that BINOL, (*i*-PrO)$_2$TiCl$_2$, and AgClO$_4$ catalyzes the ene reaction of **177** to give a mixture of **178** and **179** in modest *ee*.[126] Enal **180** with an oxygen in the tether gives a mixture of **181** and **182** in 84% and 74% *ee*, respectively. This catalyst is also effective for a type II ene reaction leading to a seven-membered ring alcohol. Jacobsen found that Cr(III) complex **183** formed from tridentate Schiff base catalyzes the asymmetric ene reaction of **180** to give **181** and **182** in 85–92% *ee*.[132] This catalyst is also effective for type I ene reactions leading to five-membered ring alcohols in 77–96% *ee* and for type II ene reactions leading to six-membered ring alcohols in 94–95% *ee*. It is also effective for the type I and type II ene reaction desymmetrization of bis(alkenyl) aldehydes and alkenyl dialdehydes.

Laschat explored a series of type I ene reactions with nitrogen in the tether.[133] FeCl$_3$ catalyzes ene reactions of **184a** and **184b** to give **185a** (51%) and **185b** (52%), respectively (see Scheme 25).[133a] The isomer with an equatorial isopropenyl group and axial alcohol is formed almost exclusively, possibly through transition state **186b** with the Lewis acid chelated to the nitrogen and carbonyl group. A similar ene reaction of **187** affords an 81:19 mixture of **188** and **189**.[133b] FeCl$_3$-catalyzed ene reaction of **190** gives exclusively adduct **191**.[133c] The BF$_3$·OEt$_2$-catalyzed ene reaction of **192** provides **193** in 96% yield in a rare example of the formation of a seven-membered ring in a type I ene reaction.[133c]

Snaith developed a series of ene reactions with an *N*-tosyl group in the tether.[134] MeAlCl$_2$ catalyzes the ene reaction of **194** at −78 °C to give a 3:1 mixture favoring the kinetically preferred *cis* adduct **195** (see Scheme 26).[134a,b] In CHCl$_3$ at reflux, the ene reaction is reversible and the *trans* adduct **196** is formed selectively. Hydrogen chloride at −78 °C also catalyzes the reaction to give the kinetically preferred *cis* adduct **195**. Similar results were obtained with the substituted aldehyde **197**. The *cis* adduct **198** is the major product under kinetically controlled conditions with HCl catalysis at −78 °C and the *trans* adduct **199** is the major product under thermodynamically controlled conditions with MeAlCl$_2$ in CHCl$_3$ at reflux.[134c,d]

Type I ene reactions have been used to make bicyclic β-lactams. The BF$_3$·OEt$_2$-catalyzed ene reaction of **200** gives *trans* adduct **201** selectively, whereas the SnCl$_4$-catlyzed reaction of **202** affords *cis* adduct **203** selectively (see Scheme 27).[135] Related type II ene reactions afford fused 3-methylenecyclohexanols. Robertson has shown that type I ene reactions can be carried out with a silicon or silicon and oxygen in the tether. The Me$_2$AlCl-catalyzed ene reaction of **204** or **207** affords mixtures of products



Scheme 24

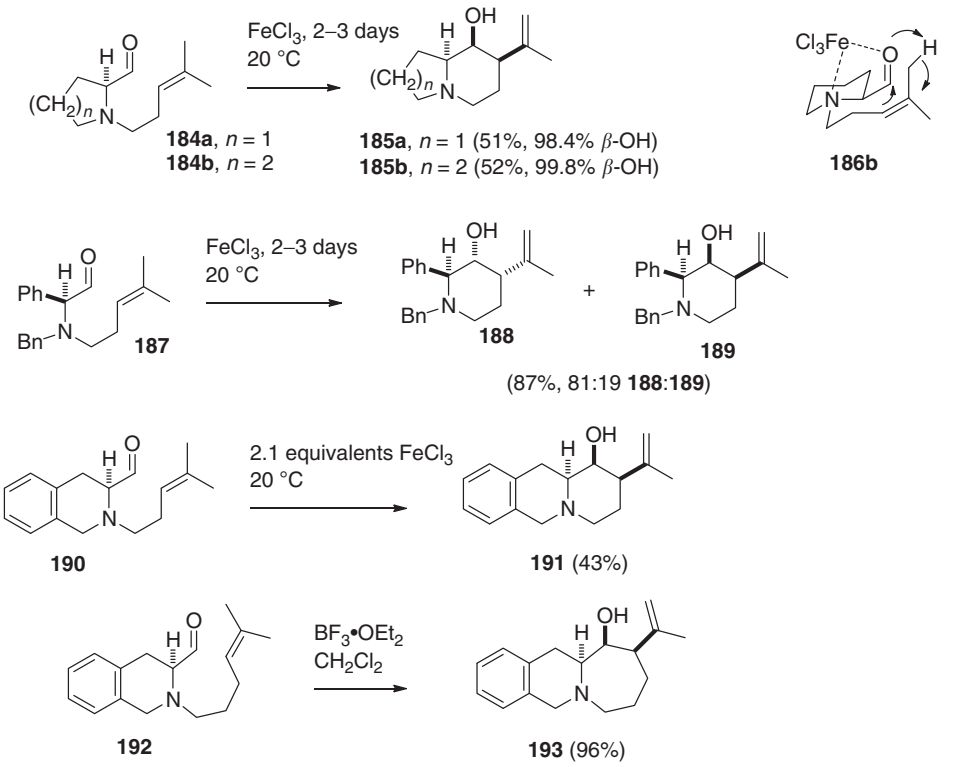
containing mostly the *trans* adducts **205** and **208**.[136a] Similarly the Me_2AlCl-catalyzed ene reaction of **210** affords mainly the *trans*, *trans* adduct **211**.[136b]

Type I ene reactions with less nucleophilic 1,2-disubstituted double bonds are more challenging. Me_2AlCl-promoted ene reactions occur in 75% yield at 0 °C.[137] Cyclization of (*Z*)-**212** gives exclusively the *cis* cyclohexanol **213**, because of geometric constraints on the transition state which preclude the formation of **214** and **215** (see **Scheme 28**). Cyclization of (*E*)-**212** gives mainly the *trans* cyclohexanols **214** and **215**. Smith has used this reaction as a key step in the synthesis of phyllanthoside.[138] Me_2AlCl-induced reaction of **216** gives **217** in 83% yield along with 5% of several stereoisomers. Not only are the hydroxy and alkenyl groups *cis* as expected from the cyclization of a (*Z*)-alkene, but they are also introduced on the face opposite the benzyloxymethyl group.

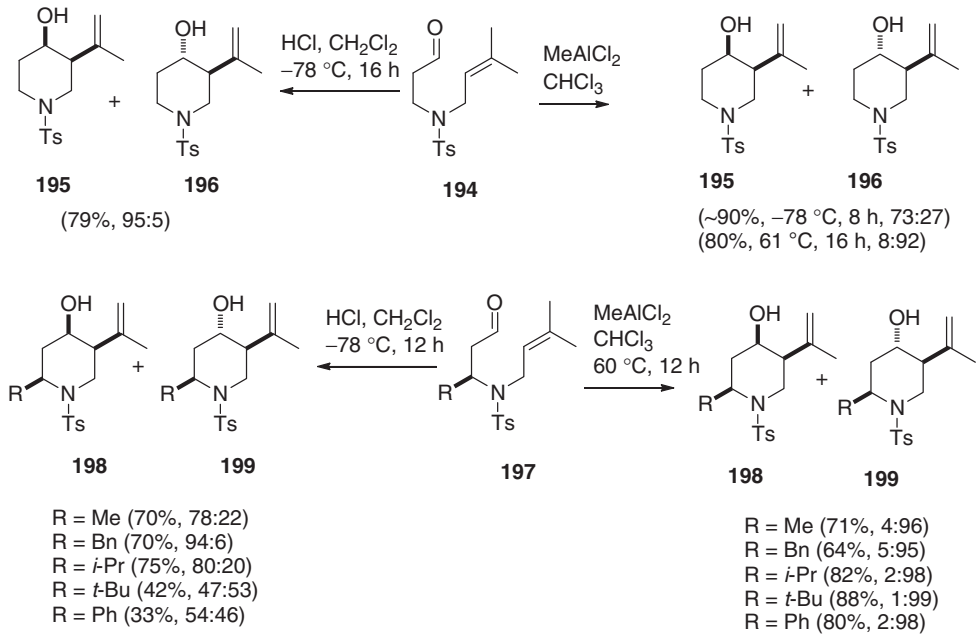
Weinreb reported the thermal intramolecular ene reactions of allenylsilane aldehydes **218a-d** to give *cis*-2-dimethylphenylsilylethynylcyclopentanols and cyclohexanols **219a–d** (see **Scheme 29**).[139] The ene reaction occurs at 140–180 °C if R=H and requires 300 °C if R=Me.

2.03.3.1.2 Formation of cyclopentanols

Intramolecular ene reactions of 1,6-dienes to give vinylcyclopentanes are much faster than intramolecular ene reactions of 1,7-dienes to give vinylcyclohexanes because of the less negative $\Delta S^{\ddagger}$ for formation of five-membered rings. Both reactions are thermodynamically favored even at elevated temperatures. Intramolecular ene reactions of unsaturated aldehydes are much faster than those of dienes because of the polarity of the carbonyl double bond. However, the ene reactions of carbonyl compounds are less exothermic than those of all carbon systems because of the greater bond strength of the carbonyl double bond. In type I intramolecular ene reactions, formation of cyclohexanols is both faster and more exothermic than formation of cyclopentanols because of the greater ring strain of cyclopentanols. Type I ene reactions to give cyclopentanols are reversible in unconstrained systems, which permits Lewis acid-catalyzed stepwise reactions to compete effectively. ΔG becomes less favorable at higher temperatures because ΔS is negative. Because of the greater ring strain of a cyclopentane than a cyclohexane, ene reactions that give cyclopentanols in unconstrained systems may be thermodynamically unfavorable at the temperatures (>100 °C) needed for thermal ene reactions.

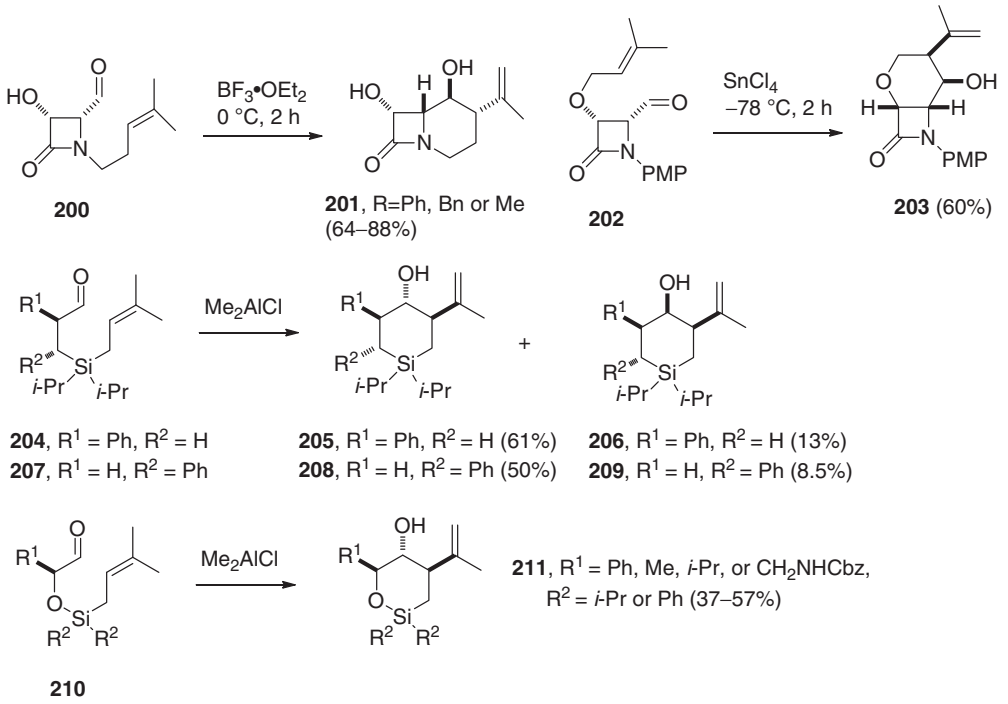


Scheme 25

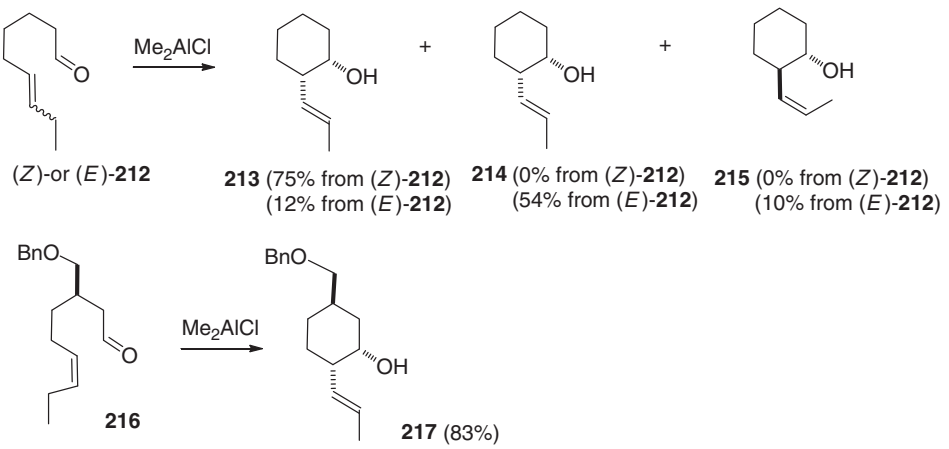


Scheme 26

Me_2AlCl-induced ene reaction of **220** at -78 °C gives primarily **221** as a 4:1 mixture of α-methyl and β-methyl isomers (see Scheme 30).[137] At 125 °C, cyclopentanol **221** is converted back to aldehyde **220**. Alcohol **221** is probably formed by a concerted ene reaction or from a π-complex rather than a zwitterionic intermediate, since concerted thermal ene reactions of 1,6-dienes give mainly *cis*-substituted cyclopentanes. A variety of other products are formed with other Lewis acids that are discussed in detail in the first edition.[1] Aldehyde **222** cyclizes cleanly to cyclopentanol **223** with 0.1 equivalent of $SnCl_4$ at 0 °C or 1 equivalent of



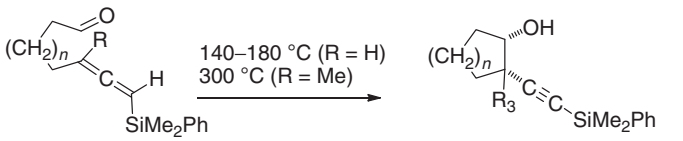
Scheme 27



Scheme 28

Me_2AlCl at −72 °C.[140] However, aldehyde **224** affords ene adduct **225** in 68% yield with 1 equivalent of Me_2AlCl at −72 °C, but not with $SnCl_4$.[140] Sarkar reported that the ene reactions of **220** and **222** catalyzed by 5 mol% Sm(III) generated *in situ* from SmI_2 in CH_2Cl_2 gives the *trans* cyclopentanols **226** and **227**, respectively rather than the *cis* cyclopentanols **223** and **225** obtained with Me_2AlCl or $SnCl_4$.[141] This Sm(III) catalyst converts citronellal into a mixture of isopulegol (**162a**) in 15% yield and neoisopulegol (**162b**) in 45% yield indicating that it behaves as large catalyst that favors the boat transition state leading to **162b** as discussed above (see Scheme 22). Presumably it also behaves as a large catalyst in the cyclization of **220** and **222**. With the smaller tether, steric interactions with the substituents on the samarium apparently now favor the *trans* rather than *cis* cyclopentanol favored with smaller Lewis acids.

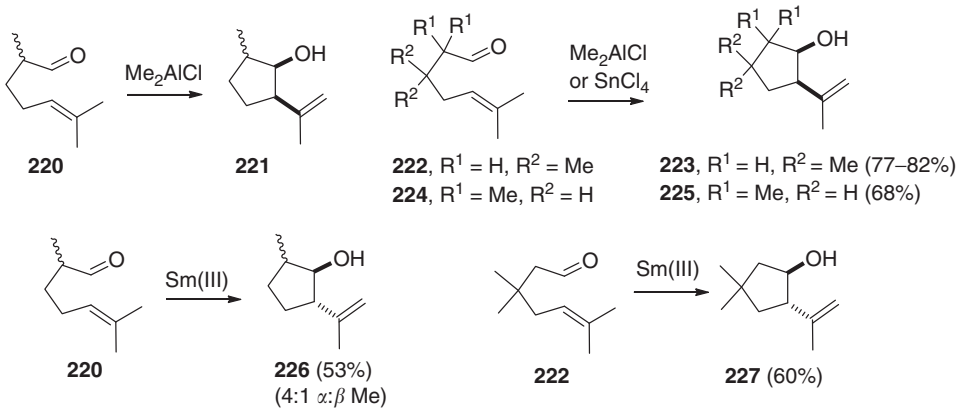
Dess–Martin periodinane oxidizes the primary alcohol of **228** to the aldehyde and catalyzes an intramolecular ene reaction to give **229** (see Scheme 31).[142] Et_2AlCl-induced ene reaction of aldehyde **230** gives a mixture of the expected *cis* isopropenyl cyclopentanols **231a** (66%) and **231b** (17%).[143] The diastereomeric aldehyde **232** gives mainly the expected *cis* isopropenyl cyclopentanols **233a** (16%) and **233b** (31%) and a small amount of the *trans* cyclopentanol **233c** (10%). Alcohol **233b**, which is formed in 49% yield with 0.1 equivalent of $Sc(OTf)_3$ as the Lewis acid catalyst, is an intermediate in a formal synthesis of the tripterpene testudinariol A.[143] Pyrolysis of **234** in toluene at 230 °C with 4 Å MS for 1.1 h affords ene adduct **235** in 60% yield,



218a, n = 2, R = H
218b, n = 2, R = Me
218c, n = 1, R = H
218d, n = 1, R = Me

219a, n = 2, R = H (51%)
219b, n = 2, R = Me (67%)
219c, n = 1, R = H (49%)
219d, n = 1, R = Me (41%)

Scheme 29



220
221
222, R^1 = H, R^2 = Me
224, R^1 = Me, R^2 = H
223, R^1 = H, R^2 = Me (77–82%)
225, R^1 = Me, R^2 = H (68%)
220
226 (53%)
(4:1 α:β Me)
222
227 (60%)

Scheme 30

which was elaborated to (+)-crinamine, (–)-haemanthidine and (+)-pretazettine.[144] Treatment of aldehyde **236** with Me_3Al provides ene adduct **237** in 77% yield, which was used for the synthesis of (+)-kuhistaferone.[145]

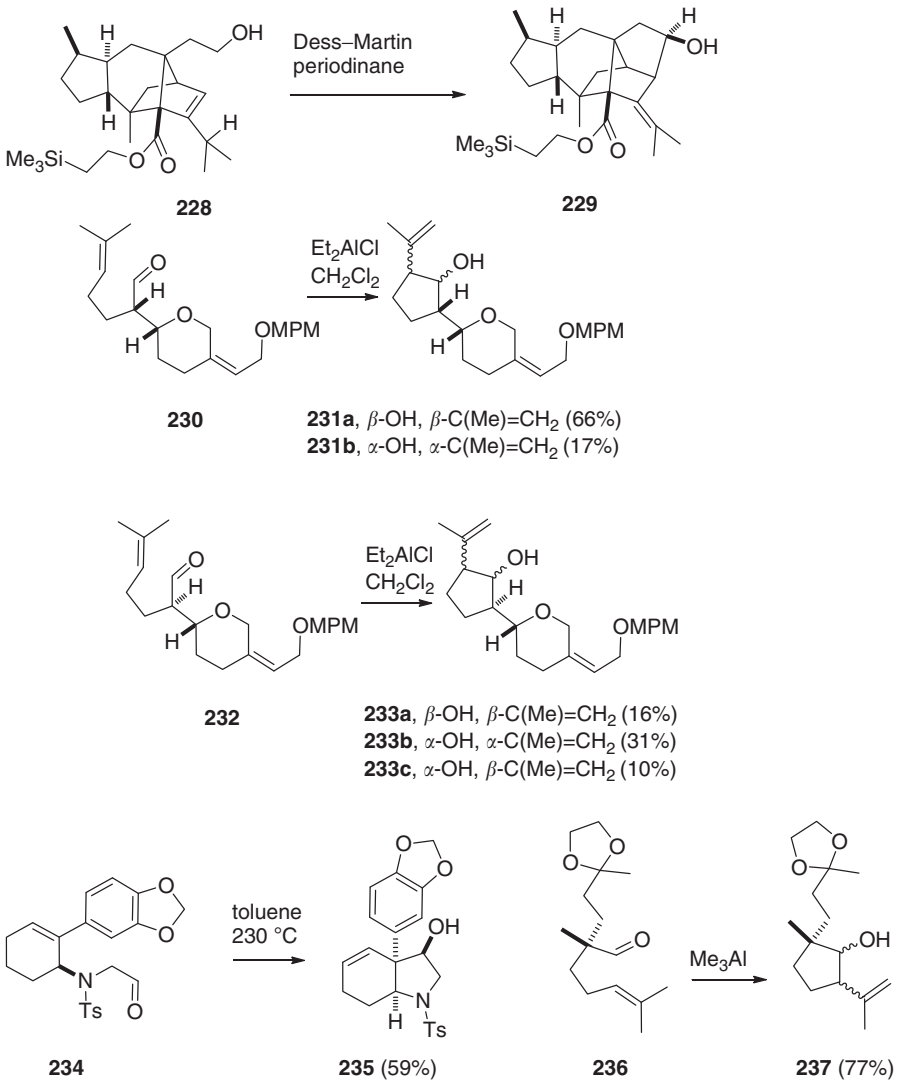
2.03.3.1.3 Formation of larger cycloalkanols

Type I ene reactions have rarely been successfully used for the formation of medium and large rings. In addition to the formation of **193** discussed above (see Scheme 25),[133c] Bulman Page reported that the ene reaction of **238** catalyzed by $BF_3{\cdot}OEt_2$ or $Yb(OTf)_3$ gives a mixture of *cis* 2-isopropenylcycloheptanols **239** and **240** (see Scheme 32).[146] Marshall reported a series of ene reactions of alkynals that form large rings.[147] For instance the $EtAlCl_2$-induced ene reaction of **241** afforded **242** as a 1:1 mixture of diastereomers. Similar treatment of epoxy alkynal **243** resulted in the pinacol rearrangement of the epoxide, but a milder 1:1 mixture of $EtAlCl_2$ and Et_2AlCl effected ene reaction to give **244** in 50–60% yield.[147] Mikami reported the thermal ene reaction of **245** in toluene at 200 °C for 30 min to give adduct **246** that undergoes dehydration.[148]

2.03.3.1.4 Formation of cycloalkanols from ketones

Ketones are generally not sufficiently electrophilic to undergo intramolecular ene type I ene reactions. However, excellent results have been obtained with ketones bearing an electron-deficient terminal substituent. Hiersemann has extensively explored ene reactions of α-keto esters.[149] For instance, heating **247** for 3 days at 180 °C afforded *cis* isopropenyl cyclopentanol **248** in 62% yield (see Scheme 33). Under the same conditions, **249** undergoes an oxy-Cope rearrangement to give **250**, which then undergoes an intramolecular ene reaction to give **251** in 74% yield. It is noteworthy that this reaction proceeds even with a less nucleophilic 1,2-disubstited alkene as the ene component. The α-keto esters can also be generated by Claisen rearrangements.[150] For instance, treatment of **252** with Cu-BOX catalyst **49c** induces a Claisen rearrangement with high enantioselectivity to give keto ester **253** as an 89:11 mixture of enantiomers, which undergoes an ene reaction in 98% *ee* affording **254** and **255**.[150] Chelation of the catalyst was proposed to account for the high degree of selectivity. Yang reported asymmetric ene reactions of keto esters of **256a** and **256b** with the same catalyst to give cyclopentanol **257a** (71% *ee*) and cyclohexanol **257b** (91% *ee*), respectively.[151] The thermal ene reaction of **258** afforded **259** (63%) and **260** (11%).[152] The major product **259** was used for the synthesis of jatrophane diterpenes.

Trifluoromethyl ketones are also sufficiently electrophilic to undergo type I intramolecular ene reactions.[153,154] $RAlCl_2$-induced intramolecular ene reaction of the electron-deficient trifluoromethyl ketones **261** and **263** gives cyclopentanol **262** and cyclohexanol **264**, respectively (see Scheme 34).[154] The phenyl substituent on the ene component makes it more electron rich and may be important for reactivity. At first glance, the formation of the *cis* cyclohexanol **264**, is surprising in comparison with the selective formation of isopulegol **162a** from citronellal under these reaction conditions. However, the hydrogen must be abstracted from a methyl group *cis* to the tether so the stereochemistry of this ene reaction should be analogous to that observed with (*Z*)-**212**,



Scheme 31

which gives exclusively *cis* cyclohexanol **213**. The rigid bicyclic framework holds the ketone and alkene of **265** in close proximity so that the ene reaction occurs to give a mixture of *cis* cyclopentanols **266** and **267** on heating at 170 °C or with $SnCl_4$ or R_2AlCl at 0 °C.[155,156] Keto allene **268** is formed by an intermolecular Diels–Alder reaction at 70–75 °C. The ketone and allene are held in close proximity by the bicyclic framework and **268** therefore undergoes an intramolecular ene reaction to produce dienol **269** with the chloropupukeanolide D skeleton.[157]

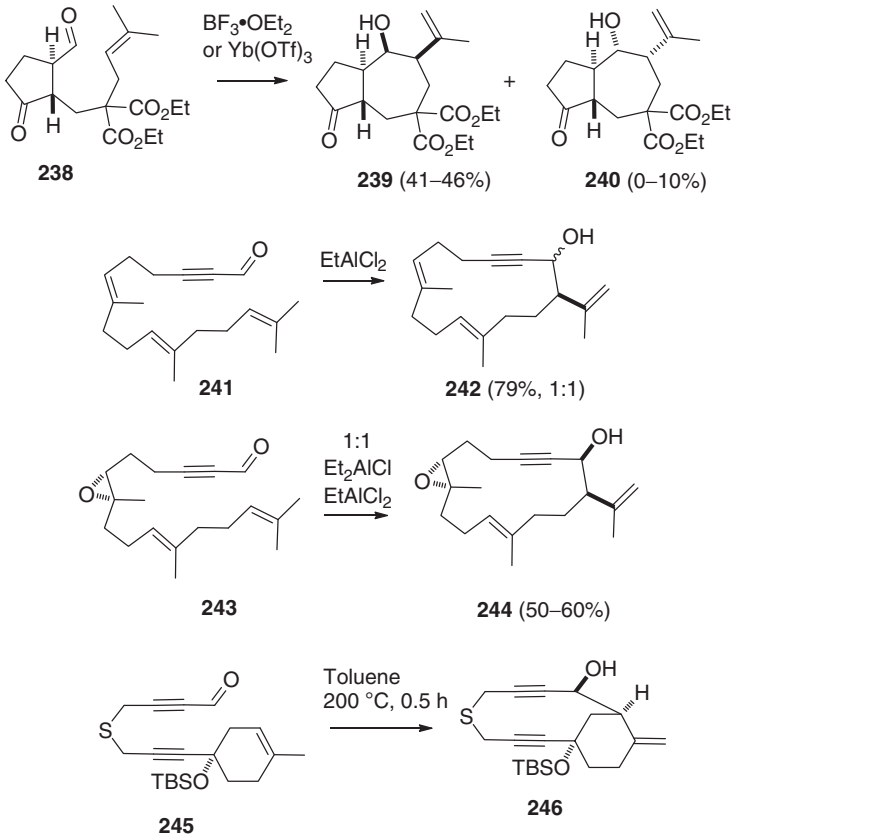
2.03.3.2 Type II Reactions

Type II intramolecular ene reactions of unsaturated aldehydes and ketones have been extensively investigated. Ene reactions occur thermally or with Lewis acid catalysis to give 3-methylenecyclohexanols or 3-methylenecycloheptanols. 3-Methylenecyclopentanols cannot be formed in type II reactions because the length of the tether precludes an intramolecular hydrogen transfer. The formation of cyclopentanols by stepwise reactions with intermolecular loss of a proton is covered in the section on Prins reactions.

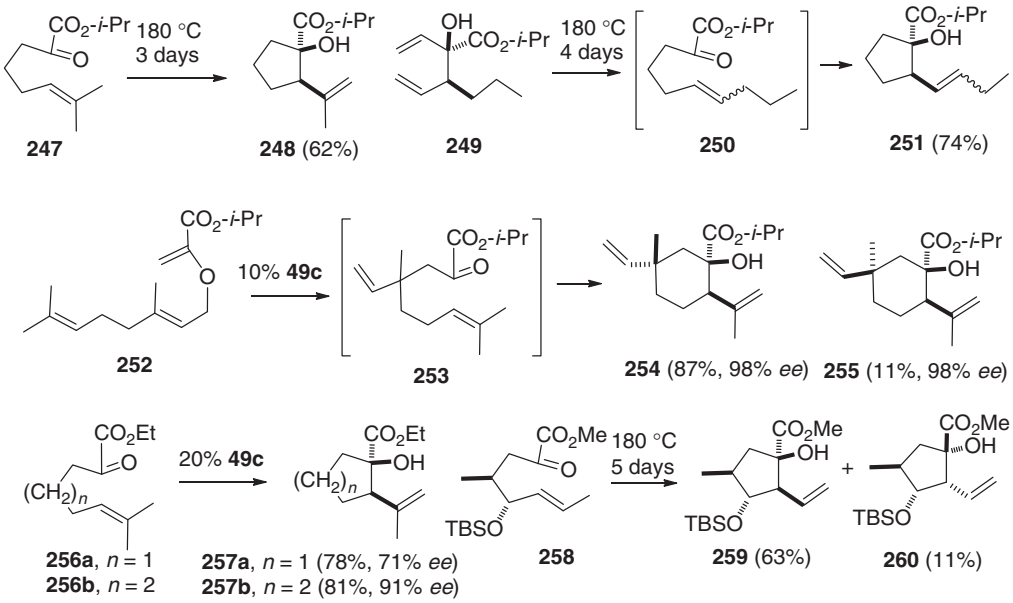
As with type I ene reactions, these cyclizations have been extensively studied for many years and the examples below update, but do not replace, the first edition.[1]

2.03.3.2.1 Formation of cyclohexanols

The Me_2AlCl-induced type II ene reactions of a series of substituted 5-methyl-5-hexenals such as **272** were examined (see Scheme 35). The cyclization proceeds through transition state **271** with a chair cyclohexane ring leading to **270** with an equatorial

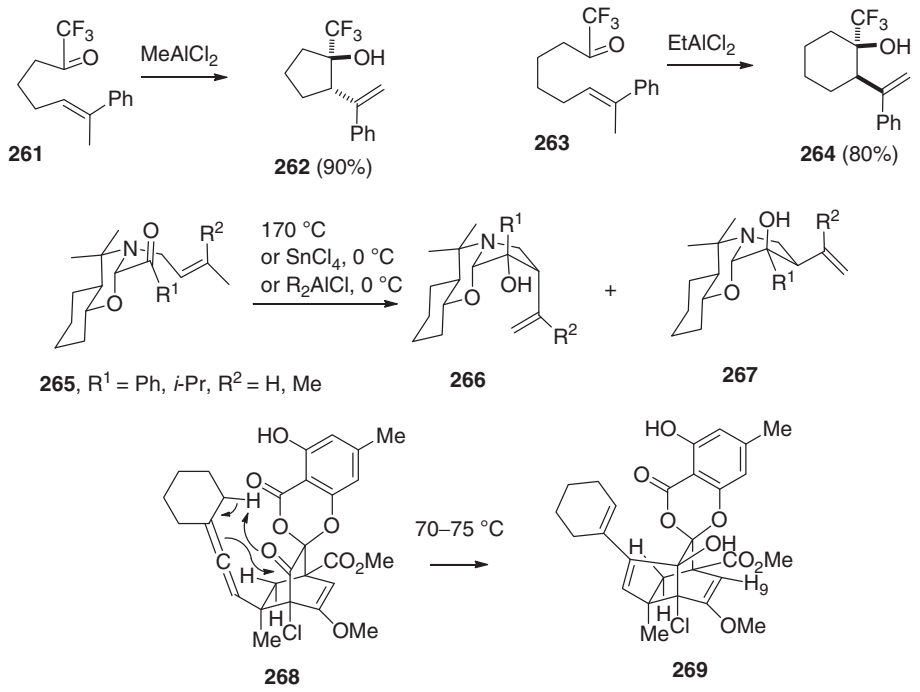


Scheme 32

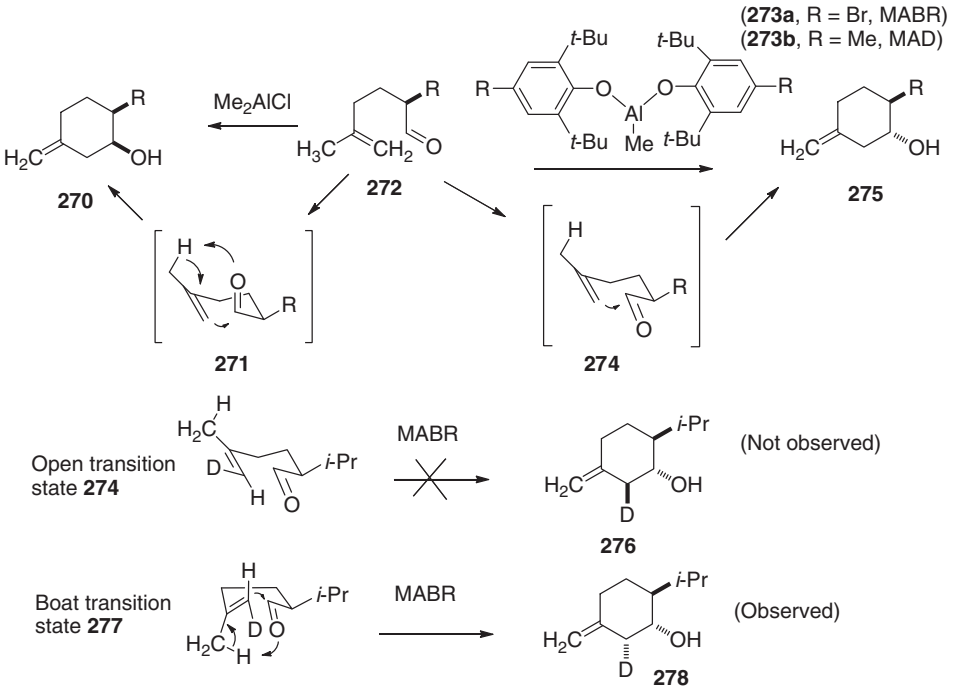


Scheme 33

methyl group as the major (90%) product.[158] Hexanals with substituents on carbons-3 or 4 also form 3-methylenecycloalkanols with axial alcohols and equatorial substituents. *Ab initio* calculations are consistent with these results.[159] Yamamoto found that hindered aluminum Lewis acids **273a** (MABR) and **273b** (MAD) lead to the opposite stereoisomer **275** from **272**.[160] They proposed that this occurs by an open transition state **274** in which both the R group and oxygen are equatorial and that proton



Scheme 34

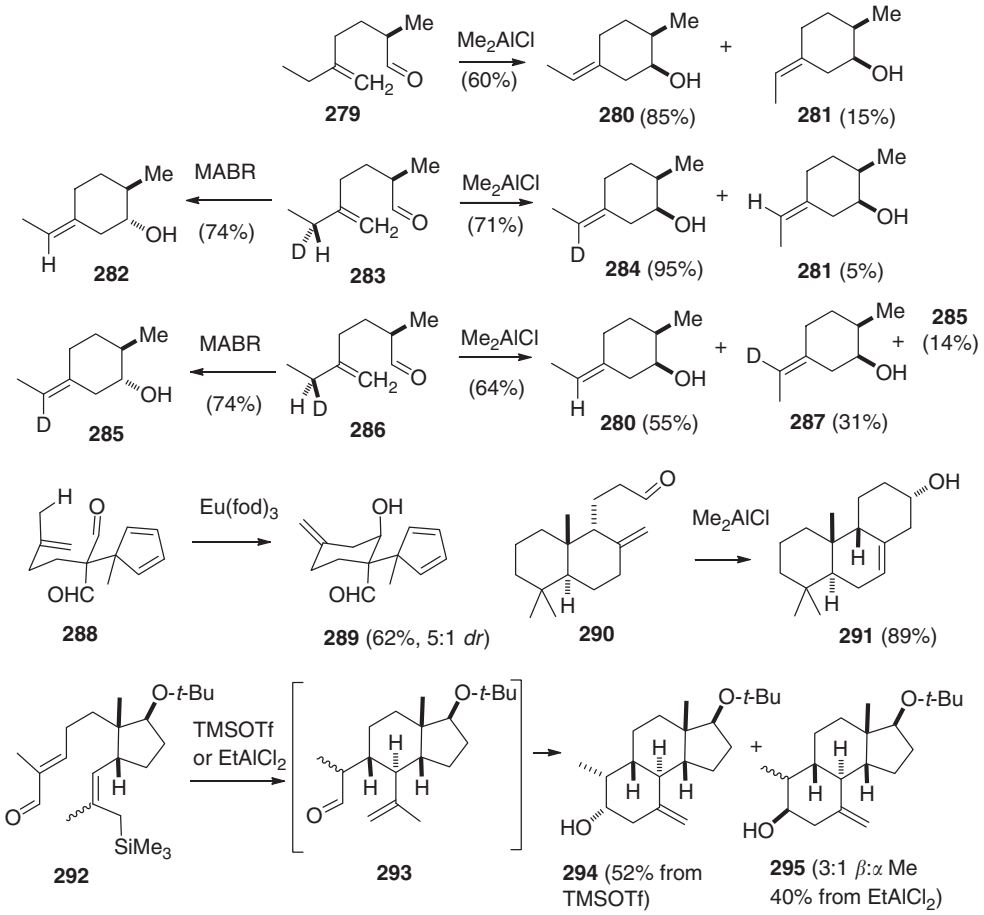


Scheme 35

transfer is intermolecular. Brown and coworkers established that the *trans* product **275** is formed through closed boat transition state **277** rather than through open chair transition state **274** using a deuterium labeled substrate that gives **278** and not **276**.[161] The boat transition state is preferred to minimize steric interactions with very bulky Lewis acids.

Marshall studied the ene reactions of **279** and the two diastereomeric deuterium-labeled aldehydes **283** and **286** with the Lewis acids Me_2AlCl and MABR (see **Scheme 36**).[162] Aldehyde **279** affords exclusively the expected *cis* products **280** and **281** with

Me_2AlCl. Labeled aldehyde **283** is more selective for **284** and labeled aldehyde **286** is less selective for **280** indicating that there is a significant primary deuterium isotope effect on the ene reaction. With MABR, the *trans* products **282** and **285** are formed exclusively as expected from Yamamoto's and Brown's results,[160,161] indicating that the preference for this product with MABR is so great as to overcome any isotope effects.

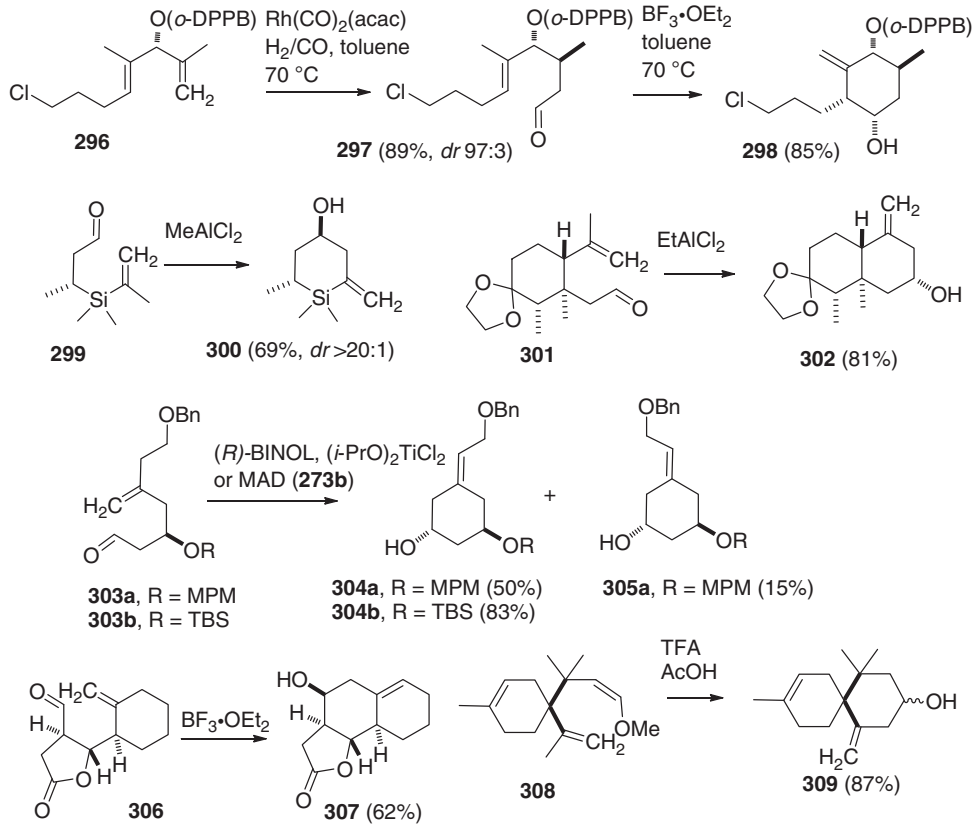


Scheme 36

Intramolecular type II ene reaction of prochiral dialdehyde **288** with $Eu(fod)_3$ as the Lewis acid catalyst for one week in CH_2Cl_2 gives a 5:1 mixture of the diastereomers of **289**, a potential intermediate for the synthesis of anguidine.[163a] The larger methylcyclopentadienyl substituent is equatorial in the major diastereomer. Use of $Eu(hfc)_3$, (+)-$Eu(DPPM)_3$, or BINOL and $(i\text{-PrO})_2TiCl_2$ as the catalyst affords **289** with 20–38% enantiomeric excess. Treatment of **290** with Me_2AlCl for 20 min at $-78\ ^\circ C$ provides axial cyclohexanol **291** in 89% yield.[163b] On treatment with TMSOTf, allylic silane enal **292** undergoes an intramolecular Sakurai–Hosomi reaction to give aldehyde **293** which reacts further to give **294** in 52% yield as the only product. The formation of the equatorial alcohol indicates that the reaction proceeds through either a boat or open transition state such as **277** or **274**, respectively.[164] In contrast, treatment of **292** with $EtAlCl_2$ also generates **293**, which now undergoes an ene reaction through a chair transition state analogous to **271** to give axial alcohol **295** as a 3:1 mixture of isomers.[164]

Breit prepared ene substrate **297** by diastereoselective and regioselective hydroformation of diene **296** (see **Scheme 37**).[165] $BF_3{\cdot}OEt_2$-catalyzed ene reaction of **297** in toluene at 70 °C provides the expected ene adduct **298** with an equatorial hydroxy group and all other substituents equatorial. Further elaboration led to several lycopodine alkaloids.[165b] Type II ene reactions can also be carried out with silicon in the tether.[166] For instance, treatment of aldehyde **299** with $MeAlCl_2$ provides **300** in 69% yield as a 20:1 mixture of diastereomers favoring the isomer shown with an axial alcohol and equatorial methyl group.[166] Type II ene reactions have been used to prepare intermediates for the synthesis of clerodane diterpenes. $EtAlCl_2$-induced reaction of **301** affords alcohol **302** in 81% yield without hydrolysis of the ketal.[167]

Mikami used a type-II ene reaction to prepare Vitamin D analog precursors by reaction of optically pure **303a** with (*R*)-BINOL and $(i\text{-PrO})_2TiCl_2$, which gives the desired product **304a** in 50% yield and the alkene stereoisomer **305a** in 15% yield.[168] Mixtures of all four (*E*)/(*Z*) and *cis* and *trans* isomers are obtained with the mismatched (*S*)-BINOL and $(i\text{-PrO})_2TiCl_2$. Uskoković found



Scheme 37

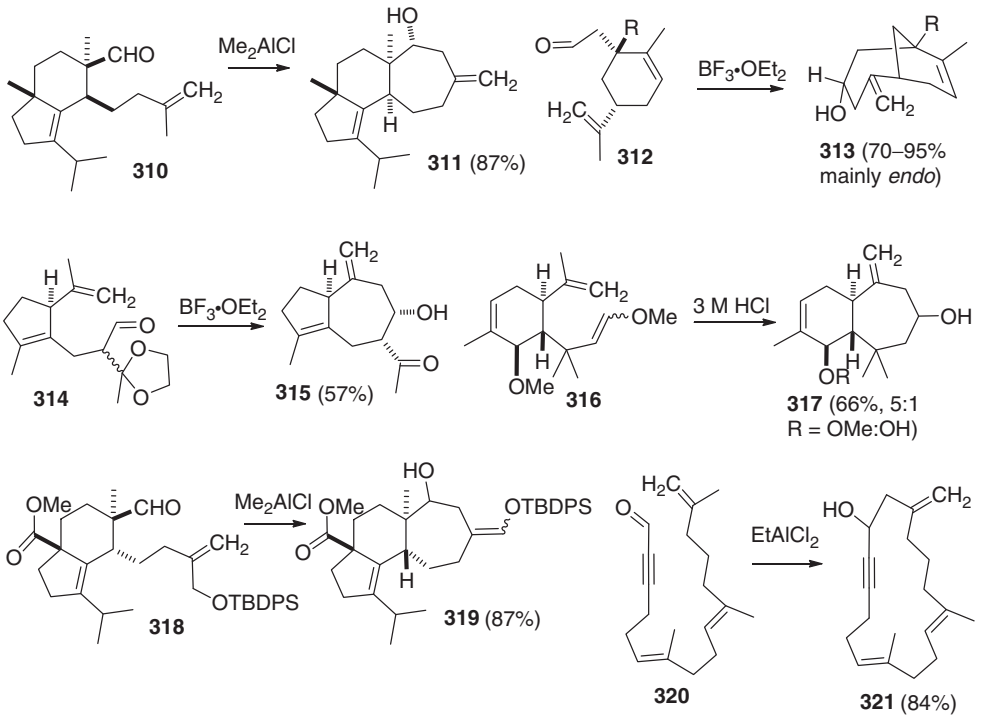
that treatment of **303b** with 2 equivalents of Yamamoto's bulky Lewis acid MAD (**273b**) gives exclusively **304b** in 83% yield.[169] The BF_3-catalyzed ene reaction of **306** gives **307** with the eudesmane nucleus in 62% yield.[170] Treatment of enol ether **308** with TFA, AcOH, and water hydrolyzes the enol ether to give an aldehyde that undergoes a Brønsted acid-catalyzed ene reaction to give **309** as a mixture of isomers that was elaborated to *β*-chamigrene and laurencenone C.[171]

2.03.3.2.2 Formation of cycloheptanols

Marshall showed that type II cyclizations of unsaturated aldehydes are well suited to hydroazulene synthesis as covered in first edition.[1] Some recent examples are presented in Scheme 38. Me_2AlCl-induced ene reaction of **310** affords 3-methylenecycloheptanol **311** (94%), which was elaborated to (±)-allocyathin B and (+)-erinacine A.[172] A wide variety of bicyclo[4.3.1]decanes were prepared by the BF_3-catalyzed ene reactions such as that of **312** to give **313**.[173] The *exo* alcohol is usually the major product. Treatment of aldehyde **314** with BF_3 effects an intramolecular ene reaction and ketal hydrolysis to give aciphyllene precursor **315** in 57% yield as the only product.[174] Treatment of **316** with 3 M HCl hydrolyzes the enol ether to give an aldehyde that undergoes an ene reaction to give *trans*-α-himachalene precursor **317**.[175] Under the acidic reaction conditions the allylic methyl ether undergoes partial solvolysis to give the alcohol. Me_2AlCl-induced ene reaction of **318** affords enol ether alcohol **319** in 87% yield, which was elaborated to (−)-scarbonine G.[176] Marshall has shown that type II ene reactions of alkynals can be used to form 12-, 14-, and 16-membered rings.[147] For instance, treatment of **320** with $EtAlCl_2$ affords **321** with a 16-membered ring in 84% yield.

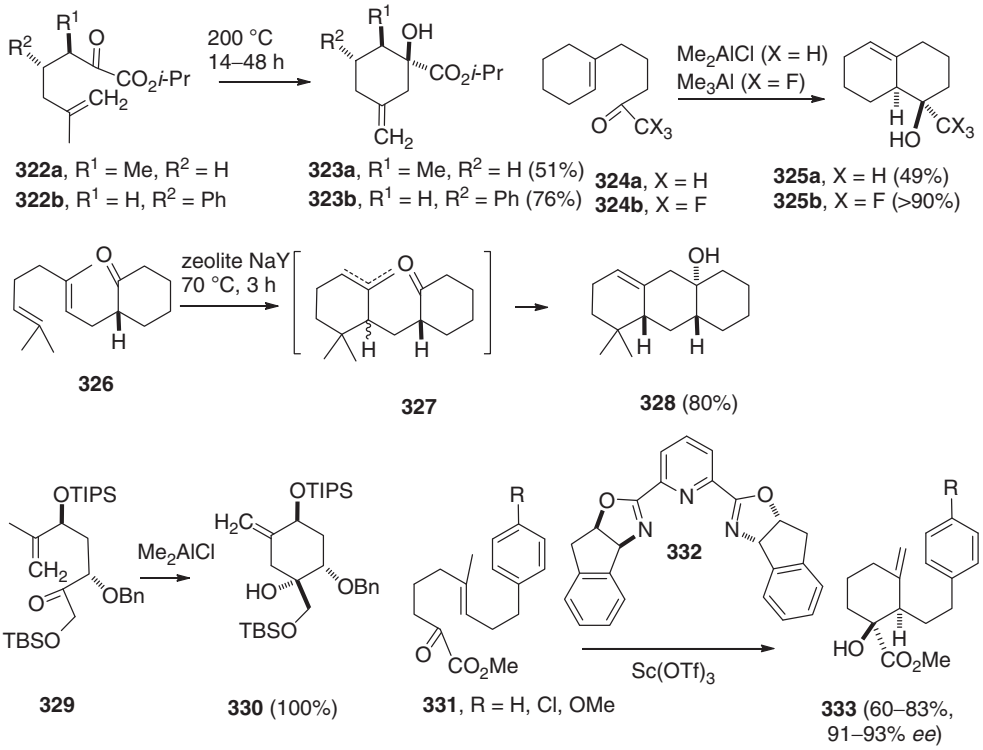
2.03.3.2.3 Formation of tertiary cyclohexanols from ketones

Type II reactions of ketones have been widely used to form tertiary axial cyclohexanols. For instance heating **322a** and **322b**, which contain an electron-deficient α-keto ester, at 200 °C for 14–48 h affords cyclohexanols **323a** (51%) and **323b** (76%), respectively (see Scheme 39).[149] Treatment of methyl ketone **324a** (generated *in situ* from an ene reaction of methyl vinyl ketone and methylenecyclohexane) with Me_2AlCl for 1 h at 25 °C provides ene adduct **325a** (49%).[177] Electron-deficient trifluoromethyl ketone **324b** cyclizes to give **325b** (>90%) at −78 °C even with the weak Lewis acid Me_3Al.[153] A series of α-geranyl-substituted carbonyl compounds undergo an acid-catalyzed cyclization followed by an intramolecular ene reaction on treatment with the mildly acidic zeolite NaY at 70 °C.[178] For instance **326** is converted to **327**, which undergoes a type II ene reaction to give **328** in 80% yield as the sole diastereomer. Presumably the stereo- and double-bond position isomers of **327** equilibrate under the



Scheme 38

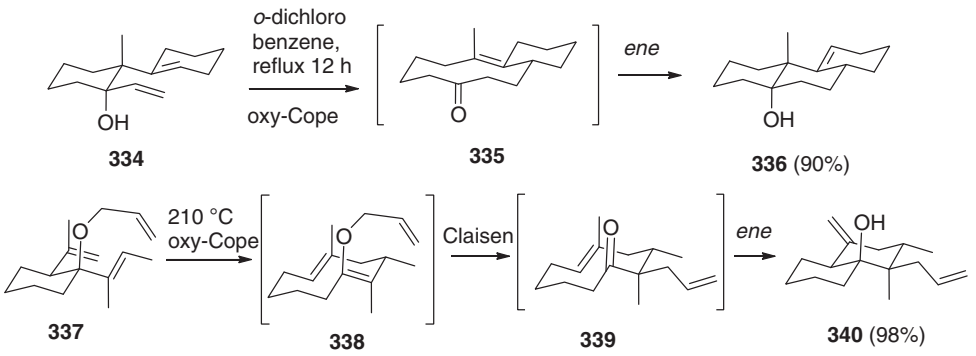
reaction conditions. Only the isomer with both hydrogens up and an exocyclic double bound can undergo an ene reaction. Ketone **329** undergoes an Me_2AlCl-induced ene reaction to give **330** (100%) stereospecifically.[179] Electron-deficient α-keto ester **331** undergoes an asymmetric type II ene reaction catalyzed by $Sc(OTf)_3$ and PyBOX ligand **332** to give **333** in 60–83% yield and 91–93% *ee*.[180]



Scheme 39

2.03.3.3 Transannular Ene Reactions

Transannular ene reactions provide an effective route to bicyclic rings with a ring fusion hydroxy group from unsaturated medium-sized ring ketones.[1] Recent examples include cyclodecenones generated as intermediates in domino sequences. For instance, **334** undergoes an oxy-Cope reaction on heating at reflux for 12 h in *o*-dichlorobenzene to give **335**, which undergoes a transannular ene reaction to give **336** (see Scheme 40).[181] Barriault reported many examples of domino oxy-Cope/Claisen rearrangement/transannular ene reactions.[182] For instance, on heating at 210 °C, **337** undergoes an oxy-Cope reaction to give **338**, which undergoes a Claisen rearrangement to give **339**, which undergoes a transannular ene reaction to give **340** in 98% overall yield.

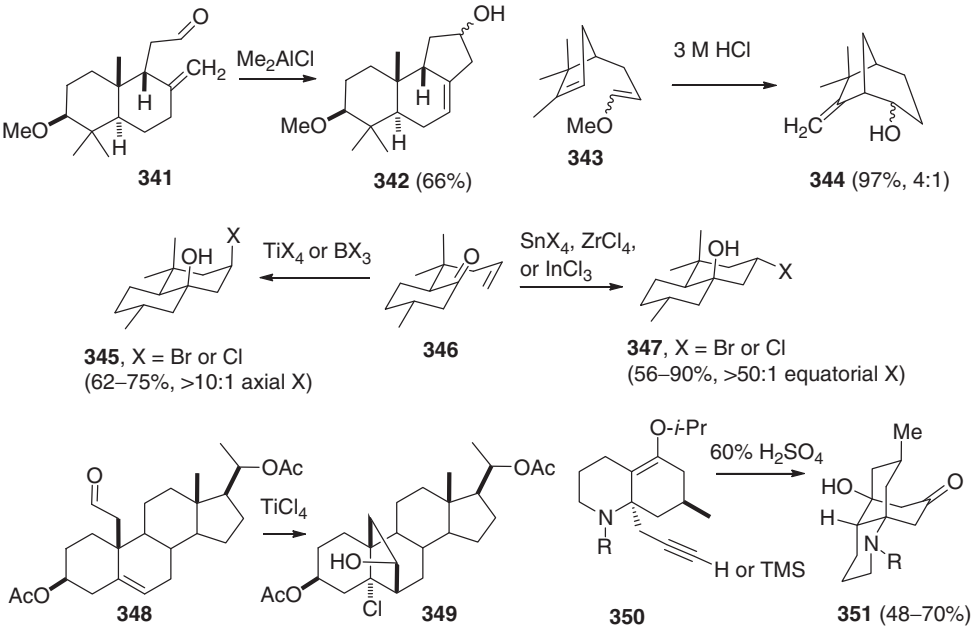


Scheme 40

2.03.3.4 Intramolecular Prins Reactions, Including Those Leading to Ene-Type Products

The type I and II intramolecular ene reactions discussed in Sections 2.03.3.1 and 2.03.3.2 are either concerted or involve the formation of an intermediate that undergoes a rapid intramolecular proton transfer to give a homoallylic alcohol ene adduct as the major or exclusive product. In contrast, intramolecular Prins reactions involve the Lewis or Brønsted acid-catalyzed cyclization of an unsaturated ketone or aldehyde to give a carbocation that can react with water or a halide nucleophile, undergo Wagner–Meerwein type shifts, or lose a proton to give a mixture of allylic and homoallylic alcohols.[140,183–193] In some cases complex mixtures are obtained, whereas in other cases a single, synthetically useful product predominates.

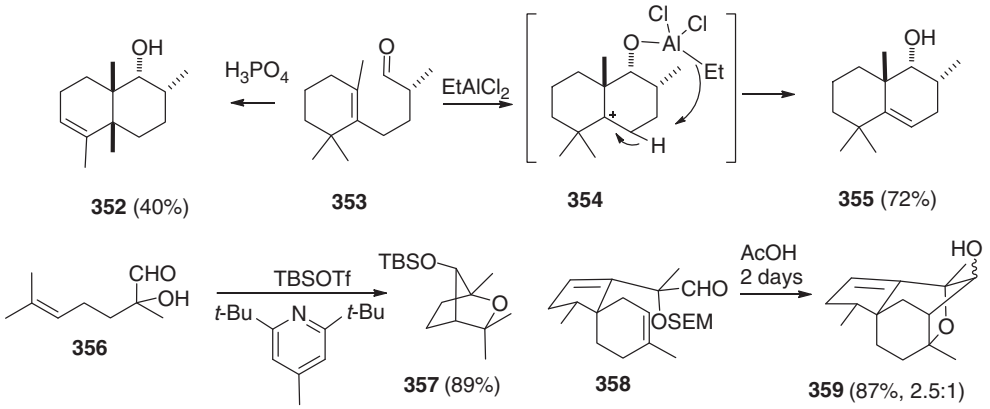
Treatment of **341** with Me_2AlCl affords cyclopentanol **342** (66%) as a mixture of stereoisomers (see Scheme 41).[183] Although this is formally a type II ene reaction, intramolecular proton transfer cannot occur to give 3-alkylidenecyclopentanols and the formation of both alcohol isomers suggests that the reaction occurs by cyclization and intermolecular proton transfer. Similarly,



Scheme 41

hydrolysis of **343** with 3 M HCl affords the aldehyde with cyclizes to give **344** (97%) as a 4:1 mixture of alcohols.[184] The *endo* product could be formed by a type II ene reaction, but the *exo* product cannot be. Coates showed that unsaturated ketones such as **346** react with TiX_4 or BX_3 (X=Cl or Br) at −78 °C to give mainly the axial chloride or bromide **345**, probably by intramolecular halide transfer from OMX_n to the tertiary cation intermediate. However, other Lewis acids such as SnX_4, $ZrCl_4$, or $InCl_3$ give the equatorial halide **347**.[191] The $TiCl_4$-induced Prins reaction of **348** affords chloro alcohol **349**.[192] Intramolecular Prins reactions have also been explored with alkynes.[194–196] Stirring **350** in 60% sulfuric acid hydrolyzes the enol ether to give the *trans*-fused bicyclic ketone. The protonated ketone adds to the triple bond to give a vinylic cation that reacts with water as the nucleophile to form 7-hydroxylycopodine intermediate **351** in 48–70% yield.[196]

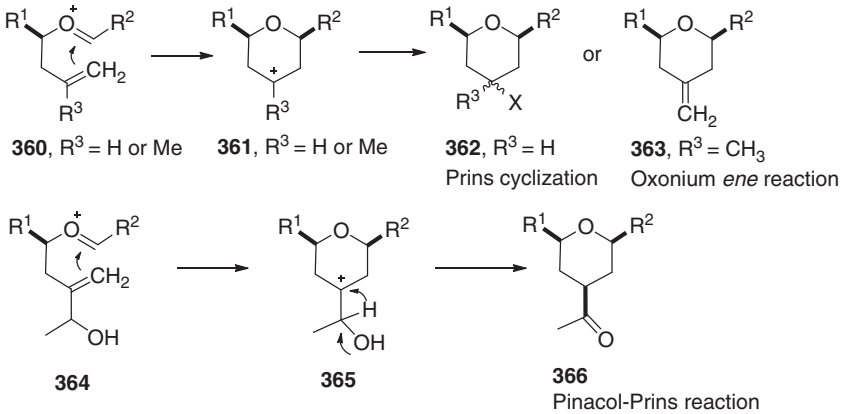
Reaction of unsaturated aldehyde **353** with phosphoric acid induces a Prins reaction (see Scheme 42). The tertiary cation undergoes a 1,2-methyl shift and loss of a proton to give alcohol **352** in 40% yield.[197] Treatment of **353** with $EtAlCl_2$ induces a Prins reaction to give cation **354**, which loses a proton to give alkene **355** (72%).[197] It was suggested that the ethyl group of **354** abstracts a proton β to the cation in an 8-membered ring transition state to give ethane and the dichloroaluminum alkoxide of **355**. Jung explored intramolecular Prins reactions of α-hydroxy aldehydes in which an alcohol traps the cation intermediate to form a cyclic ether.[198] Treatment of **356** with TBSOTf and 2,6-di-*t*-butyl-4-methylpyridine generates **357** in 89% yield. Sorensen used a similar Prins reaction of **358** to give **359** as a key step in the synthesis of hispidospermidin.[199] The 2-trimethylsilylethoxymethyl (SEM) ether is not deprotected under these conditions suggesting that the protonated aldehyde adds to the alkene to give a cation that reacts with the oxygen of the SEM ether to give an intermediate that reacts further to give **359**.



Scheme 42

2.03.4 Oxonium Ene Reactions, Prins Cyclizations, and Prins-Pinacol Reactions

Unsaturated alkoxonium ions such as **360** can cyclize to give cations such as tetrahydropyranyl cation **361**, which can react with a nucleophile to give **362** or lose a proton to give alkene **363** (see Scheme 43). The formation of **362** is usually referred to as a Prins cyclization, whereas the less common formation of **363** is referred to as an oxonium ene reaction. If there is a hydroxy group on a carbon adjacent to the cation as in **365** formed from cyclization of allylic alcohol **364**, a 1,2-hydride or alkyl shift can occur to give



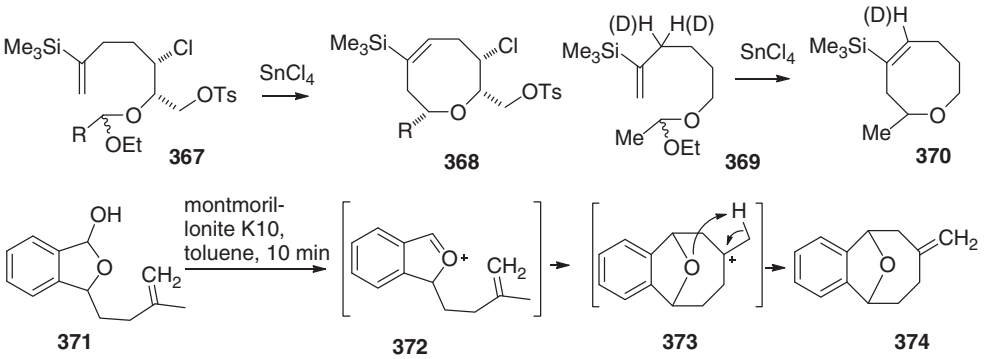
360, R^3 = H or Me; **361**, R^3 = H or Me; **362**, R^3 = H, Prins cyclization; **363**, R^3 = CH_3, Oxonium *ene* reaction

Scheme 43

a ketone such as **366**. These reactions are referred to as Prins-pinacol reactions. Recent comprehensive reviews of both the Prins cyclization[9,11,12] and the Prins-pinacol reaction[13,14,200] provide more complete coverage of these reactions than is possible here.

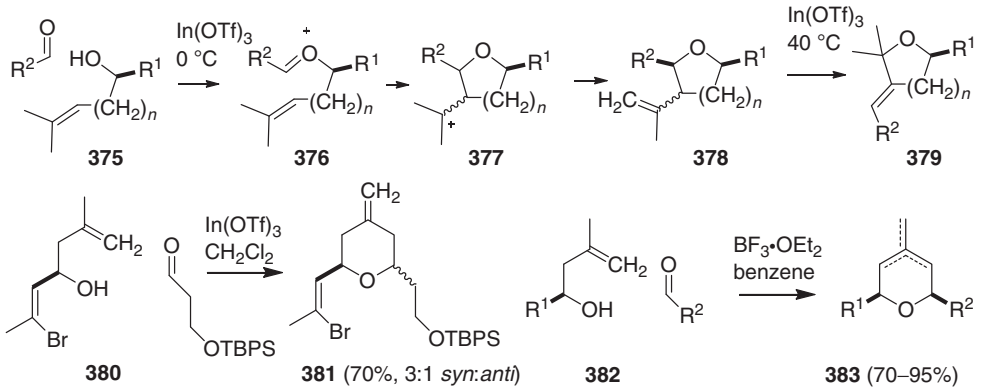
2.03.4.1 Oxonium Ene Reactions

Overman reported that treatment of acetal **367** with $SnCl_4$ generated cyclic ether **368**, which was elaborated to (–)-laurenyne (see Scheme 44).[201a] Loss of the ethoxide-$SnCl_4$ complex from **367** affords the alkoxonium ion which adds to the alkene with transfer of an allylic hydrogen to the ether oxygen to give **368** after loss of a proton. A similar cyclization of **369** afforded **370**.[201b] Both the intermolecular and intramolecular kinetic isotope effect is 1.65 which indicates the reaction proceeds through a concerted ene mechanism. Mikami reported several intermolecular oxonium ene reactions[202] and the (2,5) intramolecular oxonium ene reaction leading to **374**.[203] Treatment of **371** with montmorillonite K10 forms alkoxonium ion **372** which can cyclize to **373**, which can under a 1,5-proton transfer to give cyclic ether **374** after deprotonation. The formation of the protonated cyclic ether could also proceed by a concerted mechanism. Ether **374** is the major product at short reaction times. At longer reaction times **374** is reprotonated to give **373** which loses a proton to give the more stable endocyclic alkenes.



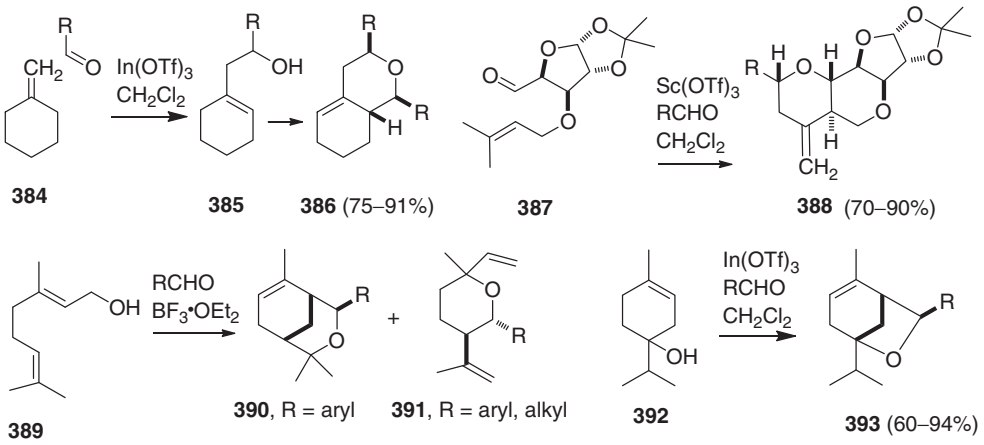
Scheme 44

Loh found that $In(OTf)_3$-catalyzed reaction of alcohol **375**, $n=1$ or 2, with an aldehyde at 0 °C generates alkoxonium cation **376** which cyclizes to give **377**, which loses a proton to give 378 by a (3,5) intramolecular oxonium ene reaction (see Scheme 45). At 40 °C, **378** is reprotonated to regenerate **377** which rearranges to **379**.[204a] Tetrahydropyran **378**, $n=2$, $R^1=H$ can also be obtained starting with 5-methyl-5-hexen-1-ol rather than 5-methyl-4-hexen-1-ol using $PtCl_2$ and AgOTf in toluene at 100 °C or $Cu(OTf)_2$ and a biphosphine as the catalyst. Under these conditions the disubstituted double bond is isomerized to the more stable 5-methyl-4-hexen-1-ol (**375**, R=H, $n=2$), which reacts with the aldehyde to give **378**.[204b–d] $In(OTf)_3$-catalyzed reaction of homoallylic alcohol **380** and 3-TBDPSOpropanal affords methylenetetrahydropyran **381** as a 3:1 mixture of *syn* and *anti* isomers by a (2,5) intramolecular oxonium ene reaction.[205] $BF_3{\cdot}OEt_2$-catalyzed reaction of aldehydes with homoallylic alcohol **382** generates **383** as a mixture of endocyclic and exocyclic double-bond isomers. Geometric constraints and the formation of several isomers suggest that this reaction is stepwise and that the proton transfers intermolecularly rather than intramolecularly to the ether oxygen.[206]



Scheme 45

Tandem carbonyl ene-oxonium ene reactions have also been reported. $In(OTf)_3$-catalyzed reaction of an aldehyde with methylenecyclohexane (**384**) affords ene adduct **385**, which reacts with a second molecule of aldehyde to generate the alkoxonium ion which cyclizes to give **386** after deprotonation (see Scheme 46).[207] Similarly, **387** undergoes a $Sc(OTf)_3$-catalyzed intramolecular ene reaction to give an allylic alcohol that reacts with an aldehyde to give an alkoxonium ion, which undergoes an oxonium ene reaction to give **388**.[208] Treatment of geraniol (**389**) with $BF_3{\cdot}OEt_2$ generates the allylic cation, which cyclizes to the alkene to form a cation that reacts with an aldehyde to give an alkoxonium ion that undergoes a (3,5) intramolecular oxonium ene reaction to give **390**.[209] The allylic cation also reacts with the aldehyde at the tertiary carbon to give an alkoxonium ion that undergoes an oxonium ene reaction to give **391**. Terpinen-4-ol (**392**) undergoes an $In(OTf)_3$-catalyzed reaction with an aldehyde to give an alkoxonium ion that undergoes a (3,5) intramolecular oxonium ene reaction to give **393**.[210] Oxonium ene reactions have been used to desymmetrize 1,4-cyclohexadienes[211] and to prepare 2,3,5,6-tetrasubstituted tetrahydrofurans.[212]



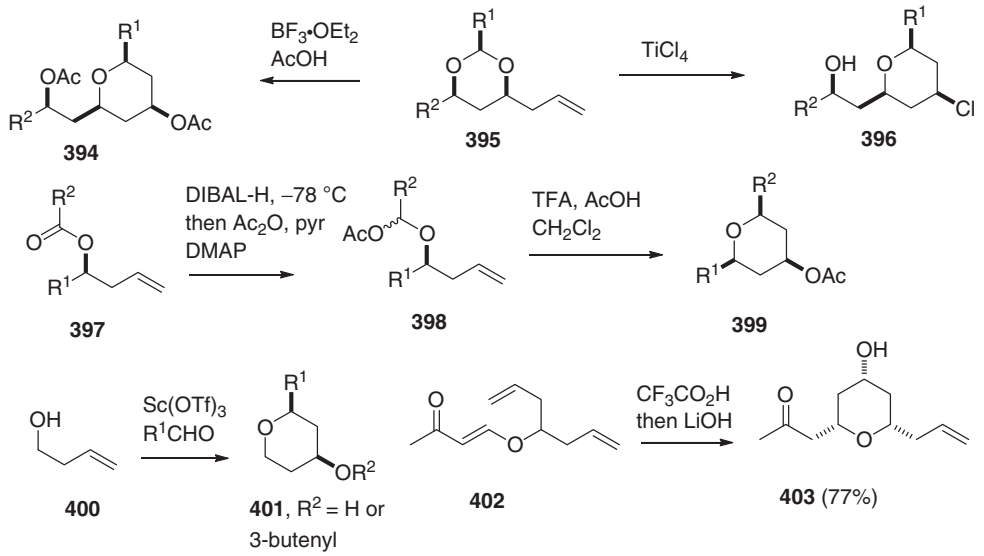
384 **385** **386** (75–91%) **387** **388** (70–90%)

389 **390**, R = aryl **391**, R = aryl, alkyl **392** **393** (60–94%)

Scheme 46

2.03.4.2 Prins Cyclizations

The Prins cyclization, the cyclization of unsaturated alkoxonium ions, has been known since the 1950s but has been only developed as a synthetically useful reaction and widely used in natural product synthesis in the last two decades. Recent reviews on the synthesis of tetrahydropyrans by Prins cyclization[11] and Prins type macrocyclizations[12] provide more complete coverage than is possible here. Rychnovsky prepared acetal **395** from a 1,3-diol and treated it with $TiCl_4$ to generate an alkoxonium ion that cyclizes to form the tetrahydropyranyl cation (see Scheme 47). Trapping with chloride gives the all *cis* 4-chlorotetrahydropyran **396**. Use of $BF_3{\cdot}OEt_2$, and AcOH as the catalyst leads to the all *cis* 4-acetoxytetrahydropyran **394**.[213] Ester **397** can be reduced by



394 **395** **396**

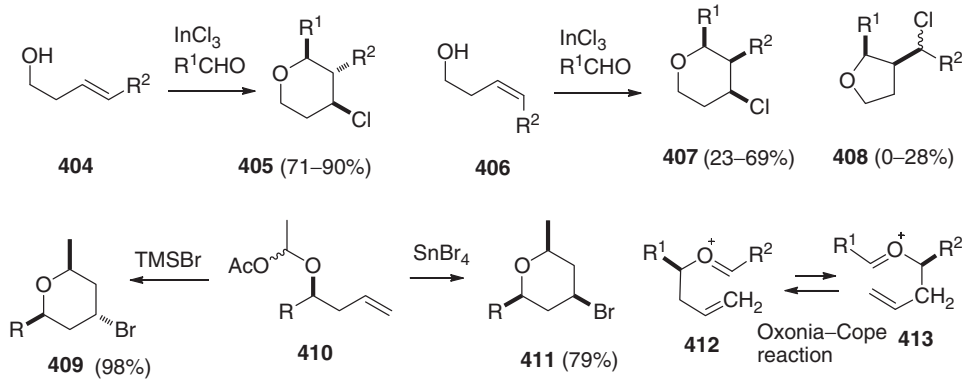
397 **398** **399**

400 **401**, R^2 = H or 3-butenyl **402** **403** (77%)

Scheme 47

DIBAL to give an intermediate that is trapped with Ac_2O to give **398**. Treatment of **398** with TFA and AcOH generates the alkoxonium ion, which cyclizes to give 4-acetoxytetrahydropyran **399**.[214] The alkoxonium precursor can be generated by reaction of homoallylic alcohol **400** and an aldehyde catalyzed by $Sc(OTf)_3$ as in the formation of **401**.[215] The alkoxonium ion precursor can also be generated by protonation of a vinylogous ester as in the conversion of **402** with TFA into a 4-acetoxytetrahydropyran that was hydrolyzed to give leucascandrolide A precursor **403** in 77% yield.[216]

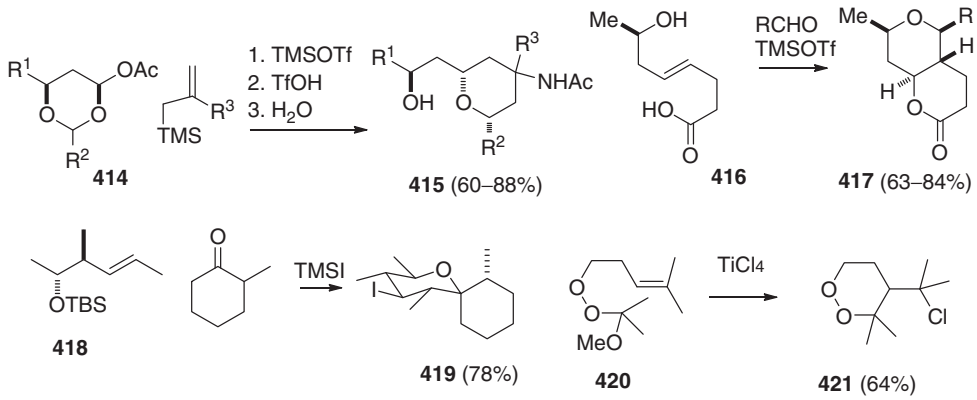
More highly substituted tetrahydropyrans can be prepared with excellent stereocontrol starting with homoallylic alcohols containing 1,2-disubstituted double bonds. $InCl_3$-catalyzed reaction of (*E*)-homoallylic alcohol **404**, R=alkyl, with an aldehyde affords **405** stereospecifically with all substituents equatorial (see Scheme 48).[217] The (*Z*) homoallylic alcohol **406**, R=alkyl, affords a mixture of tetrahydropyran **407** with R^2 axial and tetrahydrofuran **408**.[217] However, reaction of (*E*) homoallylic alcohol **407**, R=phenyl, with an aldehyde, $SnBr_4$, and TMSBr in CH_2Cl_2 at $-78\,^{\circ}C$ affords exclusively the stabilized bromalkyltetrahydrofuran analogs to **408** as a mixture of isomers, because the exocyclic secondary benzylic cation is much more stable than the secondary 4-tetrahydropyranyl cation.[218] Alkynyl alcohols have also been used in Prins cyclizations with aldehydes and TMSOTf in CH_2Cl_2 at $-78\,^{\circ}C$.[219] In these cases cyclization is exclusively 5-*exo* and 6-*exo* leading to vinyl cations that are trapped as triflates. Hydrolysis of the vinyl triflate affords all *cis* 2,5-disubstituted 3-acyltetrahydrofurans and all *cis* 2,6-disubstituted 3-acyltetrahydropyrans.[219]



Scheme 48

Rychnovsky found that **410** can be converted into either axial bromide **409** or equatorial bromide **411** by proper choice of reagent.[220] With TMSBr, a tight ion pair is formed that prefers to attack axial by a least motion pathway to give **409**. With $SnBr_4$, a solvent separated ion pair is formed with a less nucleophilic $SnBr_4X^-$ anion that adds from the preferred equatorial direction to give **411**. Rychnovsky has also shown that homoallylic alkoxonium ion **412** can undergo an oxonia-Cope reaction to give **413**.[221] This process can result in racemization of some substrates and leads to more complex product mixtures than would otherwise be expected.

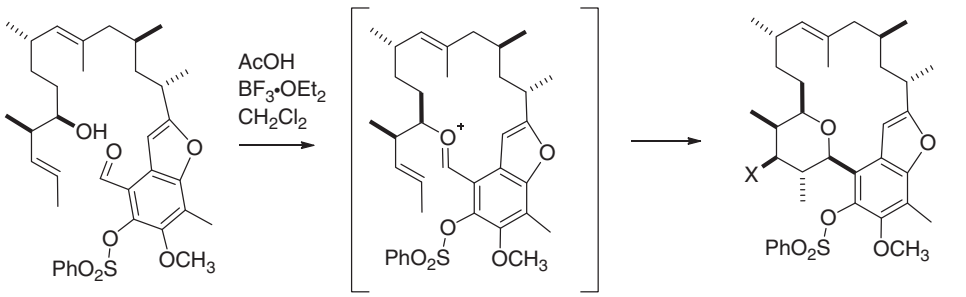
Rovis found that the TMSOTf-catalyzed reaction of **414** with an allylic silane in CH_3CN afforded a 4-allyl-1,3-dioxane analogs to **395** (see Scheme 49). Addition of TfOH generated the alkoxonium ion which cyclized to the tetrahydropyranyl cation, which was trapped by acetonitrile to give amide **415**.[222] The equatorial amide is the major product when R=H as expected from preferred equatorial attack. The axial amide is the major product when R=Me, because trapping of the cation with acetonitrile is now reversible and the isomer with an equatorial methyl and axial $NCCH_3$ is more stable.[222] Prins cyclizations have been carried out in ionic liquids and the tetrahydropyranyl cations have been trapped by Friedel–Crafts addition to 1,2- or 1,4-dimethoxybenzene.[223]



Scheme 49

An internal nucleophile can also be used to trap the tetrahydropyranyl cation as in the conversion of unsaturated hydroxy acid **416**–**417** with an aldehyde and TMSOTf.[224] Alkoxonium ions have also been formed by Mukaiyama aldol reactions. Treatment of a dimethyl acetal with $TiBr_4$ generates $RCH=OMe^+$, which adds to a homoallyl vinyl ether to give the alkoxonium ion precursor for a Prins cycyliczation.[225] The rhenium(VII) complex $O_3ReOSiPh_3$ is particularly effective for the Prins cyclizations of aromatic and α,β-unsaturated aldehydes leading to 4-tetrahydropyranols.[226] Alkoxonium ion precursors for Prins cyclizations can also be generated by oxidation of homoallylic benzyl ethers with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in the presence of $SnBr_4$ or $In(OTf)_3$.[227] Use of TiF_4 as the Lewis acid leads to 4-fluorotetrahydropyrans.[228] Prins cyclizations of ketones and homoallylic alcohols are less common, but many examples are known such as the reaction of **418** with 2-methylcyclohexanone and TMSI to generate spirocyclic 4-iodotetrahydropyran **419** stereospecifically.[229] Dussault has generated a peralkoxonium ion that undergoes a Prins cyclization by reaction of **420** with $TiCl_4$ or $SnCl_4$ to generate 1,2-dioxane **421** in 64% yield.[230]

If the unsaturated alcohol and carbonyl compound are in the same molecule, intramolecular alkoxonium ion formation will form one ring that can then undergo a Prins cyclization to form a fused or bridged bicylic system containing a tetrahydropyran. Remarkably formation of macrocyclic alkoxonium ions works quite well.[12] For instance treatment of **422** with $BF_3{\cdot}OEt_2$ and AcOH in $CHCl_2$ generates macrocyclic alkoxonium ion **423**, which cyclizes to give a mixture acetate **424a** (36%) and fluoride **424b** (48%) (see Scheme 50).[231] Hydrolysis of **424a** affords a kendomycin precursor.



422 **423**

424a, X = OAc (33%)
424b, X = F (48%)

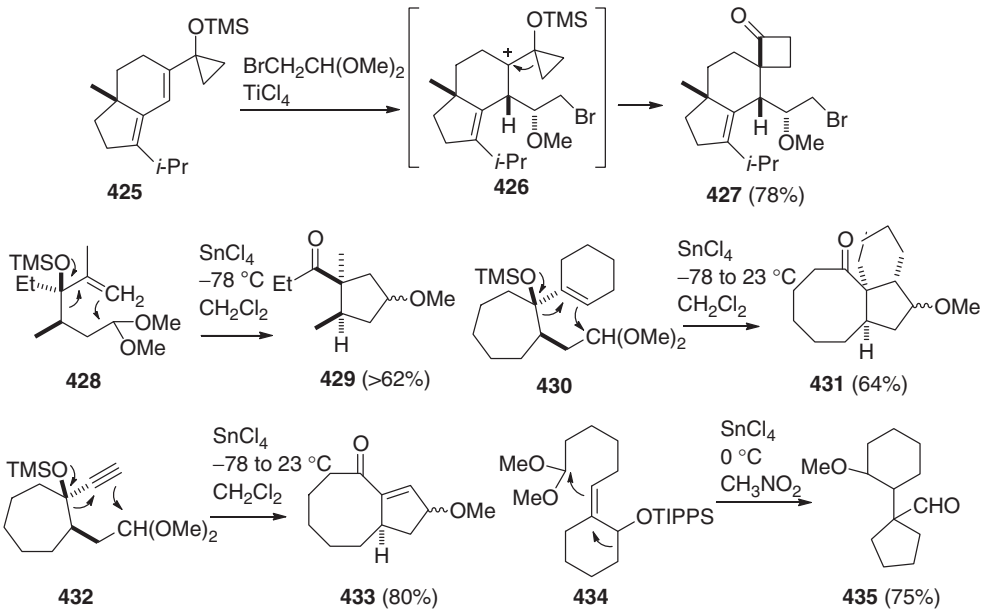
Scheme 50

2.03.4.3 Prins-Pinacol Reactions

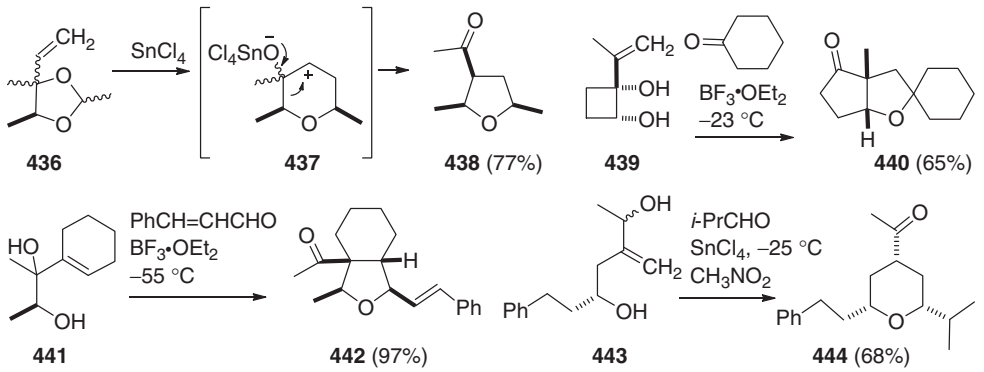
If the cation generated by an intermolecular or intramolecular Prins additions or Prins cyclizations is adjacent to a hydroxy group, a pinacol rearrangement, a 1,2-hydride, or alkyl shift generating a ketone or aldehyde, can occur to terminate the reaction. The synthetic utility of this reaction has been developed primarily by the Overman group and has been extensively reviewed.[13,14,200] Therefore only an overview is provided here. Cha carried out an intermolecular Prins addition by adding the alkoxonium ion generated from treatment of the dimethyl acetal of bromoacetaldehyde with $TiCl_4$ to diene **425** to generate cation **426**, which undergoes a pinacol rearrangement to form cyathin diterpene precursor cyclobutanone **427** in 78% yield (see Scheme 51).[232] The cations can also be generated by intramolecular Prins reactions. Treatment of **428** with $SnCl_4$ generates an alkoxonium ion which cyclizes to give a cyclohexyl cation, which undergoes a 1,2-alkyl shift to generate cyclopentyl ketone **429** in 62% yield.[233] A similar sequence converts **430** into **431** in 64% yield.[233] The cation generated from **432** cyclizes to give a vinyl cation that undergoes a 1,2-alkyl shift to give cyclooctanone **433** in 80% yield.[234] The alkoxonium ion generated from **434** cyclizes to give a cation that undergoes a 1,2-alkyl shift to generate cyclopentanecarboxaldehyde **435** in 75% yield.[235]

Overman showed that the Prins-pinacol reaction is particularly useful in terminating Prins cyclizations leading to heterocycles useful for natural product synthesis. For instance, treatment of acetal **436** with $SnCl_4$ generates the alkoxonium ion, which cyclizes to form tetrahydropyranyl cation **437** (see Scheme 52). A 1,2-alkyl shift generates tetrahydrofuryl ketone **438** in 77% yield.[236] The secondary alcohol of **439** undergoes a $SnCl_4$-catalyzed reaction with cyclohexanone to generate an alkoxonium ion, which cyclizes to give a tetrahydropyranyl cation, which undergoes a 1,2-alkyl shift to generate cyclopentanone **440** in 65% yield.[237] A similar sequence with cinnamaldehyde and $BF_3{\cdot}OEt_2$ converts **441** into **442** in 97% yield.[238] The stereochemistry of **438** and **442** with the substituents on carbons 2 and 5 and the ketone on carbon 3 in the all *cis* orientation is typical of the Prins-pinacol sequence.[13] The homoallylic alcohol of **443** undergoes an $SnCl_4$-catalyzed reaction with isobutyraldehyde to generate a tetrahydropyranyl cation, which undergoes a 1,2-hydride shift to generate all *cis* tetrahydropyranyl ketone **444** in 68% yield.[239]

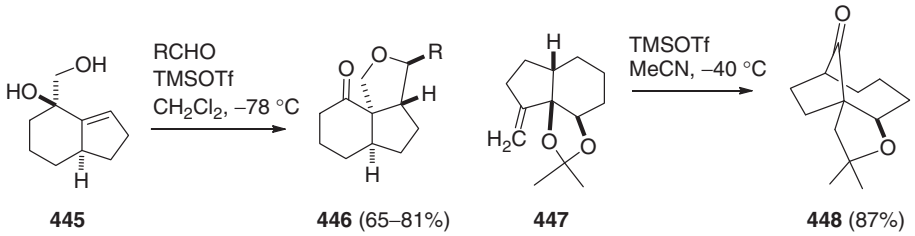
Cho synthesized a series of oxaspirobicycles by Prins-pinacol reactions.[240] For instance, treatment of **445** with an aldehyde and TMSOTf generates **446** in 65–81% yield (see Scheme 53).[240] Barriault generated bicyclo[m.n.1]alkanones by Prins-pinacol reactions.[241] For instance, treatment of **447** with TMSOTf opens the dioxolane to generate an alkoxonium ion, which cyclizes to a tetrahydropyranyl cation, which undergoes a 1,2-alkyl shift to form **448** in 87% yield.[241] The Prins-pinacol sequence has been used for desymmetrization of cyclohexa-1,4-dienes[242] and for the synthesis of a 3-oxabicyclo[3.3.1]nonan-7-one.[243] Overman recently showed that an oxonia-Cope reaction followed by an aldol reaction can give the same product as a Prins cyclization followed by a pinacol rearrangement.[244]



Scheme 51



Scheme 52



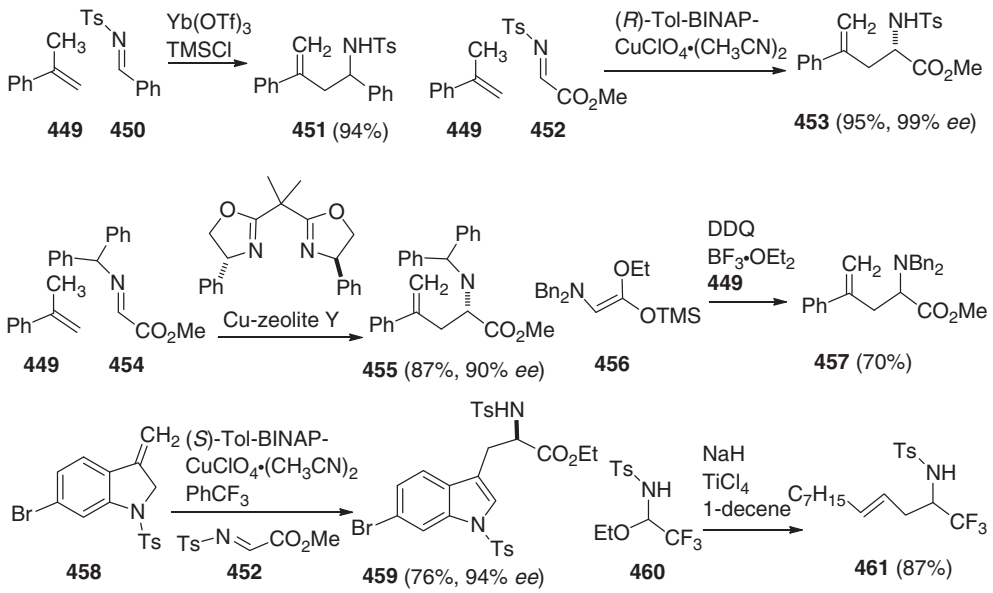
Scheme 53

2.03.5 Imine Ene Reactions

Like carbonyl compounds, imines can function as enophiles forming amines in an ene reaction. However, the C=N double bond is less electrophilic than the C=O double bond so that imines generally need to be activated by additional electron-withdrawing groups on either the carbon, nitrogen, or both in intermolecular reactions. Unactivated imines will react in more facile intramolecular reactions. The mechanism of imine ene reactions has recently been studied theoretically.[245] The coverage here updates a

comprehensive 1995 review of imino ene reactions.[15] *N*-Acyliminium cyclizations, which are analogous to Prins cyclizations and have been extensively studied and recently reviewed[17,18] are outside the scope of this chapter.

The *N*-tosyl imine of benzaldehyde (**450**) undergoes an ene reaction with α-methylstyrene (**449**) catalyzed by $Yb(OTf)_3$ and TMSCl to give ene adduct **451** in 94% yield (see **Scheme 54**).[246] Ene adducts are also obtained under these conditions with a variety of other 1,1-disubstituted alkenes. The ene reaction of **449** and **450** can also be catalyzed by TMSCl and $Cu(OTf)_2$ or $Sn(OTf)_2$.[247]

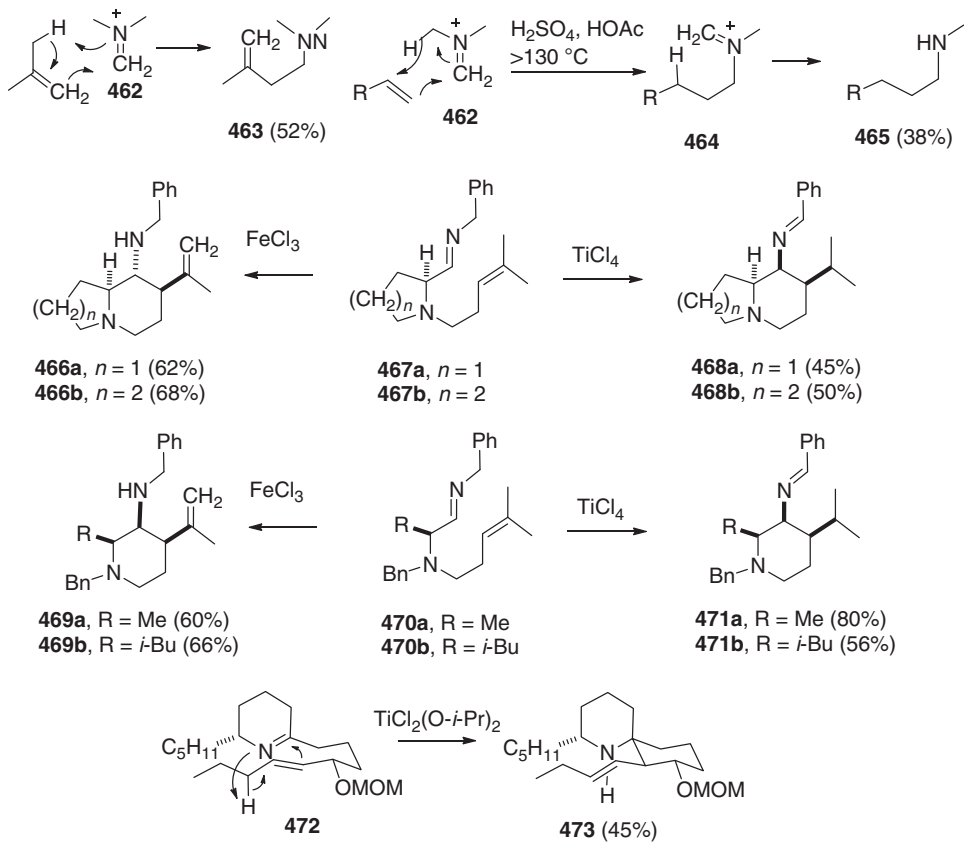


Scheme 54

N-Tosyl imines of glyoxylate esters are activated by electron-withdrawing groups on both the C and the N of the C=N bond. Lectka showed that (R)-Tol-BINAP and $CuClO_4{\cdot}(CH_3CN)_2$ catalyze the ene reaction of **449** and **452** to give protected amino acid **453** in 95% yield and 99% *ee*.[16,248] This reaction works equally well with other 1,1-disubstituted alkenes. Jørgensen reported similar results with $CuPF_6$-BINAP complexes.[249] Mikami examined the use of imines of 8-phenylmenthylglyoxylates.[250] Hutchings showed that the copper-zeolite Y bis(oxazoline) complex catalyzes the ene reaction of the *N*-benzhydryl imine of methyl glyoxylate (**454**) with **449** to give **455** in 87% yield and 90% *ee*.[65d] The unactivated *N*-benzylimine of isobutyraldehyde reacts with **449** under these conditions to give the ene adduct in 83% yield and 92% *ee*.[65d] Tobey found that 2% diethyl phosphoramidite catalyzes the reaction of **452** with a variety of 1,1-disubstituted alkenes and ethylidenecyclohexane in 25–91% yield.[251] The *N*,*N*-dibenzyliminium cation that is formally derived from ethyl glyoxylate can be generated *in situ* by oxidation of **456** with DDQ in the presence of $BF_3{\cdot}OEt_2$. This iminium cation reacts with α-methylstyrene (**449**) to give ene adduct **457** in 70% yield.[252] Rich used the Lectka conditions[16,248] to catalyze the ene reaction of **452** with 3-methyleneindoline **458** to give protected 6-bromo-D-tryptophan **459** in 76% yield and 94% *ee*.[253] Finally, the $TiCl_4$ complex of the *N*-tosylimine of fluoral generated *in situ* by treatment of **460** with NaH and $TiCl_4$ reacts with 1-decene to give ene adduct **461** in 87% yield.[254] Other terminal alkenes work equally well, but the reaction fails with cyclohexene or 2-octene.

Surprisingly, the *N*,*N*-dimethylmethyleneammonium ion **462** can react as either the ene or enophile component (see **Scheme 55**). With 1,1-disubstituted alkenes such as isobutylene, **462** undergoes the expected reaction as an enophile to give homoallylic tertiary amine **463** in 52% yield. However, Cohen showed that the reaction takes a different course with terminal alkenes.[255a] On heating with H_2SO_4 in HOAc at >130 °C the alkene reacts as the enophile and **462** reacts as the ene component to give iminium ion **464** which loses formaldehyde on hydrolysis to give secondary amine **465**. Mayr showed that **462** as the SbF_6 salt reacts with allyltrimethylsilane as the enophile in CH_2Cl_2 to give products analogous to **464**, which were reduced with $NaBH_4$ to the tertiary amine.[255b] *N*,*N*-Dibenzylmethyleneammonium pentachlorostannate reacts similarly with alkynes as the enophile to give products analogous to **464** which can be reduced to tertiary amines with $NaBH_4$ or hydrolyzed to secondary allylic amines analogous to **465**.[255c]

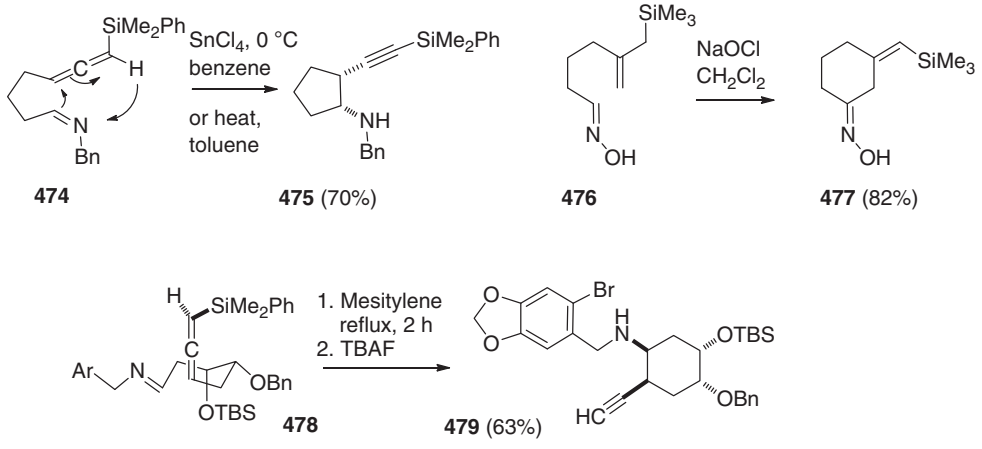
Laschat has observed a similar dichotomy in Lewis acid-catalyzed intramolecular ene reactions of imines.[133a,b,256] *N*-Benzylimines **467a** and **467b** undergo the expected intramolecular ene reactions with the imine double-bond acting as the enophile to give *trans* products **466a** and **466b** when $FeCl_3$ is used as the Lewis acid catalyst. Similar results are obtained with $SnCl_4$. However, the alkene double bond acts as the enophile to give *cis* imine products **468a** and **468b** when $TiCl_4$ is used as the Lewis acid catalyst. Mixtures of products are obtained with $ZnCl_2$, $EtAlCl_2$, and Et_2AlCl. A similar dichotomy was observed in the reactions of **470a** and **470b**, which give the expected *cis* products **469a** and **469c** with $FeCl_3$ and the *cis* imine products **471a** and **471b** with



Scheme 55

$TiCl_4$. The reasons for the differing behavior of the Lewis acids are not clear. The $SnCl_4$-catalyzed ene reactions of imines derived from citronellal give amine products analogous to **466**.[257] Tanner used the $TiCl_2(O\text{-}i\text{-}Pr)_2$-catalyzed intramolecular ene reaction of **472** to give **473** in 45% yield as the key step in a synthesis of perhydrohistrionicotoxin.[258]

Weinreb developed intramolecular imino ene reactions of allenyl silanes as a powerful method for alkaloid synthesis.[15,139,259–261] Heating **474** in toluene or treatment with $SnCl_4$ in benzene at 0 °C affords ene adduct **475** in 70% yield (see **Scheme 56**). The homolog gives the cyclohexylamine under thermal, but not Lewis acid-catalyzed conditions.[260] Although the silyl group is not transferred, its electron-donating character activates the allene as an ene component since the reaction does not occur without the silyl group. Heating **478** in mesitylene at reflux for 2 h and desilylation affords the ene adduct **479** which was elaborated the *Amaryllidaceae* alkaloids (–)-pancracine and (–)-coccinine.[261] Finally, oxidation of oxime **476** with NaOCl generates the nitrile oxide,

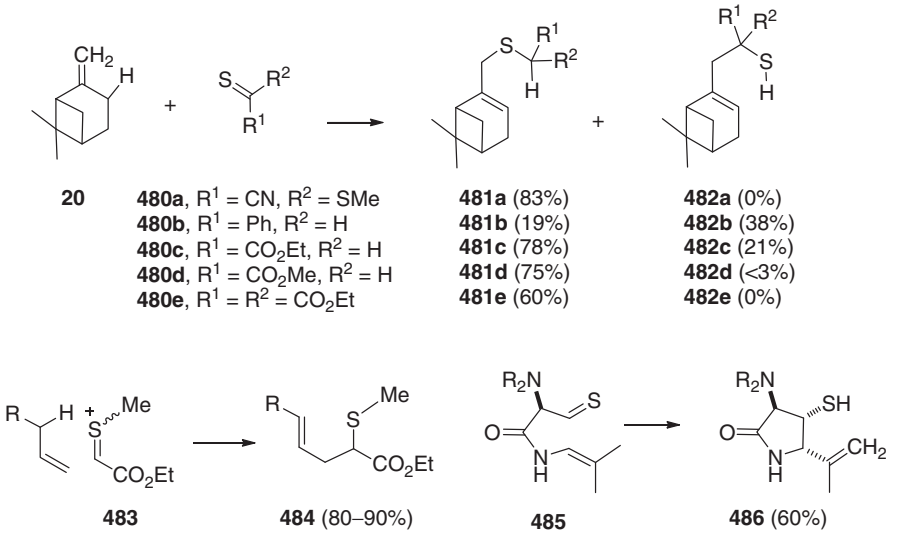


Scheme 56

which undergoes an intramolecular ene reaction to give unsaturated oxime **477**.[262] The silyl group is needed for this reactivity and a wide variety of substituents on the tether are tolerated.

2.03.6 Thiocarbonyl Ene and Prins Reactions

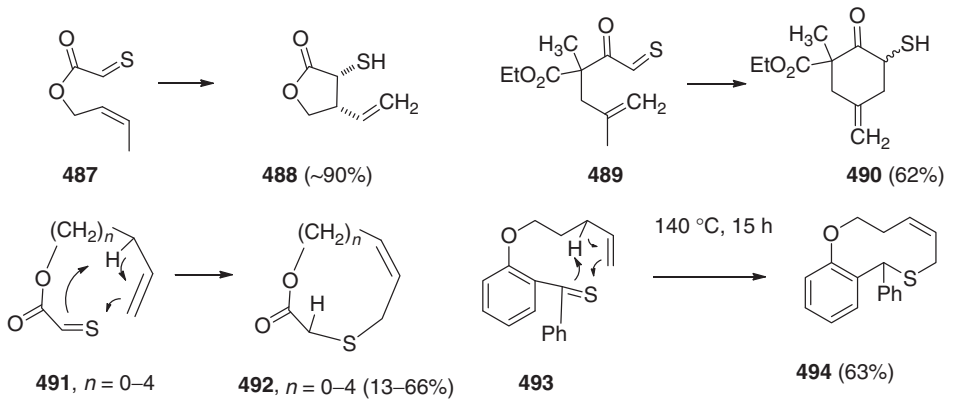
Thiocarbonyl compounds can react as enophiles, not only analogously to carbonyl compounds to give homoallylic thiols such as **482**, but also by formation of a carbon–sulfur bond to give allylic sulfides such as **481** (see Scheme 57). The situation is further complicated by the instability of thiocarbonyl compounds often necessitating their generation *in situ*. The thiocarbonyl ene reaction has been studied theoretically.[263] Hexafluorothioacetone, generated *in situ* by reaction of tetratrifluromethyl-1,3-dithietane with KF in DMF reacts with most classes of alkenes to give allylic sulfides analogous to **481**, $R^1=R^2=CF_3$ in 43–90% yield.[264,265] Methyl cyanodithioformate (**480a**) reacts with most classes of alkenes in toluene at 100 °C to give allylic sulfides such as **481a** from *β*-pinene (**20**).[266] Baldwin showed that thiobenzaldehyde (**480b**), generated *in situ* by pyrolysis of the anthracene adduct, reacts with *β*-pinene (**20**) to give sulfide **481b** in 19% yield and thiol **482b** in 38% yield.[267] Kirby found that ethyl thioxoacetate (**480c**), generated *in situ* by pyrolysis of the anthracene adduct, reacts with *β*-pinene (**20**) to give sulfide **481c** in 78% yield and thiol **482c** in 21% yield.[268] Similarly diethyl thioxomalonate (**480e**) affords sulfide **481e** in 60% yield.[269] Vedejs found that generation of methyl thioxoacetate (**480d**) *in situ* by pyrolysis of the cyclopentadiene adduct or irradiation of the phenyl sulfide gave almost exclusively the sulfide **481d**.[270] These results indicate that formation of the sulfide is favored by electron-withdrawing groups on the thiocarbonyl compound. Carbonyl sulfide undergoes ene reactions with 1,1-disubstituted alkenes catalyzed by R_2AlCl to give *β*,*γ*-unsaturated thioacid ene adducts.[271] Alkylated thioaldehydes such as **483**, generated by Pummerer rearrangements or treatment of *α*-chloro sulfides with $SnCl_4$, undergo ene-type reactions with terminal alkenes to give homoallylic sulfides **484** in 80–90% yield.[272–274]



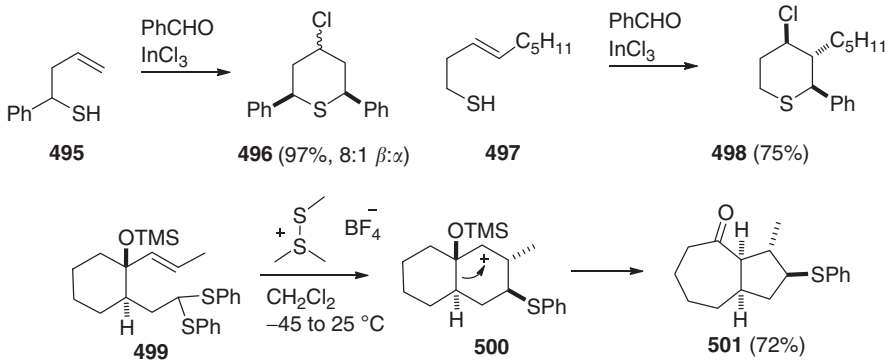
Scheme 57

Intramolecular type I ene reactions of thiocarbonyl compounds give homoallylic thiols. Pyrolysis of a penicillin derived hemithioaminal for 10 min at 176 °C generates thioaldehyde **485**, R_2=phthaloyl, which undergoes an ene reaction to give **486**, R_2=phthaloyl, in 60% yield.[275] Thioaldehyde **487**, generated *in situ* by a retro Diels–Alder reaction of the anthracene adduct of the thiocarbonyl group in toluene at reflux, gives **488** in approximately 90% yield (see Scheme 58).[276] The *trans* isomer does not give any ene adduct. Thioaldehyde **489** generated *in situ* by a retro Diels–Alder reaction from the cyclopentadiene adduct at 140 °C forms the type II intramolecular ene adduct **490** as mixture of stereoisomers in 62% yield.[270] Unsaturated thioxoacetate **491** generated *in situ* by a retro Diels–Alder reaction from the cyclopentadiene adduct undergoes a type III ene reaction to give homoallylic sulfide **492** in 13–66% yield.[277] Thioketone **493** behaves similarly giving allylic sulfide **494** in 63% yield on heating at 140 °C for 15 h.[278]

Thia Prins cyclizations have been explored by Li.[217a,279] For instance, treatment of homoallylic thiol **495** with benzaldehyde and $InCl_3$ affords the cyclization product **496** in 97% yield as an 8:1 mixture of *β*:*α* chlorides (see Scheme 59). However, more complex product mixtures are obtained from substituted benzaldehydes indicating that [3,3]-sigmatropic rearrangements are faster than the cyclization. A similar reaction of homoallylic thiol **497** affords **498** in 75% yield as a single stereoisomer.[217a,279] Overman examined thionium ion-initiated Prins-pinacol reactions.[280] For instance, treatment of **499** with the Me_2SSMe cation forms PhSSMe and the RCH=SPh cation, which cyclizes to give **500**. A pinacol rearrangement gives ketone **501** in 72% yield.



Scheme 58



Scheme 59

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2.04 Heteroatom-Stabilized Allylic Anions

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This chapter is a revision of the previous edition chapter by Yoshinori Yamamoto, Vol. 2, pp 55–79, © 1991, Elsevier Ltd.

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Glossary

(–)-Sparteine A natural tetracyclic diamine that often shows high performance in enantioselective reactions with organolithium reagents.

1,2-Migration Transfer of a group from the atom that the group is connected with to one of the neighboring atoms. Usually the neighboring atom should have a leaving group or a vacant orbital.

Homoaldol reaction Nucleophilic addition of a homoenolate to a carbonyl compound.

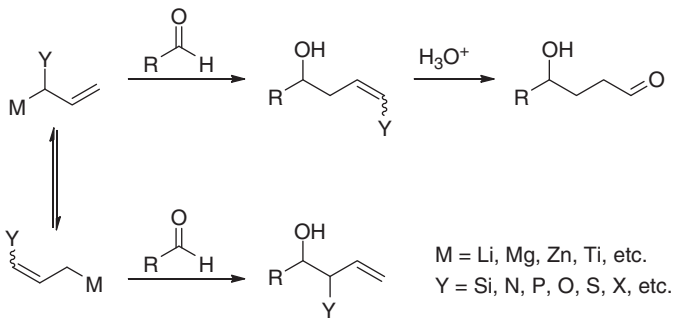
Homoenolate A reagent that is equivalent to 3-oxopropyl anion or its analog with any substituents.

***N*-Boc allylamine** A family of allylic amines in which the nitrogen atom is protected with a *t*-butoxycarbonyl group.

***O*-allyl carbamate** A family of allylic alcohols in which the oxygen atom is protected with an amidocarbonyl group. Equivalent to *O*-allyl urethane.

2.04.1 Introduction

Heteroatom-stabilized allylic anions are useful as homoenolate equivalents and/or nucleophiles providing vicinally diheteroatom-substituted skeletons as exemplified in Scheme 1. The control of α/γ regioselectivity has been extensively investigated. Focusing on the regioselectivity, the previous edition[1] summarizes the reactivity and synthetic use of heteroatom-stabilized allylic anions. For the last two decades, stereocontrol has been the main topic in this field. Two representative advances reside in (1) diastereoselective reactions of heteroatom-stabilized allylic anions bearing a chiral auxiliary and (2) enantioselective generations of heteroatom-stabilized allylic anions by chiral metalating agents. This chapter classifies allylic anions in terms of the heteroatoms and mainly deals with recent advances with emphasis on stereoselective transformations. In addition to this chapter, there are several good reviews that summarize the recent chemistry of allylic anions.[2,3]



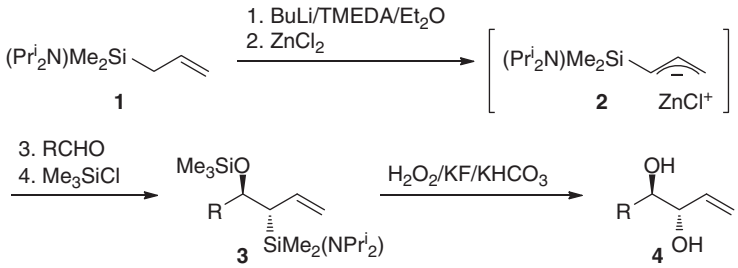
Scheme 1 Heteroatom-stabilized allylic anions in organic synthesis.

2.04.2 Silicon-Substituted Allylic Anions

The substituents on silicon can dictate the regioselectivity. Several allylic silanes were developed to this end.

 doi:10.1016/B978-0-08-097742-3.00205-6

Tamao and Ito developed (dialkylamino)allylsilanes for regioselective allylation of aldehydes.[4,5] Allyl(diisopropylamino)dimethylsilane (**1**) is deprotonated with BuLi/TMEDA, and the resulting organolithium is then transmetalated with zinc chloride to yield silicon-substituted allylic zinc species **2** (Scheme 2). Allylic zinc **2** reacts with aldehydes with high α- and *anti*-selectivities (Table 1). The aminosilyl moiety of **3** is readily converted into a hydroxy group by Tamao–Fleming oxidation with retention of configuration to afford *anti*-1,2-diols **4**. Interestingly, allylic copper species **6**, generated by the reaction of lithiated diethylaminosilane **5** with CuCN, reacts with aldehydes with completely opposite regioselectivity to yield **7** bearing a vinylic silane moiety (Scheme 3 and Table 2).

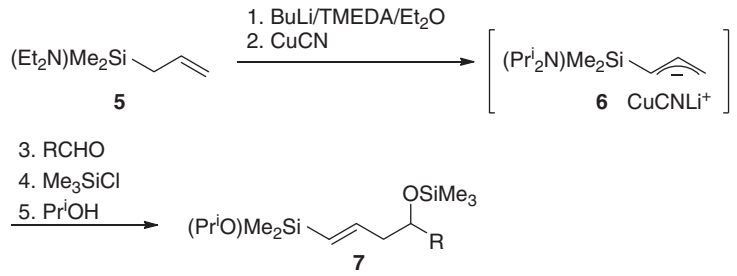


Scheme 2 α- and *anti*-selective allylation of aldehyde with (diisopropylamino)allylsilane **1** via **2**.

Table 1 α- and *anti*-selective allylation of aldehydes with **2** (Scheme 2)

R	*Yield of **3** (%)*	*Yield of **4** (%)*[a]
C_6H_{13}	53[b]	78[b]
Cyclohexyl	54	61
Ph	97	80
2-Thienyl	87	72[c]
3-Pyridyl	75	93

[a]Overall yield from aldehyde without isolation of **3**.
[b]A 4:1 mixture of regioisomers is obtained.
[c]Yield from **3**.



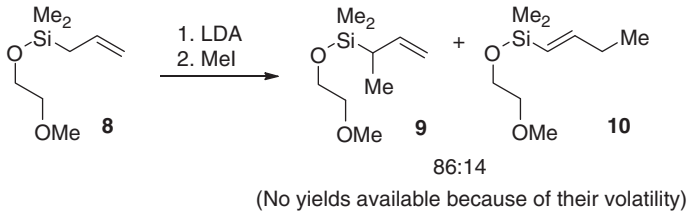
Scheme 3 γ-Selective allylation of aldehydes with (diethylamino)allylsilane **5** via **6**.

Table 2 γ-Selective allylation of aldehydes with **6** (Scheme 3)

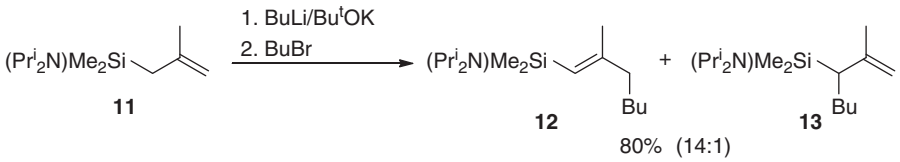
R	*Yield (%)*
C_7H_{15}	82[a]
Cyclohexyl	76
Ph	94
2-Thienyl	57
3-Pyridyl	76
2-Furyl	75

[a]A 5.6:1 mixture of regioisomers is obtained.

Chan developed regioselective alkylation reaction of metalated allylic silanes.[6,7] For instance, lithiation of allyl(2-methoxyethoxy)dimethylsilane (**8**) with LDA followed by an addition of iodomethane provides an 86:14 mixture of α- and γ-methylated products **9** and **10** (Scheme 4). The regioselectivity of the alkylation is generally moderate when alkoxysilanes are used. In contrast, aminosilanes such as **11** lead to better regioselectivity in favor of the formation of γ-alkylated vinylic silanes (Scheme 5).

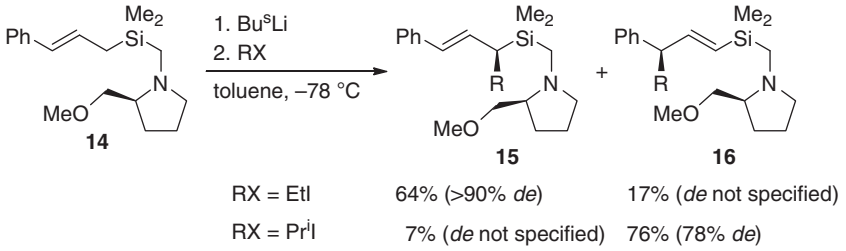


Scheme 4 Alkylation of metalated allylic alkoxysilane.



Scheme 5 Regioselective alkylation of metalated allylic aminosilane.

Cinnamylsilane **14** having a chiral auxiliary is lithiated to generate enantioenriched silyl-substituted allylic lithium species (Scheme 6).[8,9] Alkylation with methyl or primary alkyl halide takes place at the α position selectively, whereas the use of secondary alkyl halide leads to γ-selective alkylation. The diastereoselectivities of the α-alkylation are generally high, whereas the γ-alkylation proceeds with modest diastereoselectivities.



Scheme 6 Diastereoselective alkylation of cinnamylsilane **14** having a chiral auxiliary.

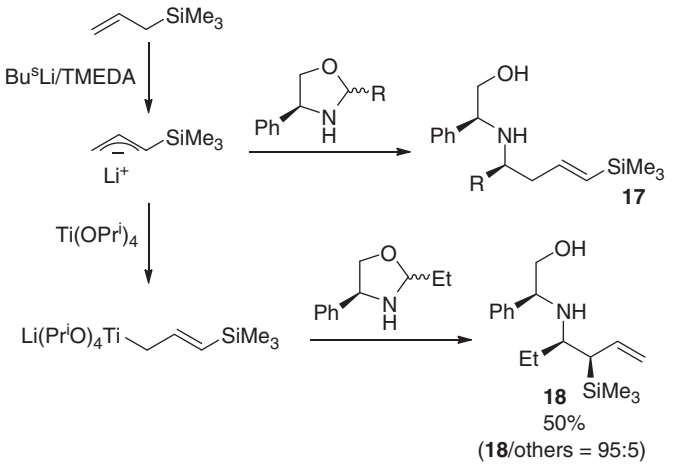
Addition of a trimethylsilyl-substituted allyllithium reagent to (*S*)-phenylglycinol-derived oxazolidines proceeds with high diastereoselectivity with forming a new C–C bond at the α position to afford β-amino alcohols **17** (Scheme 7 and Table 3).[10,11] In contrast, similar reactions with a titanium reagent lead to reversal of the regioselectivity to afford **18** since the formation of 3-trimethylsilylallyl titanate predominates.

2.04.3 Phosphorus-Substituted Allylic Anions

Hua pioneered the use of chiral phosphorous-substituted allylic anions in stereoselective synthesis.[12,13] Lithiation of chiral oxazaphospholidine oxide **19** followed by the reaction with cyclic enones provides the corresponding 1,4-adducts **20** in high yields (Scheme 8). Ozonolysis of **20** yields the corresponding ketoaldehydes **21** of high enantiomeric purity.

The allylic anion of ephedrine-derived chiral phospholidine oxide **22** is applicable to the synthesis of (–)-methyl jasmonate (**24**) and other derivatives (Scheme 9).[14]

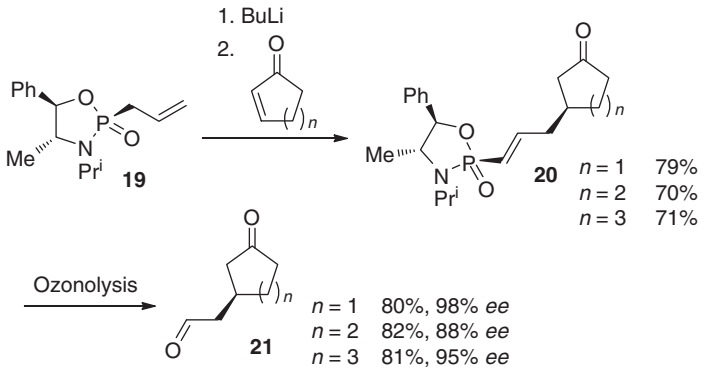
Several groups have pursued more effective chiral auxiliaries. Hanessian reported asymmetric conjugate additions of chiral allylic phosphonamide anions to α,β-unsaturated carbonyl compounds (Scheme 10 and Table 4).[15–17] Owing to the C_2-symmetric bicyclic structure originated from chiral cyclohexanediamine, the scope of the reaction is wide and the diastereoselectivities are excellent. The versatility of the strategy culminates in the generations of four contiguous stereogenic centers on acyclic motifs



Scheme 7 Addition of trimethylsilylallyllithium or titanium to (*S*)-phenylglycinol-derived oxazolidines.

Table 3 Addition of trimethylsilylallyllithium to (*S*)-phenylglycinol-derived oxazolidines (Scheme 7)

R	*Yield of* **17** *(%)*	dr
Ph	81	92:8
Et	45	80:20
Pr^i	75	90:10
Bu^t	80	95:5



Scheme 8 Asymmetric 1,4-addition of lithiated **19** to cyclic enones.

(Scheme 11). Combined with ozonolysis of the double bonds, Hanessian's C_2-symmetric reagents are easy to handle and hence useful in organic synthesis.

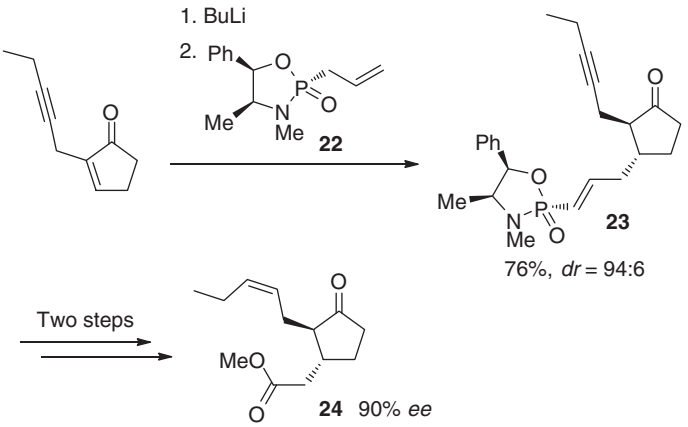
Allylic phosphorus reagents with a six-membered oxazaphosphinane oxide auxiliary also enable asymmetric conjugate addition to cyclic enones (Scheme 12).[18] Although the conjugate addition of *cis* isomers is highly regio- and diastereoselective, the relevant *trans* isomers lead to very poor diastereoselectivity.

BINOL-derived chiral allylphosphonates also undergo conjugate addition to cyclopentenone with high diastereoselectivity (Scheme 13).[19]

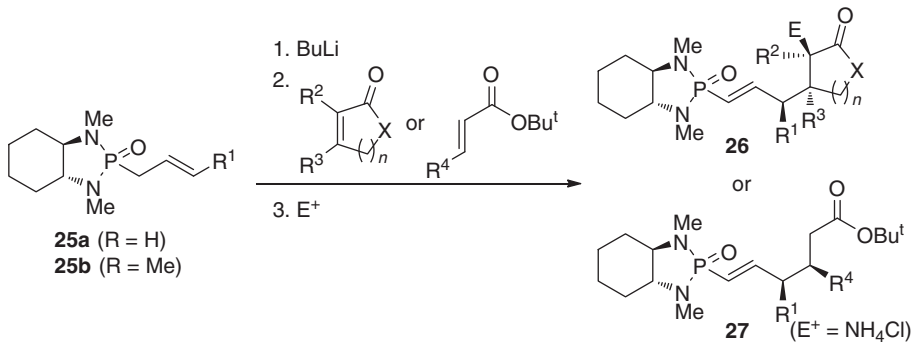
2.04.4 Sulfur-Substituted Allylic Anions

Allylic anions derived from allylic sulfoxides by deprotonation react with electrophiles at the γ positions to yield vinylic sulfoxides. For the last two decades, the chemistry of the allylic anions of allylic sulfoxides has been focusing on its application to the synthesis of bioactive compounds.

Stereoselective synthesis of (+)-juvabione from a chiral sulfoxide was achieved as shown in Scheme 14.[20] The chirality at the sulfur atom is nicely transferred onto the cyclohexanone ring and the adjacent tertiary carbon in **37** albeit the yield

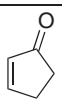
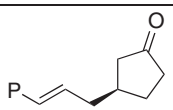
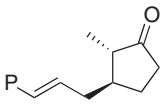
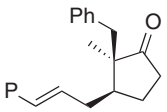
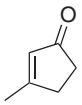
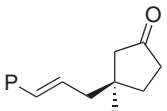
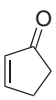
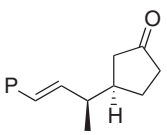


Scheme 9 Concise synthesis of (–)-methyl jasmonate.



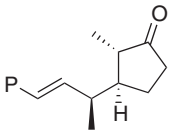
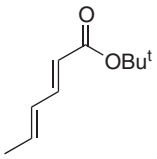
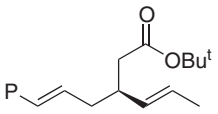
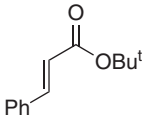
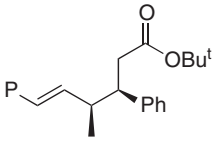
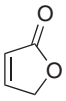
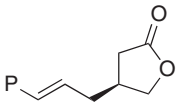
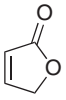
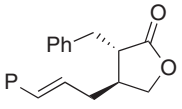
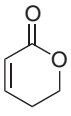
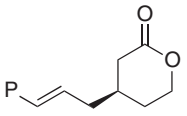
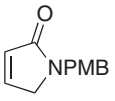
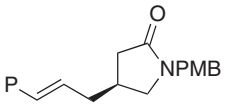
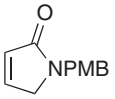
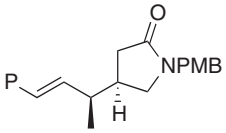
Scheme 10 Asymmetric conjugate additions of chiral allylic phosphonamide anions.

Table 4 Asymmetric conjugate additions of anions of **25** (Scheme 10)

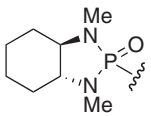
R^1	*Substrate*	E^+	*Product*[a]	*Yield (%)*	dr
H		NH_4Cl		88	93:7
H		MeOH		80	93:7
H		$PhCH_2Br$		80	>99:1
H		NH_4Cl		75	95:5
Me		NH_4Cl		96	96:4

(*Continued*)

Table 4 Continued

R^1	Substrate	E^+	Product[a]	Yield (%)	dr
Me		MeOH		74	94:6
H		NH_4Cl		76	>99:1
Me		NH_4Cl		94	>99:1
H		NH_4Cl		93	>99:1
H		$PhCH_2Br$		67	>99:1[b]
H		NH_4Cl		48	93:7
H		NH_4Cl		60[c,d]	99:1
Me		NH_4Cl		51[c]	95:5

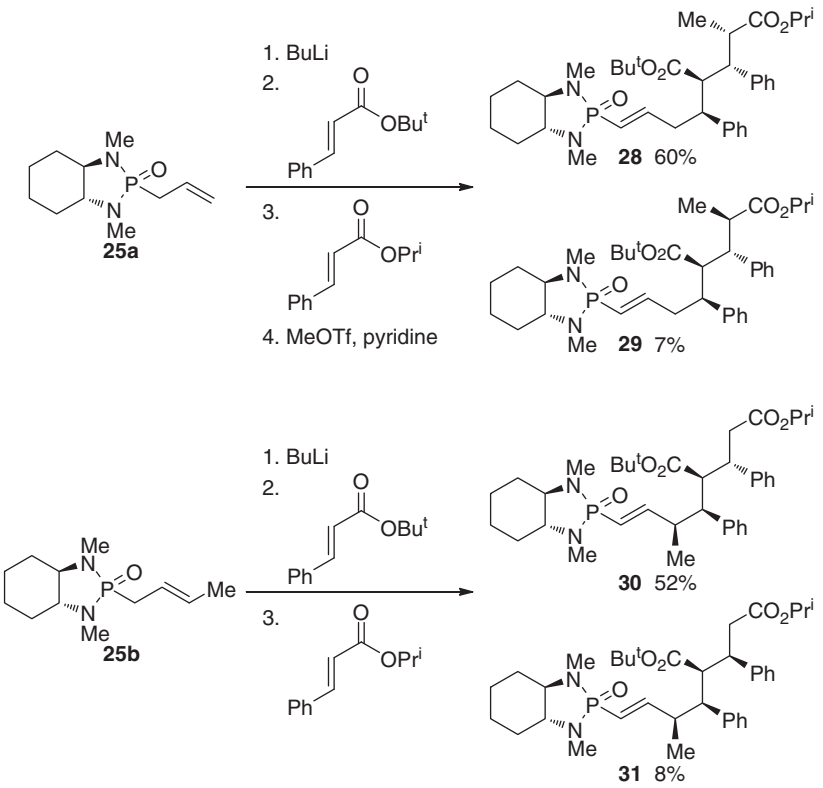
[a]

P = 

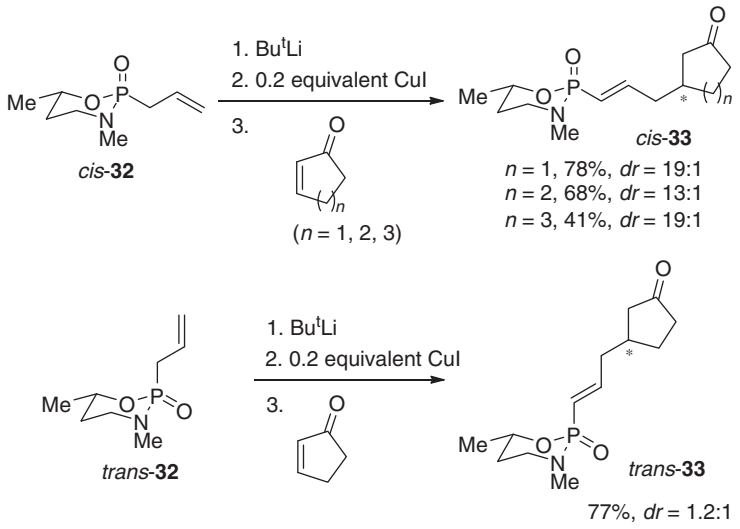
[b]After epimerization with DBU.
[c]Toluene as solvent.
[d]NaHMDS as base.

is moderate. In the synthesis of (±)-securinine (**Scheme 15**),[21] attempts on conjugate addition of allylcuprate reagents to unsaturated lactone **38** failed. The use of phenylsulfinyl-substituted allylic anion instead realized efficient allylation of **38** to yield **39** in 71% yield. The sulfinyl moiety did not interfere with the following ring-closing metathesis, and the subsequent transformations led to (±)-securinine. Other examples of sulfinyl-substituted allylic anions in organic synthesis also utilize the highly regioselective bond-forming events at the γ positions.[22,23]

An interesting method for synthesizing chiral fluorinated 1,4-dihydropyridines has been developed (**Scheme 16**).[24] Nucleophilic condensation of (*R*)-allyl *p*-tolyl sulfoxide, 2,2-difluoroalkanenitriles, and alkyl propiolates by means of KHMDS yields a variety of 1,4-dihydropyridines. The reaction involves (1) the generation of the sulfur-stabilized allylic anion of (*R*)-**40**, (2) γ-selective nucleophilic attack to 2,2-difluoroalkanenitrile and isomerization, (3) conjugate addition to propiolate, and (4) intramolecular conjugate addition to vinylic sulfoxide.



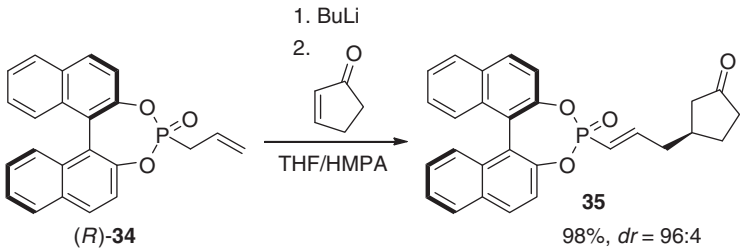
Scheme 11 Generations of four contiguous stereogenic centers from **25**.



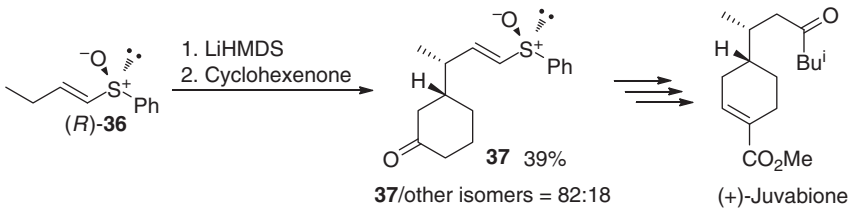
Scheme 12 Asymmetric conjugate addition of 2-allyl-1,3,2-oxazaphosphinane oxides.

The carbanions of allylic sulfones usually undergo conjugate addition at the α position. Hassner extensively investigated the reactions of lithiated 2-(bromomethyl)allyl sulfone as a trimethylenemethane equivalent.[25–27] The reactions with α,β-unsaturated carbonyl compounds provide a wide spectrum of multisubstituted methylenecyclopentanes with high diastereoselectivity (Scheme 17 and Table 5). The cycloaddition strategy is also applicable to aldehydes and imines albeit the stereoselectivities are not very high.[28,29]

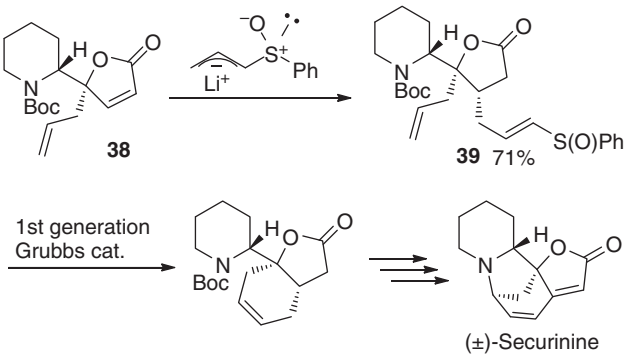
Nájera[30] and Hassner[27,31,32] examined the reactions of lithiated 2-(aminomethyl)allyl sulfones. The reactions with dihalides result in the formation of various azacycles albeit moderate yields (Scheme 18).[30] A chiral auxiliary on the nitrogen atom allows remote asymmetric induction in the reactions with unsaturated esters (Scheme 19).[31]



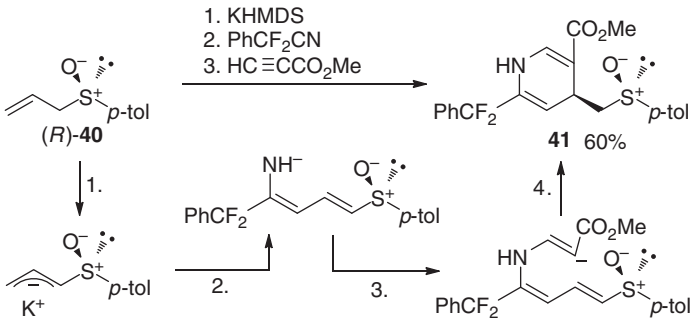
Scheme 13 Asymmetric conjugate addition of BINOL-derived chiral allylphosphonate.



Scheme 14 Stereoselective synthesis of (+)-juvabione from chiral sulfoxide.



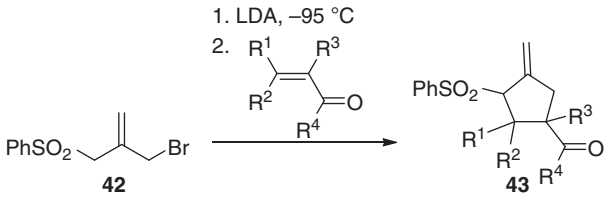
Scheme 15 Synthesis of (±)-securinine.



Scheme 16 Nucleophilic Condensation of (*R*)-allyl sulfoxide, difluoroalkanenitrile, and propiolate by means of KHMDS.

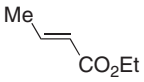
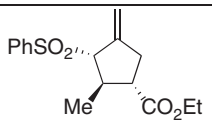
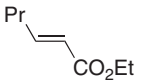
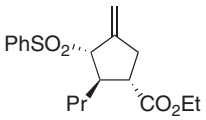
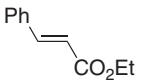
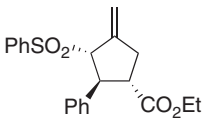
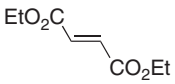
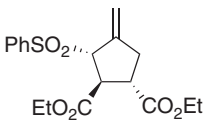
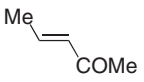
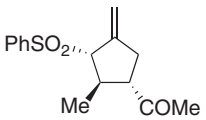
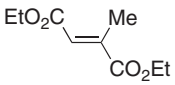
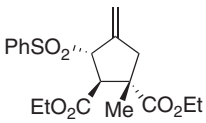
2.04.5 Nitrogen-Substituted Allylic Anions

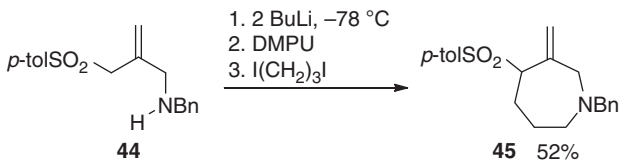
Since the pioneering work of Ahlbrecht and Enders[33] and Helmchen,[34] *C*-metalated allylic amines with a chiral auxiliary have been used as chiral homoenolate equivalents. Among them, titanated allylic oxazolidinones represent a very effective platform to



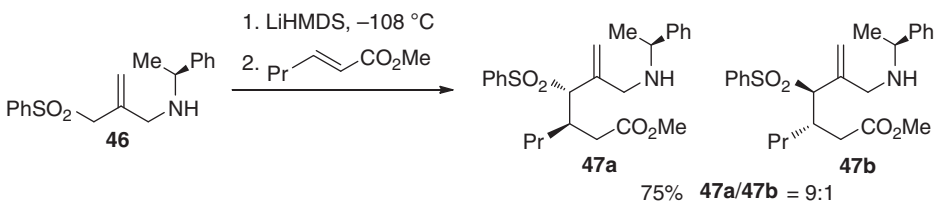
Scheme 17 Formal 3 + 2 cycloaddition of 2-(bromomethyl)allyl sulfone with unsaturated carbonyl compounds.

Table 5 Methylenecyclopentanes from **42** and unsaturated carbonyl compounds (**Scheme 17**)

Substrate	*Product*	*Yield (%)*
		93
		93
		92
		81
		95
		86

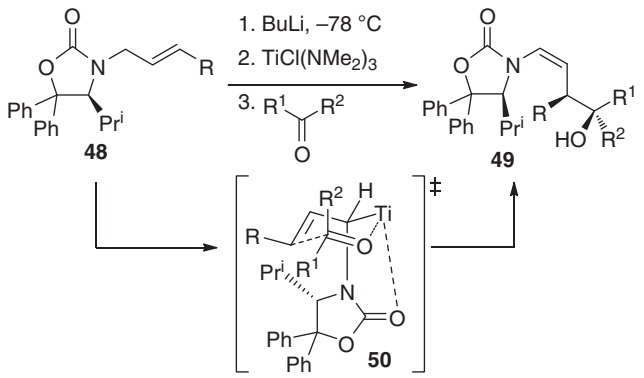


Scheme 18 Synthesis of hexahydroazepine.



Scheme 19 Conjugate addition of chiral lithiated 2-(aminomethyl)allyl sulfones.

this end.[35] Allylic titanium reagents, generated from *N*-allyl- or *N*-cinnamyloxazolidinone **48** by lithiation and the following transmetalation to titanium, react with aldehydes and ketones at the γ position (Scheme 20). The formation of enamine **49** is highly diastereoselective, even in the reactions with ketones (Table 6). The choice of the titanium complex is important and $TiCl(NMe_2)_3$ gives the best selectivity. Transition state **50** can rationalize the regio- and stereoselectivities.

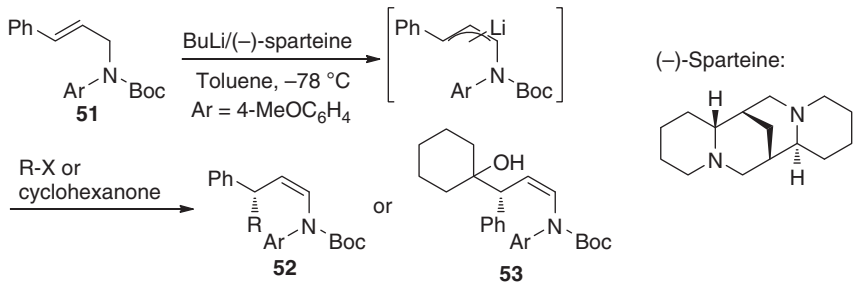


Scheme 20 Highly diastereoselective addition of metalated *N*-allylic oxazolidinones.

Table 6 Addition of titanium reagent derived from **48** to carbonyl compounds (Scheme 20)

R	R^1	R^2	*Yield (%)*	dr
H	Pr^i	H	78	94:6
H	1-cyclopentenyl	H	67	92:8
H	Ph	H	62	91:9
H	Ph	Me	74	>98:2
H	Pr^i	Me	76	91:9
Ph	Me	Me	65	>98:2
Ph	$-(CH_2)_5-$		56	>98:2

N-Boc-protected allylamines serve as homoenolate equivalents,[36,37] and a combination of butyllithium and (–)-sparteine effects enantioselective lithiation of *N*-Boc-protected cinnamylamine **51** (Scheme 21 and Table 7).[38,39] Trapping with reactive organic halide generates a stereogenic center with *S* configuration, whereas the sense of enantioselectivity in the reaction with cyclohexanone is opposite. The reaction pathway of the enantioselective reactions has been investigated in details by using NMR



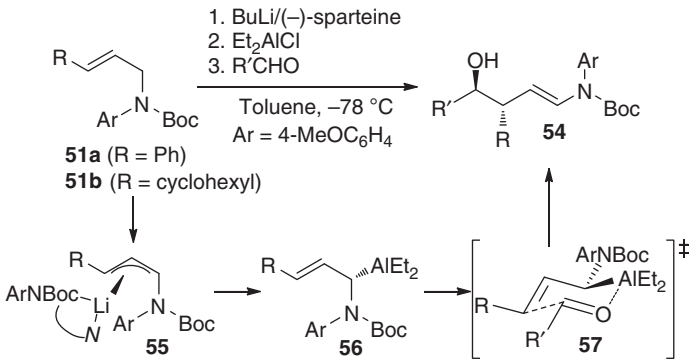
Scheme 21 (–)-Sparteine-mediated asymmetric lithiation and mucleophilic attack.

Table 7 Asymmetric lithiation and nucleophilic attack of **51** (Scheme 21)

Electrophile	*Yield (%)*	*Configuration*	*ee (%)*
CH_3I	73	*S*	95
$CH_2{=}CHCH_2Br$	72	*S*	94
$PhCH_2Br$	70	*S*	96
Cyclohexanone	77	*R*	98

spectroscopy to reveal that the enantiodetermining step can involve asymmetric deprotonation, dynamic kinetic resolution, or dynamic thermodynamic resolution.

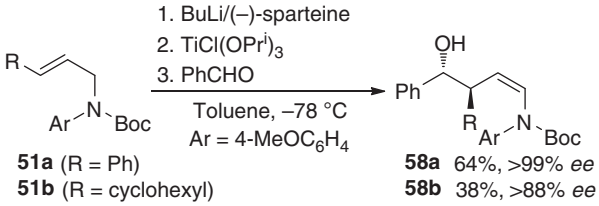
A sequence of (–)-sparteine-mediated lithiation of *N*-Boc allylic amines **51**, transmetalation to aluminum, and nucleophilic addition to aldehydes leads to highly enantioselective syntheses of *anti*-homoaldol products **54** (Scheme 22).[40] The transmetalation with diethylaluminum chloride results in the preferential formation of (*E*)-*anti*-adducts of high enantiomeric purity (Table 8). The proposed mechanism[39–41] involves enantioselective lithiation to form (–)-sparteine-ligated **55**, transmetalation to form **56** with inversion of configuration, and allylation via a favorable six-membered cyclic transition state **57**. However, transmetalation with $TiCl(OPr^i)_3$ also gives rise to *anti*-homoaldol products (Scheme 23). However, the absolute stereochemistries of the two consecutive stereogenic centers as well as the geometry of the double bond are opposite. The scope of aldehyde in the titanium-mediated reaction is limited to benzaldehyde.



Scheme 22 Transmetalation of chiral lithiated *N*-Boc allylic amines to aluminum for enantioselective synthesis of *anti*-homoaldol products.

Table 8 Enantioselective synthesis of *anti*-homoaldol products **54** (Scheme 22)

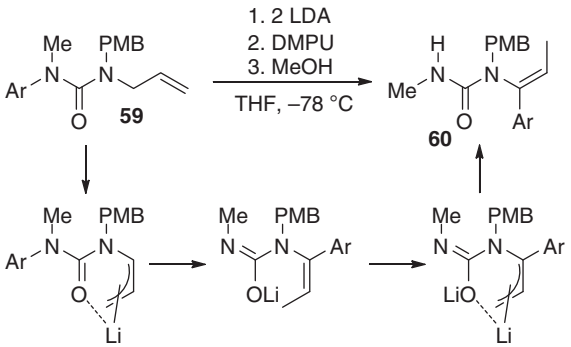
R	*R′*	*Yield (%)*	*ee (%)*	*E/Z*
Ph	Ph	85	94	90:10
Ph	Me	66	84	95:5
Ph	Pr^i	61	90	98:2
Ph	Cyclohexyl	66	96	95:5
Cyclohexyl	Ph	82	88	90:10
Cyclohexyl	Me	72	86	97:3
Cyclohexyl	Pr^i	81	88	98:2
Cyclohexyl	Cyclohexyl	84	90	98:2



Scheme 23 Transmetalation of chiral lithiated *N*-Boc allylic amines to titanium for enantioselective synthesis of *anti*-homoaldol products.

The combination of butyllithium and (–)-sparteine are applied to synthesis of heterocycles[42] and enantioenriched quaternary centers,[43] and more complex allylic compounds.[44]

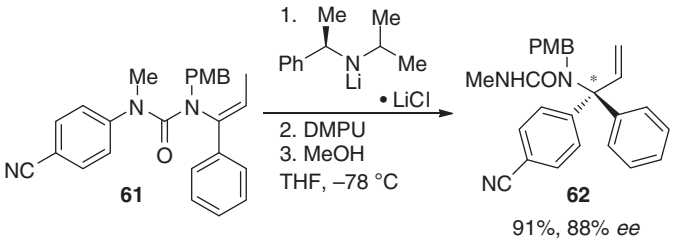
On treatment of *N*-allyl-*N′*-arylureas **59** with lithium amide in the presence of DMPU, very interesting migration of the aryl group proceeds from N to C (Scheme 24 and Table 9).[45] The newly formed N-H group in products **60** can be arylated under palladium catalysis, and the resulting *N*-(1-aryl-1-propenyl)-*N′*-arylureas such as **61** undergo similar aryl migration further to generate *N*-(1,1-diarylallyl)ureas (Scheme 25). Notably, the second aryl migration can be performed in an enantioselective manner by using chiral lithium amides.



Scheme 24 Lithiation-mediated aryl migration of *N*-allyl-*N*′-arylureas **59** to form **60**.

Table 9 Lithiation-mediated aryl migration of *N*-allyl-*N*′-arylureas **59** (Scheme 24)

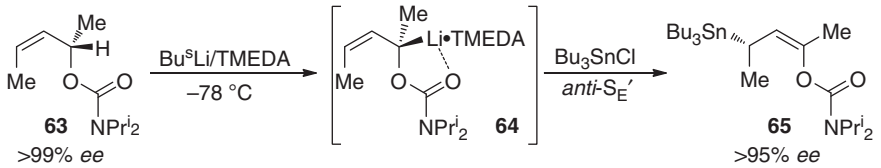
Ar	*Yield (%)*
Ph	74
p-$CH_3C_6H_4$	67
m-$CH_3C_6H_4$	95
p-$CH_3OC_6H_4$	53
m-$CH_3OC_6H_4$	68
p-ClC_6H_4	70
m-FC_6H_4	67
p-NCC_6H_4	49
m-$CF_3C_6H_4$	86
1-naphthyl	58



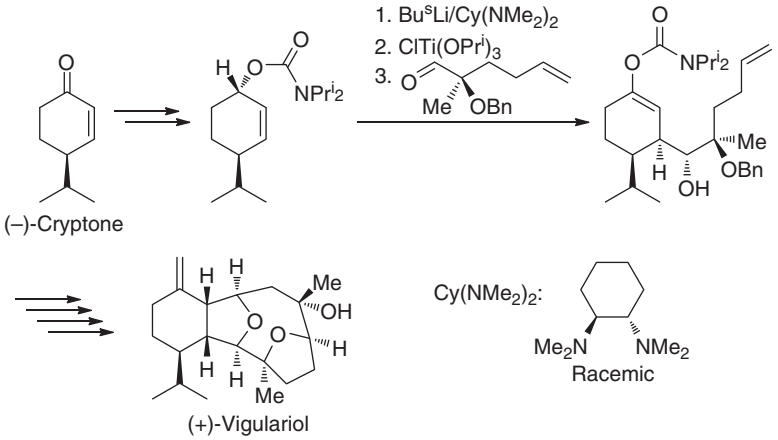
Scheme 25 Asymmetric lithiation/migration to form tertiary alkyl-substituted ureas.

2.04.6 Oxygen-Substituted Allylic Anions

Hoppe extensively investigated metalation of *O*-allyl carbamates and its application to asymmetric homoaldol reaction.[46] Starting from chiral secondary allylic carbamate **63**, deprotonation by organolithium/TMEDA yields the corresponding allylic lithium species **64** with retention of configuration (Scheme 26).[47] The following stannylation proceeds in an *anti*-S_E' fashion to yield vinyl carbamate **65**. One of the excellent applications of Hoppe's strategy is the synthesis of cytotoxic, tetracyclic diterpene (+)-vigulariol from (*R*)-(–)-cryptone (Scheme 27).[48]

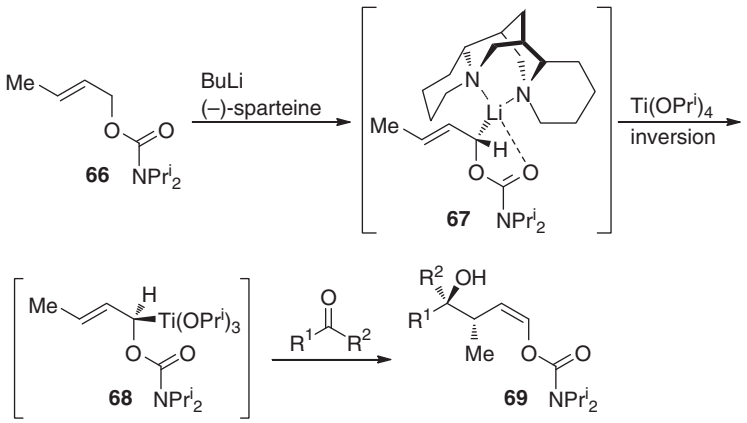


Scheme 26 Chirality transfer from allylic carbamate to allylic stannane.



Scheme 27 Synthesis of (+)-vigulariol.

Organolithium/(–)-sparteine promotes enantioselective deprotonation (Scheme 28).[49–51] After transmetalation to titanium with inversion of configuration, the resulting allylic titanium species **68** reacts with carbonyls with high enantioselectivity (Table 10). Not only *O*-crotyl carbamate **66**, but also *N*,*N*-diisopropylcarbamates with other *O*-substituents such as 3-silyl-2-alkenyl[52] or 2-cyclohexenyl[53,54] participate in the reaction. The Hoppe reaction is powerful and hence applicable to the syntheses of a variety of biologically active compounds,[46] one of which is illustrated in Scheme 29.[55]



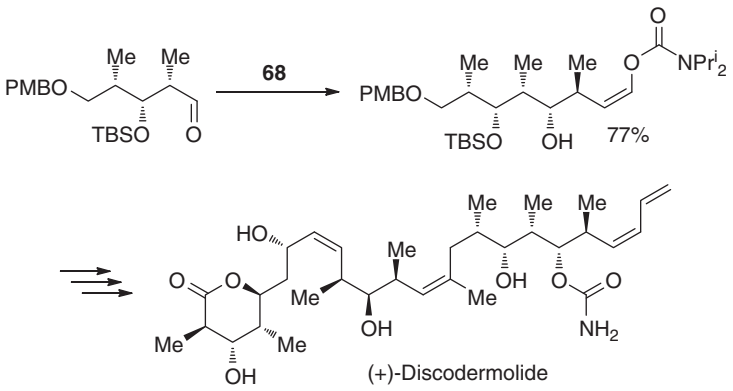
Scheme 28 Enantioselective deprotonation of *O*-crotyl carbamate and its application to homoaldol reaction.

Table 10 Enantioselective homoaldol reaction of *O*-crotyl carbamate **66** (Scheme 27)

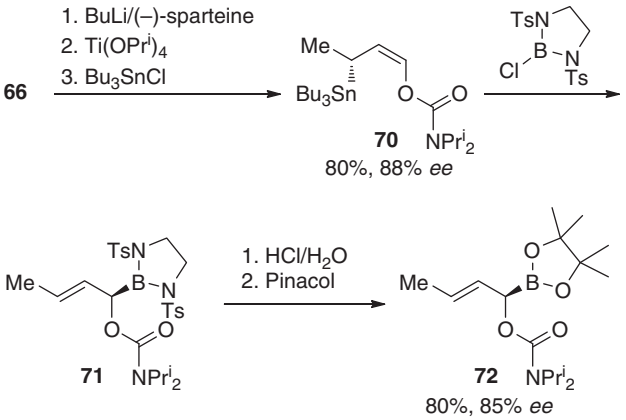
R^1	R^2	*Yield (%)*	*ee (%)*
Pr^i	H	90	90
Me	H	95	80
Bu	H	93	84
Me	Me	92	82

Carbamate **66** is converted to stable boronate **72** of high enantiomeric purity via α-lithiated **67**, titanated **68**, and γ-stannylated product **70** (Scheme 30).[56] The final transmetalation to boron proceeds in an *anti*-S_E' manner. Chiral crotylboronate **72** is subjected to homoaldol reactions with aldehydes to furnish the corresponding (*Z*)-*anti*-homoallylic alcohols with high diastereoselectivity and with complete chirality transfer.

Deprotonation of carbamates **73**, derived from enantioenriched secondary allylic alcohols, followed by the reaction with organoboronic pinacol esters results in the formation of the corresponding borate complexes **74** with retention of the stereochemistry (Scheme 31).[57] The boronates then undergo 1,2-migration leading to enantioenriched tertiary allylic boronic esters **75**

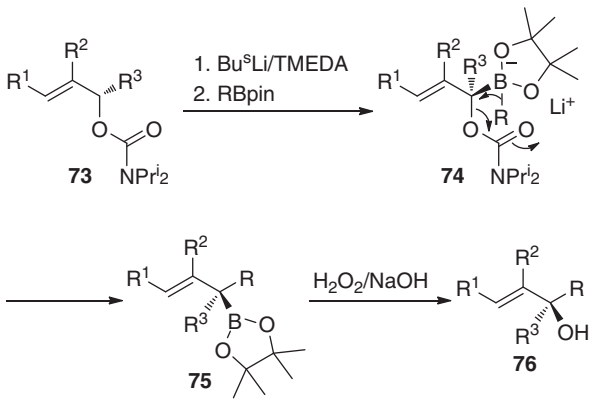


Scheme 29 Synthesis of (+)-discodermolide.



Scheme 30 Synthesis of enantioenriched α-carbamoyloxycrotylboronate.

with high stereospecificity. Boronic esters **75** are oxidized to alcohol **76** with retention of configuration by hydrogen peroxide (Table 11). This methodology is applicable to a highly efficient synthesis of botryococcene.



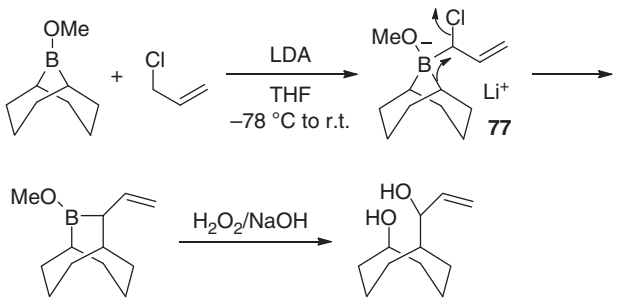
Scheme 31 Enantioselective synthesis of tertiary allylic boronic esters and alcohols from **73**.

2.04.7 Halogen-Substituted Allylic Anions

Deprotonation of allylic chloride by lithium amide in the presence of organoboranes results in the formation of α-chloroallylborates such as **77**, which then undergo 1,2-migration to yield three-carbon homologated allylic boranes of synthetic use (Scheme 32).[58–60] In addition to organoboranes, a similar transformation is achieved with zirconacyclopentanes.[61]

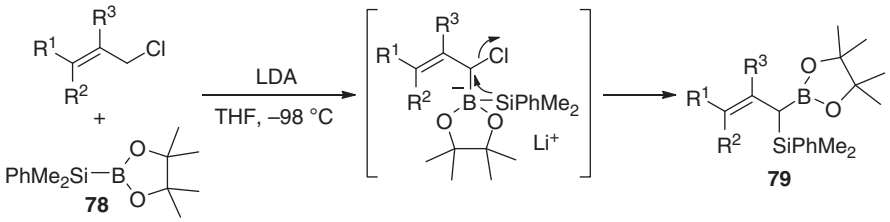
Table 11 Enantioselective synthesis of tertiary allylic alcohols **76** (Scheme 31)

R^1	R^2	R^3	R	Yield (%)	ee (%)
Me	H	Me	Bu	75	96
Me	H	Me	$(CH_2)_2Ph$	92	96
Me	H	Me	Cyclohexyl	76	98
Me	H	Me	$CH_2{=}CHCH_2$	77	96
Me	H	Me	Ph	84	96
Pr^i	H	Me	$CH_2{=}CH$	79	96
Pr^i	H	Me	Et	72	96
Me	H	Et	$(CH_2)_2Ph$	83	98
Me	Me	Me	$(CH_2)_2Ph$	81	88



Scheme 32 Three-carbon homologation of organoborane.

The reactions of lithiated allylic chlorides with silylboronate **78** resulted in *gem*-silylboration to yield **79** of synthetic use in carbonyl allylation (Scheme 33 and Table 12).[62]

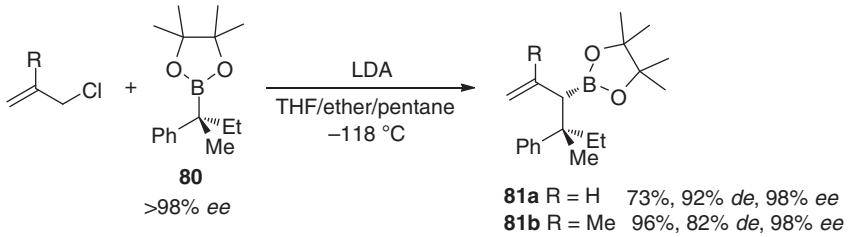


Scheme 33 *gem*-Silylboration of allylic chlorides.

Table 12 *gem*-Silylboration of allylic chlorides (Scheme 33)

R^1	R^2	R^3	Yield (%)
H	H	H	82
Pr	H	H	75
H	Pr	H	79
Ph	H	H	75
Me	Me	H	72
H	H	Me	73

The reactions of lithiated allylic chlorides with tertiary alkylboronate ester **80** give homologated allylic boronate **81** via 1,2-migration with high diastereoselectivity and complete stereospecificity (Scheme 34).[63]



80
>98% *ee*

81a R = H 73%, 92% *de*, 98% *ee*
81b R = Me 96%, 82% *de*, 98% *ee*

Scheme 34 Enantioselective construction of quaternary stereogenic centers from chiral tertiary boronic ester.

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2.05 Propargyl and Allenyl Organometallics

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This chapter is a revision of the previous edition chapter by Hisashi Yamamoto, Vol. 2, pp 81–98, © 1991, Elsevier Ltd.

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Glossary

Ate complex A complex formed between a Lewis acid and an anionic fragment usually but not always leading to a coordinationally saturated species. The term is usually applicable to elements of groups 11–13.

Chiral auxiliary A chemical compound or unit that is temporarily incorporated into a substrate in order to create new elements of chirality via chemical modification proceeding in the resulting stereodifferentiating environment.

Dynamic kinetic resolution A particular case of kinetic resolution conducted under conditions favoring equilibrium of enantiomers, which can theoretically provide 100% of enrichment with one of the chemically modified isomers.

Kinetic resolution Enrichment of a racemic mixture with one of the enantiomers via selective chemical modification of its counterpart. The concept is based on the fact that enantiomers can react with chiral reagents with appreciably different reaction rates.

Metallotropic rearrangement (shift) A sigmatropic process involving organometallic fragments.

Pincer ligand A chelating ligand that rigidly binds to three adjacent coplanar coordination sites of the metal.

Sigmatropic rearrangement (shift) A pericyclic reaction resulting in cleavage of one σ-bond and formation of another σ-bond usually accompanied by a rearrangement of the π-system.

Stereotriad A fragment consisting of three adjacent stereogenic centers.

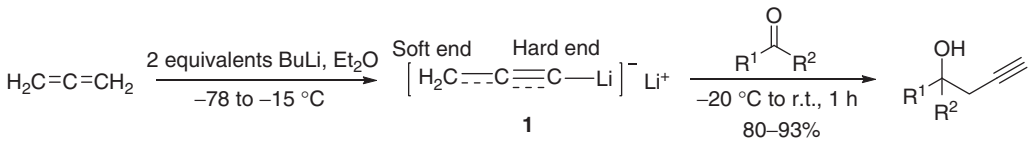
2.05.1 Introduction

Since the publication of the first edition of *Comprehensive Organic Synthesis* in 1992[1] a considerable number of useful applications of allenyl and propargyl organometallic compounds have been published; the synthetic potential of these reagents has expanded noticeably in recent years, in particular with respect to stereoselective applications. For each of the most common metals/metalloids, this chapter will thus survey some of the notable synthetic reports of the past two decades only. The selection is guided by the authors' preferences and is not supposed to be exhaustive. With regard to more detailed coverage of organometallic allenyl/propargyl reagents, a number of brilliant reviews are kindly suggested to the reader.[2–6]

2.05.2 Lithium and Magnesium

Allenyl/propargyl lithium compounds represent a particularly important class of reagents directly accessible from alkynes, allenes, and propargyl halides; this feature enables their use as precursors of other allenyl/propargyl organometallic reagents that can provide the desired reactivity and selectivity profiles. Detailed studies on the structure of allenyl/propargyllithium species in the solution and regioselectivity of metalation/silylation sequence have been conducted by Reich et al.[7]

Reactions involving allenyl/propargyllithium reagents can often raise regioselectivity issues. Generally, the dilithiated species **1**, first reported by Hooz et al., demonstrate enhanced regioselectivity in carbonyl addition reactions, leading to high yields in reactions with ketones and aromatic aldehydes (Scheme 1, Table 1). Somewhat compromised regioselectivity was detected for aliphatic aldehydes. Species **1** can be considered in light of the Pearson acid base concept, with the lithiated end of the delocalized system being 'hard' and the remote end being 'soft.'[8]



Scheme 1 Reproduced from Cabezas, J. A.; Alvarez, L. X. *Tetrahedron Lett.* **1998**, *39*, 3935–3938.

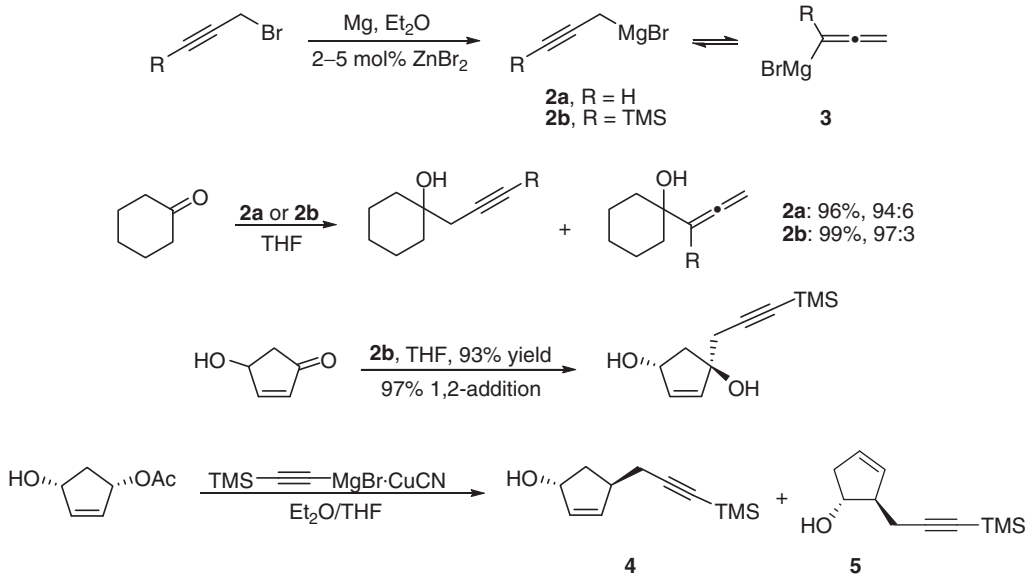
Table 1 Selected yields of homopropargylic alcohols prepared with dilithiated species **1** (Scheme 1)

No.	R^1	R^2	*Yield (%)*
1	Ph	Me	93
2	Me	CH=CH_2	80
3	Ph	Cyclopropyl	90
4	Ph	H	93
5	*s*-C_5H_{11}	H	84[a]

[a]Propargyl: allenyl 86:14.
Source: Reproduced from Cabezas, J. A.; Alvarez, L. X. *Tetrahedron Lett.* **1998**, *39*, 3935–3938.

Direct preparation of allenylmagnesium reagents from magnesium metal and propargyl halides has been used quite extensively; however, the use of catalytic amounts of mercury chloride is required (the exact nature of this beneficial effect remains poorly understood).[9]

Kobayashi and coworkers assumed that the lack of elaborated studies in some areas of propargyl Grignard chemistry could be associated with the necessity of poisonous additives; this consideration resulted in the development of an improved direct Grignard synthesis methodology for allenyl/propargyl reagents. The reaction could be carried out mercury-free in the presence of 2–5 mol% of $ZnBr_2$, rendering the protocol much more operationally convenient and environmentally benign. Carbonyl compounds furnished predominantly homopropargyl alcohols; reactions with cyclopentenones and cyclopent-2-yl acetates as substrates demonstrated high regioselectivity favoring, respectively, 1,2-addition and S_N2 substitution (with little competition from the S_N2' process, whereas the conventional mercury-assisted process provided far inferior selectivity) (Scheme 2, Table 2).[9] For a review on carbonyl additions of alkali and alkaline earth cations *see* Chapter 1.01.



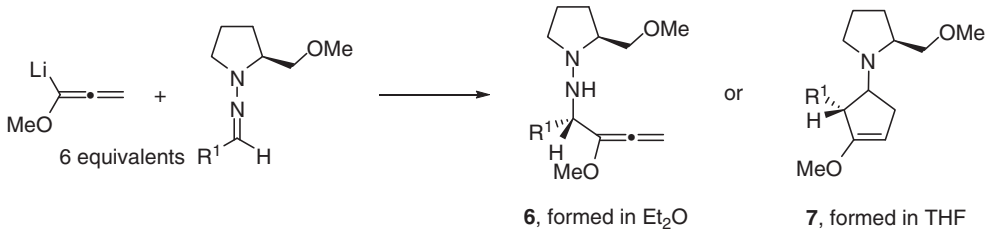
Scheme 2 Reproduced from Acharya, H. P.; Miyoshi, K.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3535–3538, with permission from ACS.

The use of propargyl/allenyllithium reagents in the enantioselective context is mostly focused on the use of chiral auxiliaries. For example, Goré and coworkers applied Enders' SAMP-hydrazone methodology to access enantiopure 3-pyrrolines as shown in equation 1.[10] The reaction outcome was found to be solvent-sensitive, and both products **6** and **7** could be obtained in a directed way. Addition proceeded with excellent diastereoselectivity leading to 3-pyrollines of excellent enantiomeric purity (equation 1, Table 3). Ketone derivatives demonstrated unsatisfactory results.

Table 2 Ratios of products **4** and **5** prepared according to **Scheme 2**

No.	*Catalyst*	*Additive (8 equivalents)*	***4*:*5***	***4*+*5* Yield (%)**
1	$HgCl_2$	None	68:32	83
2	$HgCl_2$	$MgCl_2$	94:6	76
3	$ZnCl_2$	$MgCl_2$	94:6	77
4	$ZnCl_2$	LiCl	87:13	79

Source: Reproduced from Acharya, H. P.; Miyoshi, K.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3535–3538, with permission from ACS.



(1)

Table 3 Selected examples of α-allenylhydrazines and 3-methoxy-3-pyrrolines prepared according to equation 1

No.	*Solvent*	*R^1*	***6**, Yield (%)/*de *(%)*	***7**, Yield (%)/*de *(%)*
1	Et_2O	Ph	>95/99	–
2		2-Naphthyl	>95/99	–
3		Et	>95/93	–
4		Bu^t	>95/95	–
5	THF	Ph	–	88/99
6		2-Naphthyl	–	76/99
7		Et	38/99	–
8		Bu^t	–	8/99

Source: Reproduced from Breuil-Desvergnes, V.; Compain, P.; Vatèle, J.-M.; Goré, J. *Tetrahedron Lett.* **1999**, *40*, 5009–5012.

2.05.3 Boron

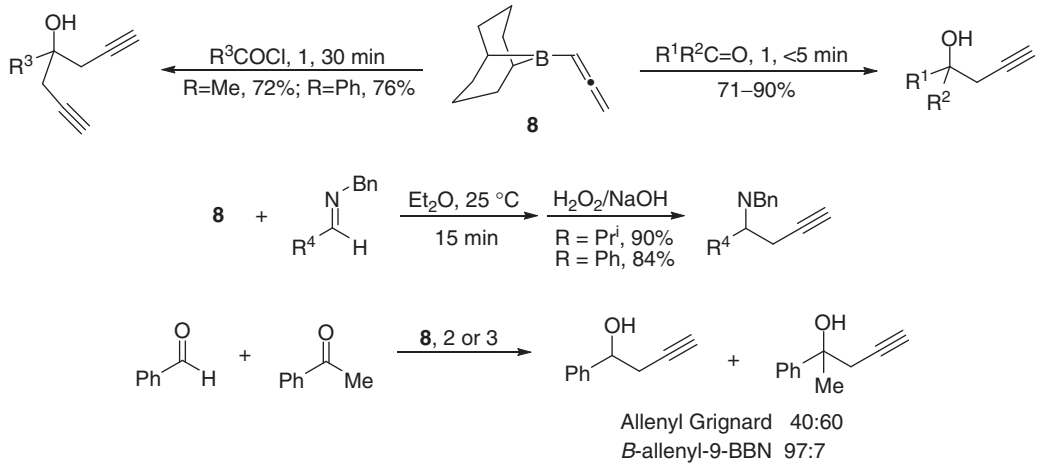
B-Allenyl-9-BBN **8**, reported by Brown in 1993, became a popular reagent for propargylation of various substrates, including aldehydes, ketones, acyl chlorides, and imines.[11] Compound **8** was found to be far superior to allenylboronates and allenyl Grignards and enabled efficient access to α-unsubstituted homopropargylic alcohols (**Scheme 3**, **Table 4**). In addition to the easy preparation and excellent regioselectivity, the reagent is notable for remarkable chemoselectivity: addition to aldehydes proceeds faster than addition to ketones and esters; moreover, less sterically challenged aldehydes and ketones can undergo propargylation in the presence of more congested ones. Addition to α,β-unsaturated carbonyl compounds proceeds in 1,2-fashion. Propargylation of acyl chlorides provided convenient access to bis-homopropargyl alcohols. Reactions with esters appeared to be significantly slower, requiring prolonged reflux, and thus they were of rather low preparative importance.

Another seminal study by Brown described the preparation and use of *B*-(γ-(trimethylsilyl)propargyl)diisopinocampheylborane **9**, which was applied in the highly enantioselective allenylation of aldehydes (**Scheme 4, Table 5**). Addition at −100 °C followed by alkaline peroxide oxidation furnished allenyl alcohols with 72–78% yields and 87–99% *ee*.[12] On oxidation of carbon–boron bonds *see* Chapter 7.22.

Corey reported a highly regio- and enantioselective methodology using chiral auxiliary **10**; both allenyl **11** and homopropargyl alcohols **12** could be prepared depending on the choice of the organotin reagent. Notably, excellent enantioselectivities were obtained in both cases for aliphatic, aromatic, and α,β-unsaturated aldehydes (**Scheme 5**, **Table 6**).[13]

Soderquist et al. published a series of studies focused on chiral auxiliaries **13** and **18**. The development of these systems was initiated by the necessity to elaborate a more convenient boron-based methodology for asymmetric allenylation and propargylation reactions. Systems **13** and **18** can be easily prepared in both enantiomeric forms from 9-MeO-BBN via an operationally simple chemistry; moreover, they are isolable in pure form, remarkably robust (air-stable), and can be recycled after the reaction, which constitute important advantages over classical boranes. Reaction of **13** with Grignards **14** or **15** furnishes allenylating and propargylating reagents, respectively, which enabled highly enantioselective preparation of homopropargylic and allenic alcohols (**Scheme 6**, **Tables 7** and **8**).[14,15] The use of pseudoephedrine after the addition enabled recovery of **13** with up to 85% yield.

Compounds **19** and **20** were likewise prepared from *N*-methylpseudoephedrine-derived **18** and were successfully utilized for the efficient and highly enantioselective synthesis of silylated α-allenyl carbinols and homopropargyl alcohols from ketones



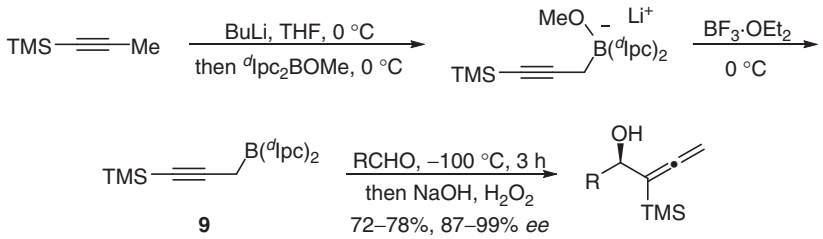
1. Et_2O, 25 °C, then H_2O_2/NaOH
2. –78 °C, Et_2O, then NaOH/H_2O_2
3. CH_2=C=CHMgBr, –78 °C, Et_2O, then NH_4Cl

Scheme 3 Reproduced from Brown, H. C.; Khire, U. R.; Narla, G.; Racherla, U. S. *J. Org. Chem.* **1995**, *60*, 544–549, with permission from ACS.

Table 4 Selected yields for the propargylation of aldehydes and ketones according to **Scheme 3**

No.	*R^1*	*R^2*	*Yield (%)*
1	Et	H	82
2	Ph	H	82
3	2-Furyl	H	79
4	Ph	Ph	90
5	CH_2=CH	Me	71
6	$(CH_2)_5$		87

Source: Reproduced from Brown, H. C.; Khire, U. R.; Narla, G.; Racherla, U. S. *J. Org. Chem.* **1995**, *60*, 544–549, with permission from ACS.



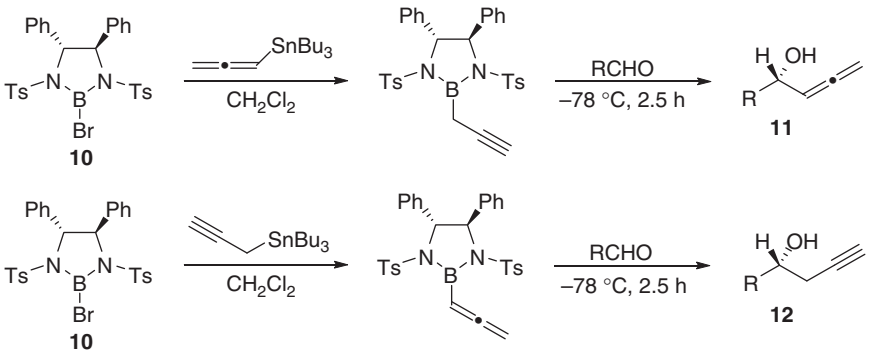
Scheme 4 Reproduced from Brown, H. C.; Khire, U. R.; Narla, G. *J. Org. Chem.* **1995**, *60*, 8130–8131, with permission from ACS.

Table 5 Allenylation of aldehydes according to **Scheme 4**

No.	*R*	*Yield (%)*	ee *(%)*
1	Me	72	87
2	Pr^i	76	99
3	Bu^t	75	92
4	Cy	78	96
5	(*E*)-MeCH=CH	68	87
6	Ph	74	89

Source: Reproduced from Brown, H. C.; Khire, U. R.; Narla, G. *J. Org. Chem.* **1995**, *60*, 8130–8131, with permission from ACS.

(Scheme 7, Tables 9 and 10). Recovery of the auxiliary was accomplished with pseudoephedrine leading to **21**, which can again be converted **19** and **20** on reaction with **14** and **15**, respectively.[16]

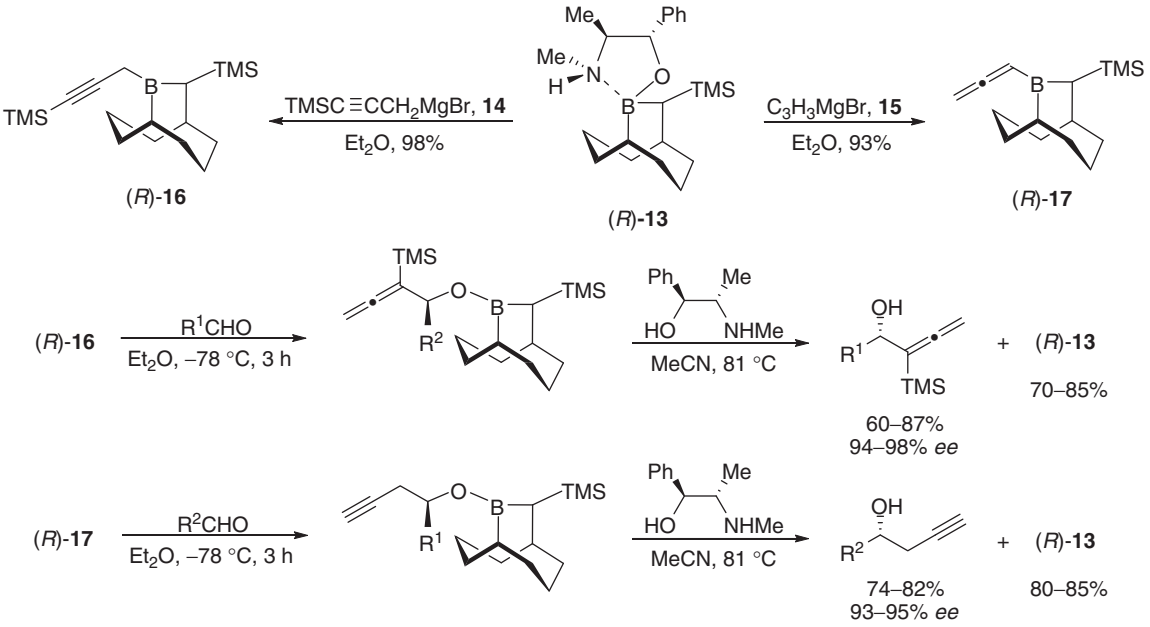


Scheme 5 Reproduced from Corey, E. J.; Yu, C. M.; Lee, D. H. *J. Am. Chem. Soc.* **1990**, *112*, 878–879, with permission from ACS.

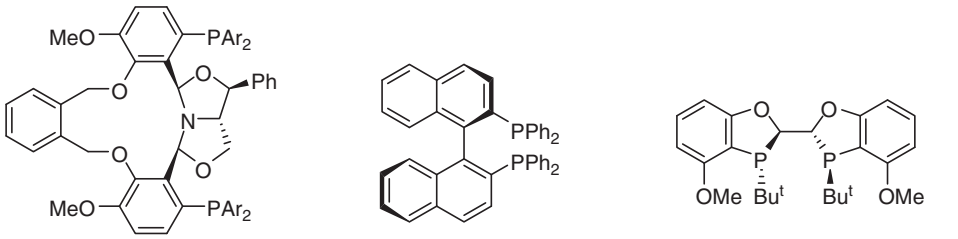
Table 6 Propargylation and allenylation of aldehydes (**Scheme 5**)

No.	*R*	***11**, yield (%)*	***11**,* ee *(%)*	***12**, Yield (%)*	***12**,* ee *(%)*
1	n-C_5H_{11}	82	>99	81	91
2	Me_2CH	74	>99	76	94
3	Cy	78	>99	82	92
4	Bu^t	78	>99	74	98
5	Ph	72	>99	76	96
6	PhCH=CH	74	>99	79	98

Source: Reproduced from Corey, E. J.; Yu, C. M.; Lee, D. H. *J. Am. Chem. Soc.* **1990**, *112*, 878–879, with permission from ACS.



Scheme 6 Reproduced from Hernandez, E.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 5397–5400, and Lai, C.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 799–802, with permission from ACS.



22, Ar = p-FC_6H_4 **23**, (*R*)-BINAP **24**, (2*R*,2′*R*,3*R*,3′*R*)-MeO-BIBOP

Table 7 Allenylation of aldehydes according to **Scheme 6**[a]

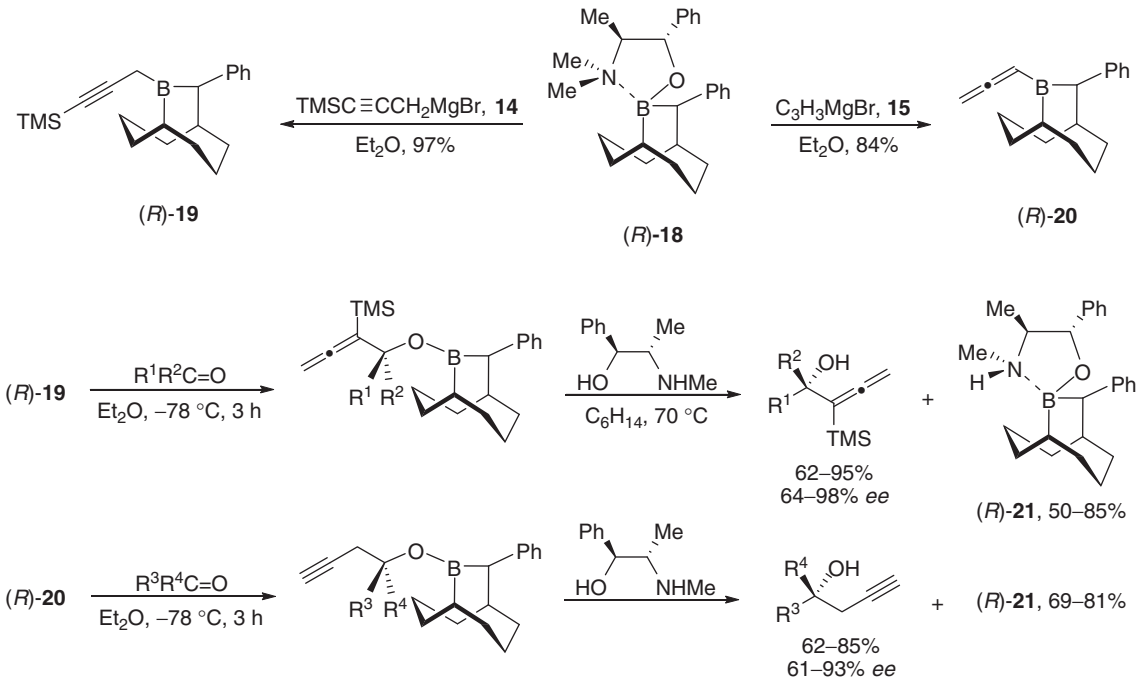
No.	R^1	*Yield (%)*	ee *(%)*
1	Me	71	94
2	Pr^n	87	98
3	Pr^i	77	97
4	Bu^t	80	98
5	Ph	60	98
6	(*E*)-MeCH═CH	87	97

[a]Screening was conducted with both (*R*)-**13** and (*S*)-**13**, which is not shown for clarity.
Source: Reproduced from Hernandez, E.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 5397–5400, with permission from ACS.

Table 8 Propargylation of aldehydes according to **Scheme 6**

No.	R^2	*Yield (%)*	ee *(%)*
1	Pr^n	82	94
2	Pr^i	81	93
3	Bu^t	75	94
4	Ph	78	93
5	CH_2═CH	74	94
6	2-Furyl	80	95

Source: Reproduced from Lai, C.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 799–802, with permission from ACS.



Scheme 7 Reproduced from Hernandez, E.; Burgos, C. H.; Alicea, E.; Soderquist, J. A. *Org. Lett.* **2006**, *8*, 4089–4091, with permission from ACS.

The first catalytic enantioselective method for the propargylation of ketones was developed by Kanai and Shibasaki. Allenyl Bpin could react with a wide range of ketones in the presence of the copper complex of the modular ligand **22**; high enantioselectivities and perfect regioselectivity were observed. Methyl ketones were found to be far superior to higher homologs in terms of enantioselectivity (equation 2, Table 11).[17]

Table 9 Allenylation of ketones according to Scheme 7[a]

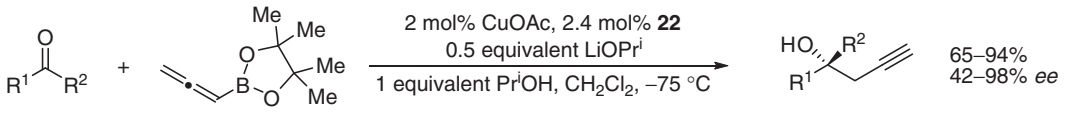
No.	R^1	R^2	*Yield (%)*	ee *(%)*
1	Ph	Me	81	97
2	Bu	Me	62	84
3	Cy	Me	67	91
4	*p*-$O_2NC_6H_4$	Me	79	98
5	2-Thienyl	Me	71	78
6	Ph	Et	63	64

[a]Screening was conducted with both (*R*)-**18** and (*S*)-**18**, which is not shown for clarity.
Source: Reproduced from Hernandez, E.; Burgos, C. H.; Alicea, E.; Soderquist, J. A. *Org. Lett.* **2006**, *8*, 4089–4091, with permission from ACS.

Table 10 Propargylation of ketones according to Scheme 7[a]

No.	R^3	R^4	*Yield (%)*	ee *(%)*
1	Ph	Me	85	93
2	Ph	Et	65	76
3	Pr^i	Me	71	84
4	Bu^t	Me	66	83
5	TMS	Me	62	90
6	$CH_2{=}CH$	Me	64	61

[a]Screening was conducted with both (*R*)-**18** and (*S*)-**18**, which is not shown for clarity.
Source: Reproduced from Hernandez, E.; Burgos, C. H.; Alicea, E.; Soderquist, J. A. *Org. Lett.* **2006**, *8*, 4089–4091, with permission from ACS.



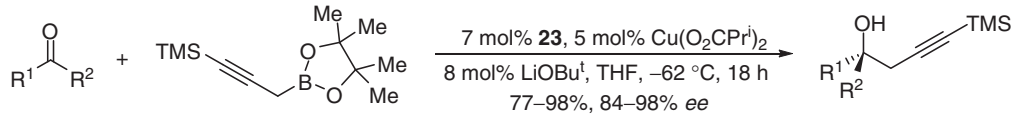
(2)

Table 11 Selected examples for the propargylation of ketones depicted in equation 2

No.	R^3	R^4	*Yield (%)*	ee *(%)*
1	Ph	Me	93	95
2	Ph	Et	94	42
3	2-Naphthyl	Me	88	93
4	(α-Tetralone)		84	98
5	2-Thienyl	Me	83	95
6	(*E*)-PhCH$=$CH	Me	90	86
7	1-Cyclohexenyl	Me	67	86
8	$PhCH_2CH_2$	Me	72	72

Source: Reproduced from Shi, S.-L.; Xu, L.-W.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 6638–6639, with permission from ACS.

Fandrick et al. developed a Cu/BINAP catalytic propargylation system with remarkable stereodifferentiating ability; methyl ethyl ketone, the substrate with minimal difference between the prochiral faces, could be converted into homopropargyl alcohol **26** with 95% *ee* in the reaction with propargylboronate **25** (equation 3, Table 12). A wide selection of methylketones (and 2-indanone) furnished the corresponding products with 84–98% *ee*.[18]



25 **26**

(3)

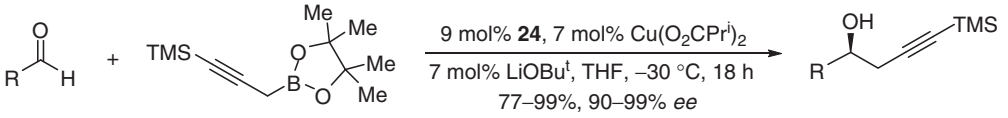
A different ligand in Fandrick's related work was utilized for asymmetric propargylation of aldehydes (equation 4). MeO-BIBOP **24** enabled high enantioselectivities and yields for aromatic and α,β-unsaturated aldehydes; slightly lower stereoselectivity values were observed for aliphatic substrates. The functional group tolerance of the protocol is notable: heterocyclic, ester, nitrile, fluoroaryl, and carbamate functionalities could be present (equation 4, Table 13).[19]

Table 12 Selected examples of Cu/BINAP-catalyzed propargylation (equation 3)

No.	R^1	R^2	*Yield (%)*	ee *(%)*
1	Et	Me	83	95[a]
2	Cyclopropyl	Me	96	98
3	$PhCH_2CH_2$	Me	77	90
4	PhCH═CH	Me	87	87
5	Ph	Me	98	96
6	2-Naphthyl	Me	96	96
7	3-Pyridyl	Me	87	91
8	2-Benzofuryl	Me	80	84

[a]Carried out at −83 °C.

Source: Reproduced from Fandrick, K. R.; Fandrick, D. R.; Reeves, J. T.; *et al. J. Am. Chem. Soc.* **2011**, *133*, 10332–10335, with permission from ACS.



(4)

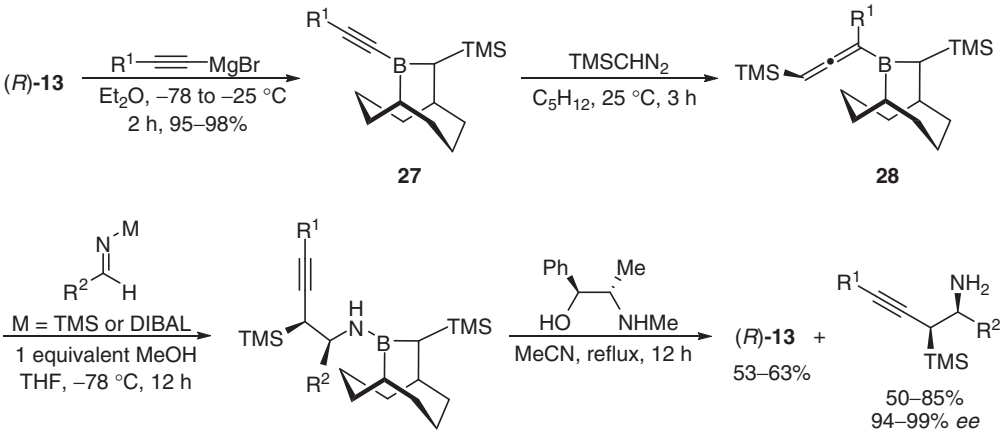
Table 13 Selected examples of Cu/Me-BIBOP-catalyzed propargylation of aldehydes (equation 4)

No.	*R*	*Yield (%)*	ee *(%)*
1	Ph	99	97
2	*p*-$MeOC_6H_4$	97	98
3	$EtO_2CCH_2OC_6H_4$	95	99
4	2-Benzofuryl	77	93
5[a]	(*E*)-PhCH═C(Me)	96	97
6	$CbzNHCH_2CH_2$	95	90

[a]Carried out at −30 to 0 °C for 48 h.

Source: Reproduced from Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T.; *et al. J. Am. Chem. Soc.* **2010**, *132*, 7600–7601, with permission from ACS.

Despite the fact that most of the developed enantioselective methods employing propargyl/allenyl organometallics are based on the addition to the carbonyl group, several protocols on addition to imines have been reported. Soderquist's system **13** was also applied for the first asymmetric allenylboration of aldimines.[20] This time **13** was initially converted into *B*-alkynylated product **27** via Grignard synthesis (pseudoephedrine is isolated back from the insoluble magnesium salt); stereospecific insertion of CH(TMS) followed by a sterically driven suprafacial 1,3-borotropic shift furnishes the propargylating agent **28**, thus alleviating the need to use allenyl/propargyl Grignards. The adduct is subject to pseudoephedrine to liberate the product and enable recovery of the chiral auxiliary (53–63% yields). A range of homopropargyl amines was prepared with good yields and excellent enantio- and diastereoselectivity (Scheme 8, Table 14). Intermediates **28** could be subject to protonolysis to furnish allenylsilanes.

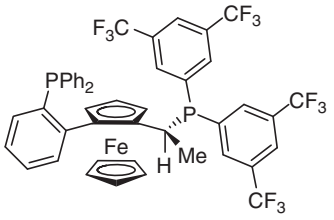


Scheme 8 Reproduced from Gonzalez, A. Z.; Soderquist, J. A. *Org. Lett.* **2007**, *9*, 1081–1084, with permission from ACS.

Table 14 Propargylation of imines according to Scheme 8

No.	R^1	R^2	*Yield (%)*	ee *(%)*
1	$(CH_2)_3Cl$	2-Thienyl	51	99
2	$(CH_2)_3Cl$	Pr^i	66	99
3	$(CH_2)_3Cl$	*p*-$MeOC_6H_4$	72	99
4	$(CH_2)_3Cl$	Ph	85	99
5	*n*-C_5H_{11}	Ph	84	99
6	Cyclopropyl	Ph	78	99
7	Me	Ph	77	94
8	Me	Me	83	92

Source: Reproduced from Gonzalez, A. Z.; Soderquist, J. A. *Org. Lett.* **2007**, *9*, 1081–1084, with permission from ACS.



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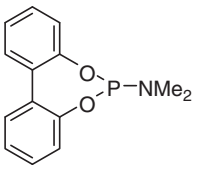

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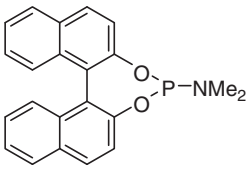
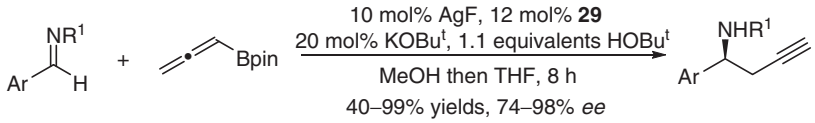


31, MonoPhos

Another study is focused on enantioselective Ag-catalyzed propargylation of imines (equation 5, Table 15). Allenyl Bpin was utilized, which is believed to undergo transmetallation to form allenyl/propargyl silver species.[21] In comparison to Soderquist's allenylboration, somewhat lower (but still excellent) enantioselectivities were obtained with a similar substrate scope; however, the important merits include the catalytic nature of the process and higher reaction temperature (− 20 °C vs. − 78 °C). *N*-tosyl aldimines were employed; however, *N*-nosyl analogs could also be used. In the latter case the relative ease of sulfonamide deprotection is synthetically advantageous.



(5)

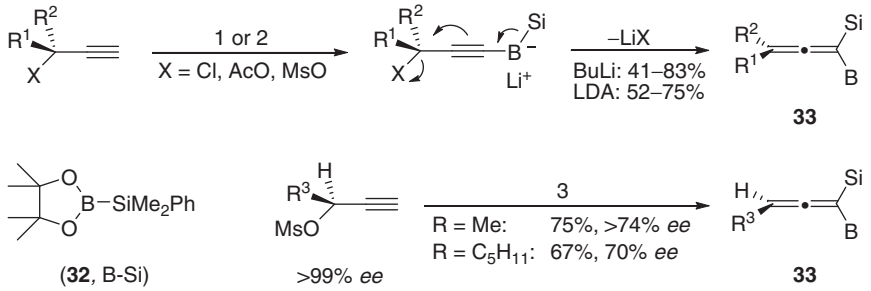
Table 15 Selected examples of Ag-catalyzed propargylation of *N*-arenesulfonyl aldimines (equation 5)

No.	*Ar*	R^1	*Yield (%)*	ee *(%)*
1	C_6H_5	Ts	91	96
2	C_6H_5	Ns	70	92
3	2-Naphthyl	Ts	81	93
4	2-Furyl	Ts	93	97
5	PhCH═C(Me)	Ts	47	89
6	CH_2═$CHCH_2CMe_2$	Ts	40	74

Source: Reproduced from Wisniewska, H. M.; Jarvo, E. R. *Chem. Sci.* **2011**, *2*, 807–810, with permission from RSC.

As *gem*-diorganometallic reagents possess enhanced synthetic versatility, Shimizu and Hiyama reported preparation of 1-boryl-1-silylallenes **33** from alkynes containing a leaving group in the propargylic position (Scheme 9, Table 16).[22] On bismetallation alkenes, alkynes and allenes *see* Chapter 4.16. Formation of the product proceeds via the ate complex, which then undergoes silyl migration. Trimethylsilyl chloride was found to accelerate the rearrangement, presumably facilitating the elimination of the leaving group. For the enantiopure starting mesylates, chirality transfer of >70% could be achieved (see Scheme 26 for an alternative outcome of the process under rhodium catalysis).

Kohn and Jarvo developed a protocol of Pd-catalyzed annulation of conjugate acceptors and allenyl Bpin, which is believed to proceed through a propargyl palladium complex.[23] A broad range of alkylidene cyano esters could be smoothly converted into cyclopentenes **34** (Scheme 10, Table 17). The reaction appeared to be tolerant to the presence of halogens; oxidative addition was not competitive with the main reaction pathway. All the products were formed as a single diastereomer. A variety of malononitriles could also be used as substrates to furnish **35**. The protocol provides access to rapid assembly of building blocks for the synthesis of natural products, as was exemplified by the formation of fused heterocyclic ring systems **36** and **37**.



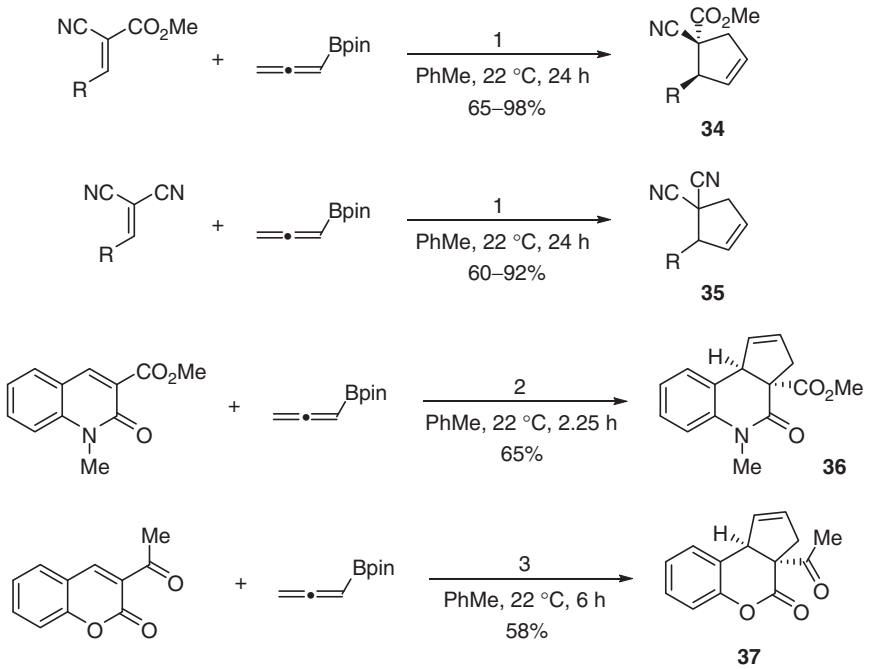
Scheme 9 Reproduced from Shimizu, M.; Kurahashi, T.; Kitagawa, H.; Hiyama, T. *Org. Lett.* **2003**, *5*, 225–227, with permission from ACS.

Table 16 Selected examples of the preparation of 1-boryl-1-silylallenes **33** according to **Scheme 9**

No.	*Base*	R^1	R^2	*X*	*Yield (%)*
1	BuLi	Me	Me	Cl	70
2	BuLi	$(CH_2)_5$		OAc	53
3	LDA	$(CH_2)_5$		OAc	60
4[a]	BuLi	Ph	H	Cl	41
5[a]	LDA	Ph	H	Cl	52
6[a]	LDA	Me	H	OMs	57

[a]Racemic substrates were used.

Source: Reproduced from Shimizu, M.; Kurahashi, T.; Kitagawa, H.; Hiyama, T. *Org. Lett.* **2003**, *5*, 225–227, with permission from ACS.



1. 20 mol% **30**, 10 mol% $PdCl_2(PhCN)_2$, 50 mol% $NaOBu^t$, 1.1 equivalents $HOBu^t$.
2. 20 mol% **31**, 10 mol% $PdCl_2(PhCN)_2$, 1 equivalent $NaOBu^t$, 1.1 equivalents $HOBu^t$.
3. 10 mol% PPh_3, 10 mol% $PdCl_2(PhCN)_2$, 50 mol% $NaOBu^t$, 1.1 equivalents $HOBu^t$.

Scheme 10

Table 17 Selected examples of the annulation leading to **34** and **35** according to Scheme 10

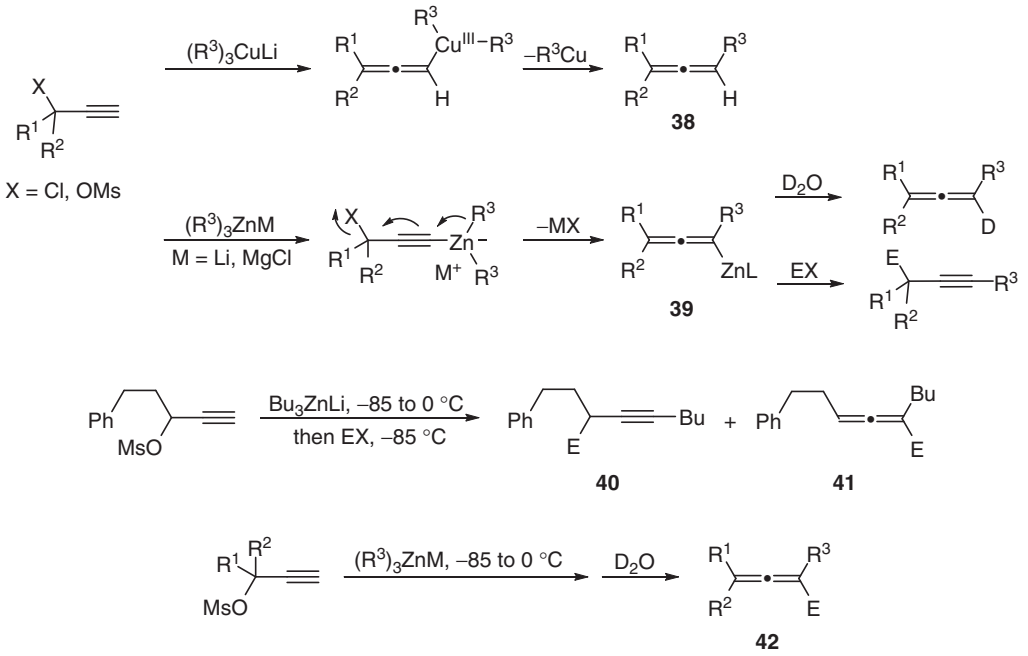
No.	*Product*	*R*	*Yield (%)*
1	**34**	C_6H_5	81
2	**34**	*m*-$(CF_3)C_6H_4$	91
3[a]	**34**	*p*-BrC_6H_4	65
4	**34**	*o*-Cl,*o*-$(F)C_6H_3$	98
5	**35**	C_6H_5	77
6	**35**	*p*-$(CF_3)C_6H_4$	80
7	**35**	2-Naphthyl	92
8[a]	**35**	2-Furyl	63

[a]1 Equivalent of NaOBut was used.

Source: Reproduced from Kohn, B. L.; Jarvo, E. R. *Org. Lett.* **2011**, *13*, 4858–4861, with permission from ACS.

2.05.4 Zinc

The work of Harada and Oku considers the contrast behavior of organozinc and organocopper reagents in allene synthesis.[24] The conventional interaction of diorganocuprates with propargylic derivatives is believed to proceed through allenylcopper(III) species, which undergo reductive elimination to form allene **38**. In contrast, triorganozincates were found to afford an allenylzinc compound **39**, which can be subject to electrophiles (Scheme 11, Tables 18 and 19). Both nucleophilic and electrophilic moieties can thus be introduced in one step into positions 1 and 3 of a propargylic substrate leading to allene derivatives. The methodology has significant advantage over lithiation of the alkynes/transmetallation sequence, as the latter can suffer from insufficient regioselectivity. For reviews on organocopper and organozinc reagents *see* Chapters 1.04 and 1.07 respectively.



Scheme 11

Table 18 Selected examples for the preparation of propargylic derivatives **40** according to Scheme 11

No.	*EX*	*E*	***40*:*41***	***40*** + ***41***, *Yield (%)*
1	I_2	I	81:6	87[a]
2	NCS	Cl	82:4	86[a]
3	TMSCl	TMS	90:10	90
4	$PhMe_2SiCl$	$PhMe_2Si$	96:4	88
5	MeCOCl	MeCO	89:11	80
6	Bu^tCOCl	Bu^tCO	95:5	91

[a]Yields corresponding to **40** only.

Source: Reproduced from Katsuhira, T.; Harada, T.; Maejima, K.; Osada, A.; Oku, A. *J. Org. Chem.* **1993**, *58*, 6166–6168, with permission from ACS.

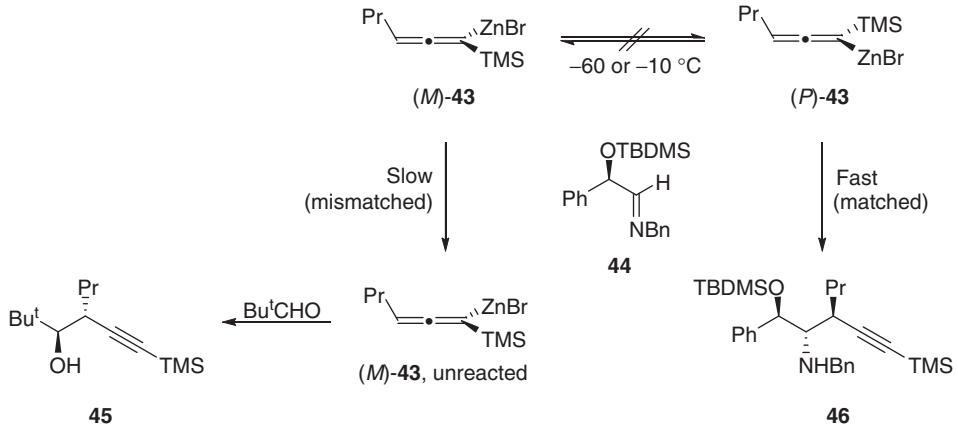
Table 19 Selected examples for the incorporation of deuterium into products **42** according to **Scheme 11**

No.	R^1	R^2	$(R^3)_3ZnM$	***42***, *Yield (%)*	*D content (%)*
1	$PhCH_2CH_2$	H	Bu_3ZnLi	97	92
2	$PhCH_2CH_2$	H	Ph_3ZnLi	77	81
3	$PhCH_2CH_2$	H	$(CH_2{=}C(Me))_3ZnLi$	77	72
4	Cy	H	Bu_3ZnLi	95	91
5[a]	$(CH_2)_5$		Bu_3ZnLi	95	86
6[a]	$(CH_2)_5$		$Bu_3ZnMgCl$	79	81

[a]Chloride was used instead of mesylate.

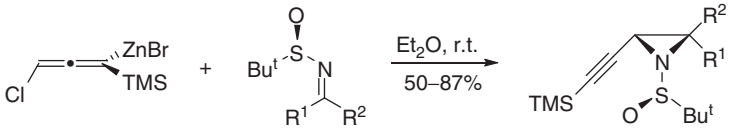
Source: Reproduced from Katsuhira, T.; Harada, T.; Maejima, K.; Osada, A.; Oku, A. *J. Org. Chem.* **1993**, *58*, 6166–6168, with permission from ACS.

Kinetic resolution of main group organometallic reagents has not been extensively studied. In this context the work of Poisson and Normant is notable:[25] kinetic resolution of allenylzinc reagents **43** was developed (**Scheme 12**). Compounds **43** were found to be configurationally stable at -60 and $-10\,^{\circ}C$; addition to imines proceeded with excellent diastereoselectivity and demonstrated a dramatic difference in the rates for matched and mismatched pairs. Although one of the isomers reacted with the substrate, the other was trapped with pivalaldehyde. The use of (*R*)-mandelic imine derivative **44** enabled enantioenrichment of **45** up to 88% *ee*. The synthetic protocol for more valuable substrates was established by the use of excess **43**: enantiomeric excess of 99% for **46** could be achieved. The preceding work demonstrated that in contrast to α-silyloxy or α-benzyloxyimines, only poor diastereoselectivities were obtained for α-silyloxyaldehydes.



Scheme 12

Allenyl organometallics have also been utilized for the preparation of optically active aziridines via the kinetic resolution approach. Racemic halogenated allenylzinc species **47** prepared via lithiation/transmetallation could react with chiral sulfinimines **48** to furnish enantiopure aziridines **49** (equation 6, **Table 20**). *N-tert*-butanesulfinimines appeared to be far superior substrates compared to analogs, for example, *N*-α-methylbenzylimines and *N*-*p*-toluenesulfinimines in the context of reactivity and stereoselectivity, respectively.[26]



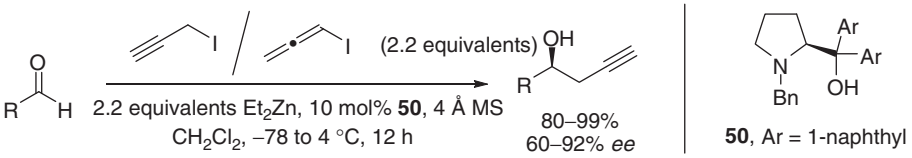
47 **48** **49** (6)

Table 20 Selected examples of aziridine **49** synthesis according to equation 6

No.	R^1	R^2	trans:cis	*Yield (%)*
1	H	Pr^n	89:11	61
2	H	Crotyl	90:10	64
3	H	Cy	90:10	58
4	H	Ph	86:14	50
5	Me	Ph	90:10	69
6	n-C_5H_{11}	n-C_5H_{11}	–	87

Source: Reproduced from Chemla, F.; Ferreira, F. *J. Org. Chem.* **2004**, *69*, 8244–8250, with permission from ACS.

While many synthetic approaches to homopropargyl alcohols involve preparation of special allenyl/propargyl sources, methods that allow the use of simple halides are particularly attractive. Trost et al. described propargylation of alkenyl, aryl, heteroaryl, and alkyl aldehydes with the system consisting of propargyl/allenyl iodide and diethylzinc in the presence of readily available ligand **50**; the products were obtained with 60–92% *ee* and excellent yields (equation 7, Table 21). A bimetallic allenylzinc catalytic species formation was assumed.[27]



(7)

Table 21 Propargylation of aldehydes according to equation 7

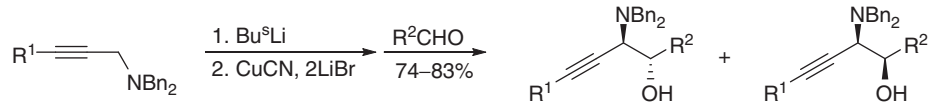
No.	*R*	*Yield (%)*	ee *(%)*
1	PhCH═CH	99	66
2	PhCH═C(Me)	99	80
3	Ph	99	86
4	*p*-$MeOC_6H_4$	98	92
5	*p*-FC_6H_4	98	86
6	2-Naphthyl	95	84
7	Furyl	80	80
8	Cy	80	60

Source: Reproduced from Trost, B. M.; Ngai, M.-Y.; Dong, G. *Org. Lett.* **2011**, *13*, 1900–1903, with permission from ACS.

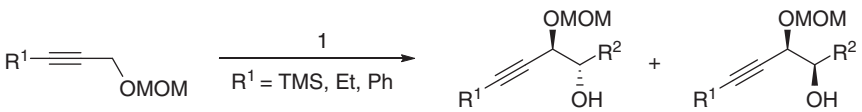
Enantioenriched allenylzinc reagents have also been successfully used in Marshall's comprehensive studies, which are reviewed in Ref. 3.

2.05.5 Copper

Despite the large amount of available information on organocopper chemistry, propargyl/allenylcopper reagents are poorly studied. Mangeney, Vrancken et al. considered the addition of hetero allenyl copper reagents to aldehydes;[28] it is noteworthy that until their reports, synthetically interesting aza-substituted allenylmetal compounds had been almost totally neglected. This approach allowed preparation of α-heteroatom-functionalized homopropargylic alcohols **52** and **54** with excellent *anti*-selectivity (equations 8–9, Tables 22 and 23). The level of stereocontrol for **54** appeared to be independent of the nature of the heteroatom, the aldehyde, or the acetylenic substituents; for the latter, the reactivity of cuprates increased in the row Et-Ph-TMS. The crucial role of lithium counterion was demonstrated by the impeding effect of added HMPA. Notably, *anti*-alkyl-substituted homopropargyl ether alcohols could not be accessed via organotin compounds. For a review on organocopper reagents *see* Chapter 1.04.



(8)



(9)

1. R = TMS: 1) Bu^tLi, 2) CuCN, 3) HMPA, 4) R^2CHO, THF, –90 °C, 30 min. 72–88%, *anti/syn* 90:10 to > 97:3.
R = Et: 1) Bu^tLi, 2) CuCN, 3) R^2CHO, THF, –60 °C, 16 h. 74–78%, *anti/syn* 90:10 to > 97:3
R = Ph: 1) Bu^tLi, 2) CuCN, 2LiBr, 3) R^2CHO, THF, –90 °C, 10 h. 82–95%, *anti/syn* 95:5 to > 97:3

Table 22 Selected examples of propargylation of aldehydes with propargylic amines **51** (equation 8)

No.	R^1	R^2	anti/syn	*Yield (%)*
1	TMS	*n*-Hexyl	>95:5	82
2	TMS	Cy	>95:5	81
3	TMS	Ph	>95:5	79
4	TMS	Propenyl	95:5	83
5	TMS	Heptynyl	93:7	74
6	Ph	Cy	>97:3	91
7	Ph	Ph	>97:3	86
8	Ph	Propenyl	95:5	80

Source: Reproduced from Vrancken, E.; Alouane, N.; Gérard, H. I.; Mangeney, P. *J. Org. Chem.* **2007**, *72*, 1770–1779, with permission from ACS.

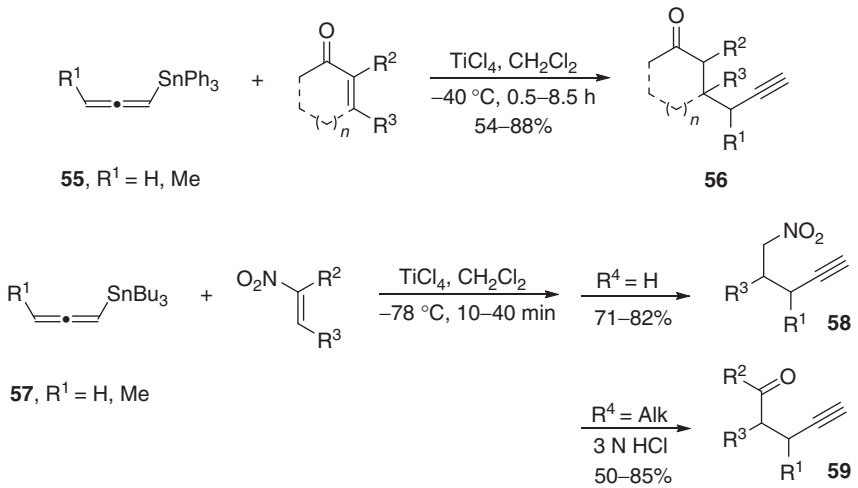
Table 23 Selected yields of products **54** according to equation 9

No.	R^1	R^2	anti/syn	*Yield (%)*
1	TMS	Pr^i	94:6	78
2	TMS	Bu^t	>97:3	72
3	TMS	Ph	97:3	88
4	TMS	Propenyl	>97:3	83
5	Et	Cy	97:3	78
6	Et	Ph	96:4	78
7	Et	Propenyl	>97:3	76
8	Ph	Cy	>97:3	93
9	Ph	Ph	>97:3	82
10	Ph	Propenyl	95:5	95

Source: Reproduced from Vrancken, E.; Alouane, N.; Gérard, H. I.; Mangeney, P. *J. Org. Chem.* **2007**, *72*, 1770–1779, with permission from ACS.

2.05.6 Tin

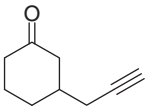
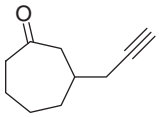
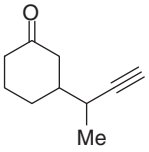
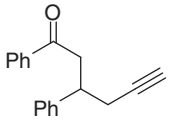
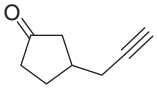
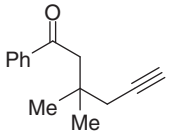
Allenyl and propargylstannanes represent a class of valuable synthetic intermediates. Haruta and Kita et al. developed conjugate addition of stannylallenes to α,β-unsaturated carbonyl compounds in the presence of titanium tetrachloride. In contrast to the analogous Danheiser's studies on allenylsilanes resulting in cyclopentene derivatives, cyclic and acyclic substrates reacted with organotin compounds to furnish propargylated ketones **56** with good yields.[29] Michael addition could also be successfully accomplished with α-nitroalkenes; α-unsubstituted and α-alkylated substrates produced synthetically interesting β-propargylic nitroalkanes **58** and α-propargylic ketones **59**, respectively (Scheme 13, Tables 24 and 25).



Scheme 13 Reproduced from Haruta, J.; Nishi, K.; Matsuda, S.; *et al. J. Org. Chem.* **1990**, *55*, 4853–4859, with permission from ACS.

S_N2' reactions of propargyl alcohol derivatives with stannyl anion equivalents provide a general approach to allenylstannanes. However, simple tin cuprate reagents react regioselectively only with terminal propargylic mesylates; internal analogs lead to

Table 24 Selected yields for products **56** prepared according to **Scheme 13**

No.	*Product*	*Yield (%)*	*No.*	*Product*	*Yield (%)*
1		78	4		60
2		86	5		86
3		59	6		59

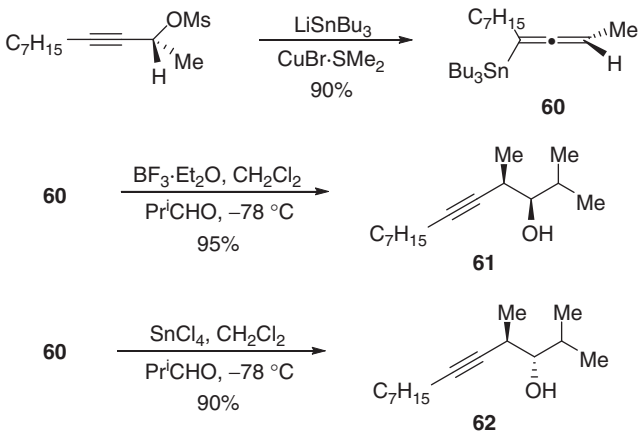
Source: Reproduced from Haruta, J.; Nishi, K.; Matsuda, S.; *et al. J. Org. Chem.* **1990**, *55*, 4853–4859, with permission from ACS.

Table 25 Selected yields for the conjugate addition to nitroalkenes according to **Scheme 13**

No.	R^1	R^2	R^3	*Yield (%)*
1	H	H	Ph	82[a]
2	Me	H	Ph	82[a]
3	Me	H	$PhCH_2CH_2$	71[a]
4	H	Me	Ph	50[b]
5	H	$(CH_2)_4$		73[b]
6	Me	$(CH_2)_4$		71[b]

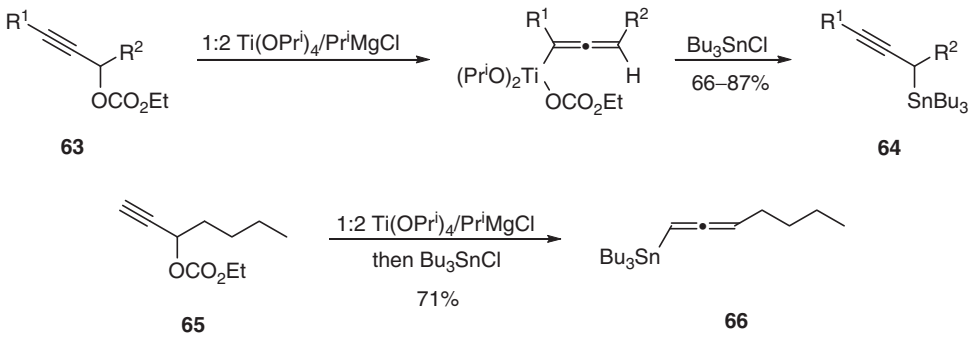
[a]Yields corresponding to **58**.
[b]Yields corresponding to **59**.
Source: Reproduced from Haruta, J.; Nishi, K.; Matsuda, S.; *et al. J. Org. Chem.* **1990**, *55*, 4853–4859, with permission from ACS.

mixture of propargyl and allenylstannanes. The latter is also true for Bu_3SnLi. This issue was overcome by Marshall, who introduced the reagent formed from Bu_3SnLi and CuBr/dimethylsulfide, which enabled exclusive formation of allenylsilanes; excellent chirality transfer was accomplished for chiral propargylic mesylates yielding compound **60**. These common chiral precursors were subsequently used to gain access to both *syn*- and *anti*-homopropargylic and allenic alcohols. Interestingly, the careful selection of a Lewis acid enabled reversal of diastereocontrol: whereas boron trifluoride led to *syn*-adduct **61**, *anti*-adduct **62** was obtained with tin tetrachloride (**Scheme 14**).[30] Remarkably, compounds **61** and **62** are epimeric at the carbinyl rather than the propargylic center. The selectivity difference was explained by the cyclic and acyclic nature of the corresponding transition states. On the basis of experimental data, the conversion of the tributylstannyl substrate to the corresponding trichlorostannane was assumed to proceed as a sequence of two S_E2' additions of $SnCl_4$ to the starting allenyltributyltin **60**.



Scheme 14

In contrast to allenylstannanes, preparation of propargyl counterparts is substantially less studied and is associated with a number of problems, including the possibility of transformation to allenyl isomers. In this context, the application of Sato's allenyltitanium methodology to the synthesis of organotin reagents is particularly noteworthy (for related studies see Scheme 25). Primary and alkyl-substituted secondary propargylstannanes **64** could be conveniently prepared in a one-pot manner from propargylic carbonates **63** (Scheme 15, Table 26). The presence of aryl groups in the substrate resulted in isomer mixtures, presumably due to isomerization occurring during work-up. Terminal propargylic substrate **65** furnished the allenyl product virtually exclusively.



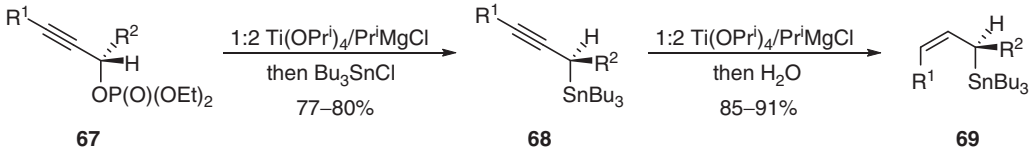
Scheme 15

Table 26 Selected yields for the preparation of propargylic stannanes **64** synthesis according to Scheme 15

No.	R^1	R^2	*Propargyl/allenyl ratio*	*Yield (%)*
1	n-C_5H_{11}	H	96:4	66
2	Bu^n	Ph	63:37	57
3	Ph	Bu^n	53:47	85
4	Me	n-C_5H_{11}	97:3	72
5	TMS	Bu^n	99:1	87
6	$Cl(CH_2)_2$	Me	98:2	82

Source: Reproduced from An, D. K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 4861–4864.

The protocol was also conducted on enantiomerically enriched secondary propargylic phosphates **67**, which enabled excellent degrees of chirality transfer; the products could then be converted into optically active allyl stannanes **69** (Scheme 16, Table 27). This methodology is particularly remarkable in light of the scarcity of the available synthetic approaches to these classes of stannanes in the enantioenriched form.[31]



Scheme 16 Reproduced from Okamoto, S.; Matsuda, S.; An, D. K.; Sato, F. *Tetrahedron Lett.* **2001**, *42*, 6323–6326.

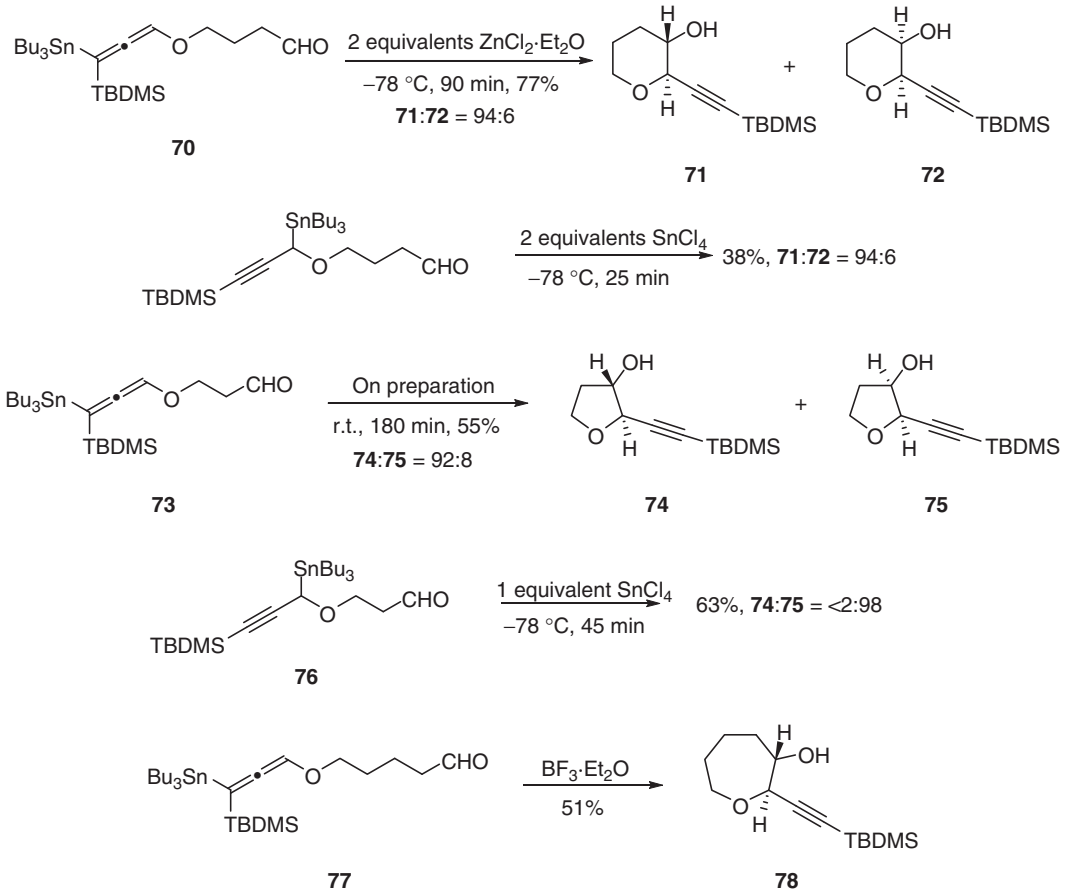
Table 27 Preparation of propargylic and allylic stannanes synthesis according to Scheme 16

No.	R^1	R^2	***67***, ee *(%)*	***68***, *Yield (%)*	***69***, *Yield (%)*	***69***, ee *(%)*[a]
1	Me	Bu^n	94	78	91	>91(>97)
2	Bu^n	Me	94	79	91	>91(>97)
3	Bu^n	Me	94	77	88	>91(>97)
4	TMS	Bu^n	92	80	85	>86(>93)

[a]The degree of chirality transfer is shown in parentheses.

Source: Reproduced from Okamoto, S.; Matsuda, S.; An, D. K.; Sato, F. *Tetrahedron Lett.* **2001**, *42*, 6323–6326.

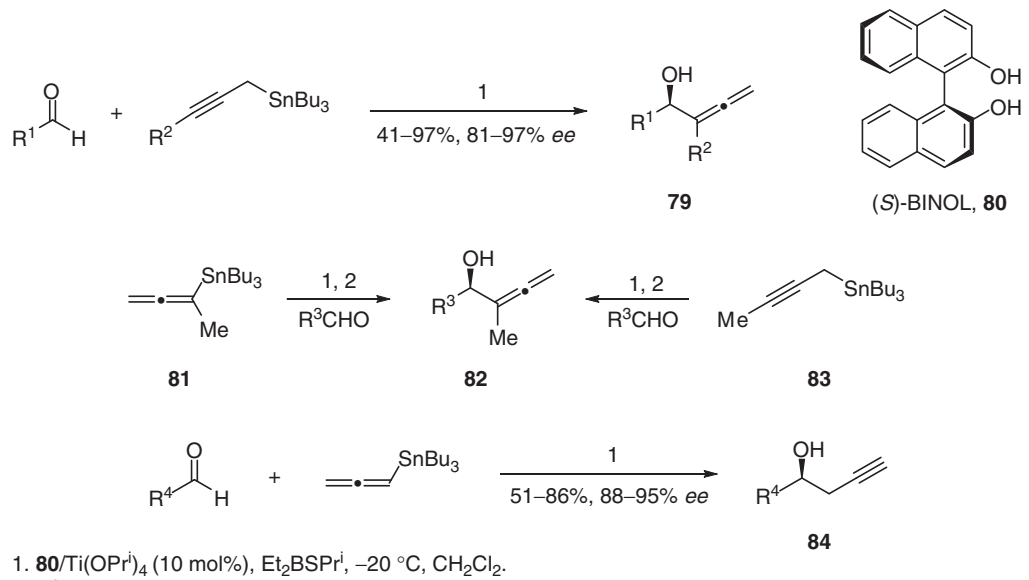
An interesting study was published by Yamamoto et al., that described intramolecular reactions of allenyl and propargylstannanes with the aldehyde group; this enabled preparation of 5-, 6-, and 7-membered cyclic ethers with generally high diastereoselectivities and good yields.[32] The optimum Lewis acids were identified for each type of substrate. For tetrahydropyrans, only allenyl substrate **70** demonstrated preparatively meaningful results. Substrate **73** spontaneously cyclized at room temperature during its preparation (oxidation of an alcohol with SO_3-py/DMSO/Et_3N) to yield *trans*-product **74** with propargyl analog **76**; the use of tin tetrachloride resulted in the exclusive formation of the *cis*-adduct. A *trans*-isomer of the seven-membered analog **78** was obtained as a sole product from substrate **77** on exposure to boron trifluoride (Scheme 17).



Scheme 17

In 1998 Yu et al. described the first catalytic enantioselective allenylation of aldehydes using a 2:1 BINOL-Ti(O^iPr)$_4$ system in the presence of superstoichiometric amounts of ^{i}PrSBEt$_2$, which was found to be an efficient rate-accelerating agent.[33] Aromatic and aliphatic aldehydes were reacted with alkyl-substituted propargylstannanes to furnish allenyl alcohols **79** with generally good yields and excellent enantioselectivities (Scheme 18, Table 28). Notably, when allenyltin reagent **81** was used instead of **83**, a virtually identical outcome was observed, which indicated an unusual case of equilibrium between organotin species. The preceding work of Yu's group demonstrated that the use of unsubstituted allenyltin reagent with aldehydes under the same conditions results in highly enantioselective propargylation (Scheme 18, Table 29).

α-Heteroatom propargylstannanes represent a poorly studied class of compounds. Within the studies on natural product synthesis, Roush et al. considered the problem of unavailability of highly diastereoselective procedures for the preparation of *anti*-propargylic diol derivatives such as **87**. As propargylstannanes can easily isomerize to allenylstannanes under Lewis acidic conditions, **85** was chosen as a suitable precursor, which can be conveniently prepared through deprotonation/transmetallation of propargylic esters. *Anti*-γ-methoxypropargylation could be accomplished with excellent diastereoselectivity; the use of reagent **86** proceeded equally well and thus furnished products with readily removable MOM-group (equation 10, Table 30). Remarkably, the authors developed an efficient work-up procedure, which involved the use of solid-supported fluoride source (KF on Celite) for the removal of tin by-products.[34]



1. **80**/Ti(OPr^i)$_4$ (10 mol%), Et$_2$BSPr^i, –20 °C, CH_2Cl_2.
2. R^3 = $PhCH_2CH_2$: **81**–81%, 91% *ee*; **83**–85%, 93% *ee*
R^3 = *n*-C_6H_{13}: **81**–78%, 92% *ee*; **83**–97%, 92% *ee*.

Scheme 18 Reproduced from Yu, C.-M.; Yoon, S.-K.; Baek, K.; Lee, J.-Y. *Angew. Chem. Int. Ed.* **1998**, *37*, 2392–2395, with permission from Wiley-VCH, and Yu, C.-M.; Yoon, S.-K.; Choi, H.-S.; Baek, K. *Chem. Commun.* **1997**, 763–764, with permission from RSC.

Table 28 Selected examples for the preparation of allenic alcohols **79** according to **Scheme 18**

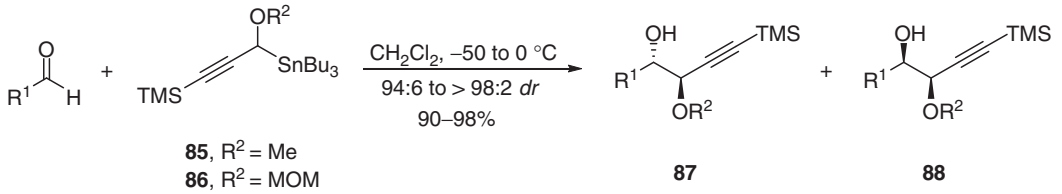
No.	R^1	R^2	***79**, Yield (%)*	***79**,* ee *(%)*
1	$PhCH_2CH_2$	Et	77	96
2	*n*-C_6H_{13}	Pr	72	90
3	Bu^i	Me	62	81
4	Ph	Me	74	90
5	Ph	Et	78	97
6	Ph	Pr	73	91

Source: Reproduced from Yu, C.-M.; Yoon, S.-K.; Baek, K.; Lee, J.-Y. *Angew. Chem. Int. Ed.* **1998**, *37*, 2392–2395, with permission from Wiley-VCH.

Table 29 Selected examples for the preparation of homopropargylic alcohols **84** according to **Scheme 18**

No.	R^4	***84**, Yield (%)*	***84**,* ee *(%)*
1	$PhCH_2CH_2$	86	94
2	C_6H_{11}	75	92
3	Cy	73	91
4	Bu^i	61	95
5	Ph	52	92

Source: Reproduced from Yu, C.-M.; Yoon, S.-K.; Choi, H.-S.; Baek, K. *Chem. Commun.* **1997**, 763–764, with permission from RSC.



(10)

Another study toward α-heteroatom propargylstannanes, conducted by Hegedus and coworkers, resulted in the development of a highly diastereoselective methodology of propargylation of aldehydes with chiral auxiliary-functionalized 1-silyl-1-allenylstannanes.[35] Standard lithiation/stannylation of propargyloxazolidinone **89** resulted in the mixture of derivatives **90** and **91**; however, the use of

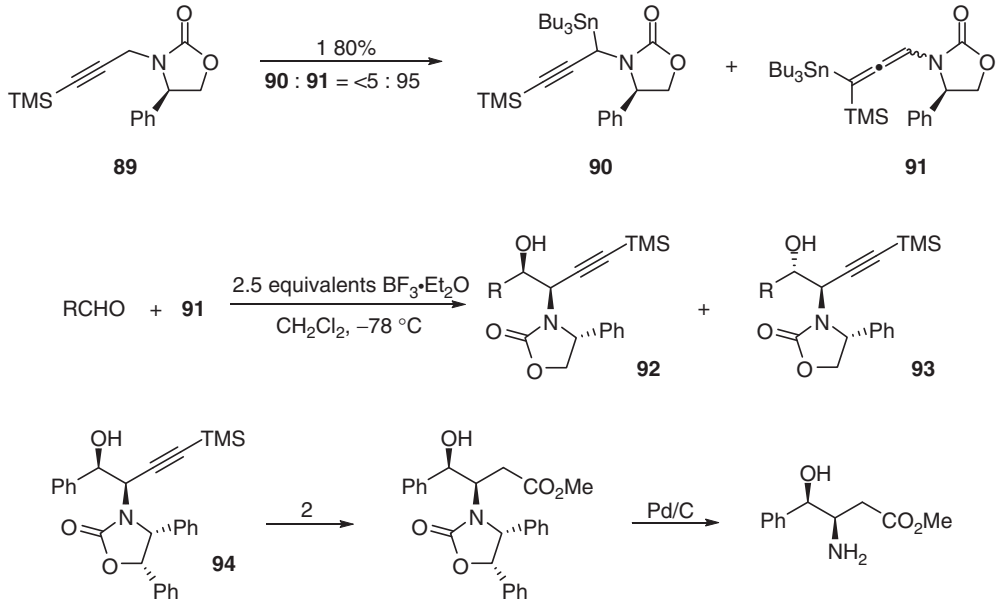
Table 30 Selected examples for the preparation of alcohols **87** according to equation 10[a]

No.	R^1	***87**, Yield (%)*	***87*:*88***
1	Pr^i	96 (95)	97:3 (98:2)
2	Ph	96 (97)	97:3 (97:3)
3	MeCH═CH	96 (90)	96:4 (94:6)
4	$PhCH_2CH_2$	98 (98)	97:3 (96:4)
5	Bu^t	96 (91)	>98:2 (>98:2)

[a]Results shown correspond to methyl esters; the data for MOM-esters are given in parentheses.

Source: Reproduced from Savall, B. M.; Powell, N. A.; Roush, W. R. *Org. Lett.* **2001**, *3*, 3057–3060, with permission from ACS.

magnesium bromide etherate before the addition of tributyltin chloride enabled highly selective formation of **91**. Although **90** did not demonstrate promising results in the addition to aldehydes, **91** enabled preparation of a wide range of *syn*-adducts **92** with high yields and diastereomeric ratios (Scheme 19, Table 31). The reaction was shown to be rather insensitive to α-chirality in the aldehyde. Neither acetophenone nor *N*-benzylidene-*N*-tosylamine could be employed as a substrate. Notably, removal of the auxiliary to liberate the free amino group would require harsh hydrolytic conditions for products **92**. Instead, a diphenyloxazolidinone moiety in **94** can be easily cleaved by mild hydrogenolysis, which enables synthetic transformations exemplified in Scheme 19.



1. 1) BuLi, 1 equivalent TMEDA, THF, –78 °C; 2) $MgBr_2$•Et_2O; 3) Bu_3SnCl, –78 °C.
2. 1) $HBCy_2$•SMe_2; 2) $NaHCO_3$, H_2O_2; 3) AcOH; 4) $TMSCHN_2$, MeOH/PhH

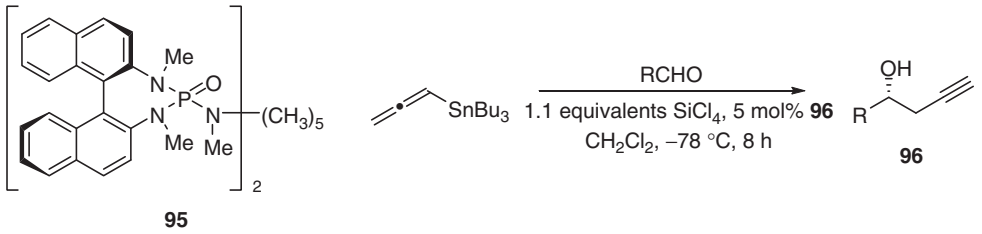
Scheme 19 Reproduced from Ranslow, P. B. D.; Hegedus, L. S.; de los Rios, C. *J. Org. Chem.* **2004**, *69*, 105–111, with permission from ACS.

Table 31 Selected examples for the preparation of products **92** according to Scheme 19

No.	*R*	***92**, Yield (%)*	***92*: *93***
1	Ph	95	>95:5
2	Pr^i	95	>95:5
3	MeCH═CH	80	>90:10
4	(*S*)-MeCH(OBn)	87	92:8

Source: Reproduced from Ranslow, P. B. D.; Hegedus, L. S.; de los Rios, C. *J. Org. Chem.* **2004**, *69*, 105–111, with permission from ACS.

Denmark considered enantioselective propargylation within the studies on Lewis base-activated chiral Lewis acids. Lewis acidity of silicon tetrachloride was increased by interaction with ligand **96**; the resulting system enabled highly enantioselective preparation of homopropargyl alcohols. The study was mostly focused on allylation and thus only three substrates were studied (equation 11, Table 32).[36]

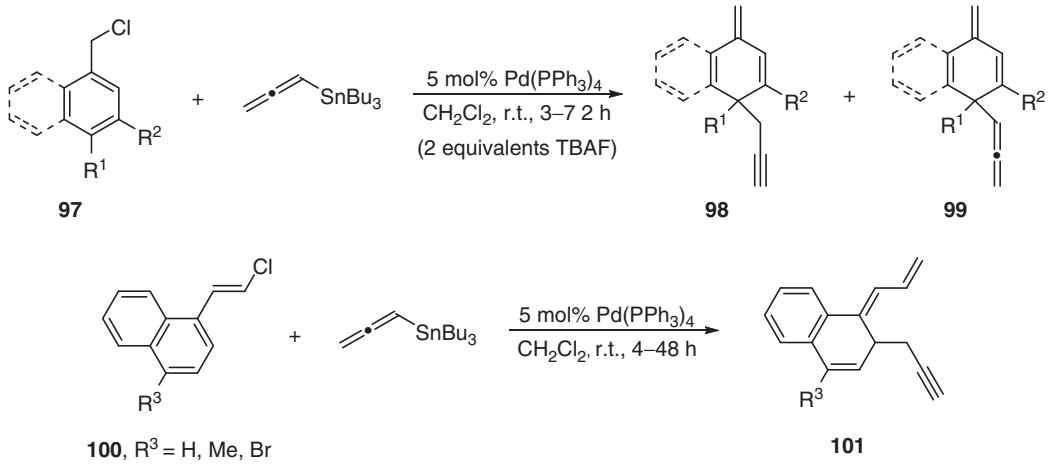


95 **96** (11)

Table 32 Propargylation of aldehydes catalyzed by **95** (equation 11)

No.	*R*	***96**, Yield (%)*	***96**, ee (%)*
1	Ph	81	97
2	PhCH=CH	90	87
3	2-Naphthyl	95	93

Feng and Bao described the use of allenyltributyltin for the Pd-catalyzed dearomatization of benzylic chlorides, chloromethylnaphthalenes, and naphthalene allyl chlorides; the procedure enables rapid construction of synthetically versatile polyunsaturated compounds.[37] Benzylic chlorides required the presence of an activator (e.g., TBAF, KF), whereas naphthalene derivatives expectedly appeared to be more reactive and thus the presence of a fluoride source was not necessary. The catalysis outcome was significantly influenced by the nature of the substrate in the context of reactivity and propargyl/allenyl ratios. Although benzylic chlorides resulted in predominance of propargylated products, the opposite trend was observed for chloromethylnaphthalenes; the incoming functionality was selectively introduced in the *para*-position with respect to the chloromethyl moiety throughout series **97** (Scheme 20, Table 33). Electron-deficient benzylic chlorides appeared to be unreactive presumably due to the high energy of the π-benzylpalladium chloride intermediate. Naphthalene allyl chlorides **100** exclusively furnished *ortho*-propargylated products **101** in good yields.



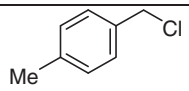
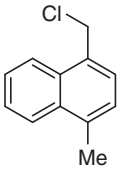
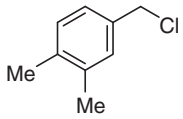
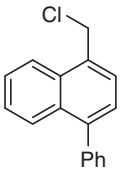
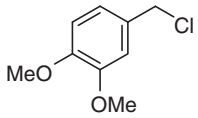
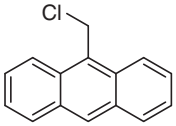
97 **98** **99**

100, R^3 = H, Me, Br **101**

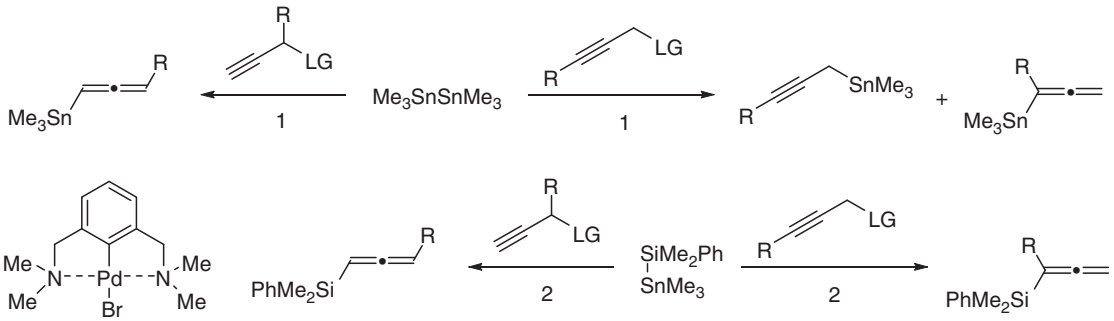
Scheme 20

It was found that the use of palladium pincer complexes rather than conventional Pd catalysts in the reaction of propargylic substrates (chlorides or mesylates) with hexamethylditin dramatically alters the reaction outcome: instead of bis-stannane addition, substitution reaction took place leading to propargyl and allenyl stannanes. The terminal substituent in the alkyne was shown to be responsible for regioselectivity; electron-donating moieties also favored propargyl products. The steric effects were demonstrated: hexamethylditin furnished only allenyl products with secondary propargylic substrates. Remarkably high functional group tolerance was observed; in addition to operational simplicity, the methodology serves as a powerful synthetic tool in the context of the importance of propargyl and allenyl organotin compounds. Further studies showed that the use of nonsymmetric reagents, for example, $PhMe_2SiSnMe_3$, exclusively favors the silyl transfer, providing easy access to allenylsilanes (Scheme 21, Table 34).[38]

Table 33 Selected examples of dearomatization of benzylic chlorides, chloromethylnaphthalenes, and naphthalene allyl chlorides (Scheme 20)

No.	*Substrate*	*Yield (%)*	***98*:*99***	*No.*	*Substrate*	*Yield (%)*	***98*:*99***
1		71[a]	98	1		85	20:80
2		67[a]	75:25	2		65	98
3		78[a]	98	3		96	99

[a]2 Equivalents of TBAF was used.



102

1. 2.5 mol% **102**, THF, 0 °C or r.t., 1.5–16 h.
2. Addition of $PhMe_2SiSnMe_3$ over 5 h, 5 mol% **102**, THF, 40–60 °C, 24 h.

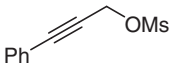
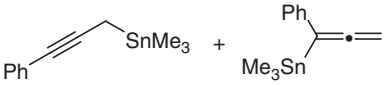
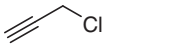
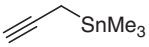
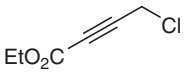
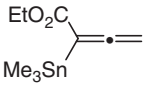
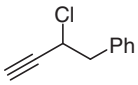
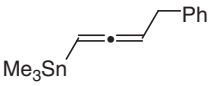
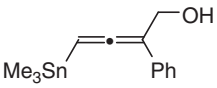
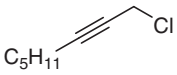
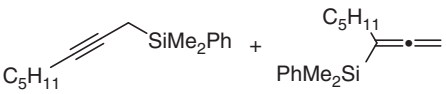
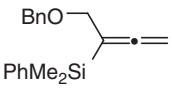
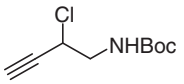
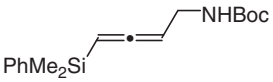
Scheme 21

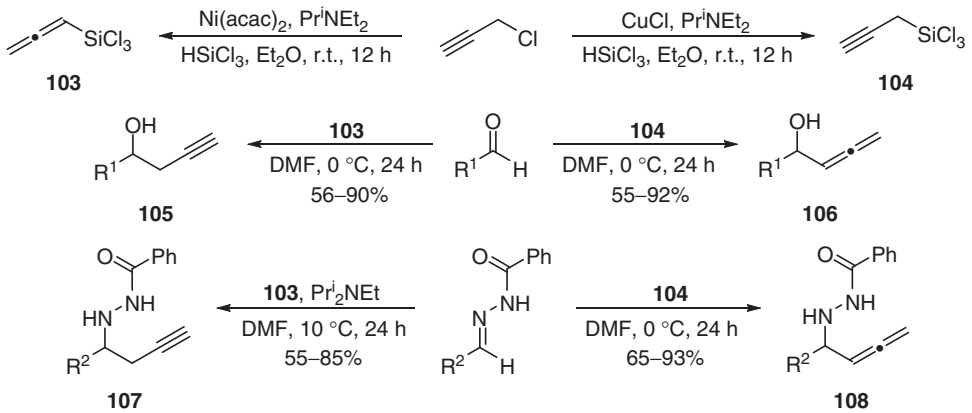
2.05.7 Silicon

Allenylsilanes, especially in the enantioenriched form, represent a versatile class of synthetic intermediates, and thus substantial effort was devoted to the development of their preparation. Kobayashi and Nishio developed a powerful methodology to prepare propargyl and allenyl trichlorosilanes from the same starting material. Thus, propargyl chloride can be directed into either of the highly regioselective reactions with chlorosilane by the choice of the catalyst; whereas copper(I) chloride furnished the propargyl derivative, nickel catalysis enabled preparation of the allenyl counterpart. Using the *in situ* formed **103** or **104** under the optimized conditions led to the exclusive formation of allenyl and propargyl alcohols, respectively; the reactions were conducted in dimethylformamide, which served as an organocatalyst. Aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldehydes could be successfully employed (Scheme 22, Table 35).[39]

Expansion of the methodology on C=N electrophiles has also been accomplished (Scheme 22, Table 36).[40] *N*-acylhydrazones were chosen as substrates in light of their stability compared to the corresponding imines in addition to convenient preparation, purification, and storage. Certain improvements over the previous protocol were introduced: propargyl bromide appeared to be superior for the generation of trichloropropargylsilane with respect to the reaction rate; the use of copper(I) fluoride over CuCl was also preferable. For both allenylation and propargylation the optimized reaction conditions were tolerated by a wide range of *N*-acylhydrazones, including aromatic, aliphatic, and α,β-unsaturated substrates, as well as α-hydrazono ester (Table 34, entry 6); propargylation generally proceeded with somewhat lower yields compared to allenylation. Control experiments demonstrated that the metal salts did not have a noticeable influence on the reaction efficiency. All the reactions proceeded with perfect regioselectivity.

Table 34 Synthesis of organotin compounds/allenylsilanes according to **Scheme 21**

No.	*Substrare*	*Reagent*	*Products*	*Yield (%)*
1		Sn/Sn	 10:1	75
2		Sn/Sn		87
3		Sn/Sn		64
4		Sn/Sn		95
5		Sn/Sn		83
6		Sn/Si	 1:4	78
7		Sn/Si		63
8		Sn/Si		70



Scheme 22 Reproduced from Schneider, U.; Sugiura, M.; Kobayashi, S. *Adv. Synth. Catal.* **2006**, *348*, 323–329, with permission from Wiley-VCH.

Table 35 Selected examples for the reactions of aldehydes with propargyl- and allenyltrichlorosilane (**Scheme 22**)[a]

No.	R^1	***105**, Yield (%)*	***106**, Yield (%)*
1	Ph	90	92
2	3-Furyl	65	55
3	Cy	56	61
4	$PhCH_2CH_2$	72	90
5	(*E*)-$Pr^nCH{=}CH$	70	79

[a]All reactions proceeded with >1:99 regioselectivity.

Source: Reproduced from Schneider, U.; Sugiura, M.; Kobayashi, S. *Tetrahedron* **2006**, *62*, 496–502.

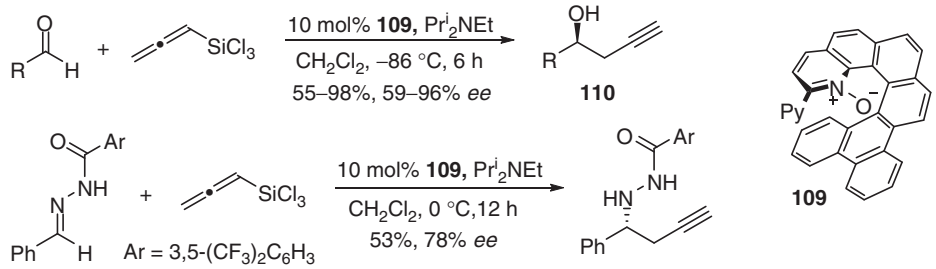
Table 36 Selected examples for the reactions of *N*-acylhydrazones with propargyl- and allenyltrichlorosilane (Scheme 22)[a]

No.	R^1	***107**, Yield (%)*	***108**, Yield (%)*
1	$PhCH_2CH_2$	85	93
2	Ph	72	85
3	(*E*)-PhCH═CH	73	80
4	Cy	58	70
5	Bu^t	63	68
6	CO_2Et	76	87

[a]Ratios of regioisomers are given in parentheses.

Source: Reproduced from Schneider, U.; Sugiura, M.; Kobayashi, S. *Adv. Synth. Catal.* **2006**, *348*, 323–329, with permission from Wiley-VCH.

Takenaka and coworkers were also interested in the applications of allenyltrichlorosilane.[41] Before their work, only one moderately enantioselective use of this reagent in asymmetric catalysis was reported. The helically chiral Lewis base catalyst **109** appeared to be a highly enantioselective and efficient mediator of asymmetric propargylation (Scheme 23, Table 37). The first case of catalytic enantioselective Lewis base-promoted addition of allenyltrichlorosilane to *N*-acylhydrazones has also been reported.



Scheme 23

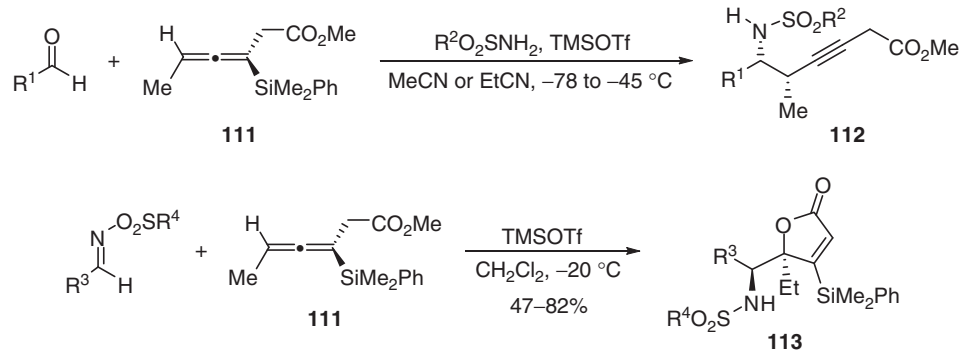
Table 37 Selected examples for propargylation of aldehydes catalyzed by **109** (Scheme 23)

No.	R^1	***110**, Yield (%)*	***110**, ee (%)*
1	Ph	87	86
2	2-Naphthyl	86	84
3	*p*-$CF_3C_6H_4$	80	90
4	*p*-MeC_6H_4	85	82
5	2-$MeOC_6H_4$	78	94
6	Cy	80[a]	59

[a]Reaction time — 36 h.

Among the recent reports on the addition of allenylmetal reagents to C═N bond, Panek's work is noteworthy,[42] as it described a three-component reaction involving addition of chiral allenylsilane **111** to *in situ* formed *N*-sulfonimines. *Syn*-adducts **112** were predominant and nearly perfect regioselectivity was observed. Aliphatic substrates were shown to be optimum, and best results were obtained with secondary and tertiary aldehydes; various sulfonamides could be used. Aromatic substrates appeared to be more challenging with diminished rates and selectivities (Scheme 24, Table 38). Interestingly, in the dichloromethane media the reaction predominantly led to the formation of γ-lactones **113**; this transformation could be accomplished with aromatic imines only (Scheme 24, Table 39). Notably, **111** is easily available on a multigram scale.

Within the brilliant comprehensive studies[3,43] of Marshall's group on the synthesis of diastereomeric stereotriad subunits of polyketides it was also found that *anti*-products can be obtained by employing allenylzinc, indium, and chlorosilane reagents, which conveniently alleviated the necessity to use toxic organotin compounds. Efficient methods to prepare these products in nonracemic form through chirality transfer from propargyl mesylates have been established. However, preparation of *syn*-analogues still required the use of tin reagents (see Scheme 14) until Marshall's work from 2000, which described the use of enantioenriched allenylsilanes in the addition reactions to enantioenriched α-substituted aldehydes. Indeed, compared to stannanes, a stronger Lewis acid ($TiCl_4$) was required to activate these reagents.[44] Allenylsilanes were prepared stereospecifically via Fleming's silylcuprate S_N2' approach. Addition of silane **114** to DPSO-substrate **115** closely paralleled a BF_3-mediated process with



Scheme 24

Table 38 Selected examples for the three-component process leading to **112** (Scheme 24)

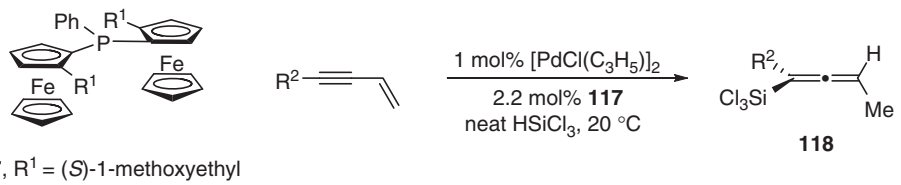
No.	R^1	R^2	***112***, *Yield (%)*	***112***, dr *(%)*
1	Pr^i	Me	81	>20:1
2	Bu^n	Me	69	5:1
3	Bu^t	Me	82	>20:1
4	Cy	*p*-Tolyl	80	>20:1
5	$PhCH_2CH_2$	*p*-$NO_2C_6H_4$	71	6:1
6	Ph	Me	47	10:1
7	*o*-$NO_2C_6H_5$	Me	28	10:1

Table 39 Selected examples for the reactions with preformed aryl sulfonyl imines leading to **113** (Scheme 24)

No.	R^1	R^2	***113***, *Yield (%)*
1	Ph	Me	47
2	*p*-Tolyl	*p*-Tolyl	69
3	2-BrC_6H_4	*p*-$NO_2C_6H_4$	49
4	Bu^t	*p*-Tolyl	0

allenylstannanes, with a matched pair giving exclusively *syn, syn*-product and a 80:20 mixture of *syn, anti*, and *anti, syn*-products for a mismatched case. Remarkably, *β*-benzyloxy substrates demonstrated rather different behavior: the mismatched pair furnished the *syn, anti*-compound as the sole product, whereas the matched reagents led to the *anti, anti*-adduct (Scheme 25). The same trends were observed for an analog of **114** (H instead of Et). No α-epimerization was observed in any of the tested cases.

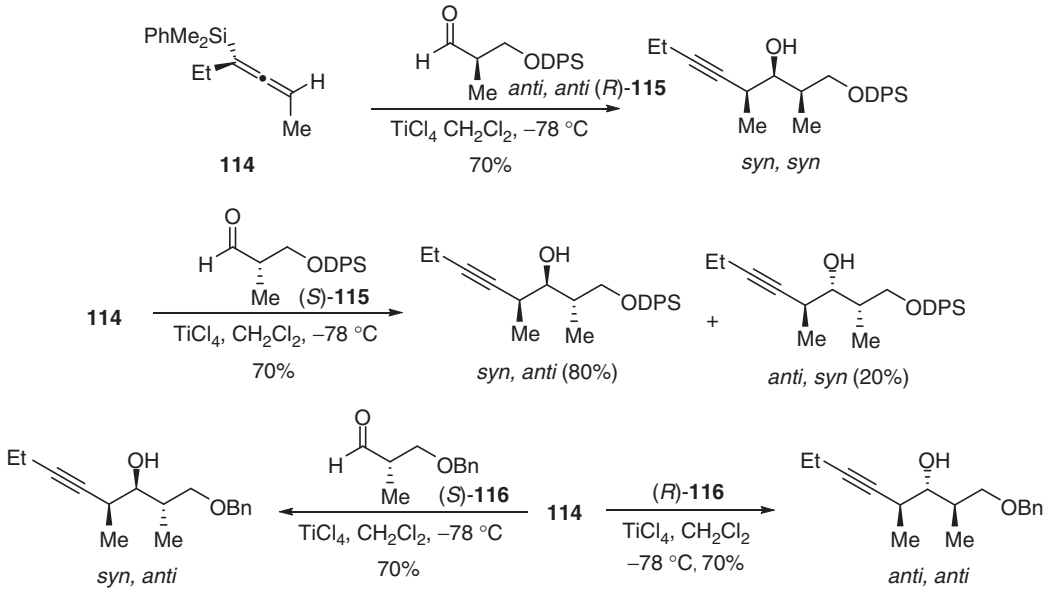
Preparation of synthetically useful chiral allenylsilanes has received considerable attention. Hayashi's study of 2001 is notable as the first report on highly enantioselective catalytic preparation of allenylsilanes **118** from enynes and trichlorosilane (with enantioselectivity induced by the catalyst).[45] Enantiomeric enrichment of up to 90% *ee* was achieved using ferrocene-derived phosphine ligand **117** (equation 12, Table 40). The catalytic cycle is assumed to include oxidative addition of chlorosilane to the palladium complex followed by hydropalladation of the alkene moiety leading to η^3-propargylpalladium species.



117, R^1 = (*S*)-1-methoxyethyl

(12)

Another study by Hayashi and Nishimura[46] described a more general catalytic enantioselective approach to chiral allenylsilanes **121**: enynamides **120** underwent 1,6-addition of arylboronic acids under rhodium catalysis resulting in excellent *ee* values (equation 13, Table 41). Triisopropylsilyl, triethylsilyl, and *tert*-butyldimethysilyl-substituted substrates worked equally well.

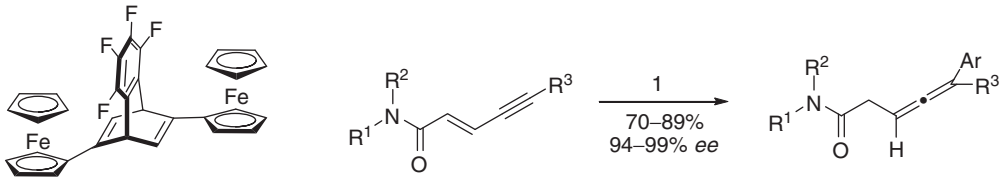


Scheme 25

Table 40 Synthesis of chiral allenylsilanes **118** (equation 12)

No.	R^2	***118***, *Yield (%)*	***118***, ee *(%)*
1	Bu^t	59	85
2	Bu^t	37	90[a]
3	Mesityl	90	77
4	Bu^tMe_2Si	40	68

[a]Conducted at 0 °C.



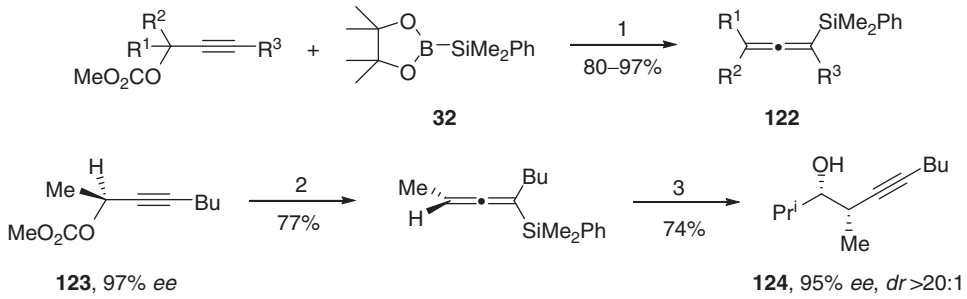
(13)

1. 5 mol% Rh –[RhCl(**119**)]$_2$, ArB(OH)$_2$, 20 mol% K_3PO_4, dioxane-water, 50 °C, 3–72 h

Table 41 Selected examples of the synthesis of chiral allenylsilanes **121** (equation 13)

No.	R^1	R^2	R^3	*Ar*	***121***, *Yield (%)*	***121***, ee *(%)*
1	OMe	Me	TIPS	Ph	87	98
2	OMe	Me	TIPS	4-$CF_3C_6H_4$	79	95
3	OMe	Me	TBDMS	Ph	80	94
4	OMe	Me	TES	Ph	75	96
5	Bn	Bn	TIPS	Ph	82	96
6	Ph	Ph	TIPS	Ph	86	99

Similarly to Shimizu and Hiyama (see Scheme 9), Sawamura's group conducted studies on the reaction between silylborate **32** and propargylic acetates, albeit in the context of rhodium catalysis, which led to the preparation of allenylsilanes **122** (Scheme 26, Table 42). In the case of chiral starting material **123**, an excellent degree of chirality transfer was observed, which was confirmed by the analysis of compounds **124**. The protocol was compatible with a variety of functional groups in the starting material. Notably, terminal alkyne moiety in the substrate was not tolerated as well as the absence of an α-substituent.[47]



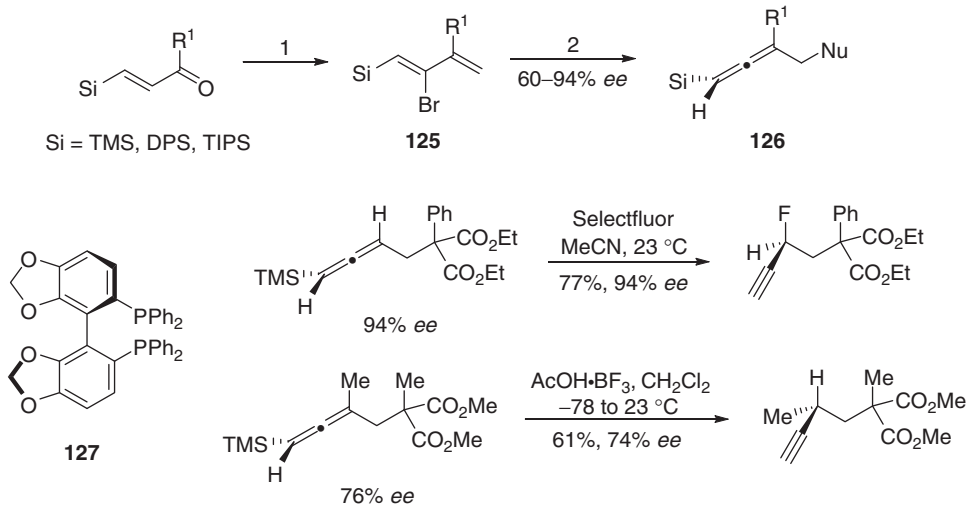
1. 5–10 mol% $[Rh(cod)_2]BF_4$, 1.5 equivalents **32**, 2.5 equivalents Et_3N, acetone, 50 °C, 12–48 h.
2. 10 mol% $[Rh(cod)_2]BF_4$, 1.5 equivalents **32**, 2.5 equivalents Et_3N, DMF/MeCN, 25 °C, 12 h.
3. 1.5 equivalents $TiCl_4$, 1.5 equivalents Pr^iCHO, CH_2Cl_2, –78 °C, 3 h.

Scheme 26

Table 42 Selected examples of the synthesis of allenylsilanes **122** (Scheme 26)

No.	*R^1*	*R^2*	*R^3*	***122**, Yield (%)*
1	Ph	H	Bu	80
2	$(CH_2)_4$		Bu	80
3	$PhCH_2CH_2$	H	H	0
4	H	H	C_5H_{11}	17
5	$PhCO_2(CH_2)_3$	Me	Bu	92
6	$HO(CH_2)_4$	H	$PhCH_2CH_2$	93

In addition to the two aforementioned studies, Ogasawara and Takahashi reported a catalytic asymmetric methodology to synthesize chiral allenylsilanes (Scheme 27, Table 43).[48] 2-Bromo-1-silyl-1,3-dienes **125** can react in S_N2' fashion with soft carbon nucleophiles under palladium catalysis; the resulting enantioenriched compounds **126** can be used for the construction of tertiary and quarternary propargylic stereocenters via the desilylative S_E2' process (selected examples are shown in Scheme 27). The silyl dienyl bromides **125** can be conveniently prepared from readily obtained *β*-silylenals/enones.



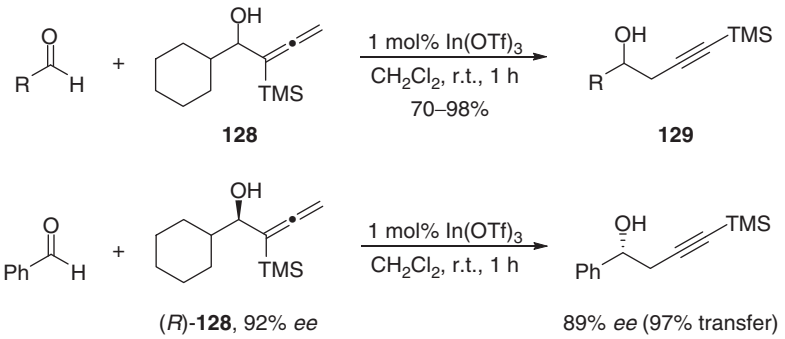
1. 1) Br_2; 2) NEt_3; 3) $TMSCH_2MgCl$; 4) AcOH-water, 60 °C.
2. NuH, base, THF or dioxane, 5 mol% Pd2(dba)4, 5.5 mol% **127**, 18 h, 40–80 °C.

Scheme 27

Loh and coworkers reported an unusual reaction of homopropargylic transfer from silylated allenic alcohol **128** to aldehydes in the presence of indium(III) triflate (Scheme 28, Table 44).[49] The presence of the silyl moiety was shown to be crucial; cyclohexyl derivative **128** provided the highest yields of cross-over product presumably due to steric factors. The process was

Table 43 Selected examples of the synthesis of allenylsilanes **126** (Scheme 27)

No.	R^1	*Si*	*NuH*	*Base*	***126***, *Yield (%)*	***126***, ee *(%)*
1	H	TMS	$CHPh(CO_2Et)_2$	$CsOBu^t$	87	94
2	H	TMS	$CH(CO_2Me)_2$	$CsOBu^t$	82	80
3	H	TMS	$CH(NHAc)(CO_2Et)_2$	$CsOBu^t$	64	85
4	H	TMS	$HC(CO_2Et)_3$	$CsOBu^t$	67	91
5	H	DPS	$CHPh(CO_2Et)_2$	$CsOBu^t$	86	91
6	Me	TMS	$CHMe(CO_2Me)_2$	NaH	71	76
7	Et	TMS	$CHMe(CO_2Me)_2$	NaH	58	60



Scheme 28

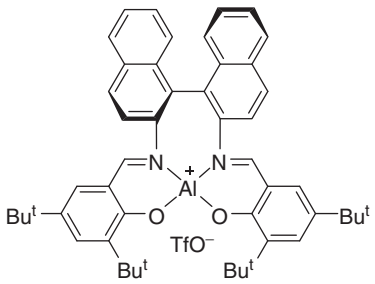
Table 44 Selected examples of the synthesis of homopropargyl alcohols **129** (Scheme 28)

No.	*R*	***129***, *Yield (%)*
1	Cy	98
2	$PhCH_2CH_2$	79
3	$BnO(CH_2)_3$	78
4	n-C_5H_{11}	71

Source: Reproduced from Lee, K.-C.; Lin, M.-J.; Loh, T.-P. *Chem. Commun.* **2004**, 2456–2457, with permission from RSC.

assumed to proceed via unprecedented oxonium [3,3]-sigmatropic rearrangement; the beneficial role of the silyl functionality was apparently associated with the β-silicon effect (stabilizing either a carbocation or a positively polarized transition state). Good-to-excellent yields were obtained for a representative range of aldehydes; the use of chiral reagent (*R*)-**128** demonstrated the feasibility of the chirality transfer (88–97%).

Evans et al. employed different modes of reaction between carbonyl compounds with allylsilanes;[50] compared to propargylation, annulation leading to dihydrofurans **132** is not extensively studied. Ethyl glyoxylate underwent both pathways depending on the size of the silyl moiety; a bulkier silyl group favored annulation. Notably, both types of catalysis provided excellent enantiocontrol (Scheme 29, Table 45).



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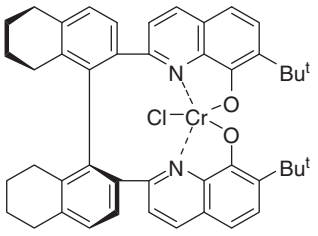

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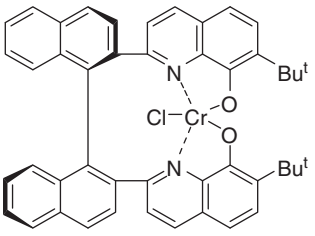
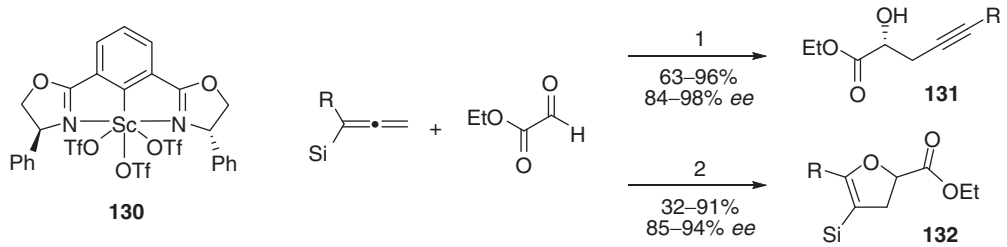


135

Another study by Evans and Aye described an elegant approach to vinyl epoxides through the reaction of propargylsilanes with glyoxamide under aluminum catalysis (equation 14, Table 46).[51] The plausible mechanism includes nucleophilic addition



1. 10 mol% **130**, 10 equivalents hexafluoroisopropanol, CH_2Cl_2, –55 °C, 16 h.
2. 10 mol% **130**, CH_2Cl_2, –48 °C, 20–65 h.

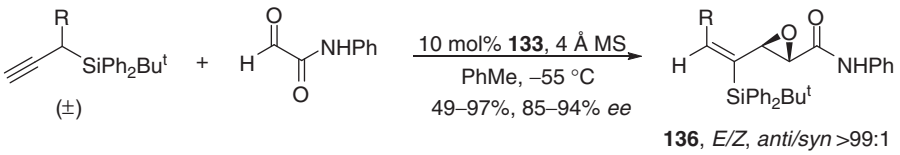
Scheme 29

Table 45 Selected examples for the synthesis of compounds **131** and **132** (Scheme 29)

No.	*Product*	*R*	*Yield (%)*	ee *(%)*
1	**131**	Me	95[a]	98
2	**131**	Ph	63	97
3	**131**	Pr^i	94[a]	84
4	**132**	Me	91[b]	94
5	**132**	Cy	63	93
6	**132**	Ph	32[c]	85

[a]Reaction run at 0 °C.
[b]Conducted with 5 mol% of **130**.
[c]Reaction run at −20 °C.

followed by a [1,2]-silyl shift and kinetic trapping, which furnished the epoxide ring. The protocol is notable for perfect *E*/*Z* and *syn*/*anti* selectivities accompanied by high levels of asymmetric induction.



(14)

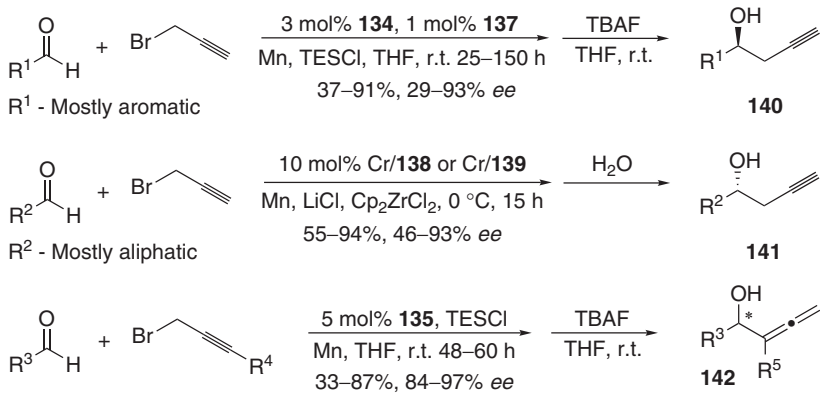
Table 46 Selected examples for the synthesis of epoxides **136** (equation 14)

No.	*R*	***136**, Yield (%)*	***136**,* ee *(%)*
1	Et	70	90
2	Bu^n	97	92
3	$H_2C{=}CH(CH_2)_2$	49	94
4	$Me_2C{=}CH(CH_2)_2$	83	85

2.05.8 Chromium

The addition of organochromium reagents to carbonyl compounds, known as the Nozaki–Hiyama reaction, is known for high regioselectivity, mild conditions, and functional group tolerance; in recent years this methodology has been successfully utilized in the context of enantioselective propargylation and allenylation. The best levels of enantioselectivity as well as the lowest catalyst loadings have been achieved for the chromium complexes of the TBOx family **134**/**135**.

Usanov and Yamamoto thus established a highly enantioselective protocol for asymmetric propargylation of aldehydes using partially reduced H_8-TBOx chromium complex **134** (Scheme 30, Table 47).[52] The background reaction caused by the *in situ* formation of some propargyl/allenyl manganese species was detected; the resulting deterioration of enantioselectivity was overcome by the introduction of cobalt cocatalytic cycle mediated by porphyrin complex **137**, which enabled acceleration of the stereoselective pathway. Derivatives of aromatic, heteroaromatic, and α,β-unsaturated aldehydes were thus obtained with 84–93% *ee*. Introduction of a terminal silyl substituent into the propargyl halide inverts regioselectivity; γ-functionalized propargyl halides furnished allenyl alcohols with excellent stereocontrol (84–97% *ee*) under the catalysis of complex **135**.[53] In addition to silyl substituents, simple alkyl and aryl counterparts could be successfully employed (Scheme 30, Table 48).



Scheme 30 Reproduced from Usanov, D. L.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 8169–8172, with permission from Wiley-VCH.

Table 47 Selected examples for the synthesis of homopropargylic alcohols using H_8-TBOxCrCl **134** (Scheme 30)

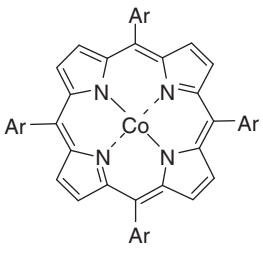
No.	R^1	***140**, Yield (%)*	***140**, ee (%)*
1[a]	Ph	75	91
2[a]	1-Naphthyl	81	86
3	(*E*)-PhCH═C(Me)	91	84
4	2-Furanyl	69	93
5	$PhCH_2CH_2$	42	34

[a]Carried out in 2-methyltetrahydrofuran in the presence of 20 mol% of $CaCO_3$.

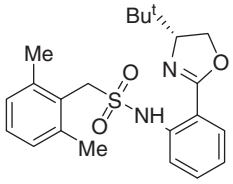
Source: Reproduced from Usanov, D. L.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 8169–8172, with permission from Wiley-VCH.

Table 48 Selected examples for the synthesis of homopropargylic alcohols using Kishi's system **138**/**139** (Scheme 30)

No.	*System*	R^2	***141**, Yield (%)*	***141**, ee (%)*
1	**139**	n-C_5H_{11}	92	81
2	**139**	$PhCH_2CH_2$	91	89
3	**139**	Bu^t	55	92
4	**138**	Ph	92	73
5	**138**	(*E*)-PhCH═CH	89	70



137, Ar = p-$MeOC_6H_4$



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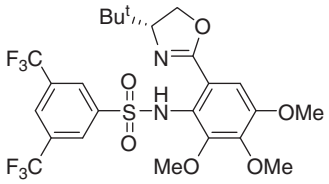


139

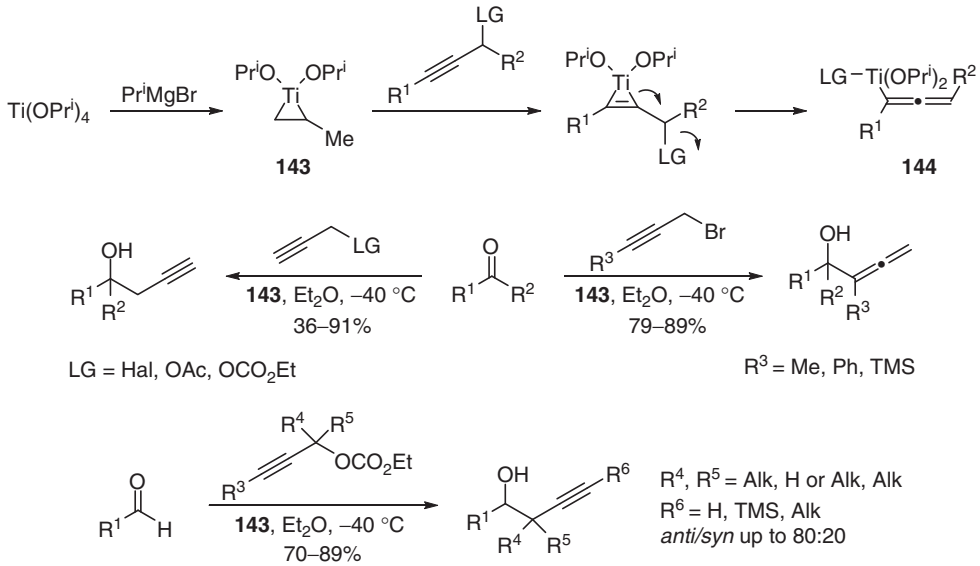
It is notable that Yamamoto's propargylation protocol appeared to be complementary to the catalytic system developed by Kishi. Interestingly, complexes **138**/**139** provided the highest enantioselectivities for aliphatic aldehydes (84–93% *ee*), whereas aromatic substrates did not exceed 73% *ee* (Scheme 30, Table 49).[54] In contrast, propargylation of aliphatic aldehydes could not be accomplished with catalysts of the TBOx family. For a review on organochromium reagents *see* Chapter 1.06.

Table 49 Selected examples for the synthesis of allenic alcohols using TBOxCrCl **135** (Scheme 30)

No.	R^3	R^4	***142**, Yield (%)*	***142**, ee (%)*
1	Ph	Me	84	97
2	Ph	Ph	58	88
3	2-Furanyl	TMS	79	97
4	(*E*)-PhCH=C(Me)	TMS	51	90
5	Cy	TMS	72	90
6	*n*-C_7H_{15}	TMS	75	85

2.05.9 Titanium and Zirconium

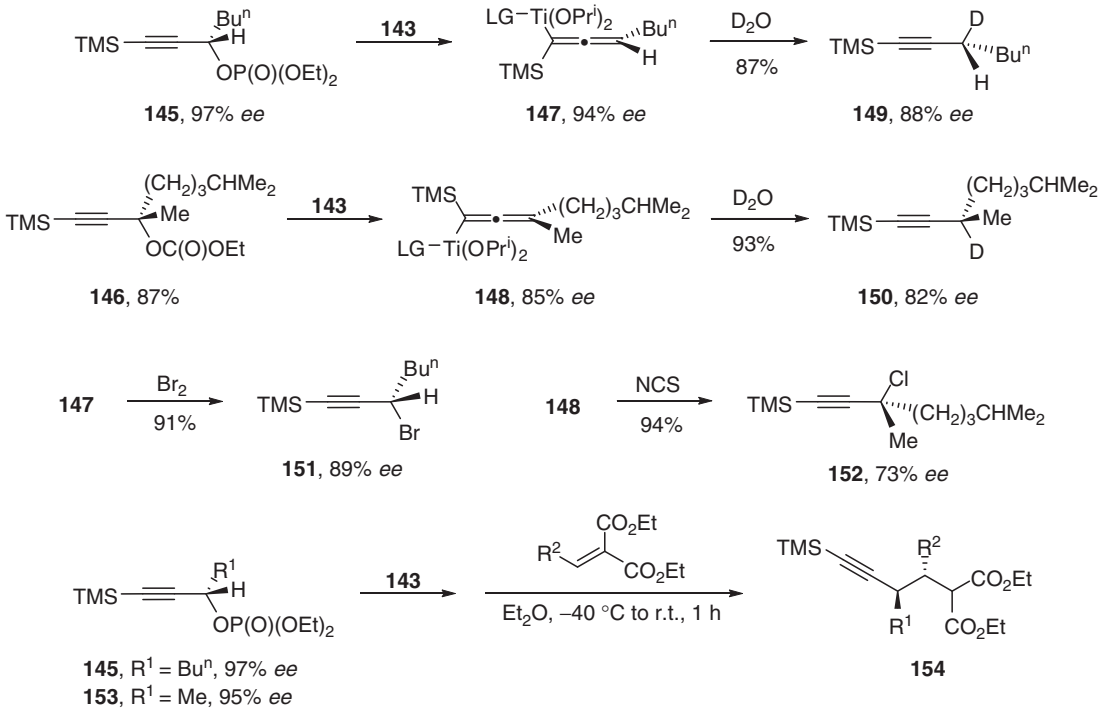
Sato et al. reported generation of propargyl/allenyltitanium reagents from propargylic halides or propargyl alcohol derivatives by means of a 1:2 mixture of titanium tetraisopropoxide and isopropyl Grignard reagent (Kulinkovich reagent).[55] Terminally unsubstituted propargyl compounds allowed good yields of homopropargyl alcohols; functionalization of the alkyne terminus reverted regioselectivity toward allenyl alcohols. Secondary and tertiary propargyl alcohols derivatives favored propargylation, which proceeded with good yields and moderate diastereoselectivity. The reaction mechanism was assumed to proceed through η^2-complex **143**, which is converted into allenyltitanium species **144** (Scheme 31). In the case of 1-substituted 3-bromo-1-propynes more stable propargyltitanium reagents were formed as a result of metallotropic rearrangement. The methodology provided certain expansion of the substrate scope available with Yamamoto's organotitanium reagents (formed via lithiation/transmetallation of propargylic ethers); however, lower levels of diastereoselectivity could be achieved. For a review on organotitanium and organozirconium reagents *see* Chapter 1.05.



Scheme 31

The use of enantiomerically enriched starting materials showed excellent degrees of chirality transfer for secondary propargylic phosphate **145** and tertiary propargylic carbonate **146**, which likely proceed via *anti*- and *syn*-elimination steps, respectively. Interestingly, the reactions involving counterparts of these substrates (carbonate vs. phosphate and vice versa) demonstrated compromised enantioselectivity. Reactions with various electrophiles enabled preparation of compounds **149–152** with a high degree of enantioenrichment preservation (Scheme 32).[56] Interestingly, protonolysis and chlorination lead to products of the opposite sense of chirality proceeding through *syn*- and anti-pathways, respectively. Synthetically challenging preparation of optically active tertiary propargylic chloride **152** is particularly noteworthy (see also Scheme 16). Reaction of chiral allenyltitanium species with alkylidene malonates proceeds with excellent stereospecificity and diastereoselectivity to furnish synthetically versatile Michael addition products **154** (Scheme 32, Table 50).[57]

Preparation of allenylmetal species has also been accomplished using low-valent metallocene complexes of titanium and zirconium. For example, propargylic ethers can react with Negishi reagent 'Cp_2ZrBu_2' to yield allenyl/propargylzirconium species; the equilibrium between isomers is dependent on the substitution pattern in the substrate. Aryl- and alkyl-substituted propargylic ethers led to allenes on hydrolysis, whereas alkynes were formed from TMS-functionalized counterparts (Scheme 33, Table 51). Organozirconium intermediates could serve as nucleophilic agents with allyl halides and could be subject to Pd-catalyzed coupling, which provides access to allenes with moderate-to-good yields.[58]

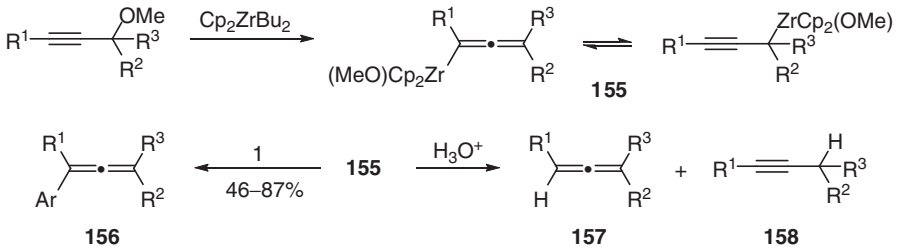


Scheme 32

Table 50 Michael addition of organotitanium reagents leading to **154** (Scheme 32)

No.	R^1	R^2	*Yield (%)*	anti.syn	ee *(%)*[a]
1	Me	Me	92	97:3	92 (94)
2	Me	Bu^n	89	98:2	96 (98)
3	Me	Ph	96	>99:1	96 (98)
4	Me	*p*-$(MeO_2C)C_6H_4$	82	>99:1	92 (94)
5	Bu^n	Me	85	97:3	88 (92)
6	Bu^n	*p*-BrC_6H_4	97	>99:1	92 (96)

[a]Values in parentheses are calculated for enantiomerically pure substrates.



1. $Pd(PPh_3)_4$, CuCl, ArI, THF, with or without DMAP, r.t., 2 h.

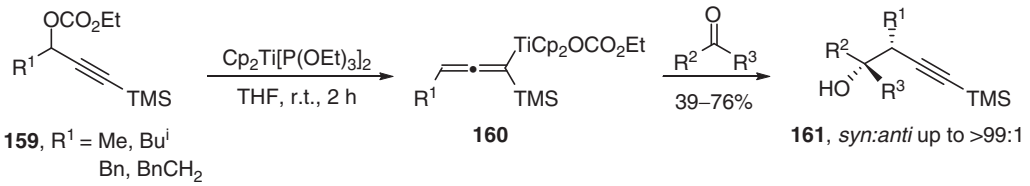
Scheme 33

Before the work of Takeda and coworkers highly diastereoselective addition of allenyl metals to ketones have not been reported. Although aldehydes tend to undergo addition leading to *anti*-homopropargylic alcohols, high levels of *syn*-selectivity were observed in the reaction of aromatic and α,β-unsaturated ketones with allenyltitanocenes **160**, which are prepared by reductive titanation of γ-trimethylsilylpropargylic carbonates **159** (Scheme 34, Table 52).[59] For acetophenones the diastereoselectivity was found to be dependent on the nature of the substituent in the aromatic ring, with electron-rich substrates demonstrating better results.

Table 51 Selected examples for protonation of organozirconium compounds according to **Scheme 33**

No.	*R^1*	*R^2*	*R^3*	*Major product*	*Yield (%)*[a]
1	Ph	$(CH_2)_4$		**157**	87
2	Bu	$(CH_2)_5$		**157**	62
3	Ph	Pr^i	H	**157**	71(9)
4	TMS	*n*-C_6H_{13}	H	**158**	69
5	TMS	Pr^n	Pr^n	**158**	60

[a]Figures in parentheses represent the yield of the minor isomer, if any.



159, R^1 = Me, Bu^i Bn, $BnCH_2$ **160** **161**, *syn:anti* up to >99:1

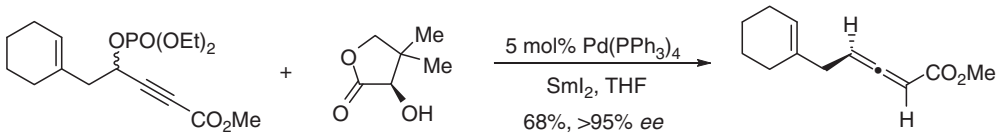
Scheme 34

Table 52 Selected examples for the addition of allenyltitanium reagents to ketones to form **161** (**Scheme 34**)

No.	*R^1*	*R^2*	*R^3*	syn:anti	*Yield (%)*
1	Me	$PhCH_2CH_2$	Me	64:36	72
2	Me	$H_2C{=}CH$	Et	81:19	49
3	Me	Cy	Me	57:43	70
4	Me	$Me_2C{=}CH$	Me	95:5	51
5	Me	Ph	Me	87:13	65
6	$BnCH_2$	Ph	Me	>99:1	71

2.05.10 Other Metals

Pd-catalyzed reaction involving allenyl/propargyl substrates has been reviewed by Ma.[5]

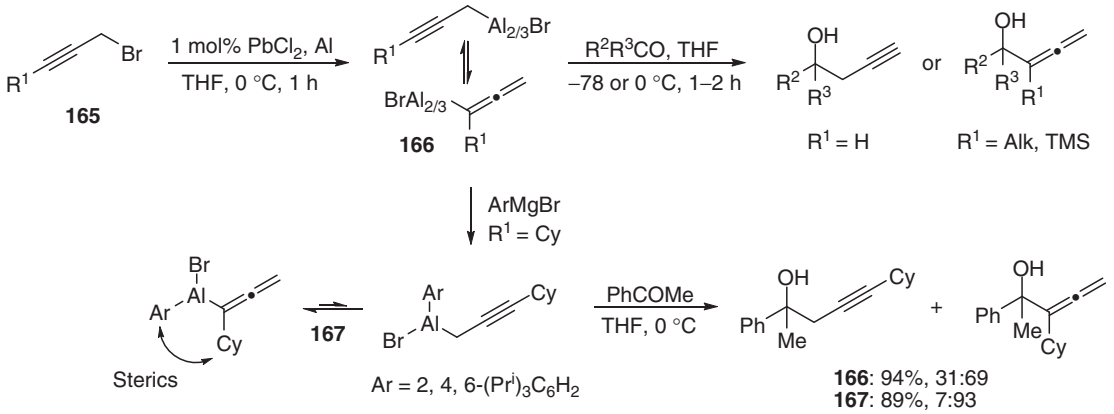


162 **163** **164** (15)

Mikami and Yoshida studied chirality transfer in SmI_2-based reductive rearrangement of propargyl phosphate **162** using palladium catalysis and *tert*-butanol. However, racemic product was obtained, which indicated racemization of allenylsamarium species occurring before the protonation step. Their attention then switched to studies on dynamic kinetic protonation, which identified **163** as the best proton source, furnishing product **164** with good yield and excellent enantioselectivity.[60]

Knochel's group reported an interesting study on the preparation of homopropargyl and allenyl alcohols via organoaluminum reagents (**Scheme 35**).[61] Aluminum powder was found to be capable of inserting into propargylic bromides under mild conditions in the presence of catalytic amounts of lead(II) chloride. The allenic isomer of the organometallic species was preferred with small R^1 groups (e.g., H), whereas propargylic analogs were favored if $R^1 \neq H$. Remarkable functional group tolerance was demonstrated, which included ester, cyano, acidic methylene, or even primary amino groups. Excellent regioselectivities were observed in nearly all cases. Notably, allenylation of benzaldehyde and acetophenone proceeded with appreciable competition from the propargylation process; this problem was elegantly solved by the treatment of the organoaluminum species with a bulky Grignard reagent to furnish modified species **167**. For a review on organoaluminum reagents *see* Chapter 1.03.

It is noteworthy that Knochel's methodology enables the synthesis of tertiary homopropargylic alcohols with high diastereoselectivity, which represents a rather challenging and underdeveloped synthetic task.



Scheme 35

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2.06 Formation of Enolates

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2.06.1 Introduction

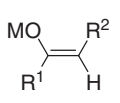
Enolates, or oxyallyl anions, are versatile reagents for the formation of α-substituted carbonyl compounds and are therefore important intermediates for the synthesis of complex molecules. The stereochemical outcome of an enolate reaction often depends on the geometry of the enolate and therefore the selective formation of enolates is a key step in many bond-forming processes.[1]

The counterion of an enolate has a pronounced influence on competing transition states of enolate reactions. The effect is often the result of cation chelation by the carbonyl oxygen atom and one or more additional basic portions of the reactants. For example, alkylation of chiral enolates may lead to more or less diastereomerically pure products and selectivity often depends on the countercation. The importance of the countercation in controlling enolate reaction product distributions requires that the synthetic chemist has at hand stereoselective methods for the preparation of enolate anions with a wide variety of counterions. This chapter is divided into several sections. The 10 following sections describe important current methods for preparing Li, Mg, B, Al, Sn, Ti, Zr, Cu, Zn and other transition metal enolates.

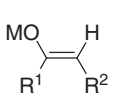
Enolates occur commonly in only two forms: the metal may be found either closer to the oxygen or closer to the carbon atom. Groups I, II and III enolates exist as O-metal tautomers. These strongly electropositive metals bind closely to the oxygen atom. Among transition metal enolates both types of enolates are observed. In a few transition metal enolates the cation is associated with a delocalized enolate anion (η^3-enolate complexes).

The structures of enolates have been examined through magnetic resonance studies (NMR) and with X-ray crystallography.[2–12] It has been observed that solvated enolates exist as dimers, tetramers or hexamers, depending on the enolate structure, the nature of the cation and the solvent.

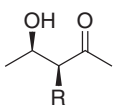
The following nomenclature for enolate stereoisomers is adopted throughout this chapter: the (*E*)/(*Z*) nomenclature is used according to the Cahn-Ingold-Prelog rules, with one change. At the carbonyl C-atom, the OM (oxy-metal) group is defined to be of highest priority without regard to the nature of the metal,[1] for example, (**1**) and (**2**). This has the advantage that changing the metal associated with a given enolate does not affect the (*E*)/(*Z*) nomenclature.



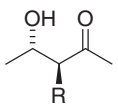
(**1**) (*Z*)



(**2**) (*E*)



(**3**) *syn/erythro*



(**4**) *anti/threo*

In the work cited here, the (*E*)/(*Z*) geometry of the enolate is sometimes not known or is not specified by the original authors. When this is the case, a wavy line is used in the representation of the enolate. Unfortunately, despite the importance of enolate geometry, many authors provide little direct information on this point. The exact nature of the countercation is also not always

specified or known. Where the counterions are rather obvious but not certainly known, they are included in the formulas but placed in brackets [ ].

For aldol products many types of nomenclature have been proposed. Throughout this chapter the *syn*/*anti* nomenclature of Masamune[13] is adopted and defined as shown in (**3**) and (**4**).

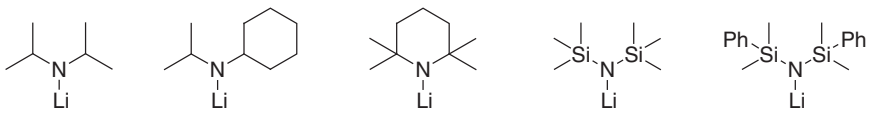
This chapter is restricted to the formation of metal and metalloid enolates that are more or less anionic and which can react with carbonyl groups without a catalyst. Silicon derivatives are therefore not described.

2.06.2 Alkali Metal Enolates

The alkali metal enolates are the most commonly employed and most useful of all enolates. Among alkali elements, lithium enolates are of greatest importance because these can often be formed under kinetic or thermodynamic conditions, as desired, and side reactions can be minimized since lithium is a small, tightly bound cation. Sodium and potassium countercations are more likely to support enolate equilibration, which is sometimes desired, but often undesired. This section is subdivided, based on the different methods of enolate formation.

2.06.2.1 Alkali Metal Enolates by Deprotonation of Carbonyl Compounds

Deprotonation of carbonyl compounds by lithium dialkylamide bases is the single most common method of forming alkali enolates. Four excellent reviews have already been published.[1,14–16] Sterically hindered amide bases are employed to retard nucleophilic attack on the carbonyl group. The most common and generally useful bases are: (i) lithium diisopropylamide (LDA; **5**); (ii) lithium isopropylcyclohexylamide (LICA; **6**); (iii) lithium 2,2,6,6-tetramethylpiperidide (LITMP; **7**); (iv) lithium hexamethyldisilylamide (LHMDS; **8**); and (v) lithium tetramethyldiphenyldisilylamide (LTDDS; **9**). Bases that are not amides include sodium hydride, potassium hydride and triphenylmethyllithium.



(**5**) (**6**) (**7**) (**8**) (**9**)

For ketone enolates, the question of the regioselectivity of deprotonation arises.[1,17] Under kinetic conditions (low temperature, typically −78 °C, excess base, small cation), the less-substituted enolate is formed. More-hindered bases give higher selectivity. Under conditions designed to provide an equilibrium mixture of product enolates ('higher' temperature, excess ketone, larger cation) the more-substituted enolate is usually formed.

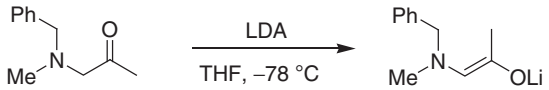
Aldehyde enolates and aldehydes are extremely reactive and therefore, to avoid undesirable side reactions, fast and quantitative conversion of aldehydes to enolates is necessary. Strong bases are needed, for example, potassium amide in liquid ammonia[18] or potassium hydride in THF.[19] Aldehyde enolates are very rarely used in organic synthesis.

Ester enolates are less reactive than aldehyde enolates but rapid and quantitative deprotonation is still necessary because of the possibility of Claisen condensation side reactions.

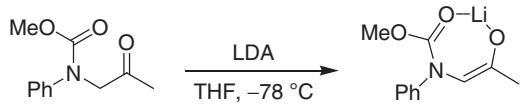
For all enolates, (*E*)- and (*Z*)-geometry is possible. Much effort has been expended to determine the geometry of enolates and to define rules to predict the outcome of carbonyl group deprotonations.[1,14–16] This knowledge is relevant to the aldol reaction because (*Z*)-enolates tend to give *syn*-products, whereas (*E*)-enolates tend to give *anti*-products with varying degrees of stereoselectivity.

Under product-equilibrating conditions the (*Z*)-enolate is always the major product (except in smaller ring systems, three to nine membered, where the (*E*)-enolate is favored). Under conditions of kinetic product control, a closer study of reactants and bases is necessary. Reactions of ketones, esters or thioesters with lithium dialkylamides like LDA, LICA or LITMP in THF give predominantly the (*E*)-enolate. Larger, bulkier bases give better (*E*)-selectivity. However, if a bulky group (e.g., *t*-butyl, phenyl) is attached directly to the carbonyl group, the (*Z*)-enolate is preferred. If lithium dialkylamide bases are used in a mixture of THF and HMPA, or if silylamide bases are employed, the (*Z*)-enolates are found to be the major products. Carboxylic acid amides always give (*Z*)-enolates with high selectivity. Ireland et al.[20] proposed a cyclic six-membered transition state between the carbonyl and the dialkylamide base to explain these results. Recently, Moreland and Dauben[21] presented theoretical calculations that support this model.

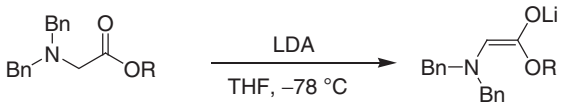
Deprotonation of α-heteroatom-substituted carbonyl compounds (at the carbon bearing the substituent) has been less studied. In several cases it has been observed that, if chelation of the counterion by the enolate is possible, the (*Z*)-enolate is the preferred compound. Garst and coworkers reported two examples in which an α-dialkylamino ketone gives (*E*)-enolates selectively, whereas the corresponding urethane gives predominantly the (*Z*)-enolate (equations 1 and 2).[22] Ireland found a similar effect with $\grave{\alpha}$-amino esters (equations 3 and 4).[20]



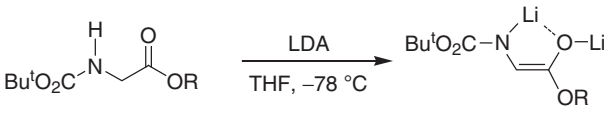
(*E*):(*Z*) > 98:2 (1)



(*Z*):(*E*) = 80:20 (2)

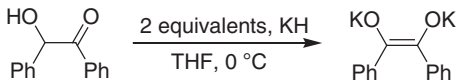


(*E*):(*Z*) = 58:42 (3)

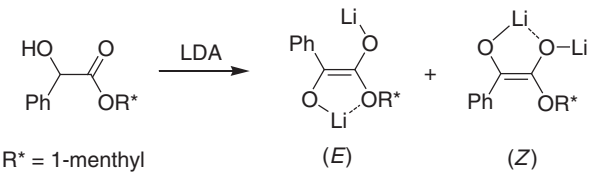


(*Z*) > 90% (4)

α-Hydroxy ketones give (*Z*)-enolates (equation 5),[23] but if α-hydroxy esters are deprotonated, the prediction of (*E*)/(*Z*) selectivity is more difficult because both enolates can be stabilized through chelation. For the reaction shown in equation 6,[24] the (*E*):(*Z*) ratio is not known.

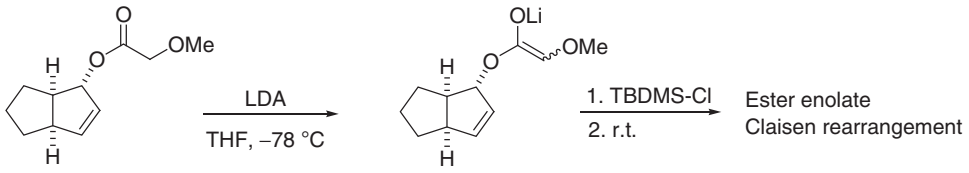


(*Z*) > 95% (5)



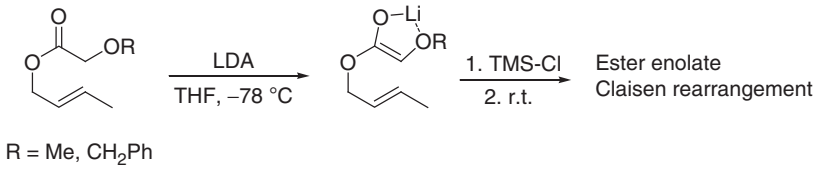
(6)

α-Alkoxy esters would give (*Z*)-enolates if chelation effects dominated but the experimental results are inconsistent. Whitesell and Helbling[25] deprotonated an α-methoxy ester with LDA to get both diastereomers in roughly equal amounts (**Scheme 1**), but Kallmerten and Gould[26] obtained the chelated (*Z*)-enolate predominantly (**Scheme 2**). Ireland et al.[27] used a cyclic α-alkoxy ester and obtained a 5:1 mixture of enolates with LDA (in favor of the chelated (*Z*)-enolate) and a 1:1 mixture with LDA-HMPA. This latter change in selectivity can be explained by loss of the chelation effect (**Scheme 3**).

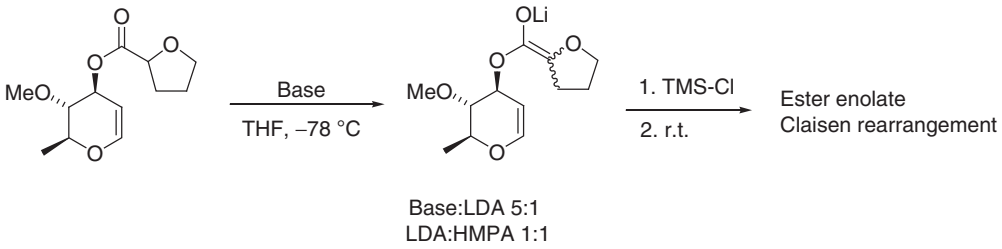


Scheme 1

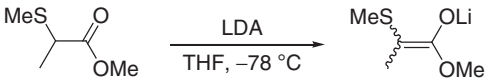
Deprotonation of one α-methylthio ester is reported to give a 75:25 diastereomer mixture, but it is not known if the (*E*)- or (*Z*)-isomer is the major product (equation 7).[28]



Scheme 2

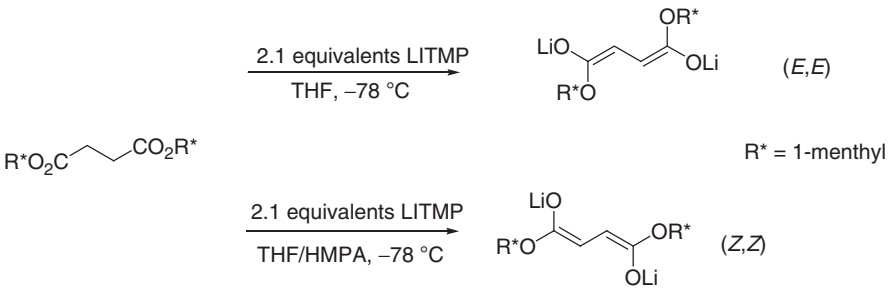


Scheme 3



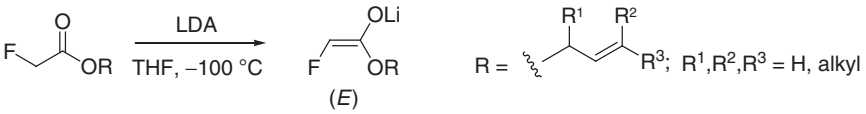
(7)

Dianion enolates of succinate diesters show the same stereochemical behavior as simple ester enolates: deprotonation with LITMP in THF gives the (*E*,*E*)-enolate and deprotonation in THF–HMPA gives the (*Z*,*Z*)-enolate (Scheme 4).[29] No mixed enolates are observed. The corresponding diamides seem to give (*Z*,*Z*)-enolates.[1,30]

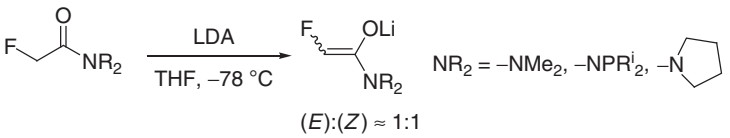


Scheme 4

Welch et al. reported successful generation of α-fluoro enolates.[31,32] Deprotonation of ester enolates in THF gave the (*E*)-enolate as expected (Scheme 5), but no effect of HMPA on the enolate geometry was observed. The α-fluoroamides reacted unselectively (Scheme 6).

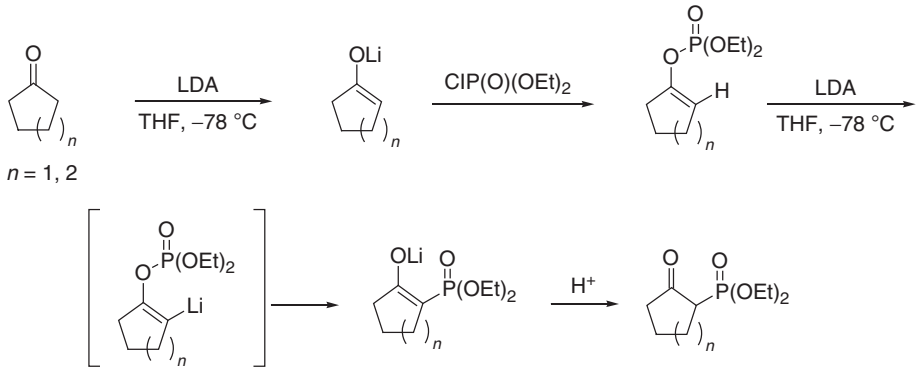


Scheme 5



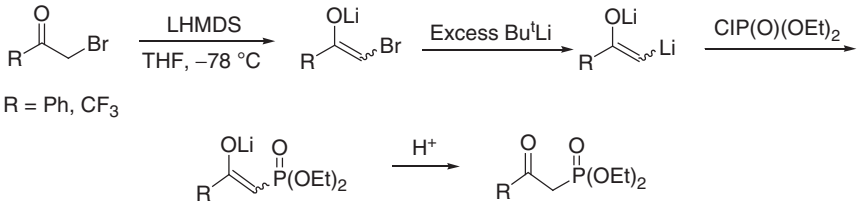
Scheme 6

A versatile method to generate β-ketophosphonates that cannot be generated through the Arbuzov reaction has been developed: α-phosphonate enolates of cyclic ketones are obtained through sequential treatment of ketones with LDA, diethyl phosphorochloridate and LDA (Scheme 7).[33,34]

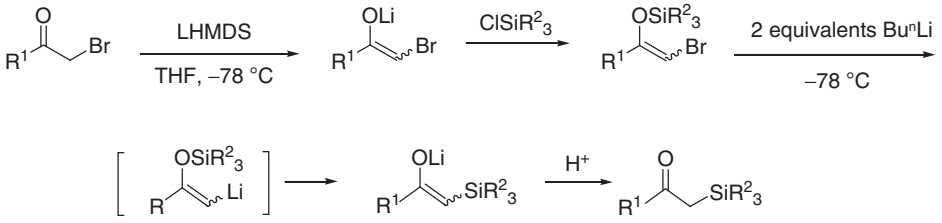


Scheme 7

Acyclic β-ketophosphonates can also be formed from α-bromo ketones (Scheme 8)[35] and in a similar reaction α-trialkylsilyl enolates can also be obtained (Scheme 9).[35,36]

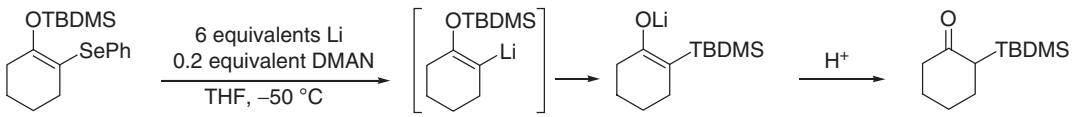


Scheme 8



Scheme 9

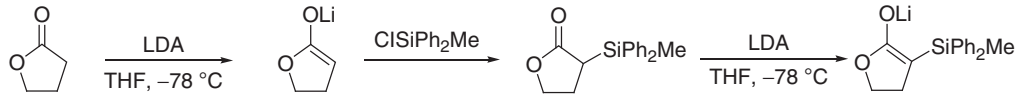
Kuwajima and Takeda employed the reaction of α-phenylselenylvinyl silyl ethers with lithium and dimethylaminonaphthalene (DMAN) to generate α-silyl enolates (Scheme 10).[37]



Scheme 10

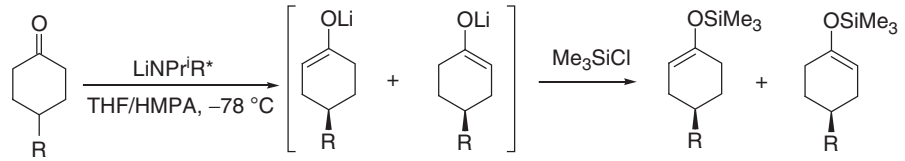
In these reactions (Schemes 7, 9 and 10) it is interesting that a strong P–O or Si–O bond is broken to get a less stable P–C or Si–C bond. The effect is apparently more than offset by the fact that a very unstable vinyl anion is converted to a relatively stable enolate anion.

The reaction of esters and γ-lactone enolates with diphenylmethylsilyl chloride is reported to be atypical and to give the *C*-silylated product (**Scheme 11**).[38]



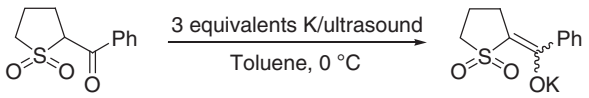
Scheme 11

Enantioselective deprotonation by chiral lithium amide bases has been reported. The degree of asymmetric induction depends on the base and on the bulkiness of the alkyl group in the cyclohexanone (**Scheme 12**).[39]

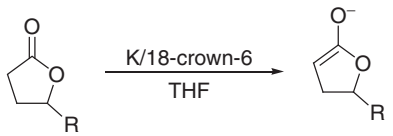


Scheme 12

Very recently, two examples of generating enolates with metallic potassium appeared. In one case potassium was dispersed ultrasonically, in the other 18-crown-6 was added to the potassium metal (equations 8 and 9).[40,41]

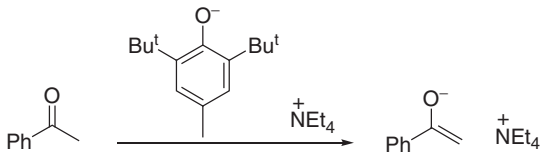


(8)

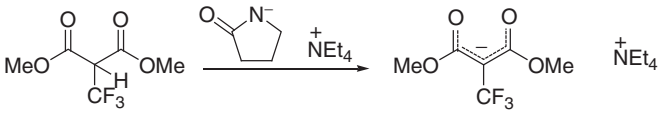


(9)

Fuchigami and coworkers have formed enolates with electrogenerated bases (equations 10 and 11).[42,43] The basic anions of 2,6-di-*t*-butyl-*p*-cresol and α-pyrrolidone were obtained by cathodic reduction. Countercations with a weak affinity for the fluorine atom (e.g., quaternary ammonium, phosphonium or tertiary sulfonium cations) had to be used in the example shown in equation 11 in order to impede defluorination.

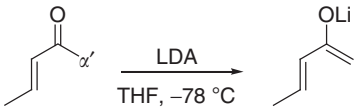


(10)

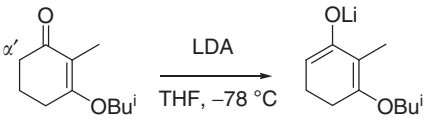


(11)

α,β-Unsaturated ketones can be deprotonated in two positions.[17] Under thermodynamic conditions the major product is that afforded by deprotonation at the γ-position, whereas under kinetic conditions the hydrogen in the α-position is usually abstracted (equations 12 and 13).[44,45]

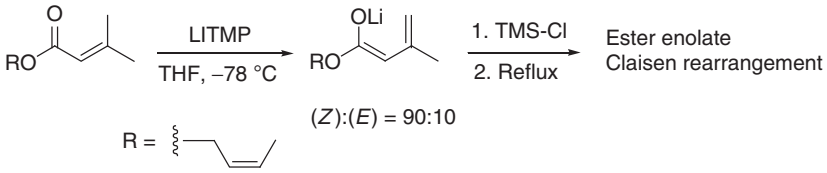


(12)

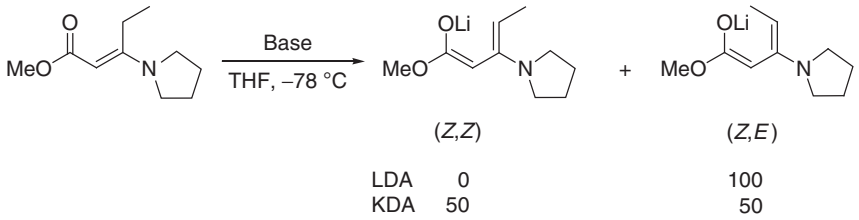


(13)

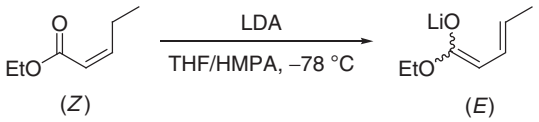
Little is known about the (*E*)/(*Z*) stereoselectivity of the enolate double bond and the newly generated Δ^3 double bond. Two experiments indicate that esters may give preferentially (*Z*)-enolates under kinetic conditions (Schemes 13 and 14).[46,47] If the Δ^2 double bond in an *α,β*-unsaturated ester has only alkyl ligands, (*Z*)-esters seem to give only enolates with (*E*)-geometry on the Δ^3 double bond and (*E*)-esters afford (*Z*)-Δ^3 double bonds (equation 14).[48,49]



Scheme 13



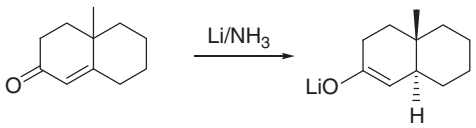
Scheme 14



(14)

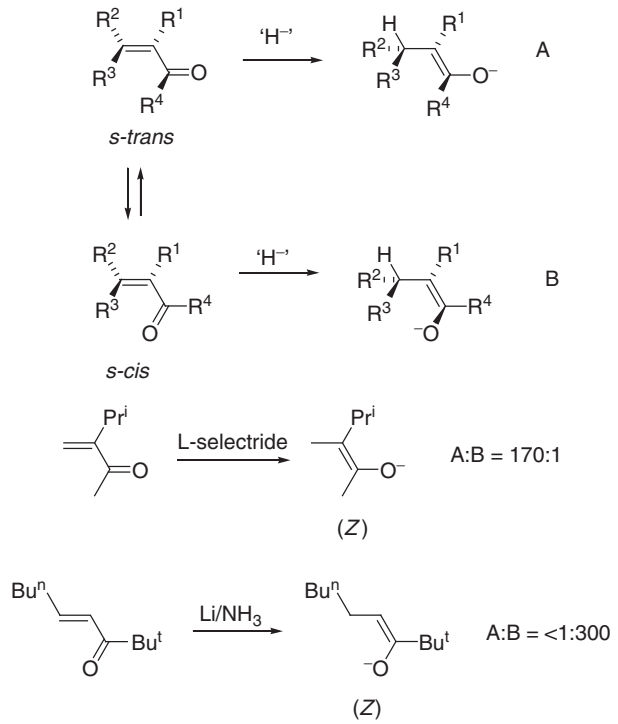
2.06.2.2 Alkali Metal Enolates by Addition to α,β-Unsaturated Carbonyl Compounds

The reduction of *α,β*-unsaturated carbonyls with lithium in ammonia is a versatile reaction of great utility.[17,50–52] The advantage of this method is that regiospecific enolates are obtained that are sometimes not accessible by other routes. This technique finds important applications in steroid-like systems (equation 15).[50]

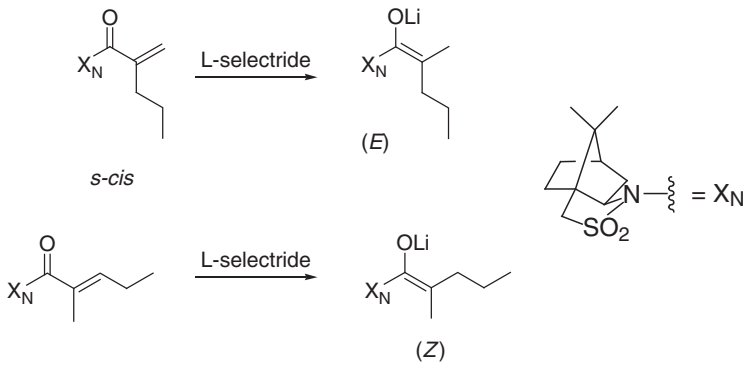


(15)

Chamberlin and Reich investigated hydride additions to *α,β*-unsaturated ketones and the correlation of conformational preferences in enones with the (*E*)/(*Z*) stereoselectivity in formation of the corresponding enolates. They found that in acyclic systems *s-trans* enones gave enolates A and *s-cis* enones gave enolates B (Scheme 15).[53] The reduction of *α,β*-unsaturated amides with L-selectride gave the same stereochemical results (Scheme 16).[54]



Scheme 15



Scheme 16

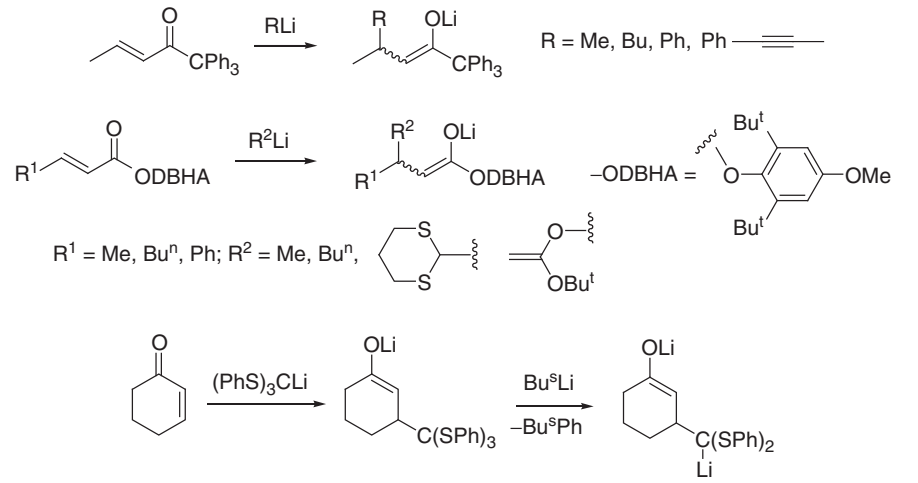
Alkyllithium reagents normally react with α,β-unsaturated carbonyls in a 1,2-fashion, but with sterically hindered substrates or reagents 1,4-addition is preferred (Scheme 17).[55–57] Of course, the presence of other metals can also affect this preference. Other examples of 1,4-additions will be seen in later sections.

2.06.2.3 Alkali Metal Enolates from Ketenes

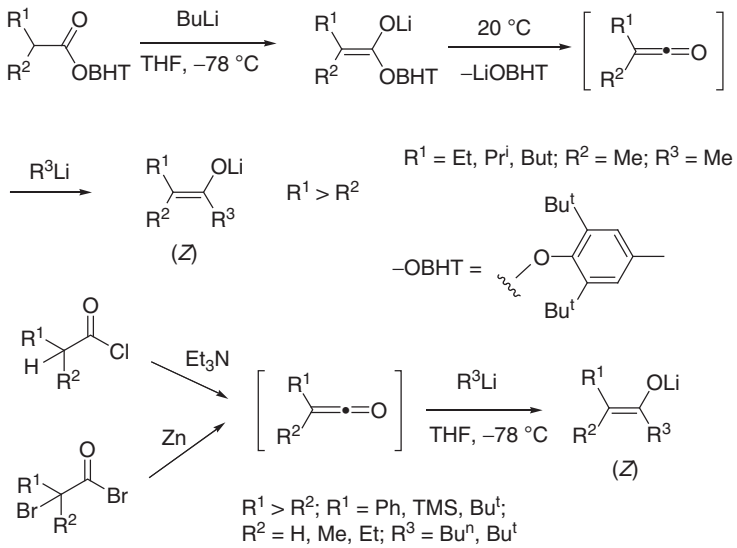
The formation of enolates from ketenes generates tetrasubstituted enolates regio- and stereo-selectively.[58–61] Deprotonation of the corresponding ketones gives mixtures of enolates. Ketenes are produced from sterically hindered esters, from α-bromoacyl bromides and zinc, or from acid chlorides and triethylamine. Alkyllithium reagents add to the ketenes from the less-hindered side to give only (*Z*)-enolates (Scheme 18).[58,60]

2.06.2.4 Alkali Metal Enolates from Enol Acetates and Silyl Enol Ethers

Enol acetates and silyl enol ethers may be prepared from enolates. This is sometimes advantageous because they are stable enolate equivalents.[17] Enol acetates can be cleaved with 2 equivalents of methyllithium (equation 16).[62] Silyl enol ethers can be cleaved

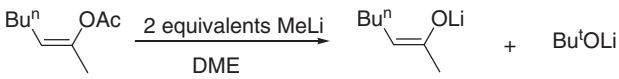


Scheme 17

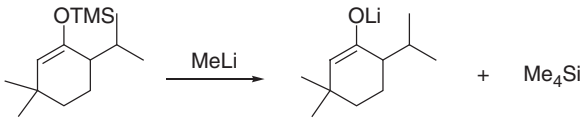


Scheme 18

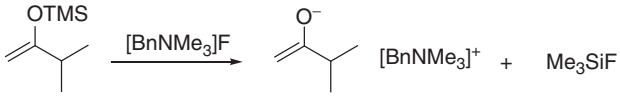
with methyllithium (equation 17),[63] with lithium or sodium amide,[64] or with benzyltrimethylammonium fluoride (equation 18).[65] These enolate formations occur without isomerization.



(16)



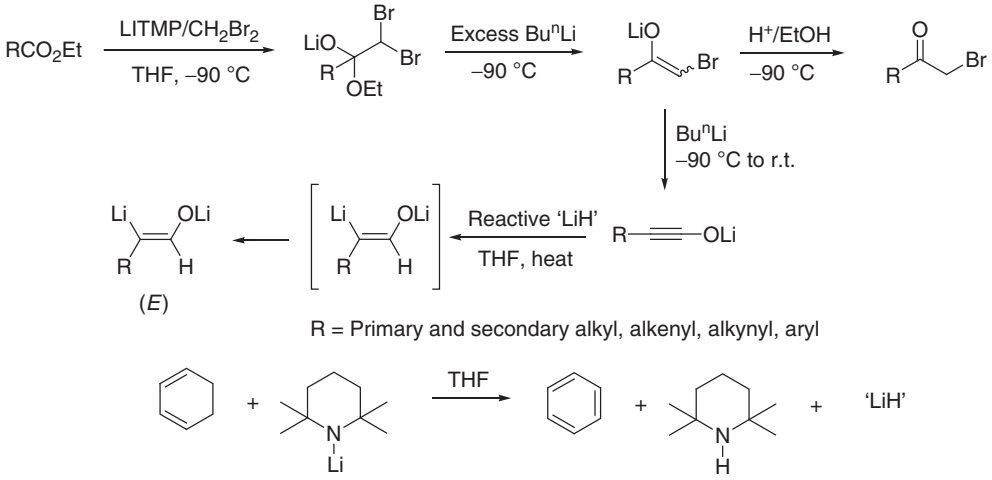
(17)



(18)

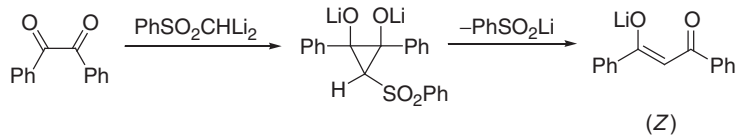
2.06.2.5 Alkali Metal Enolates by Miscellaneous Methods

Kowalski et al.[66–69] employed dibromomethyllithium (prepared *in situ*) to prepare an α-bromo ketone enolate at low temperatures. At higher temperatures and under extremely basic conditions, this enolate rearranged to give an ynolate. A mixture of 1,3-cyclohexadiene and LITMP transformed the ynolate to an aldehyde (*E*)-enolate (Scheme 19).



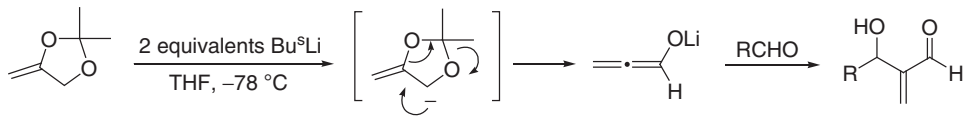
Scheme 19

Reaction of benzil with (benzenesulfonyl)methylenedilithium gives an enolate by an insertion process (Scheme 20).[70]



Scheme 20

Lithium allenolates are obtained from 2,2-dimethyl-4-methylene-l,3-dioxolane and 2 equivalents of *s*-butyllithium. These allenolates can further undergo aldol reactions (Scheme 21).[71]

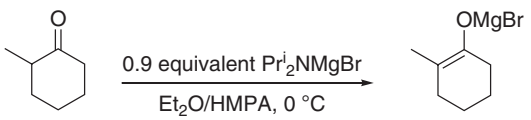


Scheme 21

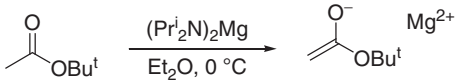
2.06.3 Magnesium Enolates

Magnesium enolates are similar to alkali metal enolates. For example, often the same stereoselectivity is observed in their formation and in the aldol reactions of these enolates.

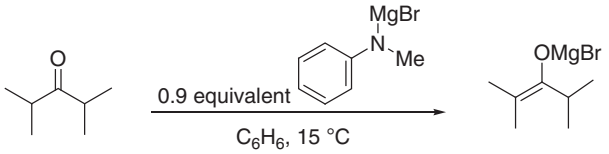
Carbonyl compounds can be deprotonated with magnesium dialkylamides, which are generated from Grignard reagents and are thus free of lithium. Again, the more-substituted enolate is obtained under thermodynamic conditions (equations 19–21).[72–74]



(19)

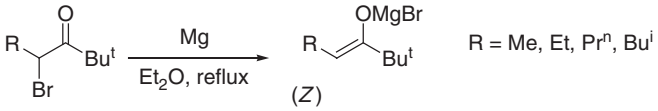


(20)

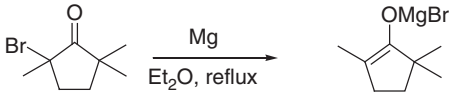


(21)

α-Bromocarbonyl compounds react with magnesium to give bromomagnesium enolates (equations 22 and 23),[75,76] and silyl enol ethers can be cleaved with methylmagnesium bromide (equation 24).[63]

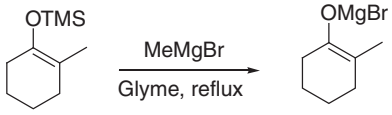


(22)



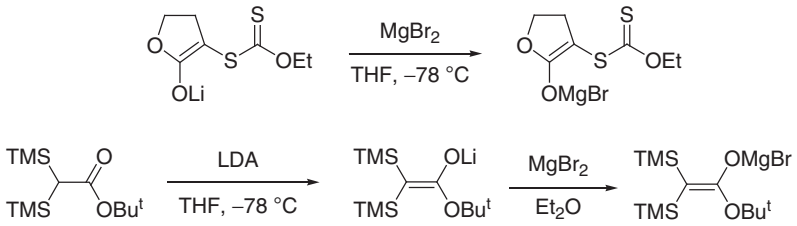
(*E*)

(23)



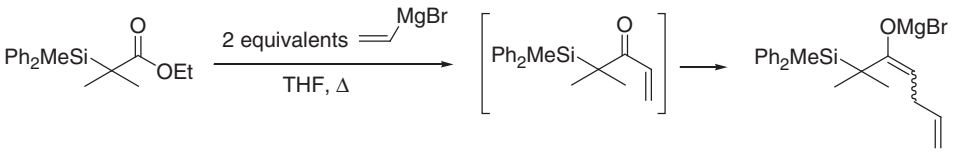
(24)

An important practical route involves the transmetallation reaction between lithium enolates and $MgCl_2$ or $MgBr_2$ (Scheme 22).[77,78] However, in such cases the true nature of the reactant (Li or Mg or both?) is obscured.



Scheme 22

A different type of reaction is the addition of 2 equivalents of vinyl Grignard reagent to an ester. This involves a conjugate addition to a sterically hindered ketone in the second step (Scheme 23).[79]

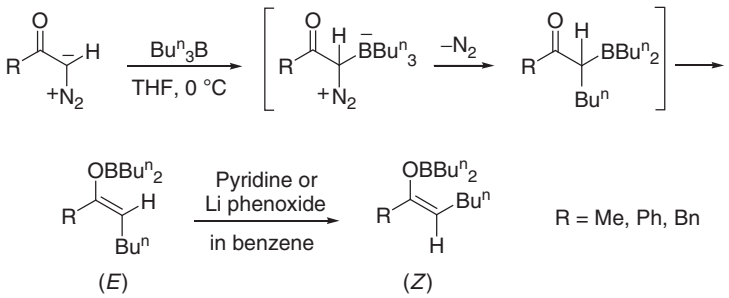


Scheme 23

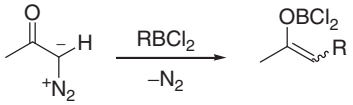
2.06.4 Boron Enolates

Boron enolates (other names are vinyloxyboranes, enol borinates, or boron enol ethers) are often employed in the aldol reaction because they show higher stereoselectivity than alkali and magnesium enolates. Extensive developmental work in this area has been carried out by Evans, Masamune and Mukaiyama, and their respective coworkers.[14–16,80,81] The correspondence between enolate geometry and aldol stereochemistry is exceptional: (*Z*)-enolates give *syn*/*erythro* aldol products, whereas (*E*)-enolates give *anti*/*threo* aldol products, although with slightly lower selectivity.

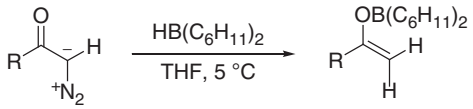
Hooz et al. produced boron enolates by treating α-diazo ketones with substituted boranes. Tri-*n*-butylborane gave almost exclusively the (*E*)-enolate, which could be isomerized quantitatively to the (*Z*)-enolate by a catalytic amount of pyridine or lithium phenoxide (Scheme 24).[82] This method has the disadvantage that only one of the three alkyl groups is utilized. If boranes with different substituents are employed, the question arises as to which substituent has the highest 'migration aptitude'. It was found that the order is aryl > alkyl > Cl (equation 25).[83] A hydride can be transferred, if a dialkylborane is used. Dicyclohexylborane proved to be the most efficient reagent to synthesize regiospecifically a terminal enolate (equation 26).[84] In a similar reaction, boron enolates can be obtained from α-halogen alkali enolates[85,86] and sulfur ylides.[87]



Scheme 24



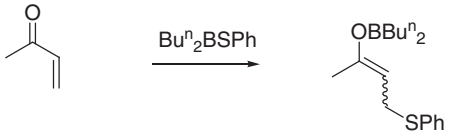
(25)



(26)

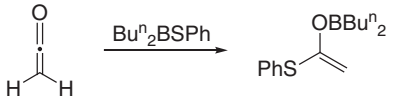
α,β-Unsaturated carbonyl compounds react with boron reagents solely through conjugate addition (equations 27 and 28).[88–90] The enolate stereochemistry, (*E*) or (*Z*), depends on the enone substituents but without useful trends in stereochemical control.[89]

(27)

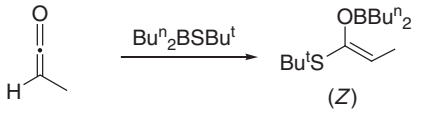


(28)

Boron enolates can be formed with good stereoselectivity by the reaction of ketenes with dibutylthioborinates (equations 29 and 30).[90–92]

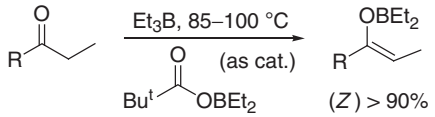


(29)



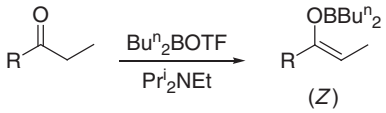
(30)

The most common route to boron enolates uses the method of carbonyl enolization. Köster and coworkers employed triethylborane with diethylboryl pivalate as a catalyst under vigorous conditions, which probably led to the thermodynamic enolates (equation 31).[93,94]

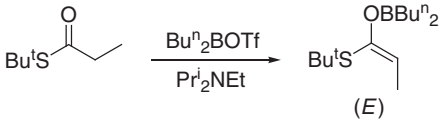


(31)

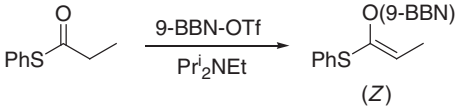
In an important experiment, Mukaiyama and coworkers enolized carbonyl compounds under much milder conditions (low temperatures) with dialkylboryl triflate and a sterically hindered tertiary amine base such as 2,6-lutidine (2,6-dimethylpyridine) or diisopropylethylamine (DPEA).[95–97] Less-hindered bases led to formation of a stable borane-amide complex (Lewis acid-Lewis base) and prevented the reaction with the carbonyl compound. Masamune et al.[98] and Evans et al.[99,100] carried out a study to investigate the reasons for the selective enolate formation. They showed that it depends on the boron ligand, base, solvent and the group attached to the carbonyl moiety. Ketones give (*Z*)-enolates with often excellent selectivity, whereas *t*-butyl thiolates give selectively the (*E*)-enolates (equations 32 and 33).[100,101] Evans suggests that reactions with 9-BBN triflate are often under thermodynamic control.[15] In equation 34, the (*Z*)-enolate could well have arisen by equilibration of the kinetic (*E*)-enolate.[102–104] Recent examples of this type of reaction often employ chiral carbonyl compounds or chiral boranes to get enantioselective aldol products (equations 35 and 36).[105–110]



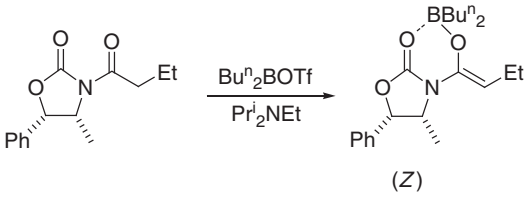
(32)



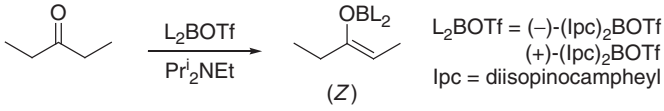
(33)



(34)

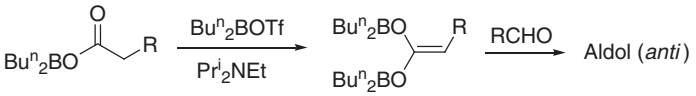


(35)



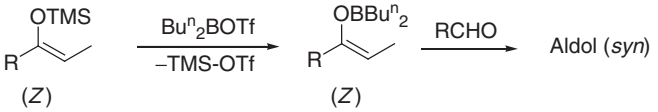
(36)

Simple alkyl esters do not react with boryl triflate reagents, but acyloxyboranes give diborane enediolates under these conditions (**Scheme 25**).[15] These diborane enediolates usually give more *anti*-aldol than *syn*-aldol product. Because aldol geometry depends on enolate geometry, it can be inferred that (*E*)-boron enolates are somewhat more reactive than the (*Z*)-isomers.



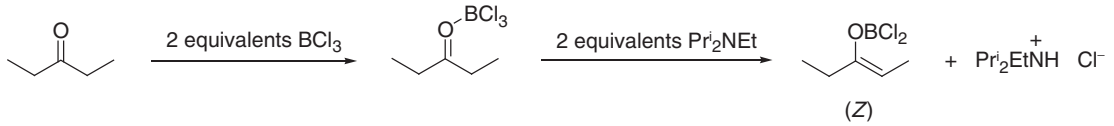
Scheme 25

Trimethylsilyl enol ethers react rapidly with boryl triflate reagents (Scheme 26).[111,112] Subsequent aldol reaction occurs with apparent stereospecificity provided that the by-product trimethylsilyl triflate is removed before the addition of the aldehyde. This seems to be a useful reaction for the synthesis of boron enolates that are not accessible by other methods, but the boryl triflate reagents are ineffective with trimethylsilyl enol ethers of amides and esters.



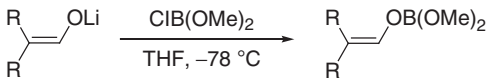
Scheme 26

Trichloroborane reacts with ketones to form a complex. Subsequent addition of DPEA leads to a dichloroboron enolate (Scheme 27).[113] If the trichloroborane and DPEA are added at the same time, direct complex formation will preclude reaction of the ketone.



Scheme 27

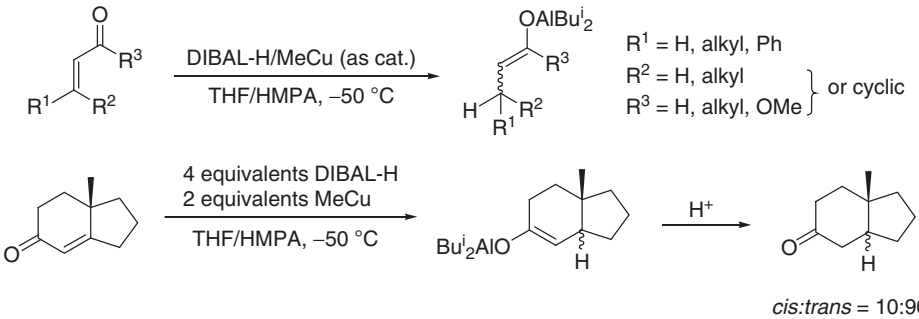
Lithium enolates react with chlorodimethoxyborane to give dimethoxyboron enolates (equation 37).[114]



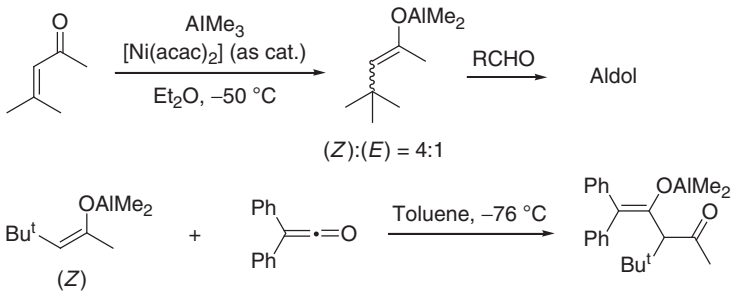
(37)

2.06.5 Aluminum Enolates

Aluminum enolates can be formed by conjugate addition with diisobutylaluminum hydride (DIBAL-H) and a catalytic amount of methylcopper in a mixture of THF and HMPA (Scheme 28).[115–117] The role of copper and HMPA is crucial, for without these 1,2-reduction of the carbonyl group takes place. The effect of copper(I) on conjugate addition is not unexpected. In regard to the solvents it is suggested that HMPA functions not as a cosolvent but as an essential ligand. Treatment of an α,β-unsaturated ketone with trimethylaluminum and a catalyst leads to a dimethylaluminum enolate with moderate (*E*)/(*Z*) selectivity. The (*Z*)-enolate reacts with diphenylketene to give another enolate (Scheme 29).[118,119]

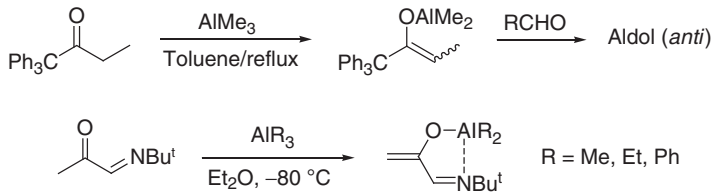


Scheme 28



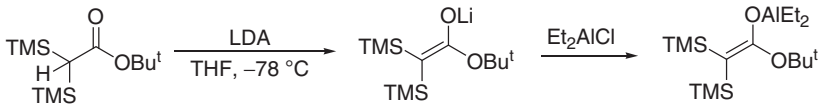
Scheme 29

Another route to aluminum enolates is through the reaction of ketones with a trialkylaluminum, usually trimethylaluminum (Scheme 30).[120,121]



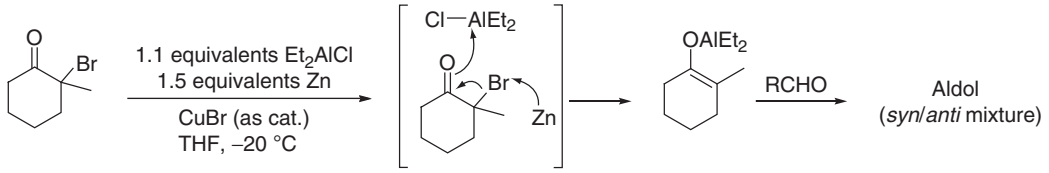
Scheme 30

Aluminum enolates can be obtained also by transmetallation of lithium enolates (Scheme 31).[73]

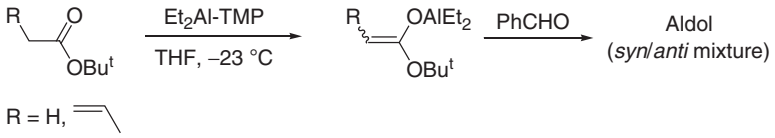


Scheme 31

Diethylaluminum enolates can be produced regiospecifically through reaction of diethylaluminum chloride and zinc dust with α-bromo ketones and esters (Scheme 32).[122] Obviously zinc is involved in this reaction, but the mild conditions are in sharp contrast to the Reformatsky reaction and support the existence of an aluminum enolate in this process. The same type of enolate can be obtained from *t*-butyl acetates and diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP), which is generated *in situ* from diethylaluminum chloride and LITMP (Scheme 33).[123]



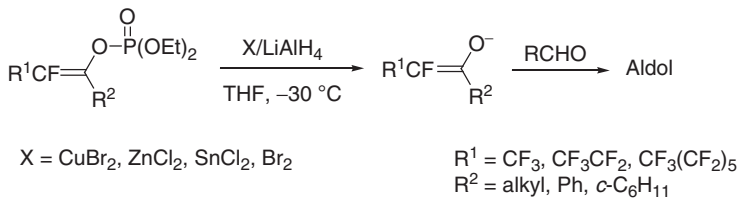
Scheme 32



Scheme 33

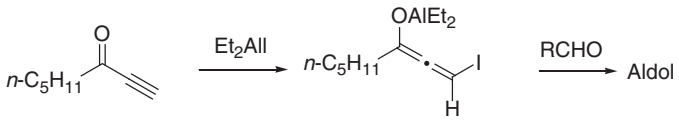
Fluorinated enolates are generally difficult to form. Ishihara and coworkers used fluorovinyl phosphates, which can be prepared from α-fluoro ketones and sodium diethyl phosphite. Reaction of these fluorinated enol phosphates with a reagent prepared from lithium aluminum hydride ($LiAlH_4$) and copper(II) bromide, zinc(II) chloride, tin(II) chloride or bromine afforded the enolate

(Scheme 34).[124] The reaction of the enol phosphate with the reagents mentioned above suggests that the metal cation of the enolate is an aluminum species, though its actual structure is not known at present.



Scheme 34

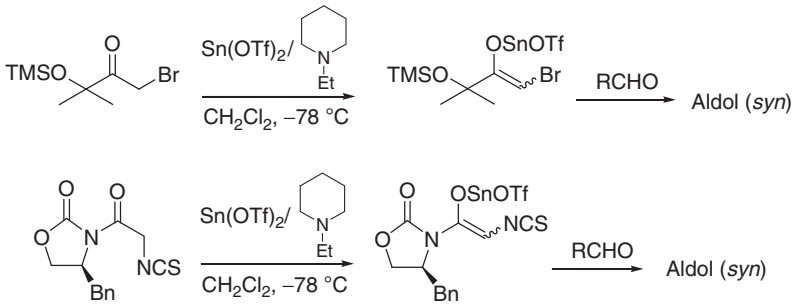
The reaction of α,β-alkynic ketones with diethylaluminum iodide gives allenolates by 1,4-addition (Scheme 35).[125] These intermediates can react with aldehydes to give aldol-type products.



Scheme 35

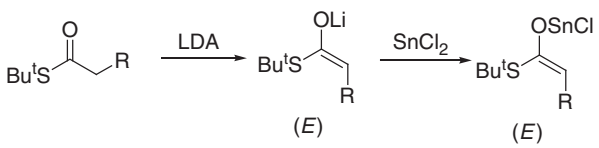
2.06.6 Tin Enolates

Tin(II) enolates can be generated by more than one method.[75,126] The most common is the method of Mukaiyama:[127–141] ketones and amides react with tin(II) triflate and *N*ethylpiperidine in methylene chloride at low temperatures to give tin(II) enolates which can have various substituents in the α-position. These divalent tin enolates have either (*Z*) or unknown configuration and produce predominantly the *syn*/*erythro* aldol products (Scheme 36).[127–136]



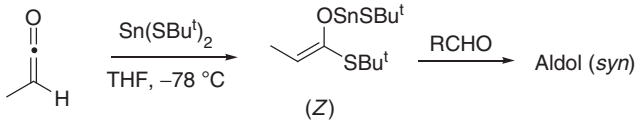
Scheme 36

Another method is the reaction of lithium enolates with tin(II) chloride, tin(II) bromide or tin(II) triflate (Scheme 37).[142,143] During the transmetallation reaction, the geometry of the enolate is believed to be unchanged.[143]



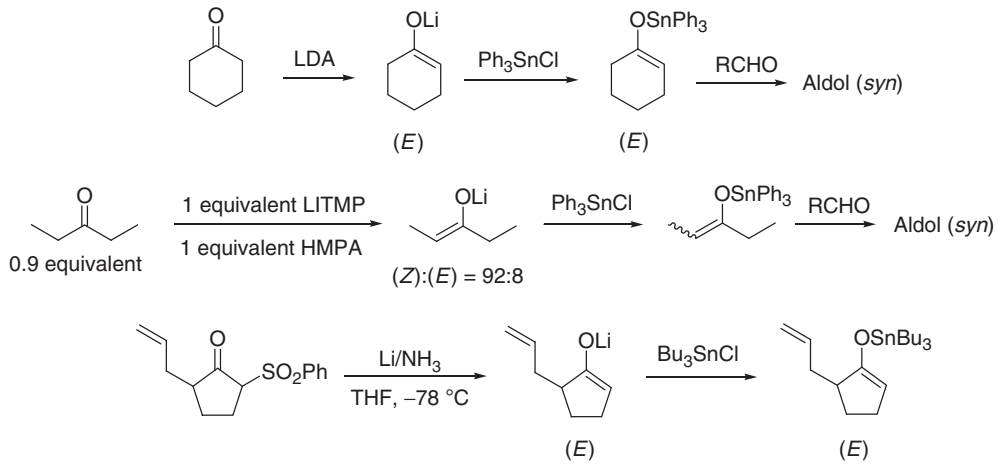
Scheme 37

The reaction of ketenes with tin(II) thiolates gives tin(II) thioester enolates with (*Z*)-configuration (Scheme 38).[144,145]

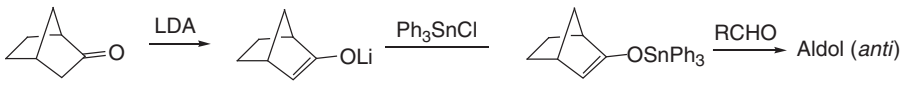


Scheme 38

Tin(IV) enolates are generated by the reaction of lithium enolates with trialkyltin chlorides.[77,136,146,147] The best stereoselectivity in the aldol reaction with tin(IV) enolates has been achieved by employing triphenyltin chloride. *Syn/erythro* aldol products were predominantly produced irrespective of the geometry of the starting enolates (Scheme 39).[146,147] However, the aldol condensation *via* the enolate derived from norbornanone gave the *anti/threo* product predominantly (Scheme 40).[146]



Scheme 39



Scheme 40

2.06.7 Titanium Enolates

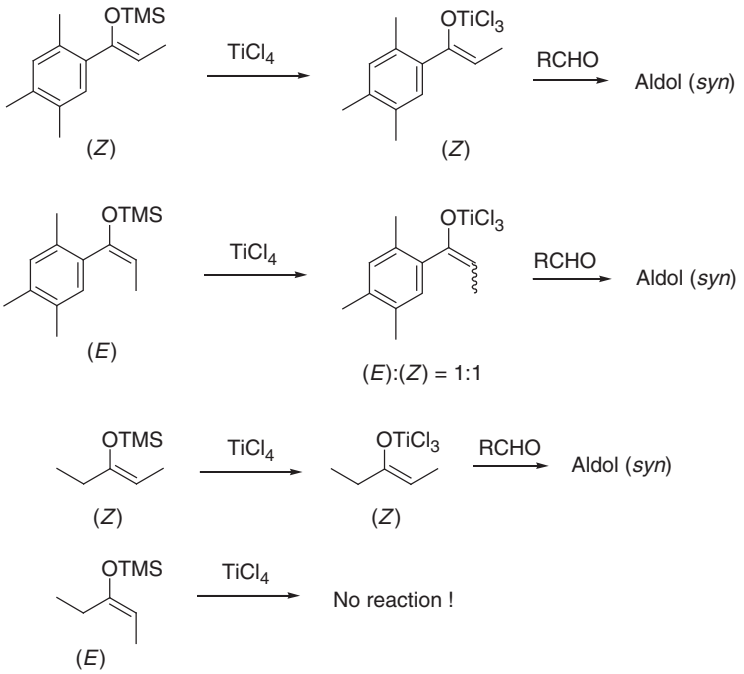
The Mukaiyama version of the aldol reaction is well known:[75] a carbonyl–titanium tetrachloride complex reacts with a trimethylsilyl enol ether. Under these conditions there is *no* titanium enolate involved. Another procedure has been reported:[148–150] a trimethylsilyl enol ether reacts with titanium tetrachloride to give the titanium enolate; addition of the carbonyl compound generates the aldol product (although with slightly lower diastereoselectivity than with Mukaiyama's procedure). (*Z*)-Enolsilanes from acyclic ketones react rapidly and stereospecifically with $TiCl_4$ to form (*Z*)-configured Cl_3Ti enolates, while the (*E*)-isomers react slowly to afford low yields of mixtures of (*E*)- and (*Z*)-Cl_3Ti enolates (Scheme 41).[149]

Another way of generating titanium enolates is the reaction of lithium enolates with titanium salts [$ClTi(OPr^i)_3$;[151–154] $ClTi(NEt_2)_3$;[153] $ClTi(NMe_2)_3$[153]]. The ratio of (*E*)- and (*Z*)-enolate remains unchanged in the exchange process (Scheme 42).

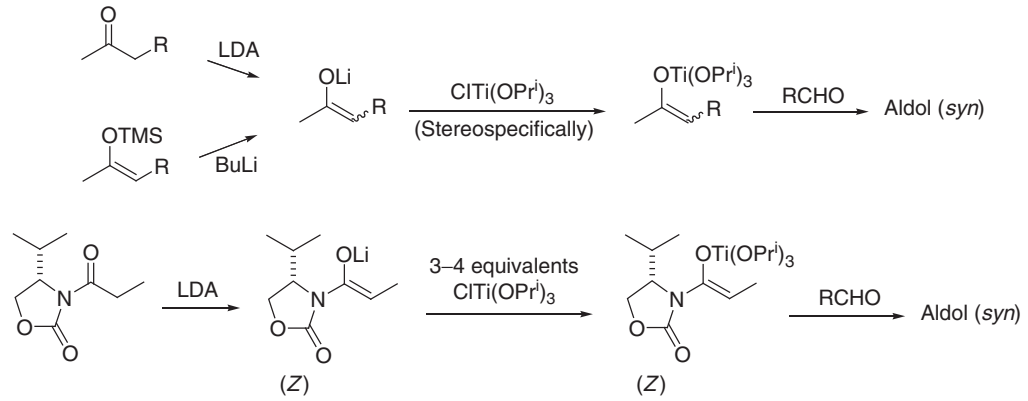
Titanium enolates generated with bis(cyclopentadienyl)titanium dichloride show *anti/threo* selectivity (Scheme 43),[155] although the corresponding zirconium enolates (*vide infra*) react *syn* selectively.

2.06.8 Zirconium Enolates

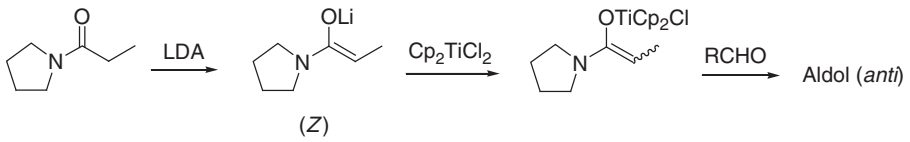
Zirconium enolates are formed by reaction of the corresponding lithium enolates with bis(cyclopentadienyl)zirconium dichloride.[146,156–163] Complete retention of enolate geometry accompanies the metal exchange.[156,157] Both (*E*)- and (*Z*)-zirconium enolates have been shown to undergo selective kinetic aldol condensation to give mainly *syn/erythro* products (Scheme 44).[156–160] Again, the enolate derived from norbornanone provides an exception to the rule (Scheme 45).[146]



Scheme 41



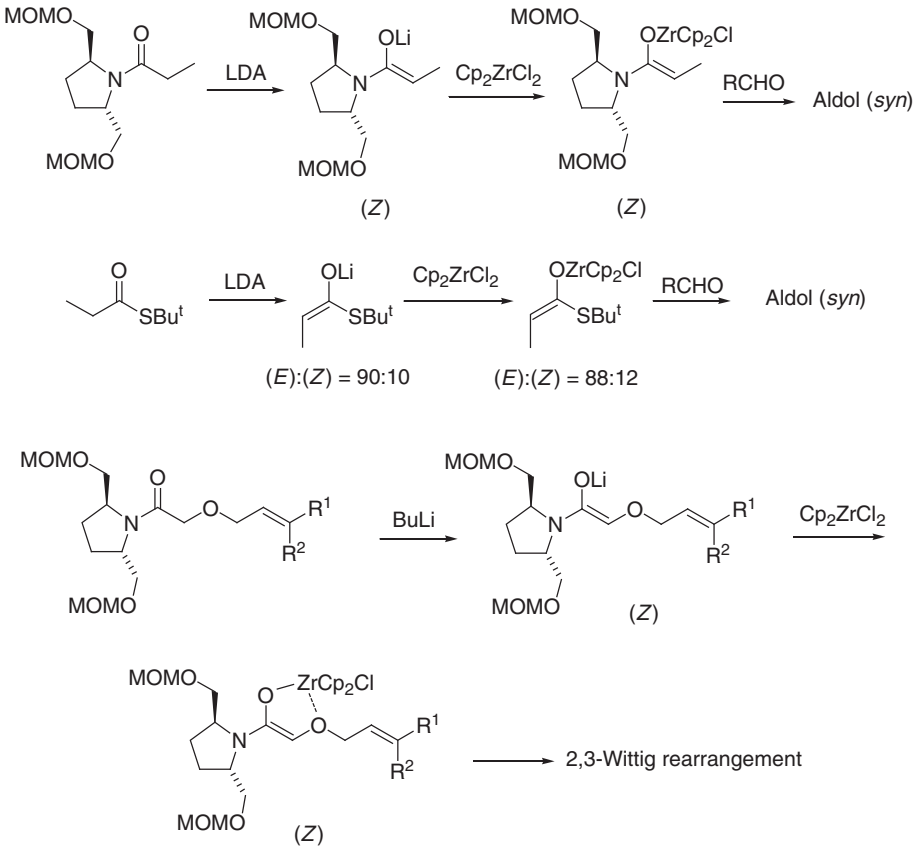
Scheme 42



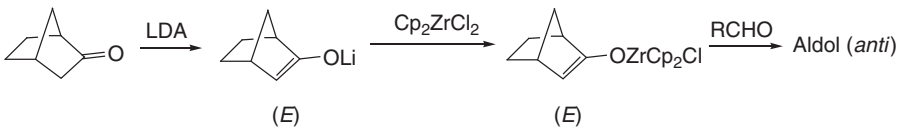
Scheme 43

2.06.9 Copper Enolates and Enolates from Cuprates

Conjugate addition to an α,β-unsaturated carbonyl compound is achieved routinely by using a lithium organocopper reagent or a copper-catalyzed Grignard reaction.[164–168] It should be noted that in many of these examples, and in particular in the case of lithium diorganocuprates, the resultant enolate has properties most consistent with a lithium enolate, and the reactivity of these enolates is unaffected by soluble copper(I) salts.[169] The chemist who desires to generate authentic copper enolates would better

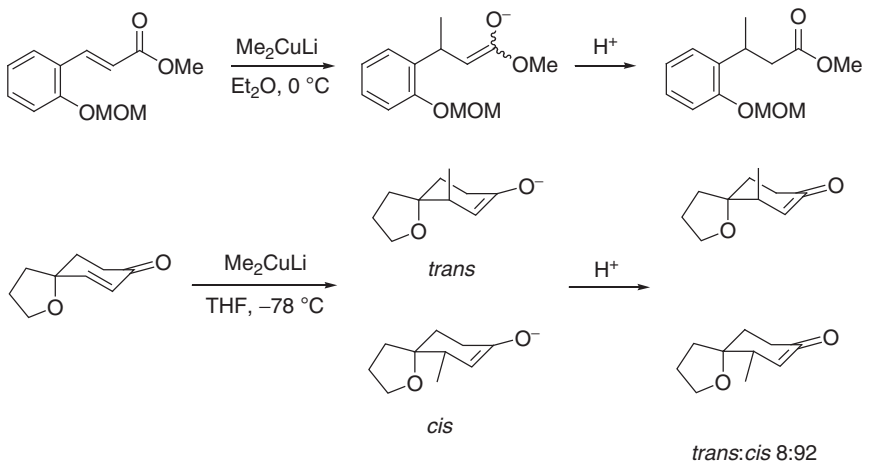


Scheme 44



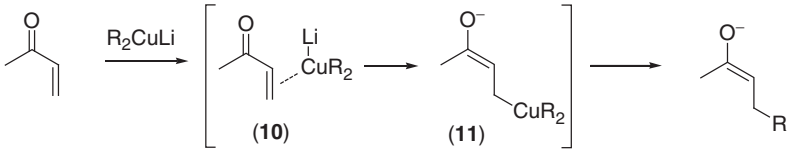
Scheme 45

avoid the use of lithium- or magnesium-ion-containing reagents. In this section, however, some discussion of lithiocuprate reagents is included. The reagent Me_2CuLi is often used (Scheme 46).[170,171] There has been considerable work done to reveal the



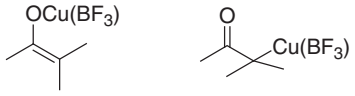
Scheme 46

mechanism of this reaction (Scheme 47). Now it seems to be certain that the first intermediate between the α,β-unsaturated carbonyl and the cuprate is a d,p^*-complex (**10**), and this is followed by a copper(III) β-adduct (**11**).[172–174]



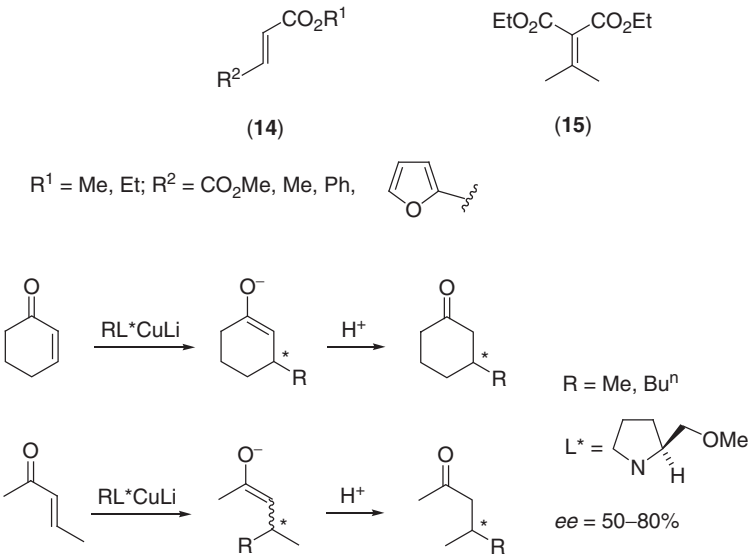
Scheme 47

An authentic copper enolate can be prepared by an alternative route, which involves the conjugate addition of $BuCu(BF_3)$.[175] Experimental results indicate clearly that the intermediate is a copper-bonded enolate (**12**) rather than an α-cupriocarbonyl derivative (**13**).



The addition of lithium diallylcuprate to α,β-unsaturated carbonyl compounds is highly substrate dependent. Good yields can only be obtained with doubly activated esters as shown in (**14**) and (**15**).[176,177]

The importance of the conjugate addition has prompted numerous searches for procedures and methods to effect asymmetric induction.[178–182] One recent example is the use of (*S*)-2-(methoxymethyl)pyrrolidine as a chiral copper ligand (Scheme 48).[181]

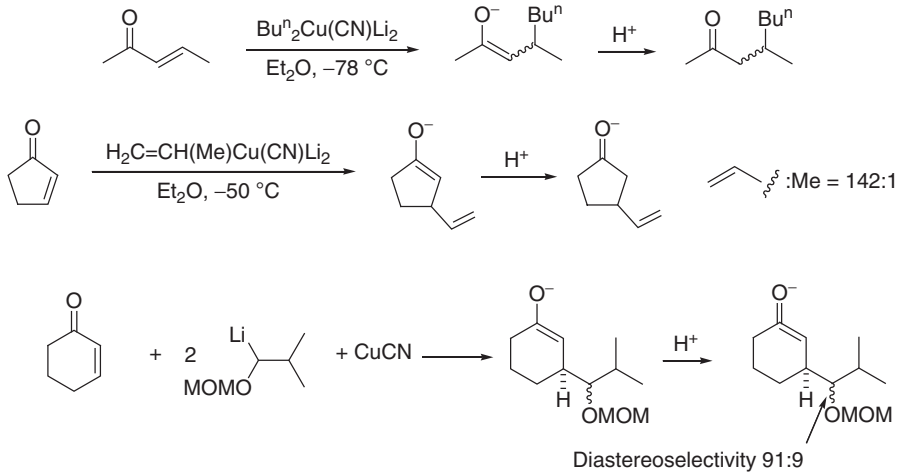


Scheme 48

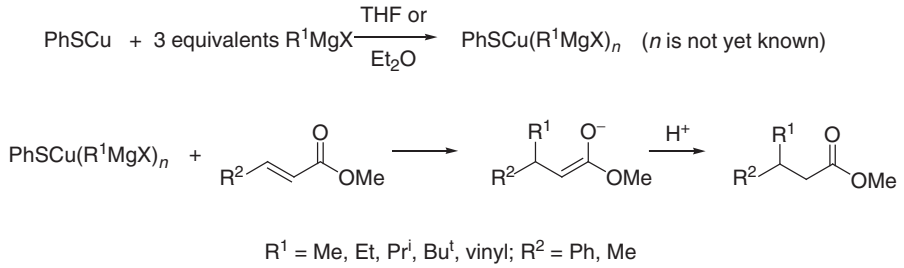
One of the mildest and most efficient reactions for effecting conjugate addition to α,β-unsaturated ketones is the use of the so-called 'mixed higher order cuprates' $R_2Cu(CN)Li_2$ and $RMeCu(CN)Li_2$. The latter have the advantage that 100% of the alkyl groups can be transferred (Scheme 49).[183–186]

The use of the mixed lithium phenylthio(alkyl)cuprates, PhSCuRLi, for conjugate addition to α,β-unsaturated carbonyl compounds is well known.[187,188] The reaction of phenylthiocuprates derived from Grignard reagents with cinnamates and crotonates has also been reported (Scheme 50).[189]

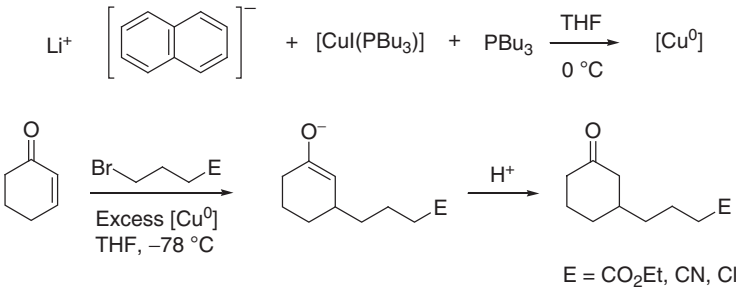
Another method to generate copper enolates through conjugate addition is the use of alkyl bromides and highly reactive zerovalent copper prepared by lithium naphthalide reduction of the CuI-PBu_3 complex (Scheme 51).[190,191] The activated copper



Scheme 49



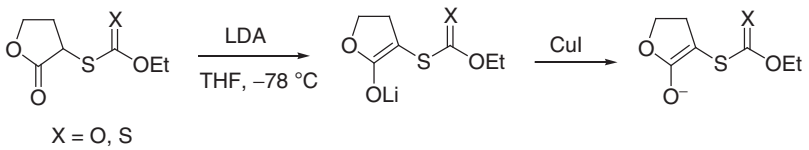
Scheme 50



Scheme 51

inserts directly into the carbon–halogen bond. The exact nature of the active copper and of the subsequent organocopper species is unknown. The advantage of this method is that the alkyl bromides can contain remote ester, nitrile, or chloride functionalities.

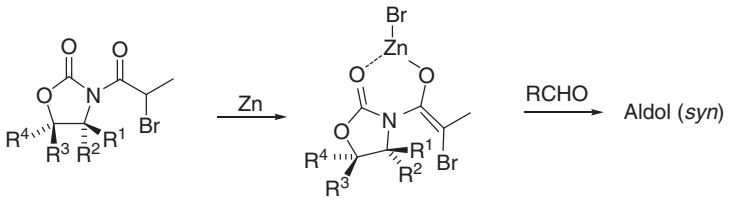
Finally, copper enolates of an α-thio lactone have been generated by the reaction of a lithium enolate with copper iodide (Scheme 52).[77]



Scheme 52

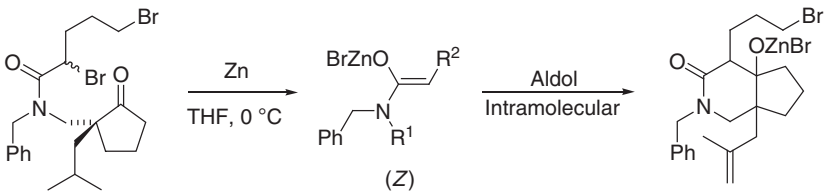
2.06.10 Zinc Enolates

The Reformatsky reaction has been known for over 100 years: α-bromo esters, ketones and amides react with activated zinc dust to give zinc enolates, which can react with carbonyl compounds to give aldol-type products.[192–194] Recent examples include the reactions with sterically crowded oxazolidone derivatives, which give predominantly *syn*-aldol products (Scheme 53),[195,196] and an intramolecular reaction (Scheme 54).[197] A zinc ester enolate has been observed to have a dimeric structure containing both Zn–O and Zn–C bonds.[198,199]



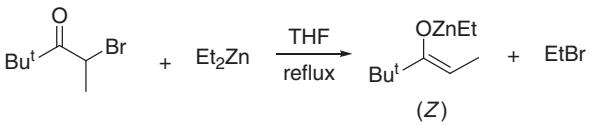
$R^1 = R^2 = Me$; $R^3 = R^4 = H$
$R^1 = R^2 = Bu$; $R^3 = R^4 = -(CH_2)_5-$

Scheme 53



Scheme 54

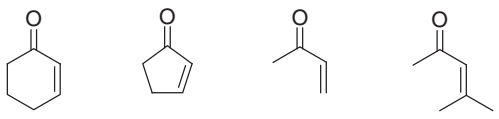
The reaction of α-bromo ketones with diethylzinc leads to an ethylzinc enolate (equation 38).[200]



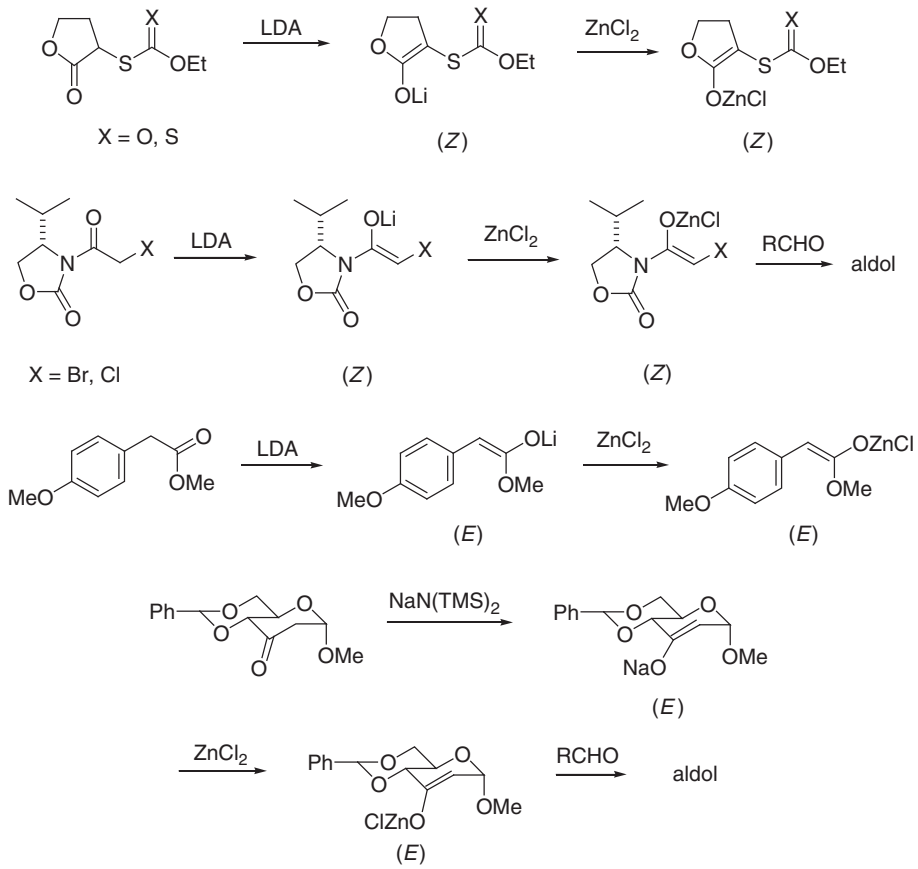
(38)

A common way to generate zinc enolates, introduced by House,[201] is the reaction of (usually) lithium enolates with zinc chloride or zinc bromide (Scheme 55)[77,136,202,203] Boersma's experiments showed that the second chlorine atom could not be replaced with an excess of lithium enolate.[204]

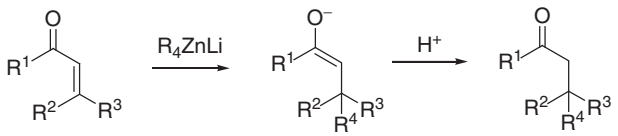
Lithium triorganozincates, R_3ZnLi, are known to effect 1,4-addition of alkyl groups to α,β-unsaturated ketones (Scheme 56).[205–208] They are an attractive alternative to the lithium diorganocuprates because of their solubility and thermal stability. A disadvantage of this method is that only one alkyl ligand can be transferred; the other two are lost. Mixed zincates of the type $R^1R^2_2ZnLi$, where R^2 is methyl, are very effective for circumventing this problem.[209] The R^1 group undergoes efficient 1,4-addition to α,β-unsaturated ketones, but the methyl groups (R^2) remain untransferred. The reactions with ketones (**16**) to (**18**) work well, when the transferring ligand is *n*-butyl or *s*-butyl, but ketones that are disubstituted on the β-carbon (**19**) give no 1,4-adduct. The mixed zincates are generated from methyllithium, zinc chloride and the lithiated transfer group (Scheme 57).[209]



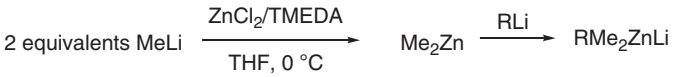
(**16**) (**17**) (**18**) (**19**)



Scheme 55

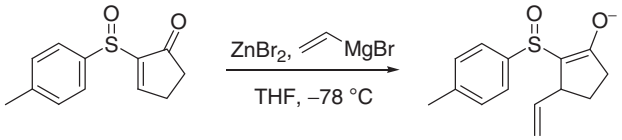


Scheme 56



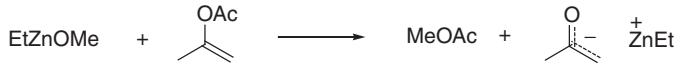
Scheme 57

A similar type of reaction has been conducted with $ZnCl_2$–TMEDA and 3 equivalents of a variety of Grignard reagents.[210] The experiments offer no real evidence for the existence of R_3ZnMgX (X=Cl, Br). The formula 'R_3ZnMgX' denotes only the stoichiometry involved in preparing the solutions used. Reactions of ketones (**16**) to (**18**) with 'R_3ZnMgX' (R=*n*-butyl, isopropyl, phenyl) give excellent yields of 1,4-adduct and usually less than 3% 1,2-adduct. Ketone (**19**) fails to react here too (see above). An example with similar reagents to achieve 1,4-addition is shown in equation 39.[211]



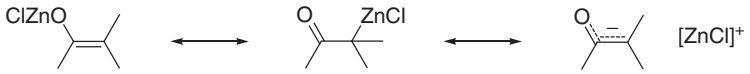
(39)

The exchange reaction between ethylzinc methoxide and enol acetates affords ethylzinc enolates, which decompose by polymerization or by reaction with the methyl acetate produced in the exchange reaction (equation 40).[204]



(40)

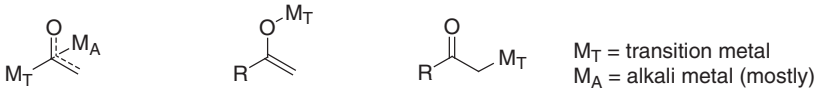
Although zinc ketone enolates are generally considered to exist with an oxygen-bound rather than a carbon-bound metal, there is still some controversy. Boersma assumes that they contain both zinc-carbon and zinc-oxygen bonds (Scheme 58).[204] One indication that they contain only an oxygen-metal bond in solution is that the ^{13}C NMR data for zinc enolates are similar to the data for alkali metal enolates.[200]



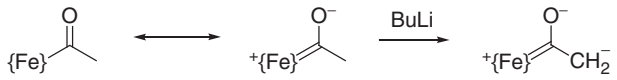
Scheme 58

2.06.11 Other Transition Metal Enolates

Three different types of transition metal enolates are known:[212,213] metallaenolates (**20**); enolates with *O*-bonded (**21**) metals; and enolates with *C*-bonded (**22**) metals.

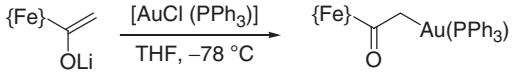


Metal-acyl complexes of iron, cobalt and rhenium have been reported to react with strong bases (BuLi or LDA) to give lithium enolates. Reaction of these enolates with various metal salts generates enolates with different countercations through transmetallation. These enolates are called metallaenolates (**20**). They are somewhat different from the usual enolates:[214–216] (i) they undergo *C*- rather than *O*-silylation; and (ii) very strong bases are needed to generate them, indicating that an ionic resonance form makes a significant contribution to the structure (Scheme 59).



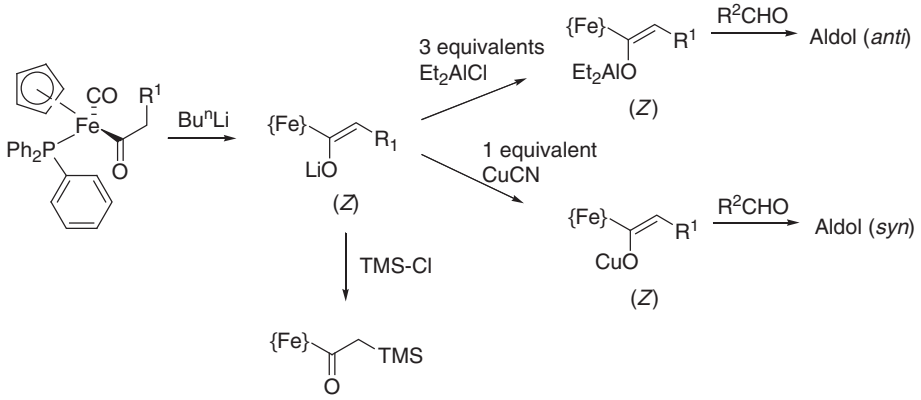
Scheme 59

Enolates of iron–acyl complexes have been studied extensively, especially by Davies and Liebeskind and their respective coworkers. The chiral complex [η^5-CpFe(PPh_3)(CO)$COCH_2R$] is usually used; it can be prepared in racemic or optically active form. The enolate usually has the *anti*-conformation with regard to CO and O^-.[217–223] Copper (*Z*)-enolates give predominantly *syn*-aldols, whereas diethylaluminum (*Z*)-enolates produce *anti*-aldols (Scheme 60).[224,225] If R^1 = H, the terms *syn* and *anti* make no sense anymore, but two diastereomers are distinguishable.[226–228] Bu^i_2A1, ClSn and BrSn enolates produce one diastereomer with good selectivity. A *C*-bonded enolate of an iron–acyl complex can be generated with [AuCl(PPh_3)] (equation 41).[229] Another way to these enolates is the diastereoselective conjugate addition of nucleophiles to chiral *α,β*-unsaturated acyl complexes of [η^5-CpFe(PPh_3)(CO)] (Scheme 61)[230] or the deprotonation of these with Bu^nLi or LDA-HMPA (Scheme 62).[231,232]

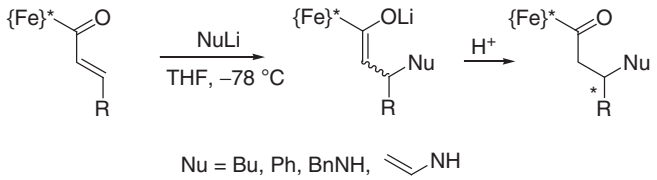


(41)

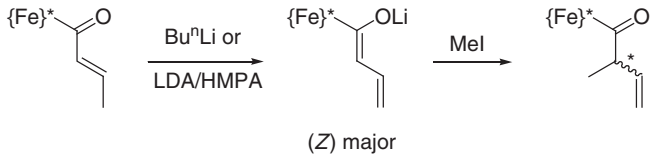
Cyclic cobalt–acyl complexes can be deprotonated, and subsequent reaction of these enolates with aldehydes gives predominantly the *anti*/*threo* product (Scheme 63).[233] Rhenium–acyl complexes can be deprotonated in the same manner. These lithium enolates can be alkylated or can react with [$M(CO)_5$(OTf)] (M = Re, Mn) to give the corresponding enolates (Scheme 64).[234,235]



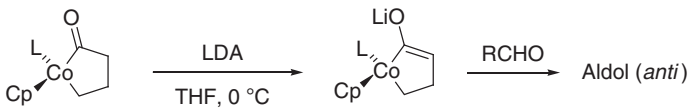
Scheme 60



Scheme 61



Scheme 62



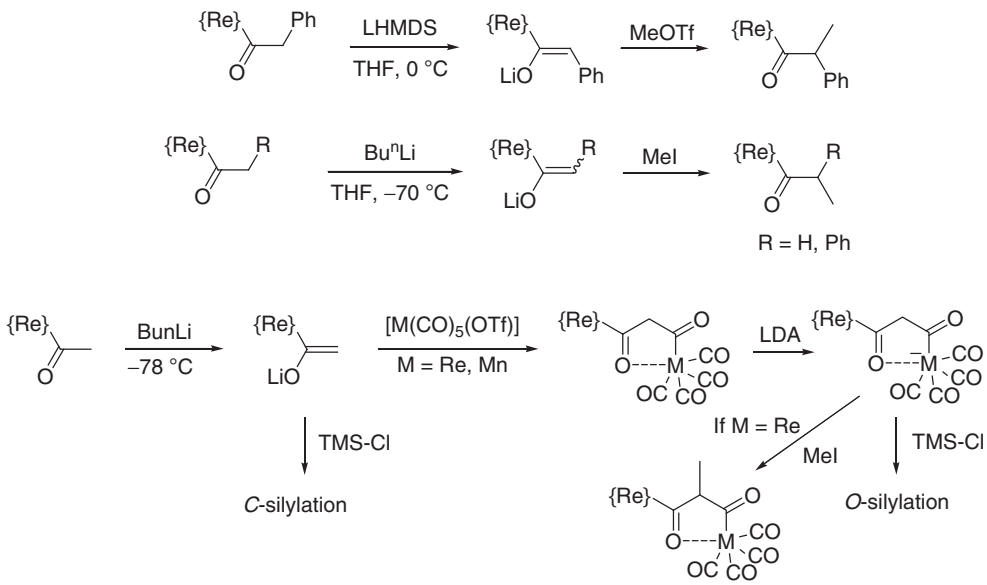
Scheme 63

Many transition metal enolates of type (**21**) or (**22**) are known,[212,213,236] but only a few have shown 'normal enolate behavior', for example, aldol reaction, reaction with alkyl halides, etc. Particularly useful examples have been developed by Molander. In a process analogous to the Reformatsky reaction, an α-bromo ester may be reduced with SmI_2 to provide excellent yields of condensation products (Scheme 65) which are generated through intermediacy of a samarium(III) enolate.[237]

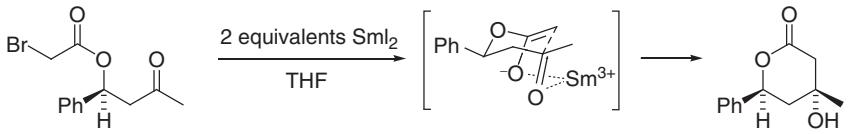
A manganese reagent prepared from RLi or RMgCl and $MnCl_2$ reacts with cyclohexenone in a 1,4-addition (Scheme 66).[238,239] The structure of the reagent is not known and the formula (e.g., 'R_2Mn') is attributed based upon the ratio of the reactants.

Molybdenum and tungsten *C*-enolates can be generated by reaction of complexes with α-chlorocarbonyls (Scheme 67).[212,213] These 2-oxaally 1(η^1-*C*-enolate) complexes react with aldehydes in a photoreaction to produce aldol products, by way of the η^3-enolate.

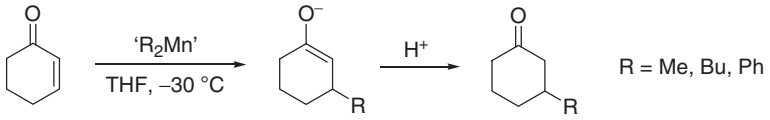
α,β-Epoxysilanes react with molybdenum(II) acetate dimer to give presumably an enolate intermediate, which can subsequently undergo aldol reaction (Scheme 68).[240]



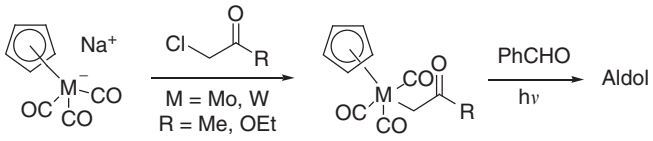
Scheme 64



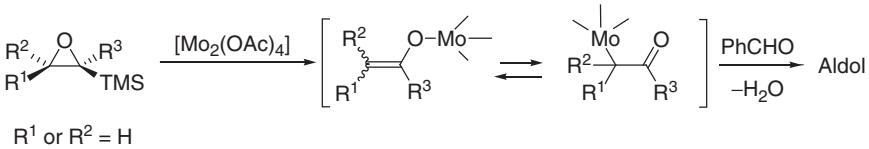
Scheme 65



Scheme 66

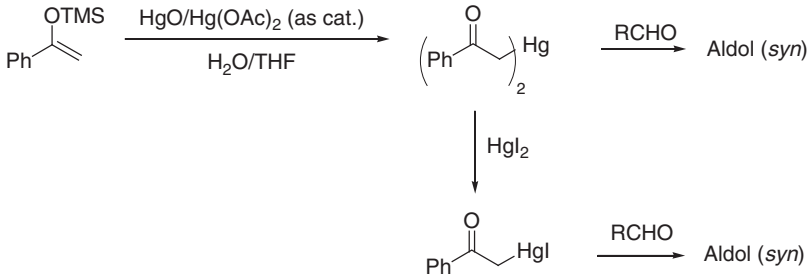


Scheme 67



Scheme 68

α-Mercurio ketones (*C*-bonded enolates) can be generated by the reaction of trimethylsilyl vinyl ethers with mercury(II) oxide, followed sometimes by further reaction with mercury(II) iodide (Scheme 69).[241,242]



Scheme 69

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2.07 The Aldol Reaction: Organocatalysis Approach

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Glossary

Direct aldol reactions Aldol reactions that take place without prior transformation of the carbonyl compound (e.g., aldol reactions using silyl enol ethers as the nucleophilic donor is not a direct aldol reaction).

Enamine An unsaturated compound derived from the reaction of an aldehyde or a ketone with a secondary or primary amine followed by loss of H_2O. Its general chemical formula is $R^1R^2C{=}CR^3NR^4{}_2$. If one of the nitrogen substituents is H, it is tautomerized to form an imine.

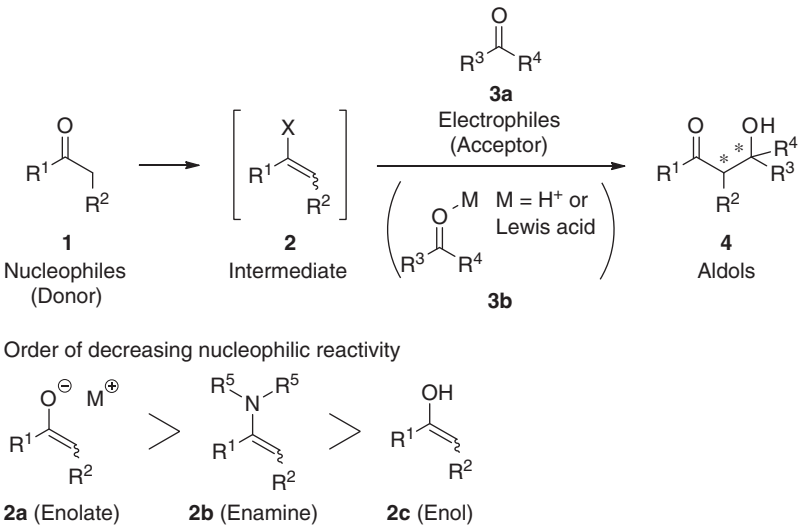
***endo* Aldol reaction** Intramolecular carbon–carbon bond formation is endocyclic to the smallest ring formed.

Enolate A reactive intermediate derived from the loss of a proton from the alpha carbon of a carbonyl group. The general formula is $R^1R^2C{=}CR^3O^-$.

***exo* Aldol reaction** Intramolecular carbon–carbon bond formation is exocyclic to the smallest ring formed.
Iminium intermediate A protonated or substituted imine, the general structure of which is $R^1R^2C{=}N^+R^3R^4$.
Transannular aldol reaction Intramolecular carbon–carbon bond formation in a large monocyclic ring to produce a bicyclic molecule.

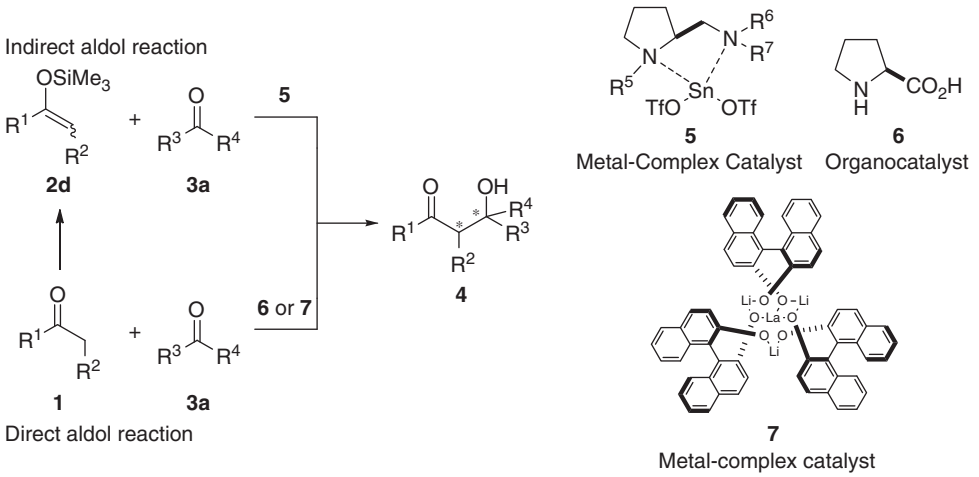
2.07.1 Introduction

Two carbonyl compounds (**1** and **3**) can combine to form *β*-hydroxycarbonyl compounds **4** with two new continuous stereocenters in the aldol reaction, discovered by Kane in 1838[1] and by Wurtz in 1872.[2] This synthetically and historically important breakthrough reaction is among the most fundamental reactions in organic chemistry; in addition, it is also an essential biological process involved in glycolysis, gluconeogenesis, and the Calvin cycle. When the carbonyl compound **1** bearing *α*-hydrogen atoms is treated with base, the nucleophilic enolate **2a** and the electrophilic carbonyl compound **3a** coincidentally exist in the reaction vessel. These two charged species **2a** and **3a** directly form a carbon–carbon bond, affording an aldol **4** through an enolate mechanism. The carbonyl compound **1** is converted to enol **2c** in the presence of acid. This enol intermediate **2c**, which is nucleophilic at the *α*-carbon but less reactive than the enolate **2a**, can attack the protonated reactive carbonyl compound **3b** through an enol mechanism. Another mechanism is called enamine mechanism. Enamine **2b**, which is derived by the reaction of the carbonyl compound **1** with a primary or secondary amine followed by loss of H_2O, reacts with the carbonyl compound **3a** to give aldol **4**. Enamine **2b** is generally more nucleophilic than the enol **2c**, but less nucleophilic than enolate **2a** (Scheme 1).



Scheme 1 Aldol reactions of carbonyl compounds.

As *β*-hydroxycarbonyl units are found in naturally occurring compounds and pharmaceuticals, many researchers have performed an asymmetric aldol reaction with frantic efforts. The Mukaiyama aldol reaction is one of the most successful and practical reactions that is the nucleophilic addition of silyl enol ethers **2d** to the carbonyl compound **3a**, commonly an aldehyde ($R^3{=}H$), catalyzed by Lewis acid such as boron trifluoride or titanium chloride, although previous aldol reactions under basic or acidic conditions have accompanied several undesired side reactions such as self-aldol, cross-aldol, aldol condensation, and double aldol condensation. In 1982, the first catalytic asymmetric version of the Mukaiyama aldol reaction through divalent tin enolates with chiral diamine ligands **5** was achieved, and then many research groups proved this methodology extremely versatile (*see* Chapter 2.09).[3] The Mukaiyama aldol reaction is beyond doubt a brilliant triumph in modern synthetic organic chemistry; however, this reaction includes preactivated silyl enol ethers **2d** derived from the carbonyl compound **1** with stoichiometric silylation agent and base (Scheme 2, indirect aldol reaction). In addition, silylated wastes are inherently formed. A better process would circumvent a preactivation process in point of atom efficiency, that is, the carbonyl compound **1** directly reacts with the carbonyl compound **3a** in the presence of a catalyst. This is generally categorized as 'direct aldol reaction' (Scheme 2). In 1971, intramolecular asymmetric direct aldol reaction of a triketone catalyzed by (*S*)-proline **6** was independently reported by the Hajos group[4,5] at Hoffmann-La Roche, Inc. and the Wiechert group[6,7] at Schering A.-G. (see also Scheme 4). A quarter century later, the Shibasaki group developed a bifunctional metal-complex catalyst **7**, which is type II aldolase mimicking, in the intermolecular direct aldol reaction in 1997.[8] In 2000, the List and Barbas group demonstrated the strategic rediscovery of proline's remarkable ability of type I aldolase mimicking intermolecular organocatalytic direct aldol reaction through the study of aldolase and antibody (see also Scheme 19).[9]



Scheme 2 Indirect and direct aldol reactions.

After these pioneering research on direct aldol reactions, a number of small metal-free organic molecules as organocatalysts in asymmetric bond-forming reactions and domino reactions have been reported.[10–17] Organocatalysts allow for the enantioselective synthesis of molecules that were not readily available by traditional methods. Research in this area has advanced rapidly over the past decade, and the versatility, simplicity, and safety of organocatalytic reactions have been demonstrated. Organocatalytic direct aldol reactions are classified into three activation modes: (1) donor activation, (2) acceptor activation, and (3) bifunctional activation (Figure 1). In donor activation, the carbonyl compounds **1** are converted to nucleophilic enols **8** in the presence of acid, which can then attack the protonated reactive carbonyl electrophiles **3b** through an enol mechanism in Brønsted acid catalysis. The second significant activation mode is called the enamine mechanism. Enamines **9** react with carbonyl electrophiles **3a** in the presence of a primary or secondary amine to give aldol **4**. The third mode of activation is through the enolate mechanism. The nucleophilic enolate **10** is formed by deprotonation of the α-hydrogen atom of a carbonyl compound **1** through Brønsted base catalysis to yield **10a** or in a phase-transfer reaction to yield **10b**. The zwitterionic ammonium enolate **11**, derived from the addition of tertiary amine or phosphine nucleophilic catalysts to a ketene, reacts with an aldehyde in a tandem aldol-lactonization process to give a β-lactone. Another zwitterionic ammonium enolate **12**, derived from the addition of nucleophilic catalyst to the α,β-unsaturated carbonyl compound, can react with carbonyl electrophiles **3**, generally called the Morita–Baylis–Hillman reaction. Acceptor activation **13** through Brønsted acid or hydrogen-bond catalysis is a powerful strategy for carbon–carbon bond formation that is similar to Lewis acid catalysis. The combination of donor and acceptor activation **14** is called bifunctional catalysis; in this mechanism, a single organocatalyst simultaneously activates both the substrates.

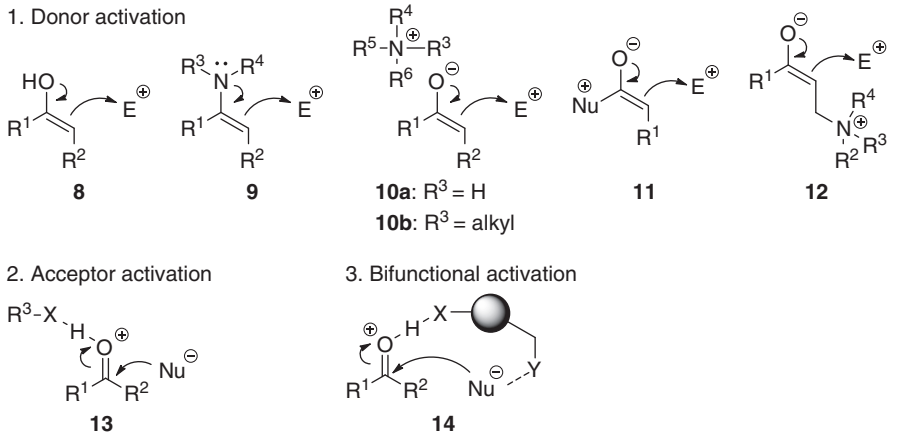


Figure 1 Activation modes and reactive intermediates.

This chapter addresses significant achievements in asymmetric syntheses focused on organocatalytic nucleophilic addition to C=O bonds, namely aldol reactions, covering the literature from 1971 to 2012.[18–24] The description is subdivided based on various classes of catalysis: enamine, Brønsted acid, hydrogen bond, Brønsted base, bifunctional phase transfer, and supported organocatalysis.

2.07.2 Enamine Catalysis

Aldolases are essential, ubiquitous enzymes involved in glycolysis, gluconeogenesis, and the Calvin cycle. They catalyze both carbon–carbon bond formation and cleavage in a stereoselective fashion in the aqueous *in-vivo milieu*. For synthetic chemists, aldolases have become useful tools in modern synthetic organic chemistry, in particular in carbohydrate synthesis; for instance, fructose-1,6-diphosphate aldolase converts D-glyceraldehyde 3-phosphate and dihydroxyacetone phosphate into D-fructose-1,6-diphosphate reversibly *in vitro*.[25–27] Native aldolases are classified into two groups based on the mechanism of nucleophilic activation. Type I aldolases activate nucleophiles through an iminium ion formation step followed by enamine formation (Figure 2, TS-1), whereas type II aldolases activate nucleophiles by forming a zinc enolate (Figure 2, TS-2). Development of a type I aldolase-mimicking antibody catalyst has provided another useful tool in organic chemistry. Aldolase antibodies such as Ab 38C2 and its antipodal antibody siblings catalyze a wide variety of crossed and self-aldol reactions, including intramolecular aldol reactions.[28,29] Type I aldolase-mimicking organocatalysts such as (*S*)-proline **6** (Figure 2, TS-3) were developed through the active research on aldolases and antibodies in 2000.[9,10]

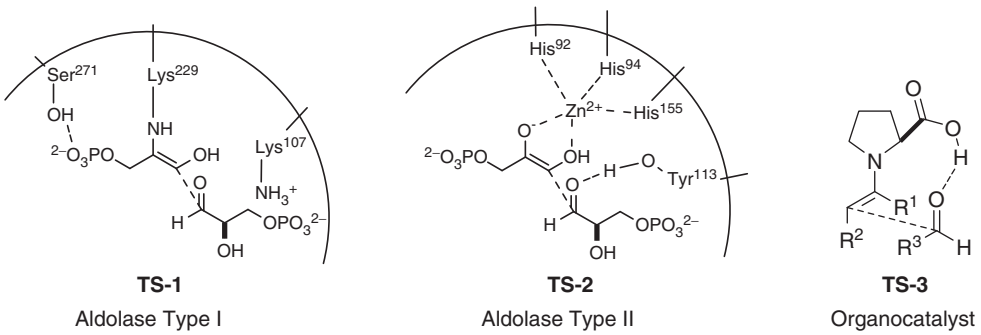


Figure 2 Transition state models of aldol reaction catalyzed by aldolases or (*S*)-proline.

Aldol reaction mechanism using aldolase or antibody is intensively investigated (Figure 3, left).[25–27] Type I aldolases activate their donor substrates **15** by the formation of imine **16** with a strictly conserved active site lysine.[229] The imine **16** to the enamine **17** tautomerization generates the nucleophilic species because of raising the energy of its highest occupied molecular orbital (HOMO). Enamine **17** attacks the appropriate face of the electrophilic aldehyde **18** with high stereoselectivity in the active site. The enzyme-bound imine **19** is then hydrolyzed, releasing the corresponding product **20** and aldolase. Similar to the aldolase, an enamine mechanism is commonly considered in (*S*)-proline-catalyzed direct aldol reaction (Figure 3, right, see also Section 2.07.2.5). The narrow substrate specificity of natural aldolases is vital for life, but not necessarily useful for organic synthesis. Altering the specificity of natural aldolases is relatively difficult and generally requires extensive directed molecular evolution;

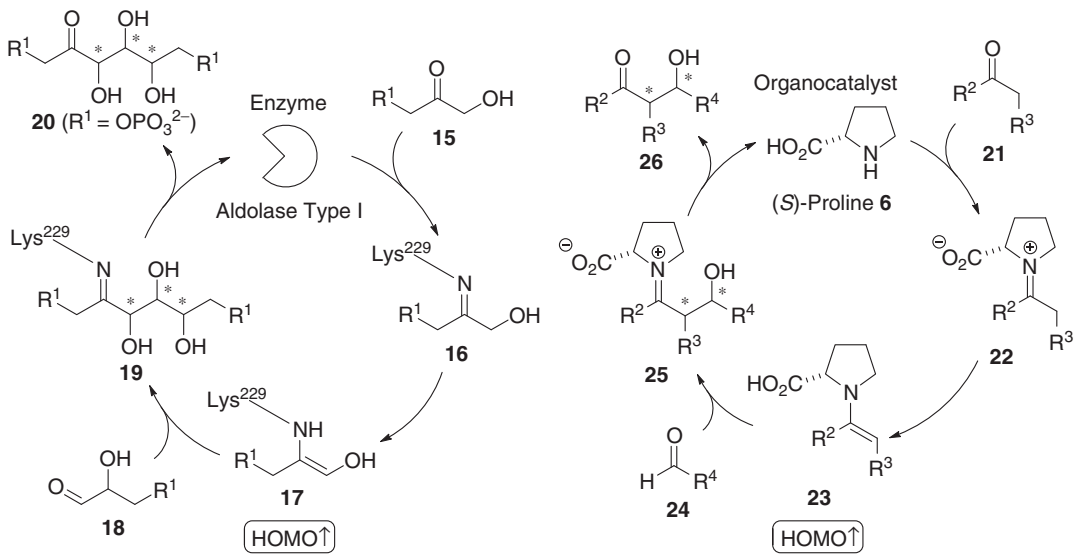
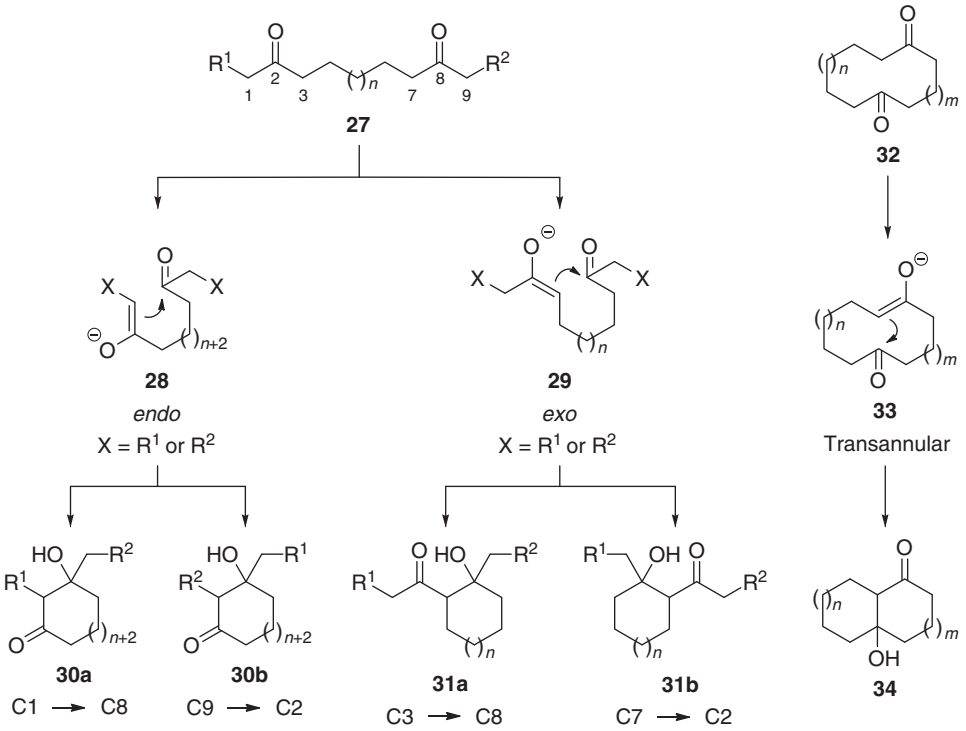


Figure 3 Enamine mechanism of aldol reaction catalyzed by aldolase or (*S*)-proline.

however, it is easy for synthetic chemists to modify a small organic molecule such as (*S*)-proline **6**. Therefore, enamine catalysis based on (*S*)-proline and its derivatives has been rapidly explored to achieve highly efficient and practical organic syntheses.[30]

2.07.2.1 Intramolecular Aldol Reactions in Enamine Catalysis

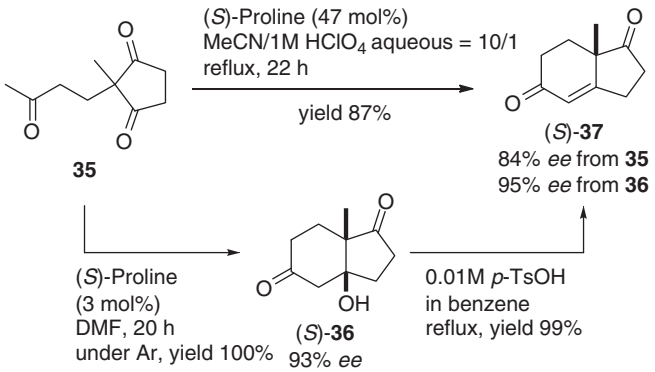
The intramolecular aldol reaction is an often used approach to the synthesis of cyclic compounds, especially, five- and six-membered rings.[31] The two carbonyl components of the substrate intramolecularly react as both electrophiles and nucleophiles; in addition, they form two different nucleophilic intermediates, namely *endo* (**27**→**28**→**30**) and *exo* (**27**→**29**→**31**) aldol reactions (Scheme 3). Another type of intramolecular reaction is the *transannular* aldol reaction (**32**→**33**→**34**) that may be considered *endo* and *exo* simultaneously. Although more than one product may be theoretically formed, excellent chemo-, regio-, and stereoselectivities have been accomplished in enamine catalysis.



Scheme 3 Intramolecular *endo*, *exo*, and *transannular* aldol reactions.

2.07.2.1.1 Cyclization of ketone nucleophiles with ketone electrophiles

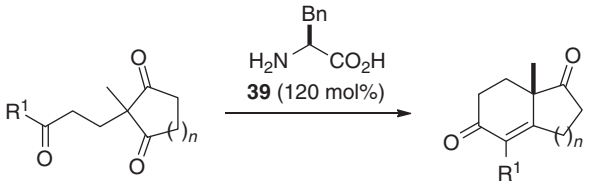
The first example of an organocatalytic asymmetric intramolecular 6-*endo* aldol reaction is the Hajos–Parrish–Eder–Sauer–Wiechert cyclization. In the early 1970s, the Hajos group at Hoffmann-La Roche, Inc.[4,5] and the Wiechert group at Schering A.-G.[6,7] independently reported the enantiogroup-differentiating 6-*endo* aldol reaction of triketone **35** catalyzed by (*S*)-proline (Scheme 4).



Scheme 4 Hajos–Parrish–Eder–Sauer–Wiechert reactions.

Hajos' anhydrous condition in dimethylformamide (DMF) affords the aldol product (*S*)-**36** in 100% yield, subsequent acid-promoted dehydration provided (*S*)-Hajos-Wiechert ketone **37** in 99% yield with 95% *ee*. In contrast, Wiechert's aqueous conditions in aqueous MeCN/1M $HClO_4$ directly produce ketone **37** in 87% yield with 84% *ee* in one-pot operation.

Although the (*S*)-proline-catalyzed intramolecular aldol reaction of triketone **35** proceeds in excellent yield and enantioselectivity, merely introducing an alkyl group or expanding the ring size led to a decrease in both yield and enantioselectivity when employing (*S*)-proline **6**. Thus, both the Hajos and Eder groups used other amino acids to effect this organocatalytic intramolecular aldol reaction, wherein phenylalanine **39** became the amino acid of choice.[4,6]

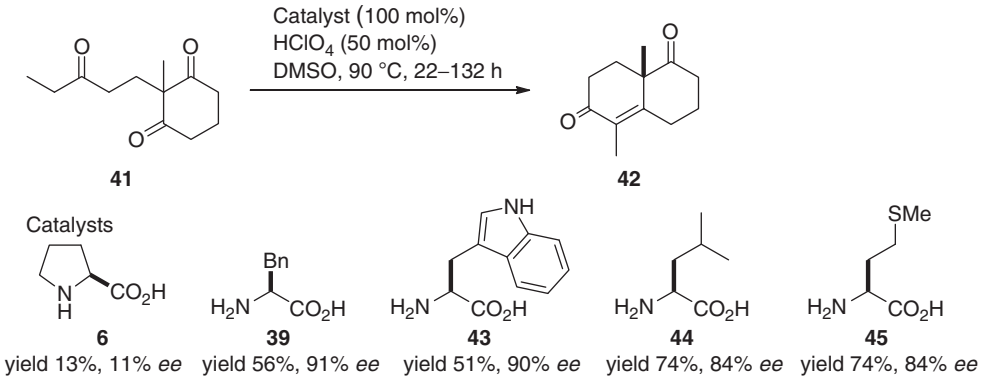


(1)

$n = 2, 3$

R^1 = Me, Et, butenyl oxygenated alkyl

Wieland–Miescher ketone analogs **42** have been synthesized using stoichiometric amounts of α-amino acids under various reaction conditions, as reported by Inomata, Paquette, and coworkers in 2007.[32] Not only phenylalanine **39** but also tryptophan **43**, leucine **44**, and methionine **45** are efficient catalysts for intramolecular aldol reactions (Scheme 5).



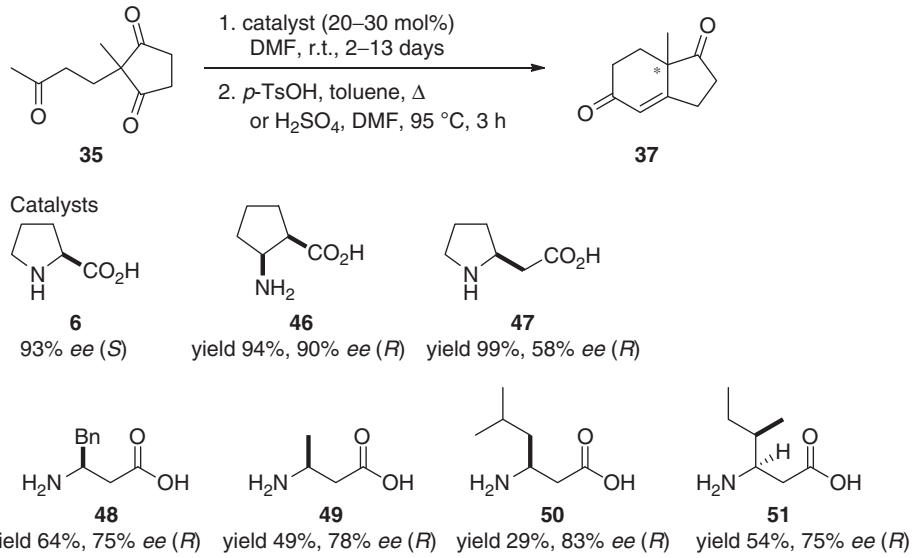
Scheme 5 Synthesis of methylated Wieland–Miescher ketone.

β-Amino acids can be used as catalysts for asymmetric aldol reactions (Scheme 6). When (1*R*,2*S*)-cispentacin **46** (30 mol%) was used as a catalyst for 6-*endo* aldol reactions of triketone **35**, the corresponding bicyclic diketone **37** was obtained in excellent yield with enantioselectivity.[33] The absolute configuration of product **37** is (*R*), whereas (*S*)-isomer **37** is obtained by use of (*S*)-proline **6**. Limbach then reported a study of different β-amino acids as aldol catalysts: β^3-homoproline **47** affords diketone **37** in excellent yields but with low enantioselectivities; however, the use of β-amino acids **48**–**51** bearing aliphatic side chains results in modest yields but with good enantioselectivities.[34]

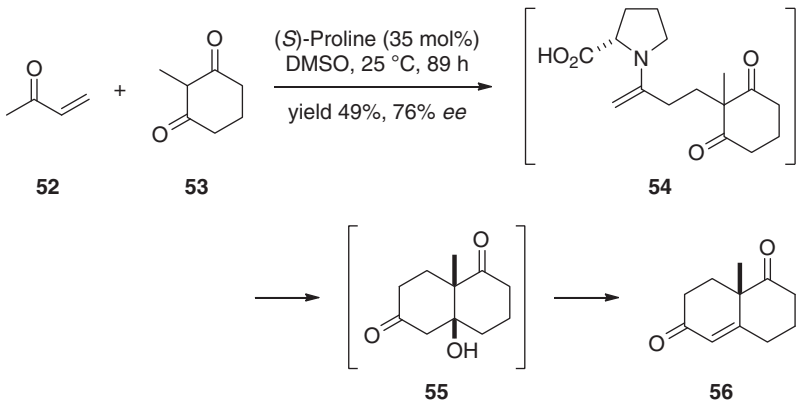
A one-pot domino Michael-aldol reaction of enone **52** and diketone **53** catalyzed by (*S*)-proline gives the Wieland–Miescher ketone **56** reported by the Barbas group (Scheme 7).[35] The iminium-based activation of the Michael acceptor **52** (*see* Chapter 4.03) and the enamine-based activation of triketone **54** are included in the entire Robinson annulation sequence.

Chiral bicyclic diketones such as Hajos–Parrish ketone **37** and Wieland–Miescher ketone **56** are extensively employed for the synthesis of biologically active complex molecules, since Hajos–Parrish–Eder–Sauer–Wiechert intramolecular aldol reaction was reported in 1971. Here, an excellent example of organocatalytic total synthesis of drugs and bioactive natural product is highlighted. Taxol **62** is a highly efficacious anticancer drug used in the treatment of breast, ovarian, lung, bladder, prostate, melanoma, esophageal, as well as other types of solid tumor cancers. Taxol is isolated from the bark of *Taxus brevifolia*, and then many research groups have tried to synthesize this structurally unique molecule through their own strategy. The Danishefsky group employed (*S*)-proline-catalyzed intramolecular aldol reaction on the first step to install all of the stereochemistry required to reach baccatin III and Taxol in a sequential manner (Scheme 8).[36] As enantiopurity of Wieland–Miescher ketone **56** is readily increased by simple recrystallization in large quantity, the concept of the Wieland–Miescher ketone matrix is favorable for taxol synthesis.

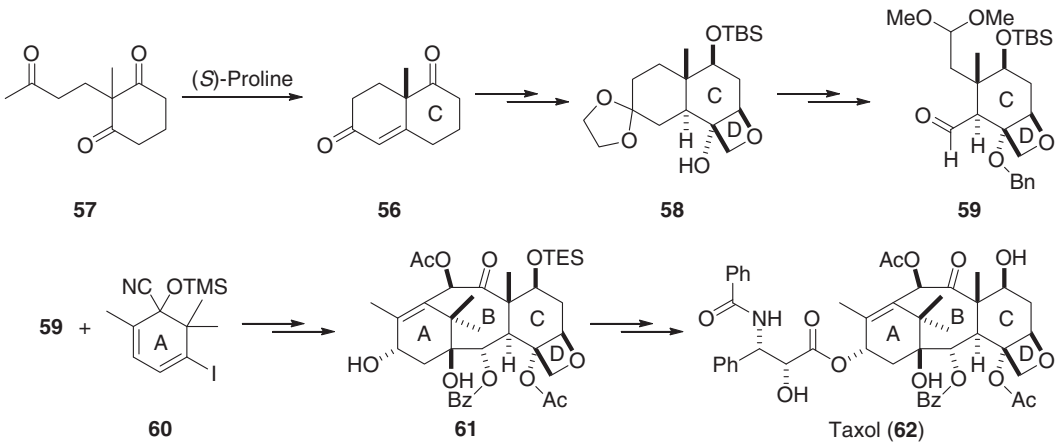
The Agami group reported (*S*)-proline-catalyzed asymmetric 6-*endo* aldol reaction of the prochiral diketone **63** in 1984.[37] Cyclization shows a stereoselective *si*-face attack with moderate enantiomeric excess (equation 2).



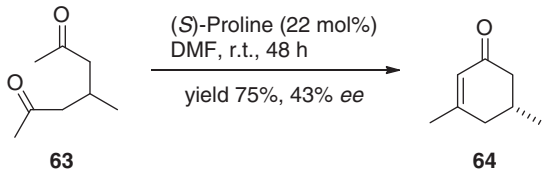
Scheme 6 β-Amino acid-catalyzed intramolecular 6-*endo* aldol reactions.



Scheme 7 One-pot domino Michael-aldol reaction.

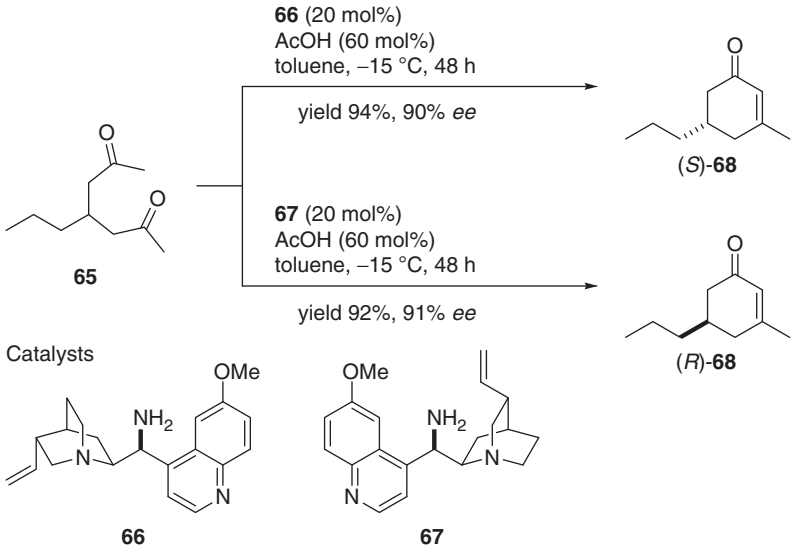


Scheme 8 Taxol synthesis from Wieland–Miescher ketone.



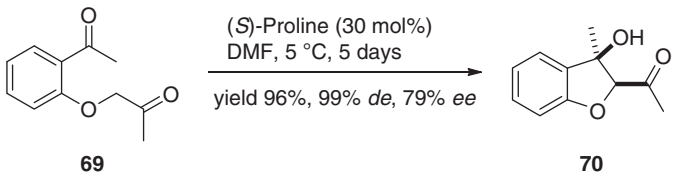
(2)

The enantioselective aldol cyclodehydration of 4-substituted 2,6-heptanediones **65** to cyclohexenones **68** has been a long-term challenge in asymmetric catalysis. In 2008 List and coworkers reported that quinine-derived primary amine **66** in the presence of acetic acid affords cyclic ketone (*S*)-**68** in 94% yield with 90% *ee* in intramolecular 6-*endo* aldol reaction of diketone **65**, whereas (*S*)-proline gives the cyclization product **68** in low yields with moderate *ee*. In addition, the pseudoenantiomeric quinidine-derived primary amine **67** delivers the opposite product, (*R*)-enantiomer **68**, with similar yield and enantioselectivity (Scheme 9).[38]



Scheme 9 Primary amine-catalyzed 6-*endo* aldol reaction of prochiral diketone.

β-Hydroxy ketones bearing tertiary hydroxy functionality are a very important class of compounds in natural product syntheses; however, ketones are generally poor electrophiles. Furthermore, even if the aldol reaction occurs, dehydration products are mainly obtained as above. The Enders group developed 5-*exo* aldol reactions of diketone **69** to synthesize *cis*-selective 3-hydroxy 2,3-dihydrobenzofurans **70** bearing tertiary alcohol (equation 3).[39]

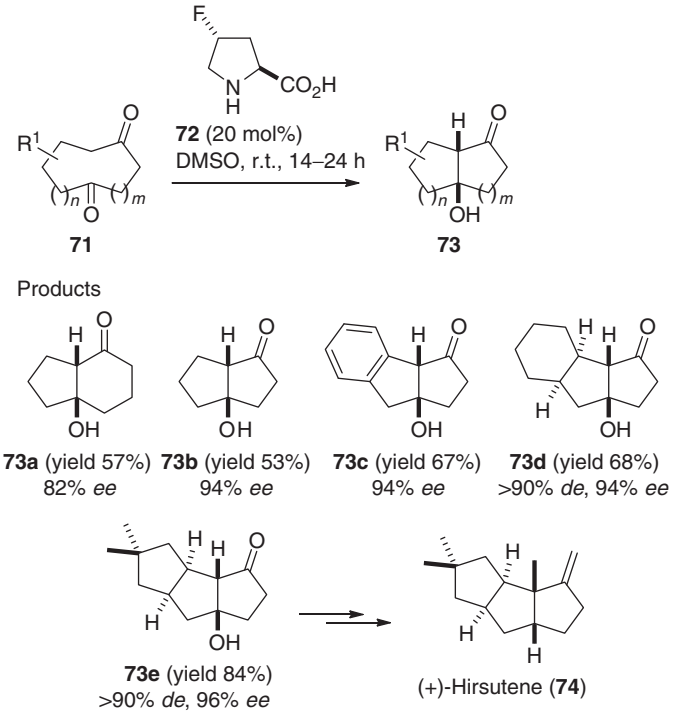


(3)

As intramolecular *transannular* aldol reactions create two new rings and at least two new stereogenic centers in a single process, the corresponding cyclic *β*-hydroxy ketones **73** are useful for the synthesis of polycyclic natural products. The List group reported that *trans*-4-fluoro proline **72** is superior to (*S*)-proline (60% conversion, 54% *ee*) in the catalysis of this type of reaction with excellent diastereoselectivity and enantioselectivity (Scheme 10).[40] The utility of this reaction has been demonstrated in a total synthesis of (+)-hirustene (**74**), which is a fungal metabolite first isolated from basidiomycete *Coriolus consors*.

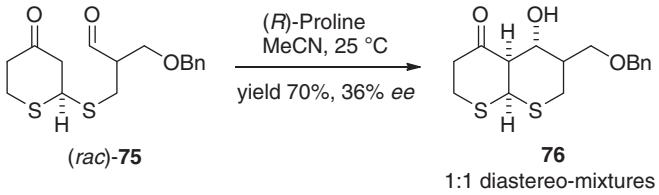
2.07.2.1.2 Cyclization of ketone nucleophiles with aldehyde electrophiles

β-Hydroxy ketone bearing secondary hydroxy group is prepared by aldol reactions of ketone nucleophiles with aldehyde electrophiles. In general, reactive *α*-unsubstituted aldehydes could not act as an efficient electrophile because of side reactions such as a self-aldol reaction; however, in the following reports chemoselectivities between ketone and aldehyde functional groups are efficiently controlled. In 1981, the Woodward group reported (*R*)-proline-mediated intramolecular aldol reaction of the racemic ketone-aldehyde **75** in erythromycin synthesis (equation 4).[41] When the racemic ketone-aldehyde **75** is submitted to



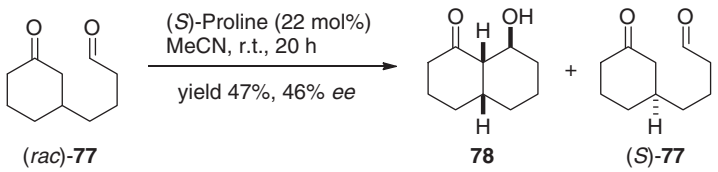
Scheme 10 Intramolecular *transannular* aldol reactions.

intramolecular aldol reaction by use of (*S*)-proline in benzene/MeOH at 25 °C, aldols **76** obtained are virtually racemic. In contrast, the use of (*R*)-proline in CH_3CN at 25 °C leads to a 1:1 mixture of aldols **76** in 70% yield with 36% *ee*.



(4)

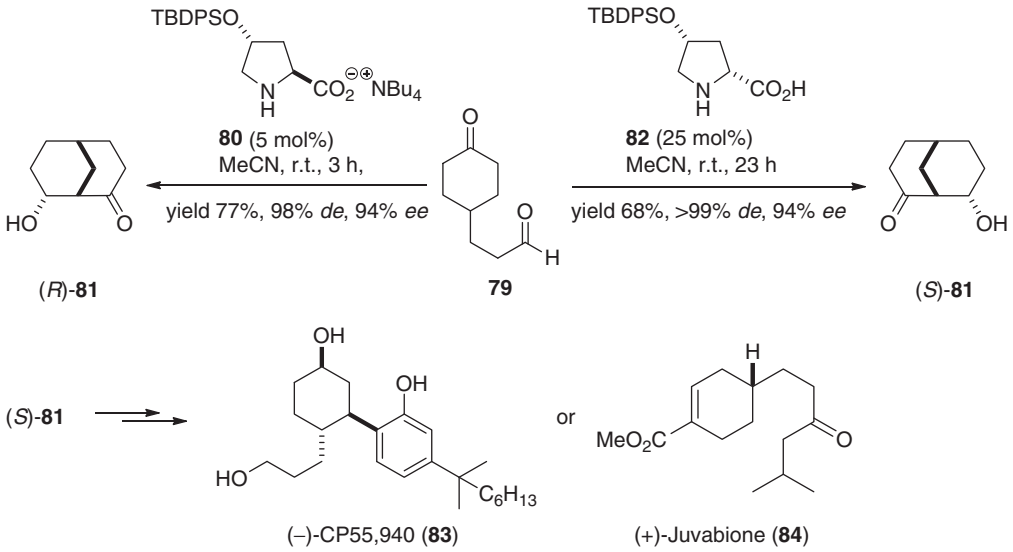
In 1987, the Agami group had demonstrated kinetic resolution of racemic ketone-aldehyde **77** through (*S*)-proline-catalyzed intramolecular 6-*exo* aldol reaction with moderate enantioselectivity (equation 5).[42]



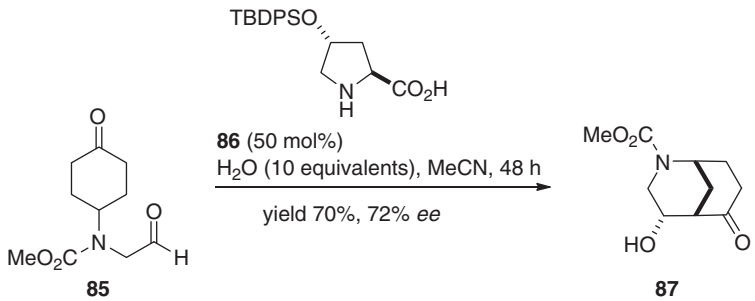
(5)

In 2005, the Iwabuchi group reported an asymmetric intramolecular 6-*exo* aldol reaction of σ-symmetric ketone-aldehyde **79** (Scheme 11). Although (*S*)-proline itself results in moderate stereoselection, *trans*-tetrabutylammonium prolinate **80** affords the corresponding (8*R*)-hydroxybicyclo[3.3.1]nonan-2-one **81** with excellent enantioselectivity at low catalyst loading. Interestingly, opposite enantiopreferences are found in the transformation of **79** to (*S*)-**81** with *cis*-siloxy proline **82**.[43] Enantiopurity of the bicyclic aldol (*S*)-**81** is increased up to 99% *ee* after recrystallization. A stereocontrolled synthesis of (−)-CP55,940 (**83**), a potent cannabinoid receptor agonist, has been attained by employing this organocatalytic asymmetric aldol reaction.[44] Furthermore, (+)-juvabione (**84**), a natural sesquiterpene exhibiting insect juvenile hormone activity, has also been synthesized from the same key compound (*S*)-**81**.[45]

Similarly, the six-membered nitrogen-containing ring of the morphan scaffold **87** is formed by an intramolecular 6-*exo* aldol reaction of the *aza*-ketone-aldehyde **85** in the presence of the siloxy proline **86** carried out by the Diaba and Bonjoch group, though very few methods are currently available to synthesize enantiopure morphans (equation 6).[46]

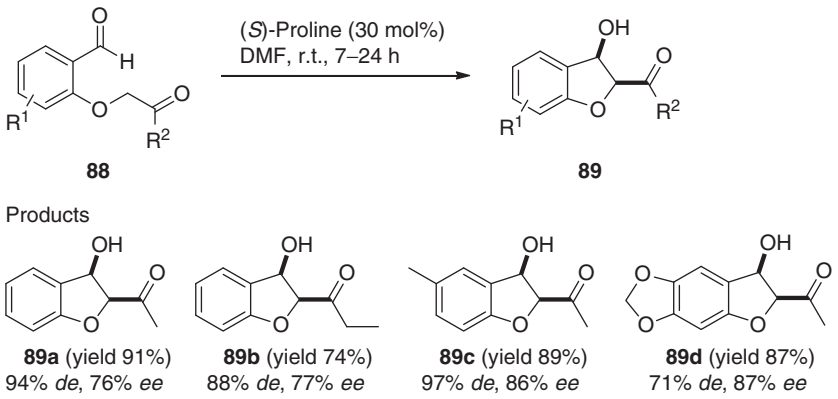


Scheme 11 Intramolecular 6-*exo* aldol reaction of σ-symmetric ketone aldehyde.



(6)

The Enders group has developed (*S*)-proline-catalyzed 5-*exo* aldol reactions of the ketone-aldehyde **88** to synthesize *cis*-selective 3-hydroxy 2,3-dihydrobenzofurans **89** that is a key structure for the synthesis of coumarin natural products (Scheme 12).[39] The diastereo- and enantiopure furans **89** are obtained after simple recrystallization from ethyl acetate/hexane.

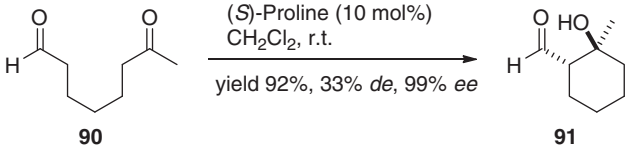


Scheme 12 *cis*-Selective 5-*exo* aldol reactions of ketone aldehyde.

2.07.2.1.3 Cyclization of aldehyde nucleophiles with ketone electrophiles

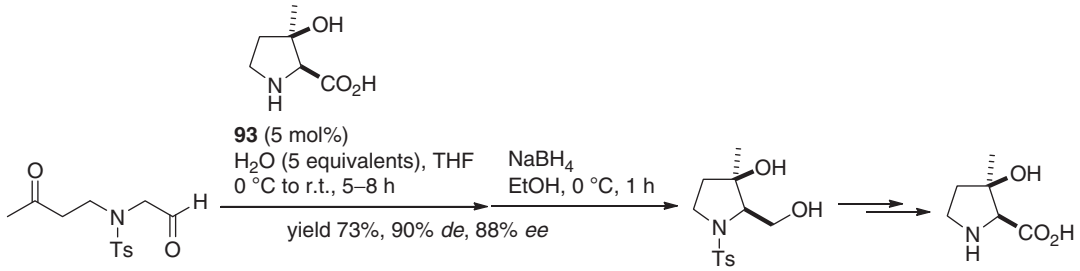
β-Hydroxy aldehydes bearing tertiary hydroxy group are prepared by aldol reactions of aldehyde nucleophiles with ketone electrophiles. Aldehydes are a more reactive electrophile than ketones; especially electrophilicity of unmodified ketones is very low. Thus, there are little reports on this mode of intramolecular aldol reactions. The List group reported (*S*)-proline-catalyzed

asymmetric 6-*exo* aldol reaction of aldehyde–ketone **90**. This process provides the substituted cyclohexane **91** with excellent enantioselectivity (equation 7).[47]



90 **91** (7)

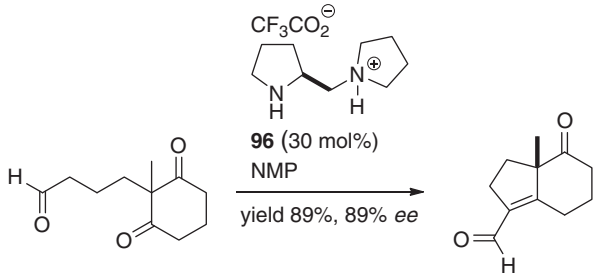
(2*S*,3*R*)-3-Hydroxy-3-methylproline **93** is an efficient catalyst for the 5-*exo* aldol reaction of aldehyde–ketone **92** reported by the Hamada group. One-pot reduction of aldol with $NaBH_4$ affords the *N*-protected pyrrolidine derivative **94**, which is converted to 3-methylproline **93** (Scheme 13).[48]



92 **94** **93**

Scheme 13 Intramolecular 5-*exo* aldol reaction of aldehyde–ketone.

The trifluoroacetic acid salt of 2-(pyrrolidinylmethyl)pyrrolidine **96** is found to be an effective organocatalyst in an asymmetric intramolecular aldol reaction of aldehyde–ketone **95**, affording bicyclo[4.3.0]nonane derivatives **97** with the creation of a quaternary carbon center with high enantioselectivity reported by the Hayashi group (equation 8).[49] In this reaction, the aldehyde and ketone act as nucleophile and electrophile, respectively, a rare reversal of their normal roles.



95 **97** (8)

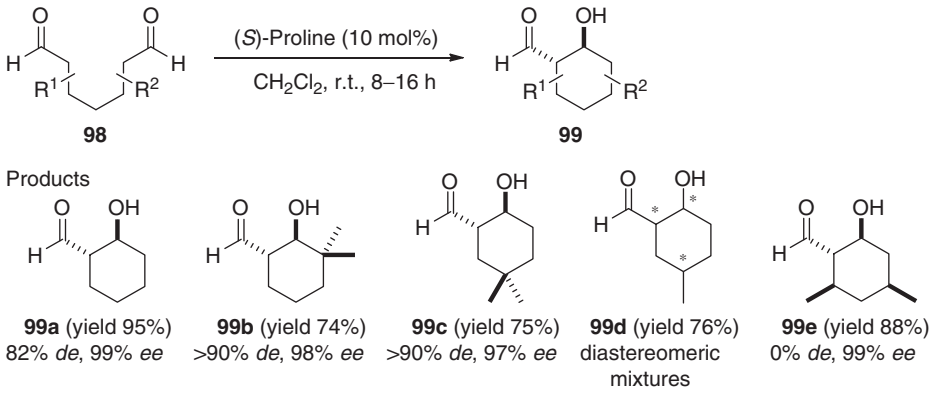
2.07.2.1.4 Cyclization of aldehyde nucleophiles with aldehyde electrophiles

β-Hydroxy aldehyde bearing secondary hydroxy group is prepared by aldol reactions of aldehyde nucleophiles with aldehyde electrophiles. (*S*)-proline-catalyzed asymmetric 6-*exo* aldol reaction of dialdehyde **98** was reported by the List group.[47] The process provides *trans*-substituted cyclohexanes **99a–c** in excellent diastereo- and enantioselectivities, though a single substituent at the 4-position has an unfavorable effect on the stereoselectivity of **99d**. The *meso*-dialdehyde is also a good substrate, giving equal amounts of two expected *anti*-configured aldols **99e** with excellent enantioselectivity in asymmetric desymmetrization (Scheme 14).

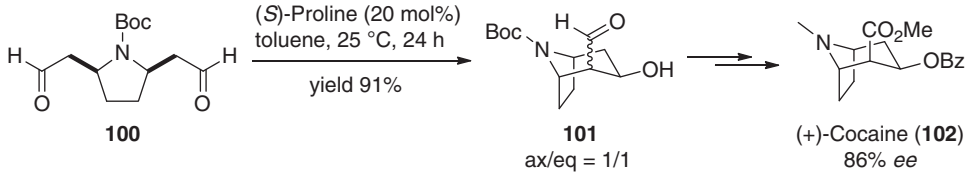
Intramolecular 6-*exo* aldol reaction has been used for the total synthesis of (+)-cocaine (**102**). The Pearson group reported aldol reaction of the *meso*-dialdehyde **100** with (*S*)-proline, giving the tropane ring skeleton **101** directly with good enantiomeric excess. (+)-Cocaine (**102**) is synthesized in 6.5% yield and with 86% *ee* over 14 linear steps starting from commercially available starting materials (Scheme 15).[50]

2.07.2.2 Intermolecular Aldol Reactions in Enamine Catalysis

Two unsymmetrical molecules of an aldehyde or a ketone combine to generate aldols, in which the carbonyl compounds **1** and **103** including *α*-hydrogen atoms form four possible aldols, that is, two self-aldol products (**104a** and **104c**) and two cross-aldol

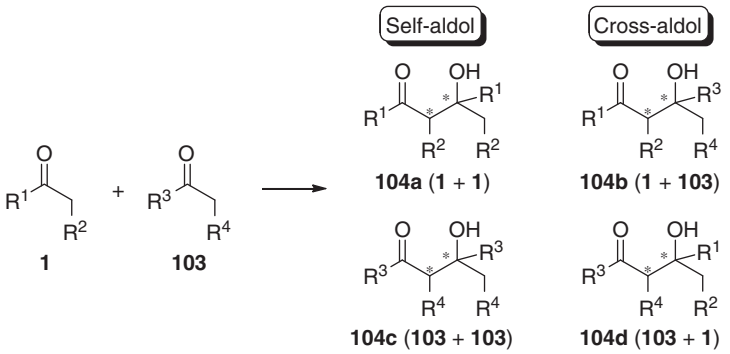


Scheme 14 Intramolecular 6-*exo* aldol reaction of dialdehyde.



Scheme 15 Intramolecular 6-*exo* aldol reaction of dialdehyde for tropane ring skeleton synthesis.

products (**104b** and **104d**) (Scheme 16). When you need a single aldol product, a highly controlled aldol reaction should be designed. A fundamental challenge of chemoselectivity as well as stereoselectivity has been unsolved in intermolecular organocatalytic direct aldol reactions for a long time; however, the List and Barbas group has reported the first intermolecular aldol reaction of a nucleophilic ketone with an electrophilic aldehyde using (*S*)-proline as an organocatalyst in 2000 (see Scheme 19).[9]

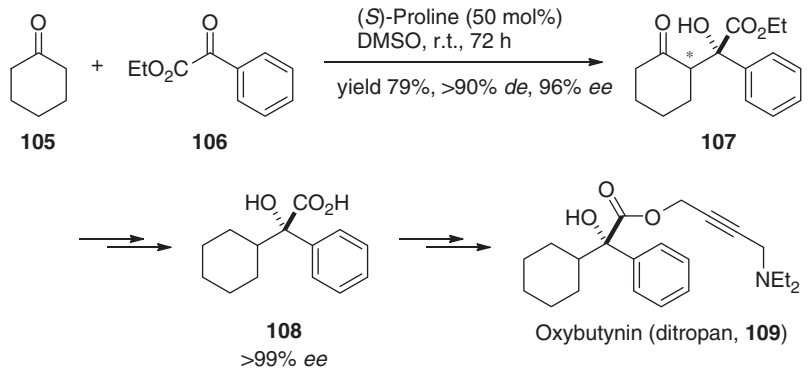


Scheme 16 Intermolecular self- and cross-aldol reactions.

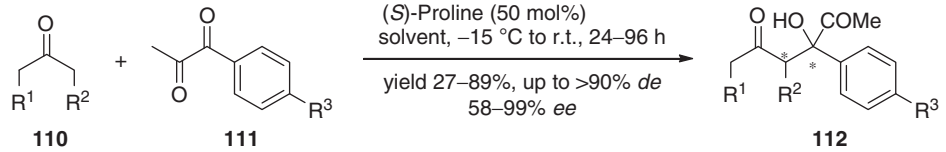
2.07.2.2.1 Ketone nucleophiles with ketone electrophiles

Unmodified ketone is generally a less reactive electrophile; therefore, activated ketones are used in the intermolecular aldol reaction of ketone nucleophiles with ketone electrophiles. The crucial asymmetric tetrasubstituted carbon center of **107** is constructed with excellent stereoselectivity through the (*S*)-proline-catalyzed direct asymmetric aldol reaction between cyclohexanone **105** and ethyl phenylglyoxylate **106** under mild conditions carried out by the Maruoka group. The asymmetric synthesis of the carboxylic acid **108** as a key intermediate for the preparation of chiral (*S*)-oxybutynin (**109**), which is a prescribed muscarinic receptor antagonist, has been achieved (Scheme 17).[51]

Similarly, 1,2-diketones **111** are good electrophiles in aldol reaction, affording the corresponding 2-hydroxy 1,4-diketones **112** with high stereoselectivities reported by the Zhao group. This reaction provides an easy access to optically active tertiary alcohols **112** bearing two carbonyl groups for further transformation (equation 9).[52]

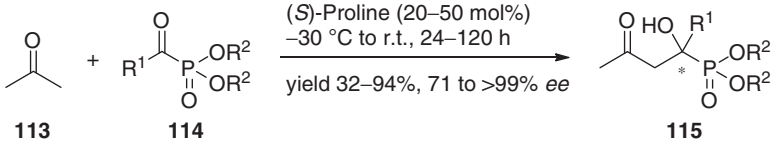


Scheme 17 Intermolecular aldol reaction of cyclohexanone with ethyl phenylglyoxylate.



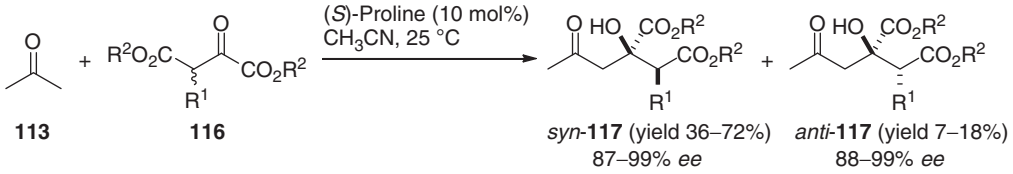
(9)

Although chiral tertiary α-hydroxy phosphonates **115** are potentially important chiral building blocks for the synthesis of bioactive compounds, there is no general method for their synthesis. The Zhao group demonstrated an (*S*)-proline-catalyzed cross-aldol reaction of acetone **113** with α-keto phosphonates **114**. Good yields and high enantiomeric purity up to 99% *ee* are observed (equation 10).[53] In addition, Hu and coworkers have presented the example of introducing primary amino acids into bispidine frameworks to generate catalysts that achieve highly enantioselective direct aldol reactions of α-keto phosphonates and α-ketoesters with acetone or cyclohexanone.[54]



(10)

The dynamic kinetic resolution of 2-oxo-3-arylsuccinates **116** has been achieved through (*S*)-proline-catalyzed aldol reaction of acetone **113** by the Zhang group, providing the desired adduct **117** in up to 72% yield with up to 99% *ee* (equation 11).[55]



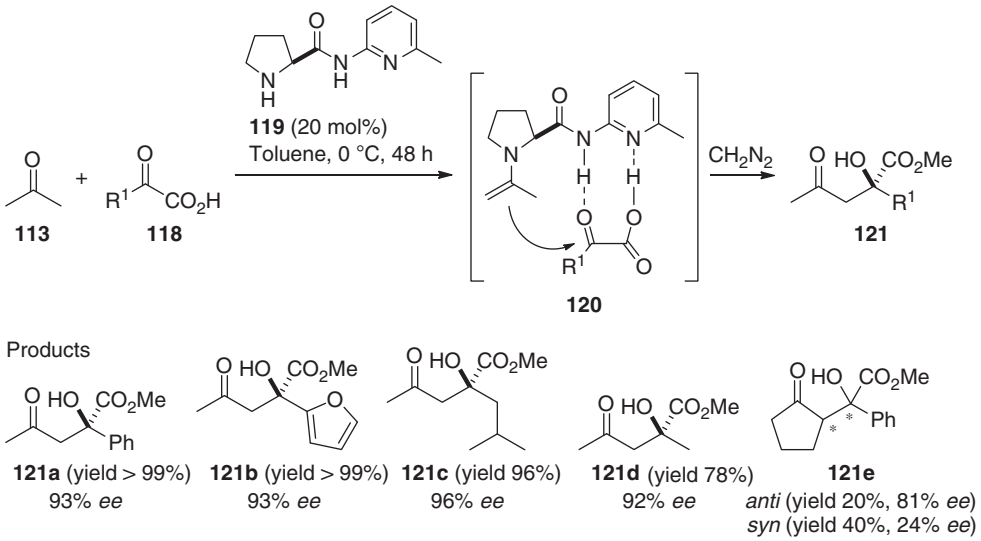
(11)

The Gong group reported interesting study using (*S*)-proline derivatives **119** as an aldolase-type organocatalyst. Prolinamide **119**, which is designed based on molecular recognition, catalyzes the aldol reaction of acetone **113** with aryl and alkyl α-keto acids **118**. The corresponding γ-keto-α-hydroxyl esters **121** with a tertiary stereogenic center are obtained with excellent enantioselectivities. It is easy to separate the acidic aldols (α-hydroxy carboxylic acids) and the basic catalyst **119** from the reaction mixture by an acid–base conversion strategy, and hence, recycling of the catalyst **119** is allowed (**Scheme 18**).[56]

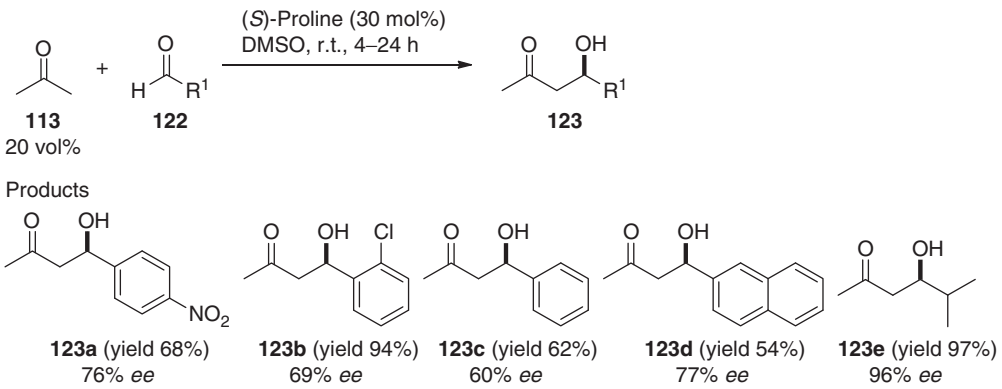
2.07.2.2.2 Ketone nucleophiles with aldehyde electrophiles

2.07.2.2.2.1 Catalyzed by secondary amine derivatives

The first intermolecular aldol reaction of a ketone with an aldehyde using (*S*)-proline was reported by the List and Barbas group in 2000 (**Scheme 19**).[9] The intermolecular aldol reaction of acetone **113** with 4-nitrobenzaldehyde **122** ($R^1 = 4\text{-}NO_2C_6H_4$) in dimethyl sulfoxide (DMSO) at room temperature for 4 h has furnished aldol **123a** in 68% yield with 76% *ee*. The significant by-product is the only α,β-unsaturated ketone formed through aldol or Mannich-type condensation. Aldol products **123** including aromatic as well as aliphatic groups are obtained, especially the reaction of acetone **113** with isobutyraldehyde **122** ($R^1 = i\text{Pr}$) gives aldol **123e** in 97% yield and 96% *ee*. These findings have made outstanding progress in proline chemistry, because it had been



Scheme 18 Aldol reaction of acetone with aryl and alkyl α-keto acids.

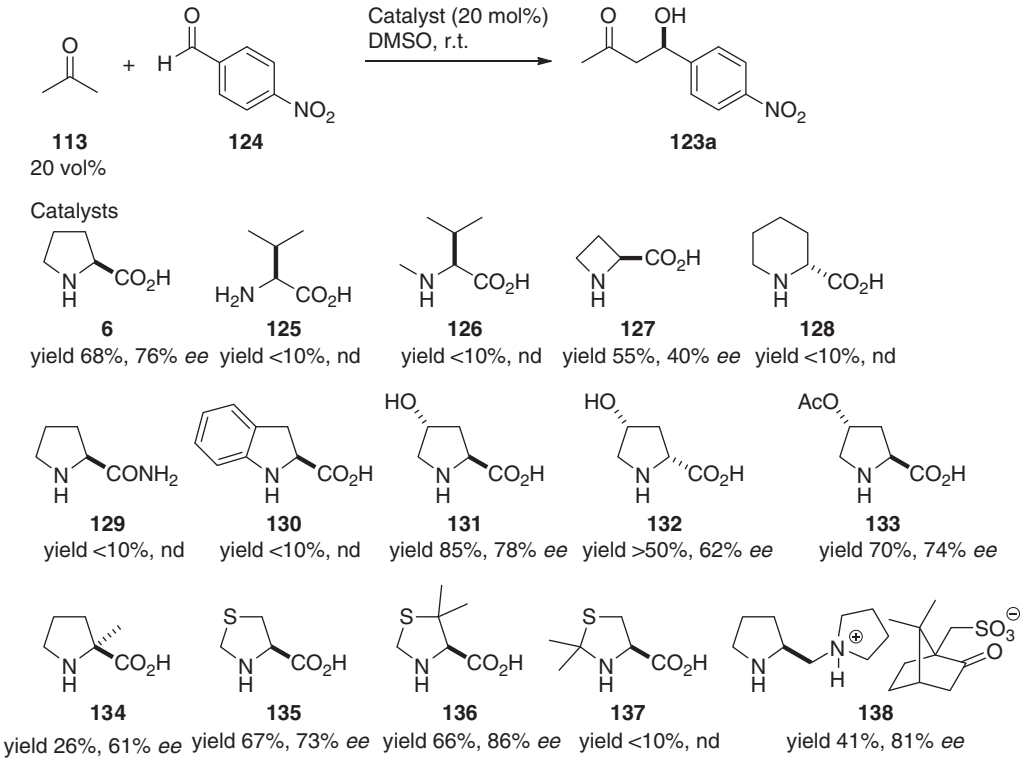


Scheme 19 First (*S*)-proline-catalyzed intermolecular aldol reaction.

known that proline reacts with an aldehyde to give several products such as the oxazolidinone, self-aldol product, and 1,3-dipolar cycloaddition product.

The five-membered pyrrolidine ring and the carboxylic acid moiety are crucial components for high reactivity and stereoselectivity (Scheme 20).[57] Simple natural amino acid such as (*S*)-valine **125** is a poor catalyst for the aldol reaction; in addition, *N*-methyl valine **126** is also ineffective. The size of the ring has significant effects on the reaction; thus, lower reactivities are shown with 2-azetidinecarboxylic acid **127** and pipecolic acid **128** than with (*S*)-proline. An acidic proton in appropriate spatial proximity is essential for efficient catalysis, because 2-pyrrolidine carboxamide **129** does not yield the desired aldol **123a**. Substituents at the 4-position of proline scaffold **131–133** do not significantly affect the reactivity and stereoselectivity; however, substituent at the 2-position **134** provides aldol **123a** in decreased yields. L-Thiaproline **135** shows approximately the same enantioselectivities as (*S*)-proline. Best enantioselectivity is achieved by 5,5-dimethylthiazolidine-4-carboxylic acid **136**; in contrast, 2,2-dimethylthiazolidine-4-carboxylic acid **137** provides the aldol product **123a** in dramatically decreased yields. Similarly, a diamine salt **138** containing ammonium ion as an acid moiety is an effective catalyst as well. Following these findings, aldol reactions using secondary amines, most of which make use of the pyrrolidine moiety, have been studied predominantly.

The initial screening of catalysts reported by Barbas for the asymmetric aldol reaction of acetone with 4-nitrobenzaldehyde illustrates the effect of a number of different modifications of the proline structure. However, there was still space for improvement, regarding yield, enantioselectivity, generality, and catalyst loading. Many catalysts have since been developed based on the structure of proline (Figure 4). For instance, 4-siloxyprolines **139**,[58–60] prolinamides **140**,[61] ethanolamine derivatives **141**,[62] sulfonamide derivatives **142**,[63,64] diamine catalyst **143**,[49,65,66] tetrazole derivative **144**,[67–70] and diarylprolinol **145**[71–74] have been reported. Some common modifications to the proline structure involve increasing the hydrophobicity to improve its solubility in organic solvents and replacing the carboxylic acid with a variety of other hydrogen-bonding groups. Small peptides and their derivatives have also been evaluated as alternative catalysts for direct catalytic asymmetric aldol reactions.[75–77]



Scheme 20 Catalyst screening in intermolecular aldol reaction.

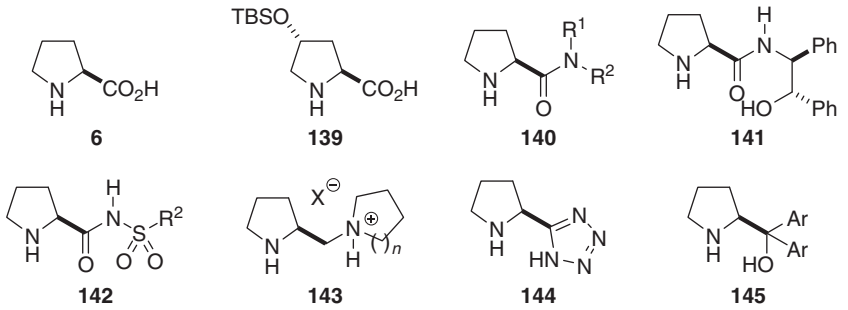
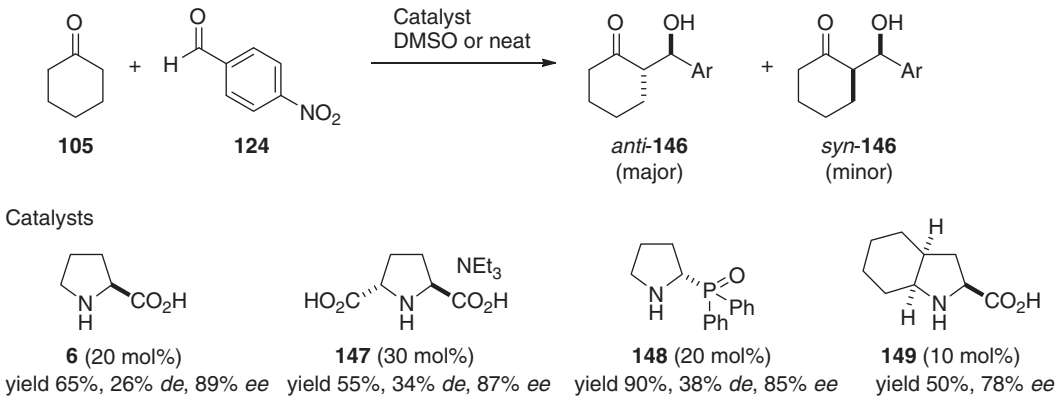


Figure 4 Organocatalysts derived from proline or hydroxyproline.

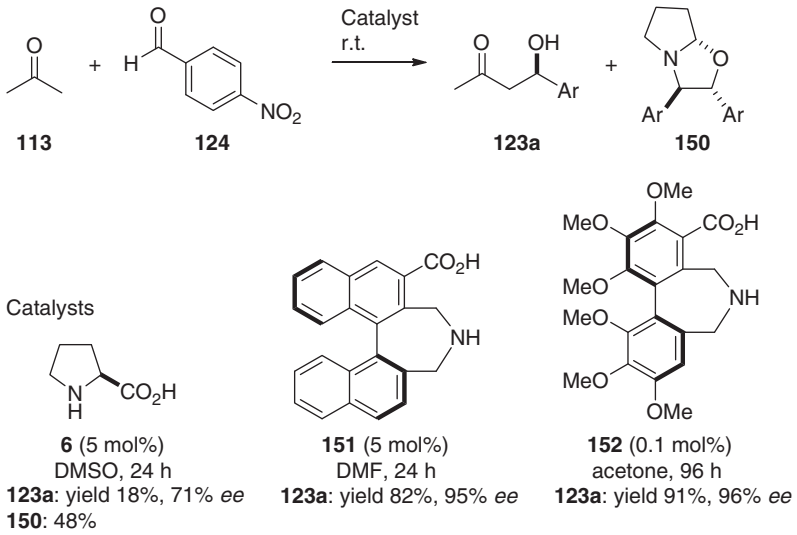
Secondary amine catalysts having pyrrolidine units that are not derived from proline exist in the literature (Scheme 21). The C_2-symmetric (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid (**147**, 30 mol%) has been used as a combination with triethylamine (30 mol%) in the intermolecular aldol reaction to afford the aldol product **146** in good yields and moderate enantioselectivities.[78] Phosphinyl oxide pyrrolidine **148** has also been reported to afford the desired aldol adduct **146** in 90% yield and in 85% *ee*.[79] Moderate yields have been obtained in aldol reactions catalyzed by (*S*,*S*,*S*)-perhydroindolic acid **149**, with the best enantioselectivities being obtained for aromatic aldehydes possessing electron-withdrawing groups.[80]

Secondary amine catalysts that do not contain pyrrolidine units also exist in the literature. Maruoka and coworkers have found that the binaphthyl-based amino acid **151** is an efficient catalyst for direct asymmetric aldol reaction of acetone **113** with the aldehydes (Scheme 22).[81,82] With 5 mol% of catalyst **151**, adduct **123a** was obtained in good yield and enantioselectivity (82%, 95% *ee*). The same reaction with (*S*)-proline **6** gave the desired aldol product **123a** in low yield with moderate enantioselectivity, as well as a side product, 1,3-oxazolidine **150** (48% yield based on proline), which is derived from (*S*)-proline itself and two equivalents of 4-nitrobenzaldehyde **124**. However, the formation of such a by-product was not observed with catalyst **151** because of its structural stability. They also designed a biphenyl-based amino acid of type **152**, which is highly substituted with electron-donating methoxy groups, with the expectation of the increasing nucleophilicity of the amino moiety. In the case of catalyst **152**, the catalyst loading could be decreased to only 0.1 mol% in acetone without loss of yield or enantioselectivity.[83]

It is always required to allow for the formation of self-aldol products as a by-product, when α-unsubstituted aldehydes **153** are used as a substrate. The List group has demonstrated the (*S*)-proline-catalyzed cross-aldol reaction of acetone **113** with

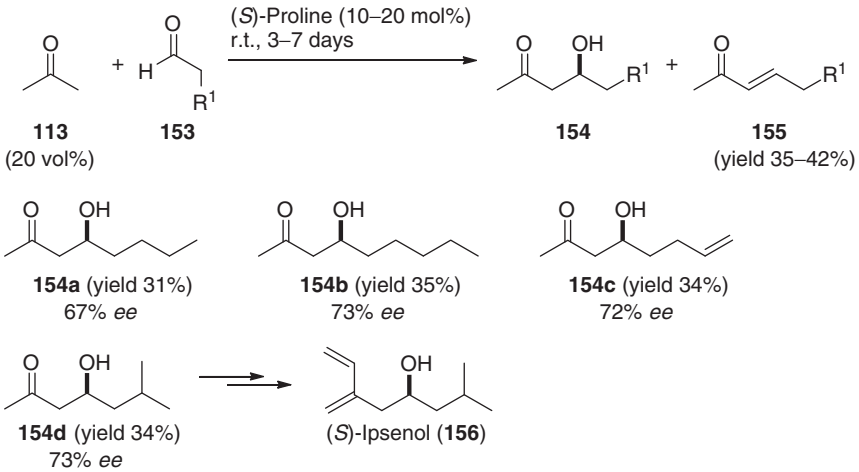


Scheme 21 Pyrrolidine-based catalysts for aldol reaction of cyclohexanone.



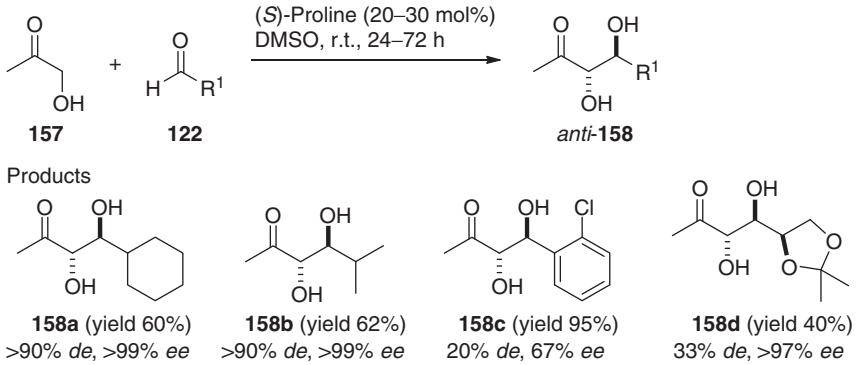
Scheme 22 Direct asymmetric aldol reaction catalyzed by (*S*)-proline vs. axially chiral catalysts.

α-unsubstituted aldehyde **153**, in which aldol products **154** are obtained with moderate enantioselectivities along with the formation of comparable amounts of α,β-unsaturated ketones **155** (Scheme 23).[84] A concise new synthesis of (*S*)-ipsenol (**156**) is developed using this strategy.



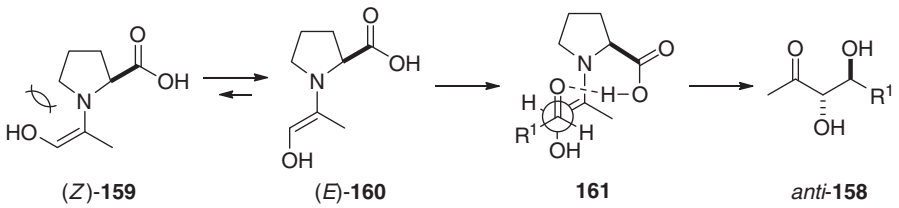
Scheme 23 Cross-aldol reaction of acetone with α-unsubstituted aldehydes.

Aldol reactions of α-hydroxyketone **157** with an aldehyde **122** create chiral *anti*-1,2-diols **158**, which are common structural motifs found in a vast array of natural and biologically active molecules. The List group reported highly diastereo- and enantioselective synthesis of the *anti*-1,2-diol **158** (Scheme 24, see also Scheme 36).[85]



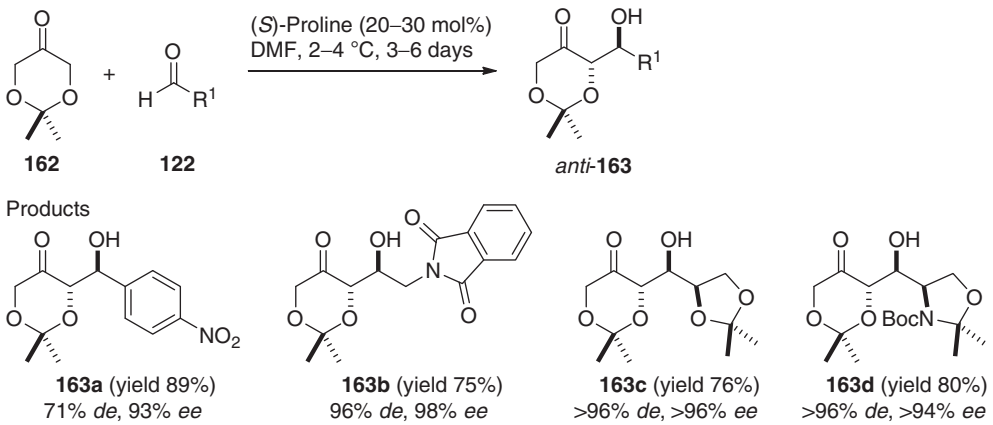
Scheme 24 *Anti*-selective aldol reactions of α-hydroxyacetone with aldehyde.

The following models account for the above *anti*-stereoselectivities (Scheme 25). (*E*)-Enamine intermediate **160** predominates because of steric interactions in (*Z*)-enamine **159** in (*S*)-proline-catalyzed reaction, thus a carbon–carbon bond is formed between the *si*-face of the (*E*)-enamine **160** and the *re*-face of aldehyde **122** to give the *anti*-isomer **158** (see also Scheme 37).



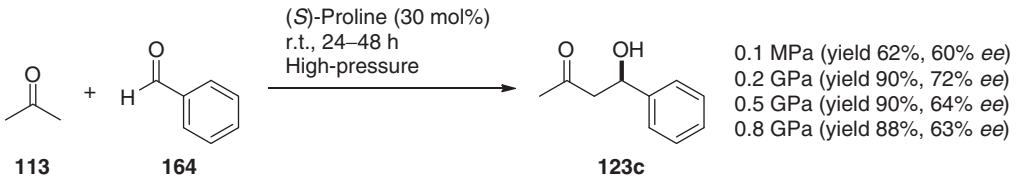
Scheme 25 Proposed transition state model for *anti*-selective aldol reaction.

A biomimetic asymmetric synthesis of carbohydrates including aminosugars has been accomplished by a proline-catalyzed aldol reaction of the protected dihydroxyacetone **162** with aldehydes **122** reported independently by the Enders[86] and the Barbas[87] group (Scheme 26, see also Schemes 38 and 39). (*S*)-proline-catalyzed aldol reaction between dihydroxyacetone equivalent **162** with aldehyde **122** gives the corresponding *anti*-polyols **163a–d** in good yields with >90% *ee*. This new organocatalytic C_3+C_n strategy leads directly to *anti*-selectively protected simple sugars and amino sugars.



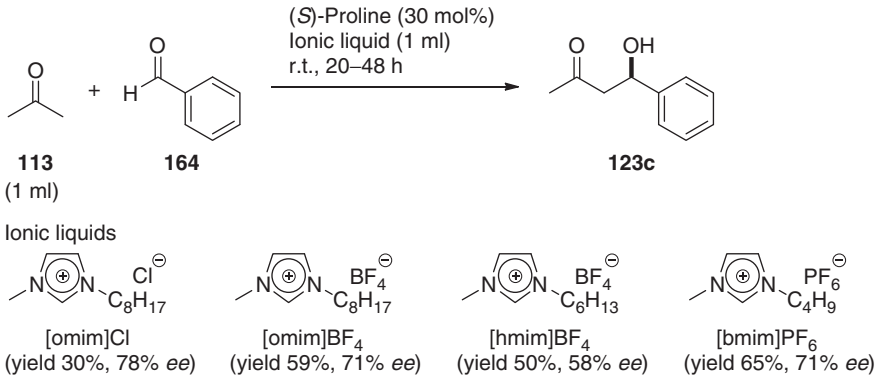
Scheme 26 *Anti*-selective aldol reactions of protected dihydroxyacetone with aldehyde.

The Kotsuki group has investigated the aldol reaction under unconventional reaction condition, that is, under high pressure (equation 12).[88] Comparable enantioselectivities are observed; however, aldol **123c** is obtained in an improved yield at 0.2 GPa. In addition, this process does not require the use of DMSO as a cosolvent.



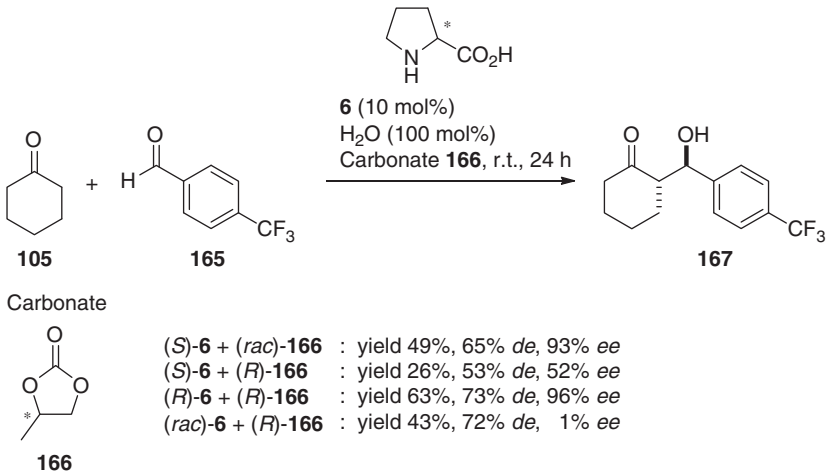
(12)

Recently, ionic liquids have attracted great interest in organic synthesis, as their properties such as nonvolatility and insolubility in some solvents are suitable for environmentally friendly synthesis. (*S*)-proline in imidazolium-based ionic liquids has been successfully used as an efficient catalyst for direct aldol reactions carried out by the Loh group (**Scheme 27**, see also **Scheme 89**).[89] Comparable or better enantioselectivities are observed compared with that in conventional organic solvents; in addition, less or no elimination product is detected.



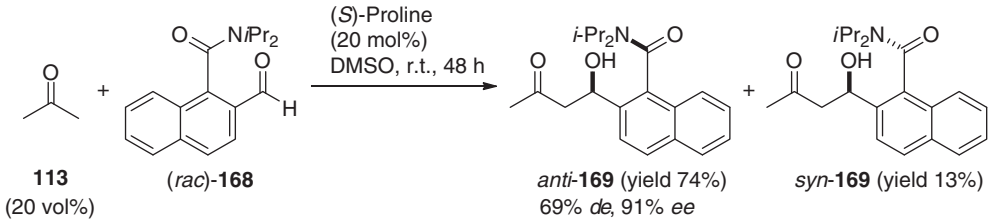
Scheme 27 Aldol reactions in ionic liquids.

Chiral solvents should have an effect on stereoselectivity. Recently, the North group reported (*S*)-proline-catalyzed aldol reaction in chiral propylene carbonate **166** as a solvent (**Scheme 28**).[90] When enantiomerically pure propylene carbonate is used, the combination of (*R*)-proline **6** and (*R*)-carbonate **166** constitutes a matched pair, whereas (*S*)-proline **6** and (*R*)-carbonate **166** constitutes a mismatched pair.



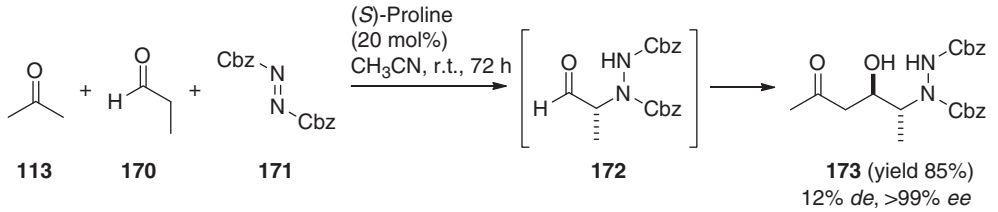
Scheme 28 (*S*)-proline-catalyzed aldol reactions in chiral solvent.

The Walsh group reported interesting dynamic kinetic resolution of racemic naphthamide **168** (equation 13).[91] Excellent stereoselectivities and good yield are observed, wherein the stereochemistry of the atropisomeric amide **169** chiral axis and a stereogenic center are simultaneously controlled.



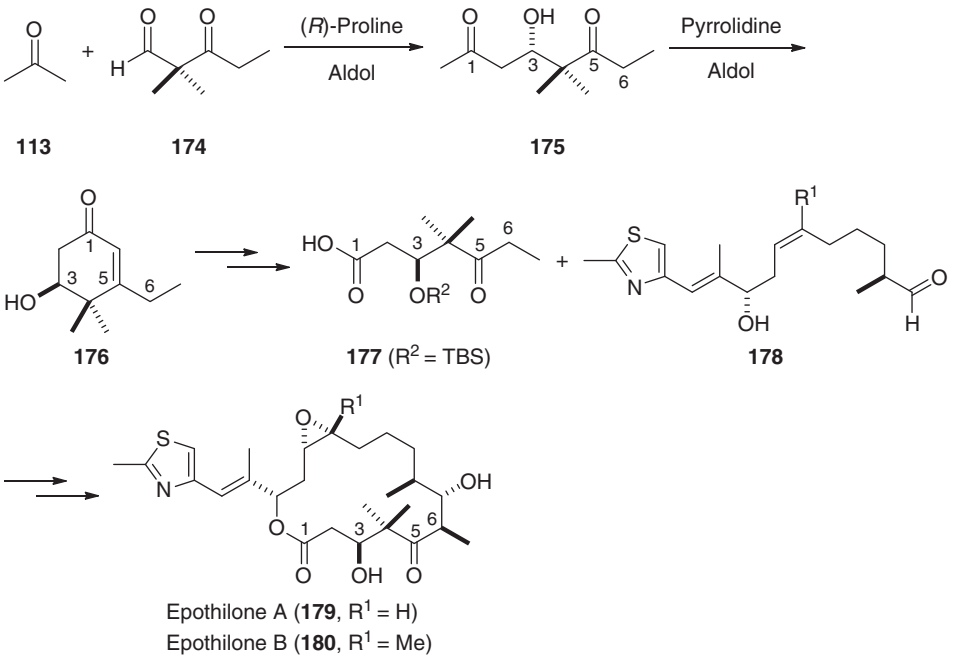
(13)

Catalysts are traditionally designed and optimized to mediate a single reaction; however, (*S*)-proline is capable of catalyzing multiple reactions in a one-pot reaction. Direct asymmetric assembly of acetone **113**, aldehyde **170**, and azodicarboxylic acid ester **171** provides an optically active *β*-amino alcohol **173** in good yields with excellent enantiomeric excess carried out by the Barbas group (Scheme 29).[92] This reaction involves stepwise reaction sequence through *α*-amination of the aldehyde **170** with the electrophilic azo compound **171** followed by aldol reaction of acetone **113** with the aldehyde intermediate **172**. Both aldehyde and ketone as nucleophiles are used in one-pot operation.



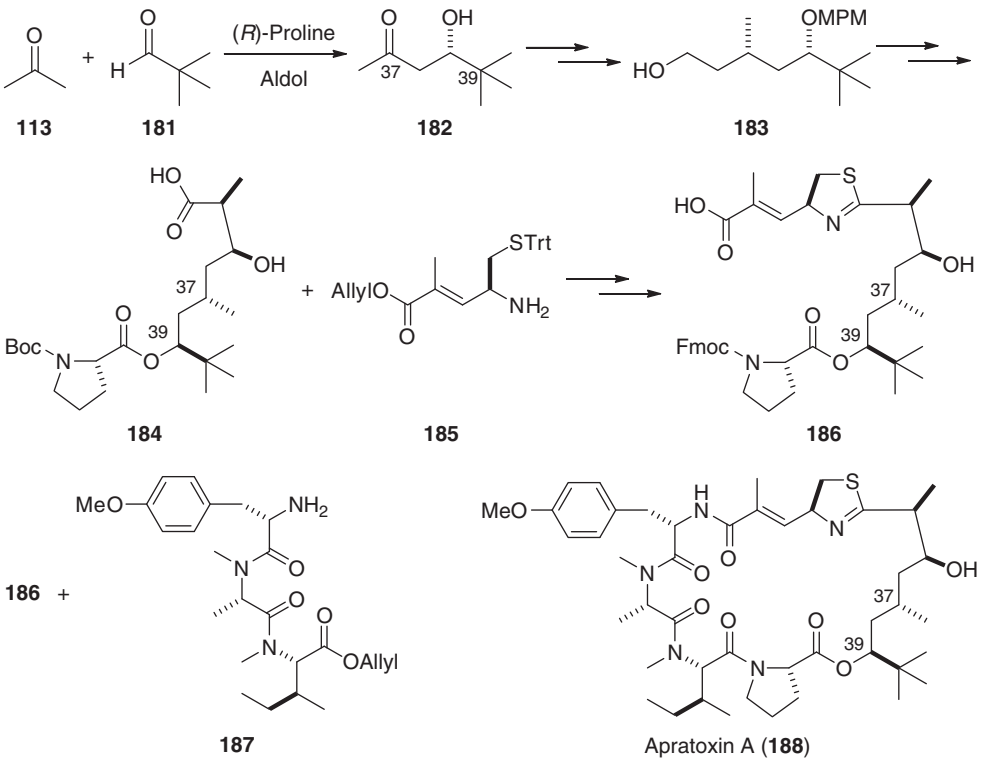
Scheme 29 Assembly reactions of acetone and dibenzyl azodicarboxylate with aldehyde.

After List–Barbas aldol reaction reported in 2000, intermolecular aldol reaction is recently employed for the synthesis of biologically active complex molecules. Epothilones A (**179**) and B (**180**) are naturally occurring 16-membered macrolides, which are produced by the myxobacterium *Sorangium cellulosum*. Although no structural similarities between epothilones and taxol **62** are observed, they exhibit similar biological activities *in vitro*. Key structure **177** of epothilones is constructed through intermolecular and intramolecular aldol reactions carried out by the Avery group (Scheme 30).[93] The *δ*-ketoaldol **175** is synthesized in 75% yield with >99% *ee* by the (*R*)-proline-catalyzed aldol reaction of acetone **113** with a pivaldehyde-like aldehyde **174**. Pyrrolidine-catalyzed intramolecular aldol reaction of *δ*-ketoaldol **175** furnishes enone **176** in 76% yield without protection of the hydroxy group. Further oxidation of the silyl-protected enone leads to the key product **177**, and then epothilones **179** and **180** could be produced according to the known procedure.



Scheme 30 Epothilone synthesis through intermolecular aldol reaction.

Apratoxin A (**188**), isolated from the marine cyanobacterium *Lyngbya majuscula* Harvey ex Gomont, possesses IC_{50} values for *in vitro* cytotoxicity against human tumor cell lines. Interestingly, this cyclodepsipeptide of mixed peptide–polyketide biogenesis bears a thiazoline ring flanked by polyketide portions including an unusual methylation pattern. The Doi and Takahashi group have employed the (*R*)-proline-catalyzed intermolecular aldol reaction of acetone **113** with pivaldehyde **181** in multigram scale to synthesize the polyketide building block **182** (Scheme 31).[94,95] The coupling of polyketide **186** with peptide **187**, followed by macrolactamization between the proline and *N*-methylisoleucine residues provides apratoxin A (**188**).

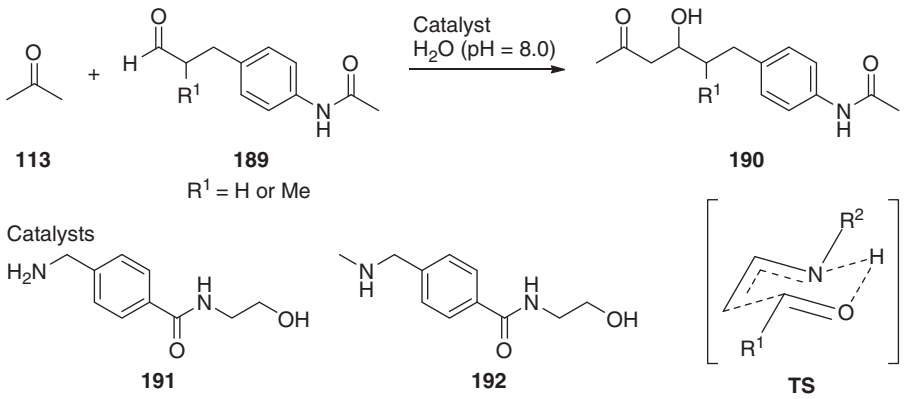


Scheme 31 Apratoxin A synthesis through proline-catalyzed aldol reaction.

2.07.2.2.2.2 Catalyzed by primary amine derivatives

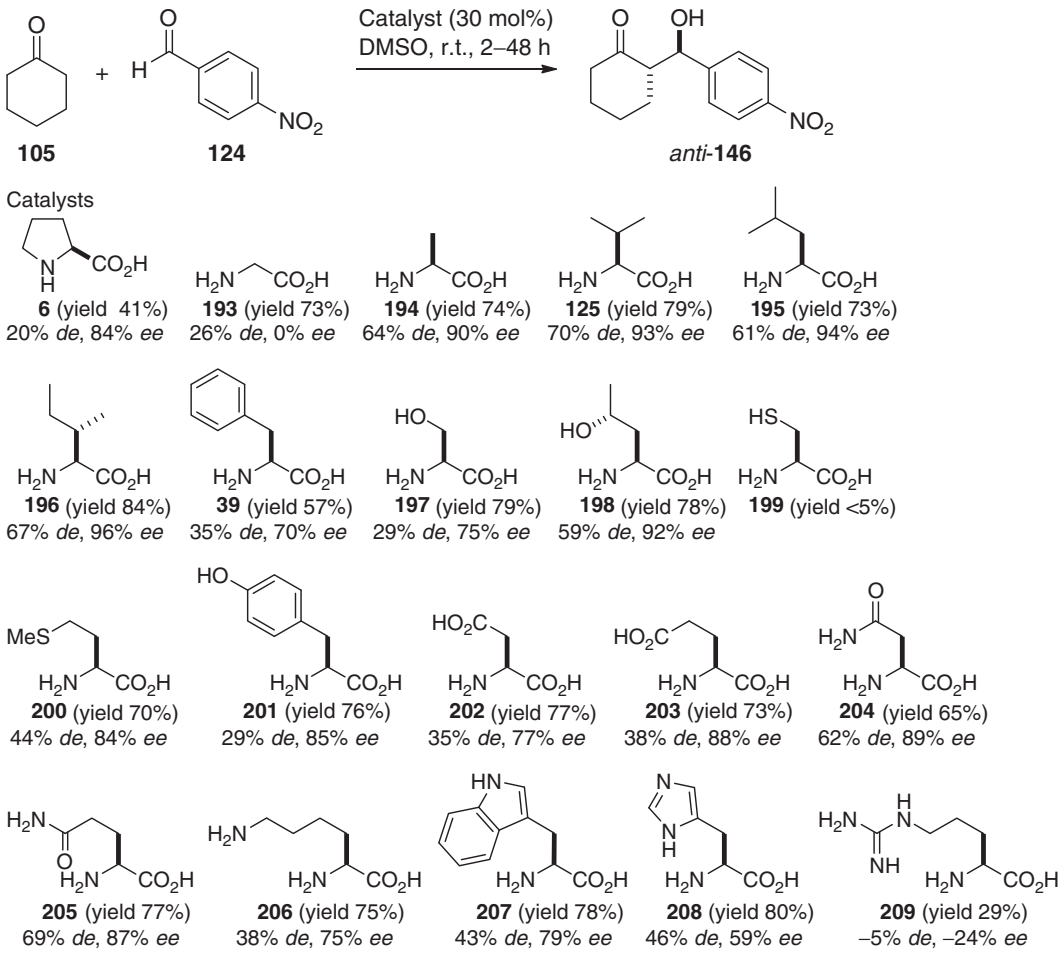
In the seminal paper by List, Barbas, and Lerner,[9,57] it has been reported that (*S*)-proline **6** promotes the enantioselective aldol reaction of acetone **113** and 4-nitrobenzaldehyde in DMSO, whereas primary amino acids such as histidine, valine, threonine, and phenylalanine do not (see Scheme 20). However, a few years earlier, in 1995, Reymond and coworkers found that intermolecular aldol reactions of acetone **113** with aldehydes **189** could be catalyzed by both primary and secondary amines.[96] They also studied a variety of amine-catalyzed aldol reactions in water and reported that primary amines react faster than secondary amines, with the exception of proline. Primary amine **191** was found to catalyze the stereoselective aldol reaction of acetone **113** to aldehyde **189** 10 times faster than secondary amine **192** (Scheme 32). For this reaction, Houk suggested that primary enamine-mediated aldol reactions involve half-chair transition states **TS** with hydrogen bonding leading to proton transfer (Scheme 32).[97] This leads to charge stabilization and low activation energies as compared with secondary enamine-mediated aldol reactions. Ever since these findings, the search for efficient organocatalysts has been extended to the family of primary amines. In this section, intermolecular aldol reactions using primary amines are reviewed.[98–101]

There have been reports that primary amino acids can promote aldol reaction, and in some cases, excellent enantioselectivities have been achieved. For instance, Córdova and coworkers have examined the aldol reaction of cyclohexanone **105** and 4-nitrobenzaldehyde **124** using 13 of the 20 natural amino acids under aqueous conditions.[102] A report by Hayashi and coworkers has shown a systematic study of all 20 proteinogenic amino acids for the aldol reaction of **105** and **124** in DMSO (Scheme 33).[103] The reaction proceeds with all amino acids except cysteine **199**, and aldol products **146** are obtained enantioselectively except with glycine **193**. The obtained yields, diastereoselectivities, and enantioselectivities depended on the amino acid tested. Even glycine **193**,[104] the simplest amino acid, allows the aldol reaction to afford the desired product **146** in good yield. Moreover, even alanine **194**, the simplest chiral amino acid, furnishes the aldol product **146** with good enantioselectivity. Perhaps surprisingly, proline **6** is not the amino acid that delivers the best results; many other amino acids, all primary amines, render higher yields and enantioselectivities. In addition, Lu and coworkers have reported 12 of the 20 proteinogenic amino acids for the aldol reaction of



Scheme 32 Intermolecular aldol reactions catalyzed by primary amines and half-chair transition state model.

105 and **124** in H_2O,[105] for which they find tryptophan **207** to be the best catalyst. After screening solvents, water is found to be the best solvent for tryptophan catalyst.



Scheme 33 Systematic studies of all 20 proteinogenic amino acids in aldol reactions.

Córdova and Himo carried out computational studies to understand the observed reactivity of amino acid-catalyzed reactions. Density functional theory calculations were performed on alanine-catalyzed aldol reactions to provide a key understanding of the reaction mechanism.[106] The carboxylic acid-associated enamine mechanism **210** is more favorable (Figure 5). The amine-mediated enamine mechanism **211** and the enaminium-mediated mechanism **212** are less favorable, as much higher activation energies are required.

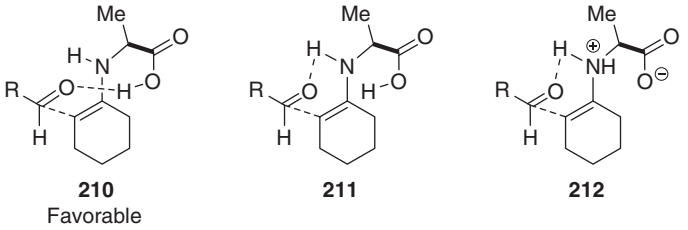
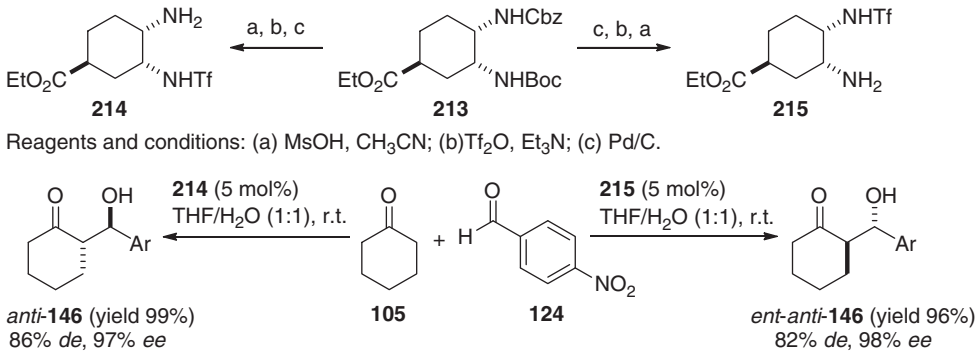


Figure 5 Possible transition state models of (*S*)-alanine-catalyzed aldol reaction.

Maruoka and coworkers reported intermolecular aldol reactions that resulted in both enantiomeric forms of the aldol product **146** by using two different chiral organocatalysts **214** and **215** (Scheme 34).[107] These catalysts can be synthesized from a common precursor **213** in a three-step sequence. The asymmetric aldol reaction of cyclohexanone **105** and 4-nitrobenzaldehyde **124** catalyzed by **214** or **215** in THF-H_2O afforded aldol products **146** in excellent yield, *anti*-selectivity, and excellent enantioselectivity, but with opposing absolute configurations. After elucidating the optimal conditions for the aldol reaction, the researchers studied the scope of aldol reactions using various cyclic ketones and substituted aryldehydes. Both catalysts generally exhibited high *anti*-selectivity and excellent enantioselectivity. In the case of cyclohexanone substrates, the catalyst loading could even be reduced to 1 mol% without compromising the high *anti*-selectivity and enantioselectivity.



Scheme 34 Asymmetric aldol reactions using two different chiral organocatalysts synthesized from common chiral source.

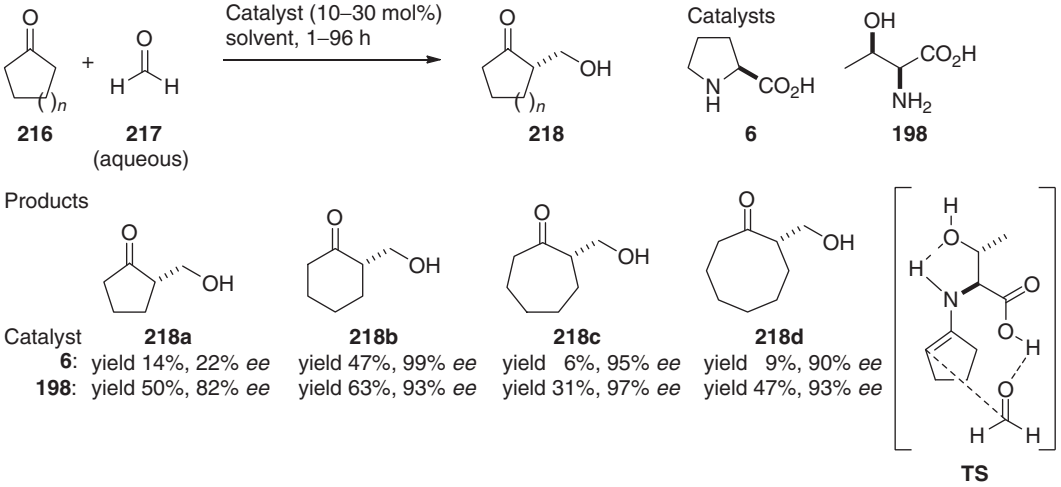
Formaldehyde **217** is one of the most important C_1 units as electrophiles in organic synthesis; in addition, aqueous formaldehyde solution, that is, formalin, is a very cheap chemical. Water-compatible Lewis acids have developed the use of aqueous formaldehyde solutions in the Mukaiyama aldol reaction.[108] Although (*S*)-proline-catalyzed direct α-hydroxymethylation of cyclohexanone with aqueous formaldehyde solution furnishes the corresponding α-hydroxymethylated aldol **218b** with excellent enantioselectivity,[109] (*S*)-proline is not an effective catalyst for aldol reaction of five-, seven-, and eight-membered cyclic ketones **216**. Recently, the Mase and Takabe group has developed enantioselective α-hydroxymethylation of these cyclic ketones **216** using simple amino acids such as (*S*)-threonine **198**. In (*S*)-proline catalysis highly strained cyclic iminium or enamine intermediates would be formed; in contrast, (*S*)-threonine catalyst forms a more flexible intermediate, but weakly fixed by intramolecular hydrogen bonding, to react with formaldehyde through the proposed transition state **TS** (Scheme 35).[110]

2.07.2.2.2.3 Syn*-selective aldol reactions*

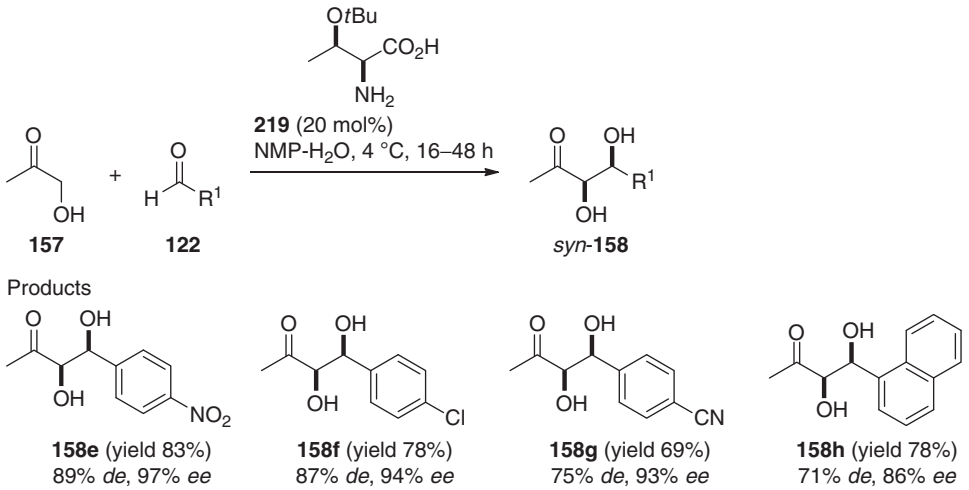
Chiral 1,2-diols are common structural motifs found in biologically active molecules. Efficient enantioselective syntheses of *anti*-1,2-diols **158** have been developed using enamine-based organocatalytic strategies with most research occurring from 2000 to 2006 as noted in Scheme 24. Before 2007, there were no reports on the synthesis of *syn*-1,2-diols **158** through an organocatalytic approach; however, use of primary amine-containing amino acid **219** derived from commercially available (*S*)-threonine overcame this synthetically important challenge. An aldol reaction catalyzed by **219** with the unmodified α-hydroxyketone **157** furnishes highly diastereomerically as well as enantiomerically enriched *syn*-1,2-diol **158** in excellent yield (Scheme 36).[111] Introduction of not only *tert*-butyl group but also siloxy groups at the hydroxyl function of (*S*)-threonine by Lu and coworkers resulted in efficient hydrophobic organocatalysts for this type of *syn*-selective reaction.[112]

When (*S*)-proline **6** is used as a catalyst, the (*E*)-enamine intermediate **160** predominates due to steric interactions in (*Z*)-enamine **159** (Scheme 25). In contrast, with primary amine-containing amino acid **219**, (*Z*)-enamine **221** of α-hydroxyketone **157** predominates over (*E*)-enamine **220** due to intramolecular hydrogen bonding, and thus, *syn*-diastereoselectivity has been observed through the bond-forming transition state **222** (Scheme 37).[111]

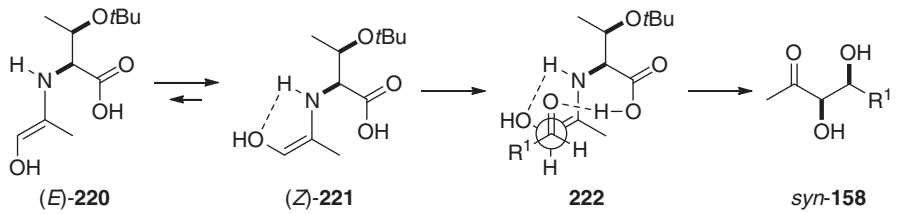
Furthermore, the (*S*)-threonine-based primary amine **219** is a powerful organocatalyst that has been used to synthesize L-rhamnulose and D-fructose derivatives **225** from protected dihydroxyacetone **223** as a donor. This new strategy offers the



Scheme 35 α-Hydroxymethylation of cycloalkanones with aqueous formaldehyde solution.



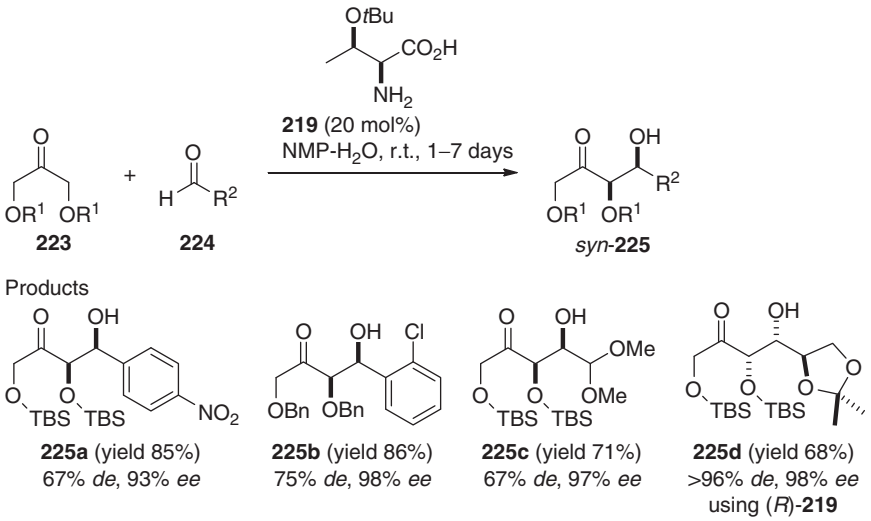
Scheme 36 *Syn*-selective aldol reactions of hydroxyacetone with aldehyde.



Scheme 37 Predicted transition state model for *syn*-selective aldol reactions.

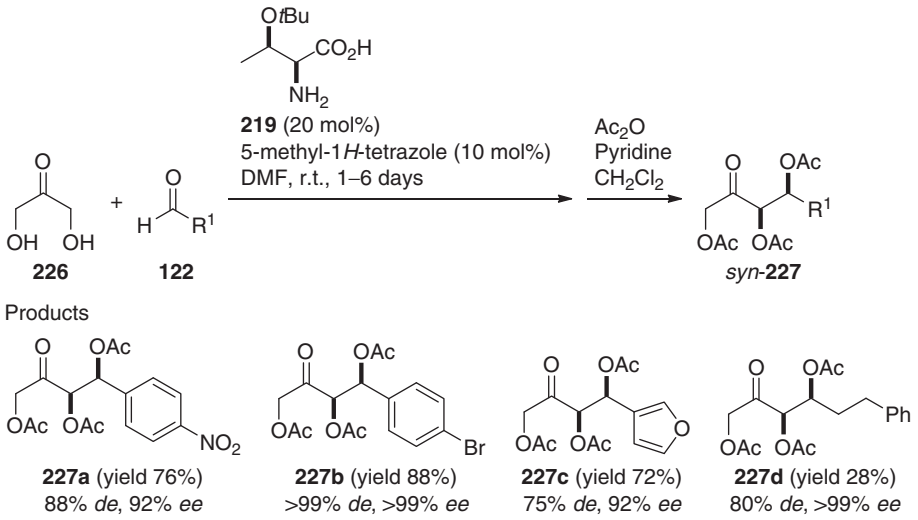
organocatalytic mimics of the enzymes L-rhamnulose 1-phosphate aldolase and D-fructose 1,6-diphosphate aldolase (Scheme 38).[113,114]

Carbohydrates play diverse and essential roles in biology, medicine, and industry and thus synthesizing them stereoselectively is an important concern in organic chemistry, and specifically in aldol chemistry. Therefore, asymmetric aldol reactions between the unprotected dihydroxyacetone **226** and aldehydes **122** have been a challenging topic in organocatalysis. For example, no enantioselection was observed in the (*S*)-proline or (*S*)-1-(pyrrolidin-2-ylmethyl)pyrrolidine-catalyzed aldol reaction of dihydroxyacetone **226** with aldehyde **122** reported by the Barbas group in 2002, though this reaction interestingly proceeded in aqueous conditions.[115] In 2007, the same group overcame this difficulty by the use of (*S*)-threonine-based primary amine **219**



Scheme 38 *Syn*-selective aldol reactions of protected dihydroxyacetone with aldehyde.

(Scheme 39).[113] DMF and 5-methyl-1*H*-tetrazole are identified as an optimal solvent and acid additive combination, in which *syn*-aldol products **227** are obtained in good yield with >92% *ee*.



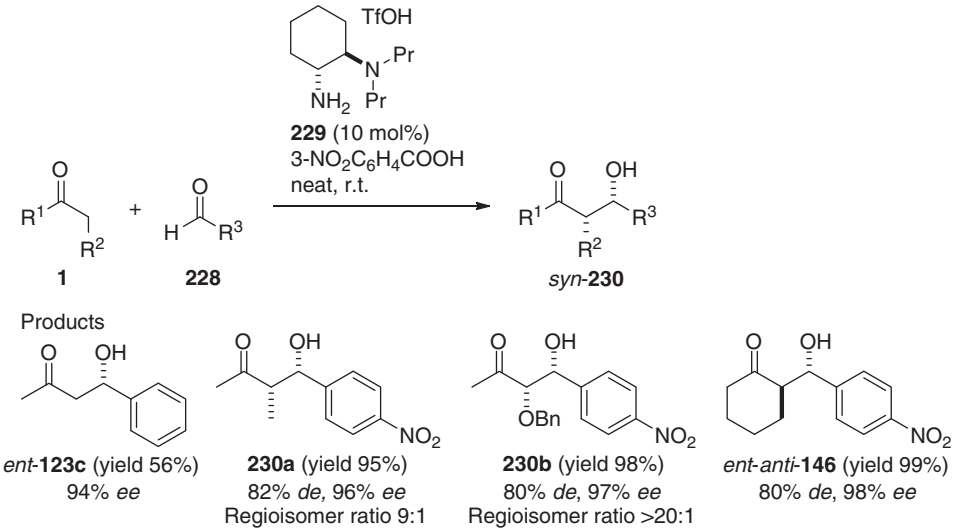
Scheme 39 *Syn*-selective aldol reaction of unprotected dihydroxyacetone with aldehyde.

Aldol reactions of linear aliphatic ketones **1** with aldehydes **228** are synthetically important; however, regioselectivity and stereoselectivity are difficult to control. The chiral primary–tertiary diamine **229**, derived from nonamino acids, in combination with trifluoromethanesulfonic acid (TfOH) catalyzes the aldol reaction with high regio-, *syn*-diastereo-, and enantioselectivity (Scheme 40).[116] The reaction of 2-butanone occurred preferentially at the methylene carbon with good regioselectivity, favoring the branched aldol product **230a** in high enantioselectivity. More interestingly, the branched product **230a** was obtained with unexpected diastereoselectivity, favoring the *syn*-isomer; in contrast, the reaction with (*S*)-proline derivatives generated *anti*-selective products with acyclic ketones. In the case of cyclic ketone as donors, *anti*-product **146** was obtained.

The (*Z*)-enamine transition state **TS-1** was proposed in the *syn*-selective reaction of an acyclic ketone donor with an aldehyde acceptor catalyzed by **229**. In this model, the protonated tertiary amine serves as a hydrogen-bonding donor. The formation of the (*E*)-enamine of the acyclic ketone is disfavored due to steric repulsion between R^1 and R^2 substituents. The reaction of cyclohexanone, which is only capable of forming (*E*)-enamine transition state model **TS-2**, gave *anti*-diastereoselectivity (Figure 6).[116]

2.07.2.2.3 Aldehyde nucleophiles with ketone electrophiles

Controlling the chemo- and stereoselectivities in intermolecular aldol reaction using aldehyde nucleophiles is one of the most challenging topics in organic synthesis. The direct catalytic asymmetric cross-aldol reaction using a nucleophilic aldehyde with a



Scheme 40 Aldol reactions catalyzed by chiral primary–tertiary diamine.

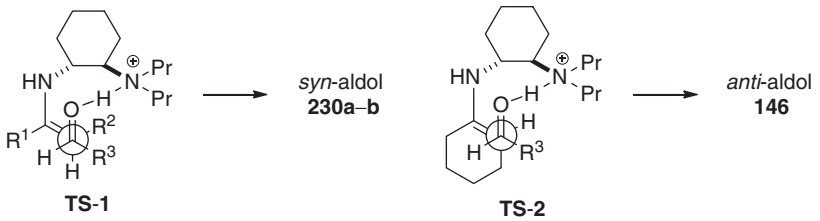
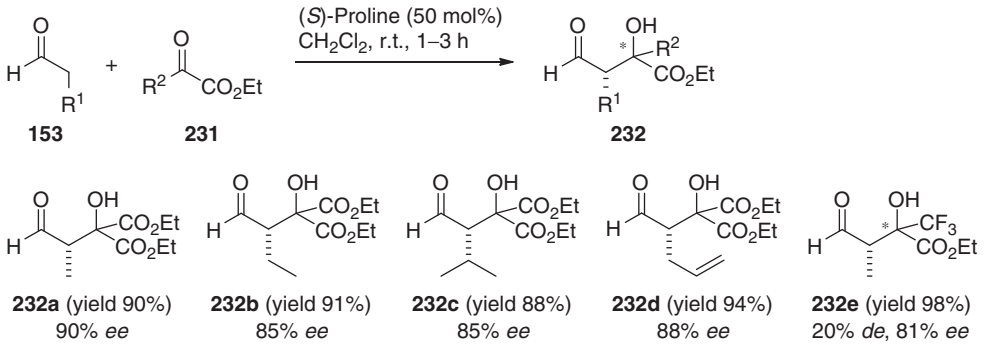


Figure 6 Predicted transition state models for aldol reactions catalyzed by chiral primary–tertiary diamine.

ketone electrophile has been reported by the Jørgensen group (Scheme 41).[117] α-Unsubstituted aldehydes **153** are used in (*S*)-proline-catalyzed cross-aldol reaction with activated ketomalonates **231**. The desired products **232** are obtained in excellent yields and enantioselectivities, though a substoichiometric amount of catalyst is required. The asymmetric intermolecular aldol reaction of aldehyde with unactivated simple ketone is still difficult to achieve (see Section 2.07.2.1.3).

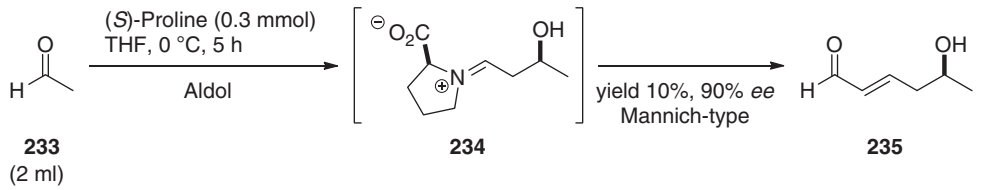


Scheme 41 Aldol reactions of aldehyde nucleophile with activated ketone electrophile.

2.07.2.2.4 Aldehyde nucleophiles with aldehyde electrophiles

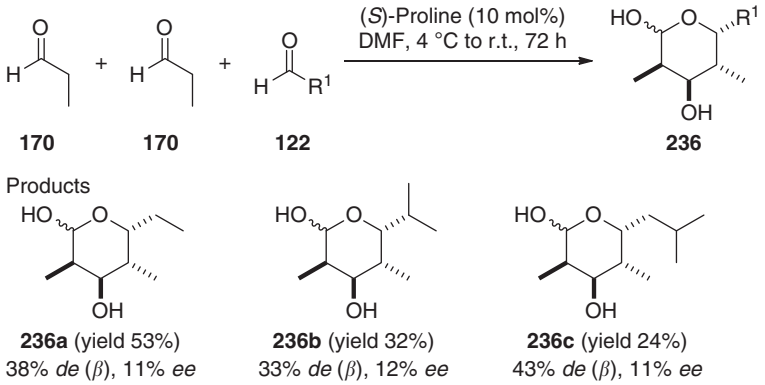
2.07.2.2.4.1 Aldol reactions of aldehyde nucleophiles

It has been a chemist's dream to accomplish the highly controlled asymmetric cross-aldol reaction of a wide variety of abundant aldehydes. Although many transformations of aldehyde functional group are well known, aldehydes apparently have a tendency to polymerize under acidic or metal-catalyzed conditions. The first (*S*)-proline-catalyzed direct self-aldol reaction of acetaldehyde **233** was disclosed by the Barbas group (Scheme 42).[118] (5*S*)-Hydroxy-(2*E*)-hexenal **235** with 90% *ee* in a low chemical yield is obtained through the self-aldol followed by Mannich-type condensation.



Scheme 42 Self-aldol reaction of acetaldehyde.

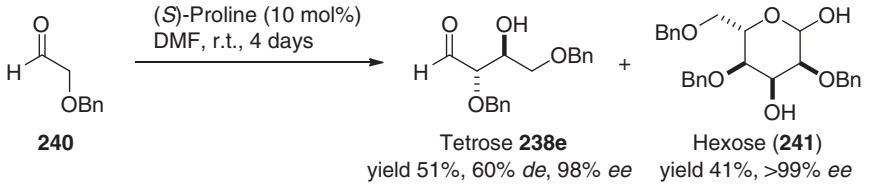
The Barbas group reported the directed asymmetric assembly of simple three aldehyde molecules into stereochemically complex triketides **236** (Scheme 43).[119] The pyranose products **236** including four asymmetric centers are constructed by (*S*)-proline-catalyzed double aldol reactions. Despite modest stereoselectivities, this approach may warrant consideration as a prebiotic route to sugars and polyketides.



Scheme 43 (*S*)-proline-catalyzed assembly of aldehydes to synthesize pyranoses.

Nonequivalent aldehydes must selectively partition into two discrete components, that is, a nucleophile and an electrophile, in cross-aldol reaction of α-unsubstituted aldehydes. The MacMillan group has achieved this challenging aldol reaction, and syringe addition of electrophilic aldehyde is a key to high reaction efficiency (Scheme 44, products **238a–238d**).[120] By slowly adding the donor aldehyde **153** to 10 equivalents of the acceptor aldehyde **237**, the desired cross-aldol product **238** was obtained in good yield and enantioselectivity with only 10 mol% (*S*)-proline. This excellent procedure is employed in producing protected erythrose using α-oxyaldehydes (Scheme 44, products **238e–238i**).[121] Furthermore, a synthetic route based on aldol coupling of three aldehydes is accomplished for the *de-novo* synthesis of hexoses in only two steps, that is, the (*S*)-proline-catalyzed self-aldol reaction of α-oxyaldehydes, followed by a Lewis acid-catalyzed Mukaiyama aldol addition-cyclization afforded the protected allose **239** (Scheme 44).[122] This strategic synthetic procedure is very helpful to prepare differentially protected glucose, allose, and mannose stereoisomers in high yields and stereoselectivities simply by changing the solvent and the Lewis acid used.

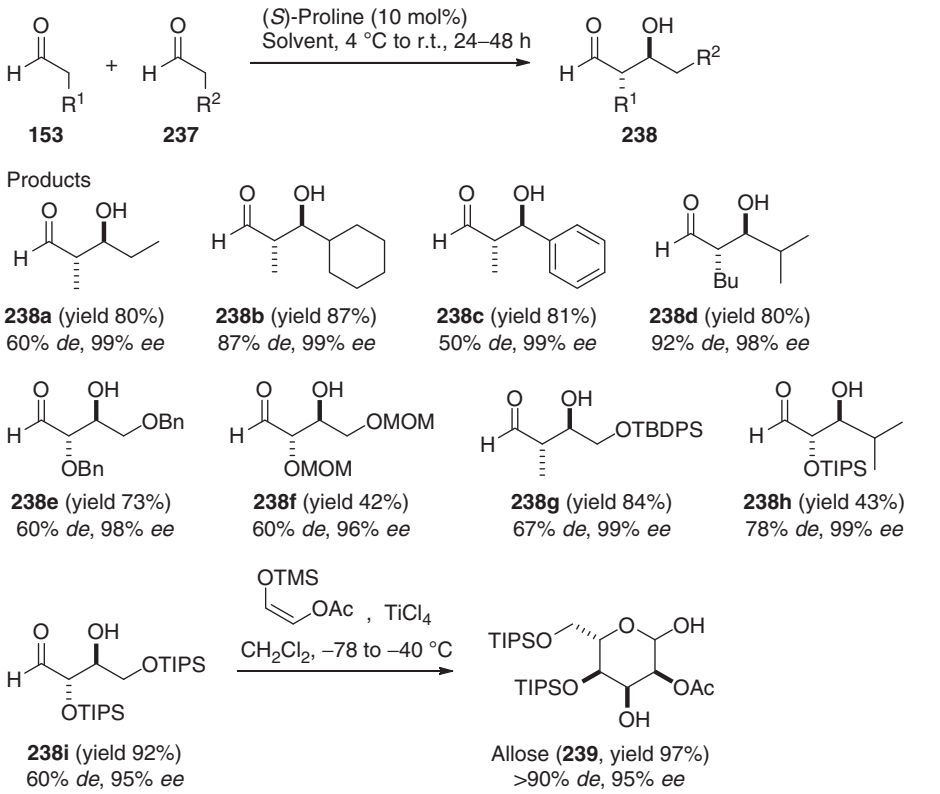
One-pot *de-novo* synthesis of carbohydrates has also been accomplished by (*S*)-proline-catalyzed trimerization of α-benzyloxyaldehyde **240** carried out by the Córdova group (equation 14).[123] Chemical yield is moderate, but absolute stereocontrol of the protected allose **241** is achieved by this direct $C_2+C_2+C_2$ methodology in one-pot operation.



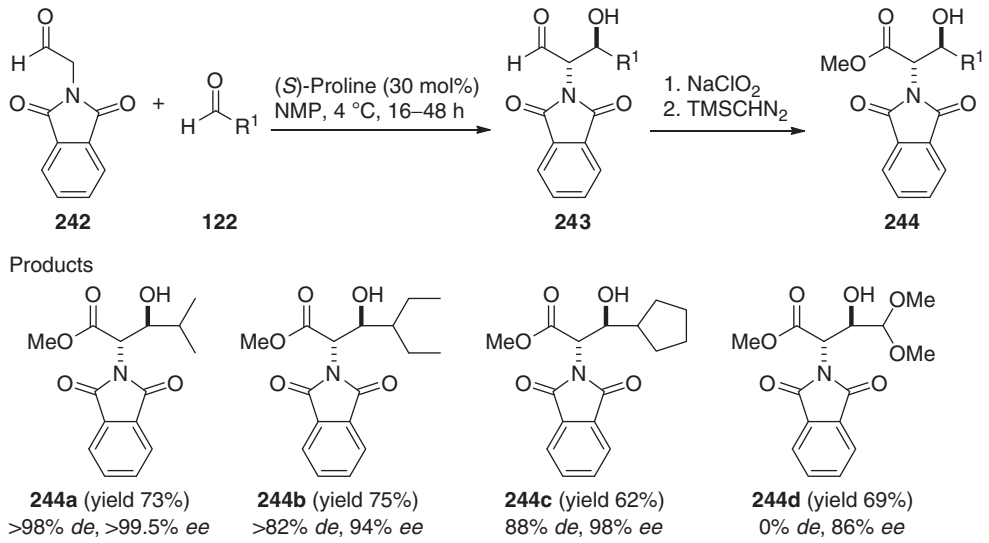
(14)

Not only α-oxyaldehydes but also α-aminoaldehydes **242** are also investigated in direct aldol reactions. The Barbas group reported that β-hydroxy-α-amino acid derivatives **244** were prepared by the (*S*)-proline-catalyzed aldol reaction of glycine aldehyde **242** with aldehyde electrophiles **122** (Scheme 45).[124] The reactions afford *anti*-β-hydroxy-α-amino aldehydes **243** in good yields with high diastereo- and enantioselectivities, which are easily transformed into β-hydroxy-α-amino acid derivatives **244**.

Although proline itself can catalyze cross-aldol reactions between different aldehydes in excellent enantioselectivities and high yields, some problems currently exist: (1) preventing self-aldol reactions without recourse to slow addition techniques and (2) development of *syn*-selective aldol reactions, as *anti*-products usually predominate. MacMillan and coworkers have reported an organocatalytic self-aldol reaction of propanal **170** using imidazolidinone catalysts **254** (Scheme 46),[125] and under these reaction conditions, the initial aldol dimerization adduct **246** undergoes rapid transformation into hemiacetal **247**. This 'self-termination'



Scheme 44 (*S*)-proline-catalyzed cross-aldol reaction of α-unsubstituted aldehydes.

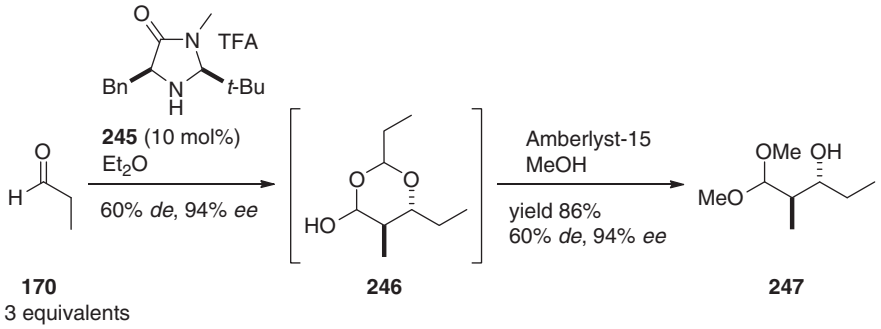


Scheme 45 Aldol reactions of glycine aldehyde derivative with aldehyde electrophile.

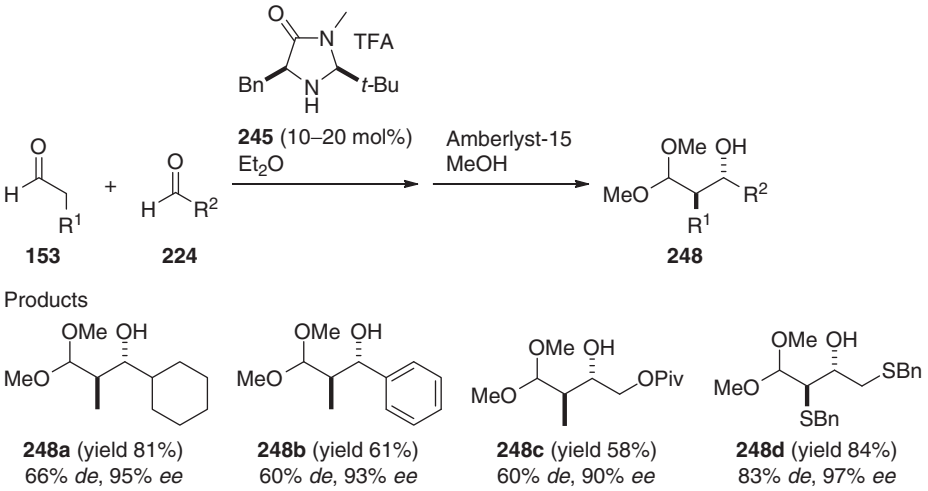
step fortuitously protects the product from participating in further aldol processes. Methanolysis of this aldol hemiacetal product **246** *in situ* then allows direct access to a stable dimethoxyacetal **247** without loss in enantiopurity or diastereoselectivity.

Addition of α-unsubstituted aldehyde **153** by means of a syringe pump to a variety of aldehyde acceptors **224** effectively prevents homodimerization while giving the desired cross-aldol product **248** in good yield and excellent enantioselectivity (Scheme 47).[125] The resulting *syn*/*anti*-selectivity was almost the same as with proline, but the opposite enantiomer was obtained.

The high selectivity of this reaction is thought to arise from the selective formation of the (*E*)-iminium isomer during the transition state to avoid nonbonding interactions with the bulky *tert*-butyl group, as well as the prevention of the *re* face of the enamine **249** from participating in carbonyl addition due to the protruding benzyl group from the catalyst framework (Figure 7).



Scheme 46 Imidazolidinone-catalyzed self-aldol reaction.



Scheme 47 Imidazolidinone-catalyzed cross-aldol reaction.

In contrast, when (*S*)-proline is used as a catalyst, the aldehyde acceptor is activated by coordination to proline's carboxylic acid moiety **250**.

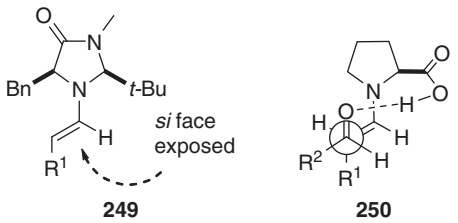
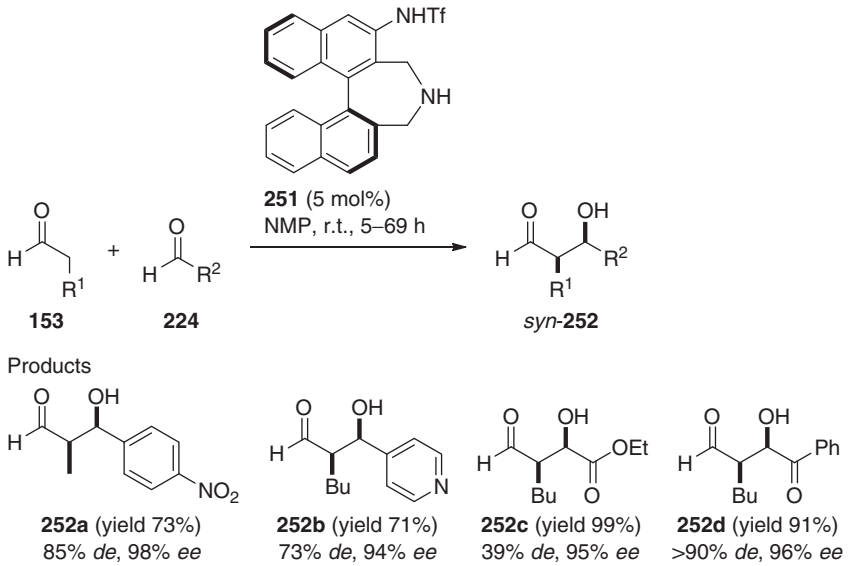


Figure 7 Proposed intermediates in the aldol reaction comparing MacMillan's catalyst to (*S*)-proline.

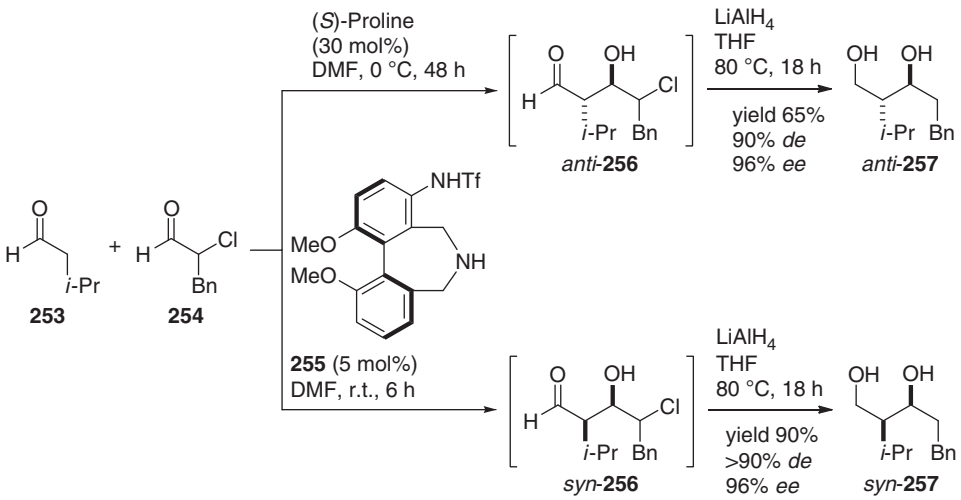
An axially chiral binaphthylsulfonamide derivative **251** has been successfully used as the catalyst in a cross-aldol reaction between aliphatic **153** and aromatic aldehydes **224** as well as ethyl glyoxylate or phenylglyoxal, affording *syn*-isomers **252** with excellent enantiomeric excess (Scheme 48).[126]

A chemo- and stereoselective direct cross-aldol reaction between aliphatic aldehydes **253** and α-chloroaldehydes **254** has been succeeded as a method for the formation of the cross-aldol adduct **257** with both diastereo- and enantiocontrol; in addition, either *anti*- or *syn*-aldol adducts **257** were obtained in good to excellent stereoselectivities by use of (*S*)-proline or the axially chiral amino sulfonamide **255** as the catalyst (Scheme 49).[127]

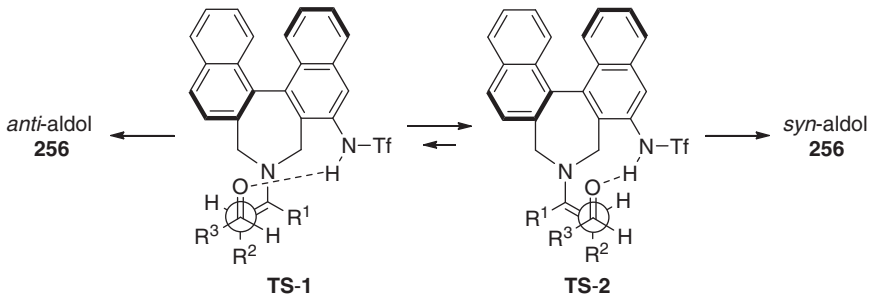
The *syn*-selectivity in the binaphthylsulfonamide-catalyzed aldol reaction is believed to proceed as follows: It would be difficult for *anti*-enamine **TS-1**, generated from a donor aldehyde and the catalyst, to react with an acceptor aldehyde that is activated by the distal acidic proton of the sulfonamide catalyst. The cross-aldol product would thus be expected to proceed through the more favorable *syn*-enamine **TS-2** (Scheme 50).[126]



Scheme 48 Binaphthylsulfonamide-catalyzed *syn*-selective cross-aldol reaction.



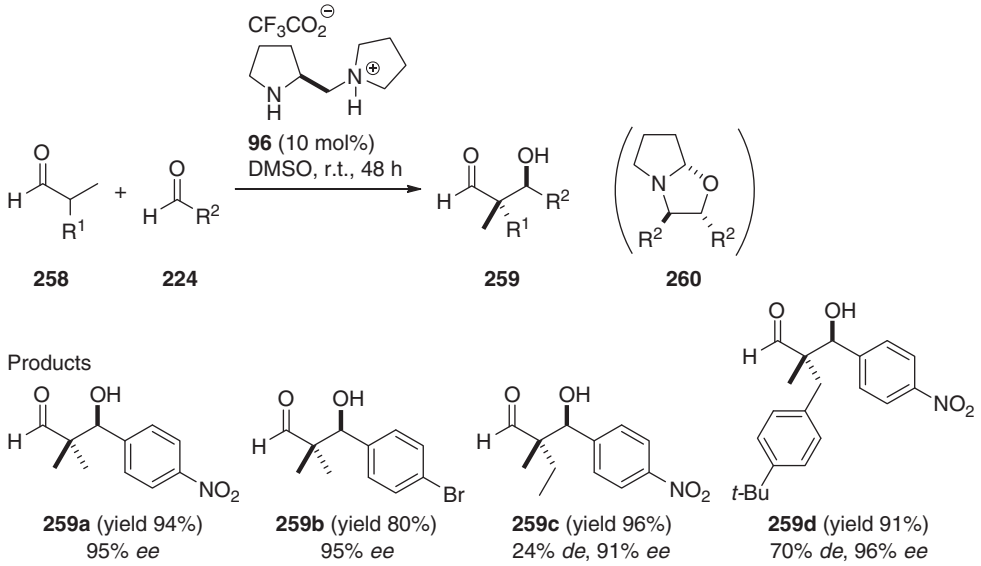
Scheme 49 Binaphthylsulfonamide-catalyzed *syn*-selective cross-aldol reaction of 2-chloroaldehyde.



Scheme 50 Predicted transition state models for cross-aldol reaction catalyzed by binaphthylsulfonamide.

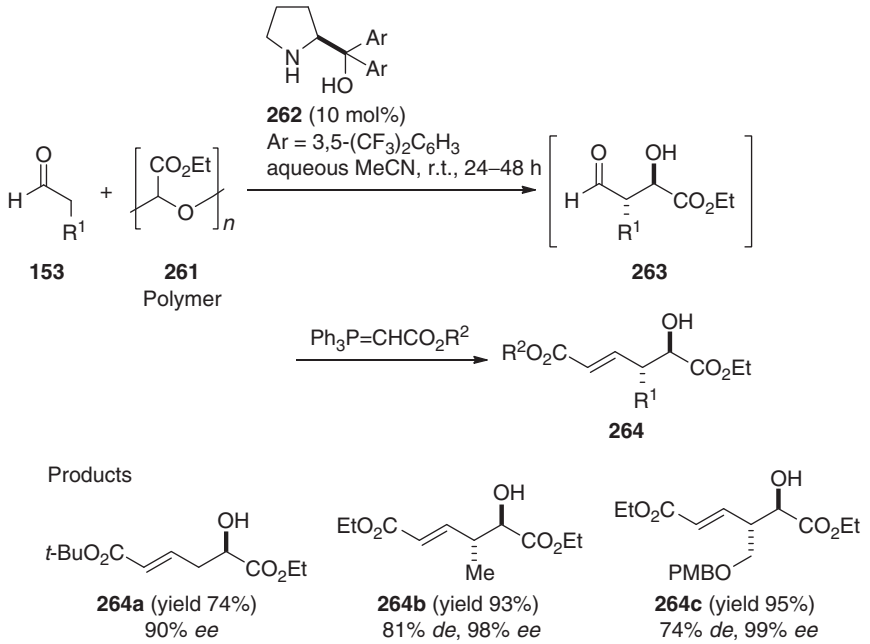
Although impressive, the synthetic scope of (*S*)-proline is not sufficient to address all aspects of the direct aldol reaction. For example, the synthesis of aldols with quaternary carbon atoms is one of the most challenging topics in asymmetric organic chemistry that is not addressed efficiently with (*S*)-proline catalysis, that is, aldol **259a** is obtained in 34% chemical yield with 80% *ee* in the presence of (*S*)-proline (30 mol%) after 72 h stirring. Enamine formation is not effective in this condition, thus

1,3-dipolar cycloaddition product **260** through decarboxylation of iminium intermediate derived from (*S*)-proline and aldehyde **224** is formed. The Tanaka and Barbas group identified chiral-amine/acid combinations **96** as a bifunctional catalyst through a fluorescence-based evaluation system for asymmetric direct catalytic aldol reactions of α,α-dialkyl aldehydes **258** with aryl aldehydes **224** (Scheme 51).[66] Aldols **259** bearing quaternary carbon atoms are obtained with excellent enantioselectivities.



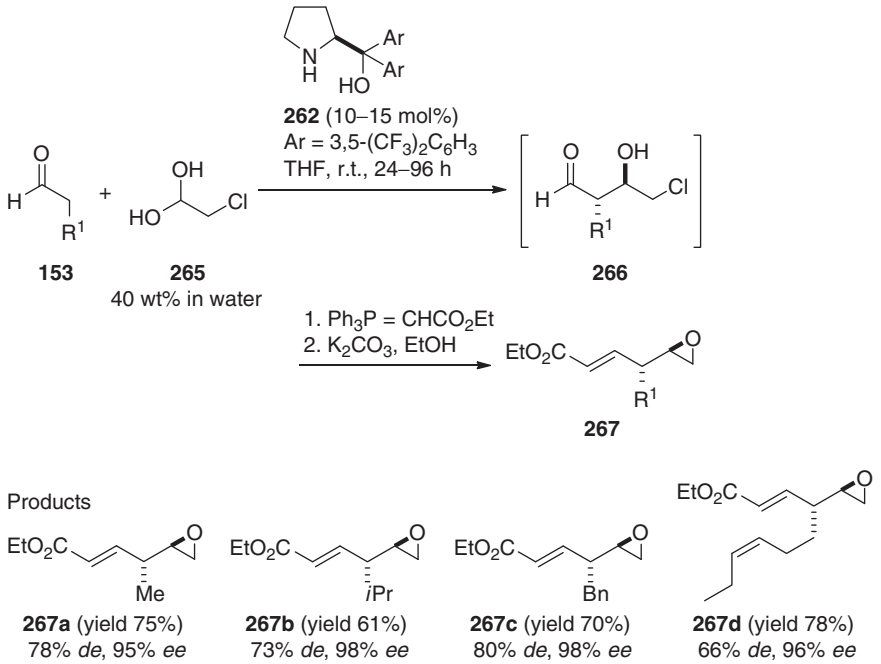
Scheme 51 Synthesis of aldols with quaternary carbon centers catalyzed by a chiral amine/acid combination catalyst.

Trifluoromethyl-substituted diarylprolinol **262**, which is easily prepared from (*S*)-proline, is an efficient catalyst in several aldol reactions, in which proline does not afford the good results. Ethyl glyoxylate is a useful electrophile, which is commercially available as its polymer form **261** in toluene solution. Usually, its monomer, prepared through pyrolysis just before use from the polymer, is used in aldol reaction, and it is a synthetic advantage if its polymer can be directly employed in the reaction. The cross-aldol reaction of ethyl glyoxylate using its polymer solution can be catalyzed by diarylprolinol **262** to afford the aldol product with excellent diasereo- and enantioselectivity (Scheme 52).[74]

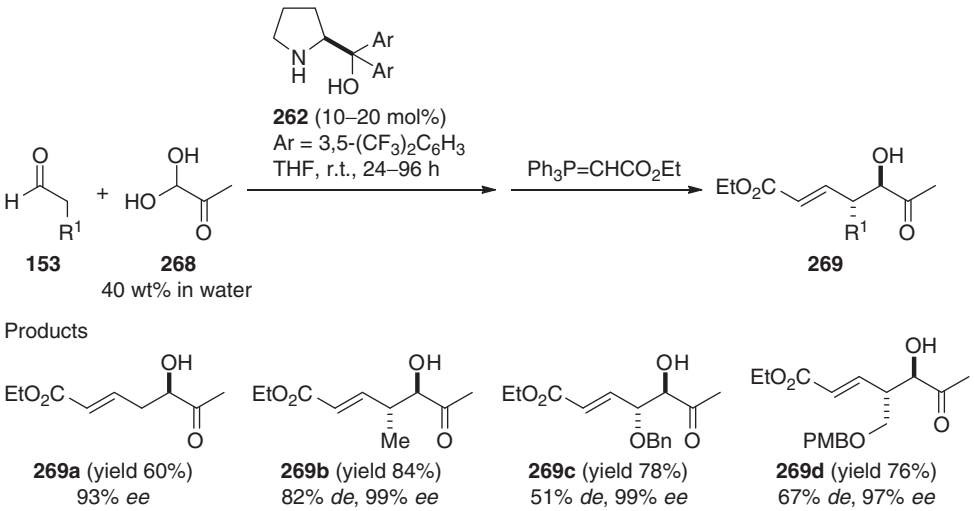


Scheme 52 Diarylprolinol-catalyzed cross-aldol reaction of aldehyde with ethyl glyoxylate using its polymer solution.

This catalyst **262** is also effective in the aldol reaction of chloroacetaldehyde hydrate **265** (Scheme 53)[128] and pyruvaldehyde hydrate **268** (Scheme 54),[129] both of which are commercially available as an aqueous solution. In the reaction of chloroacetaldehyde, aldol product **266** was treated with Wittig reagent, followed by the addition of base, which gave epoxy ester **267** with excellent enantioselectivity in one-pot operation.



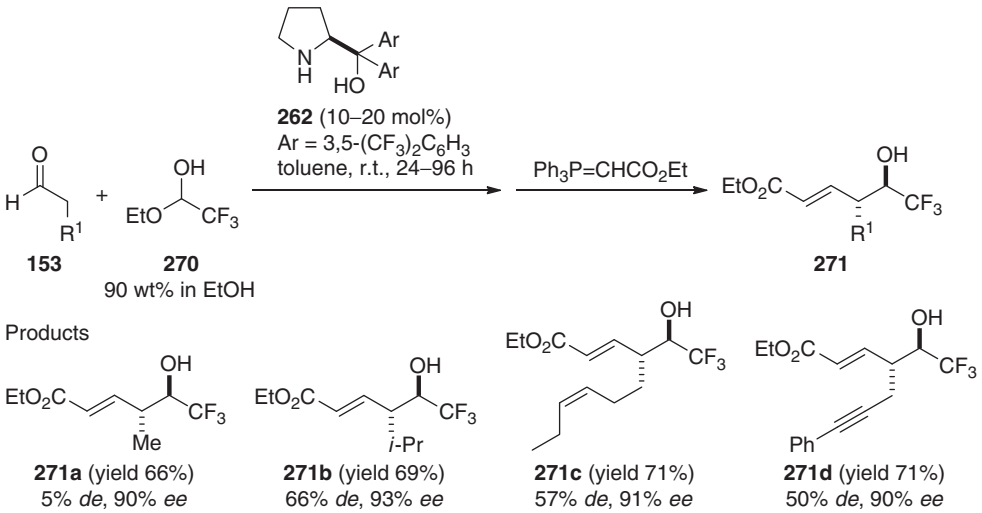
Scheme 53 Diarylprolinol-catalyzed cross-aldol reaction of aldehyde with chloroacetaldehyde.



Scheme 54 Diarylprolinol-catalyzed cross-aldol reaction of aldehyde with pyruvaldehyde.

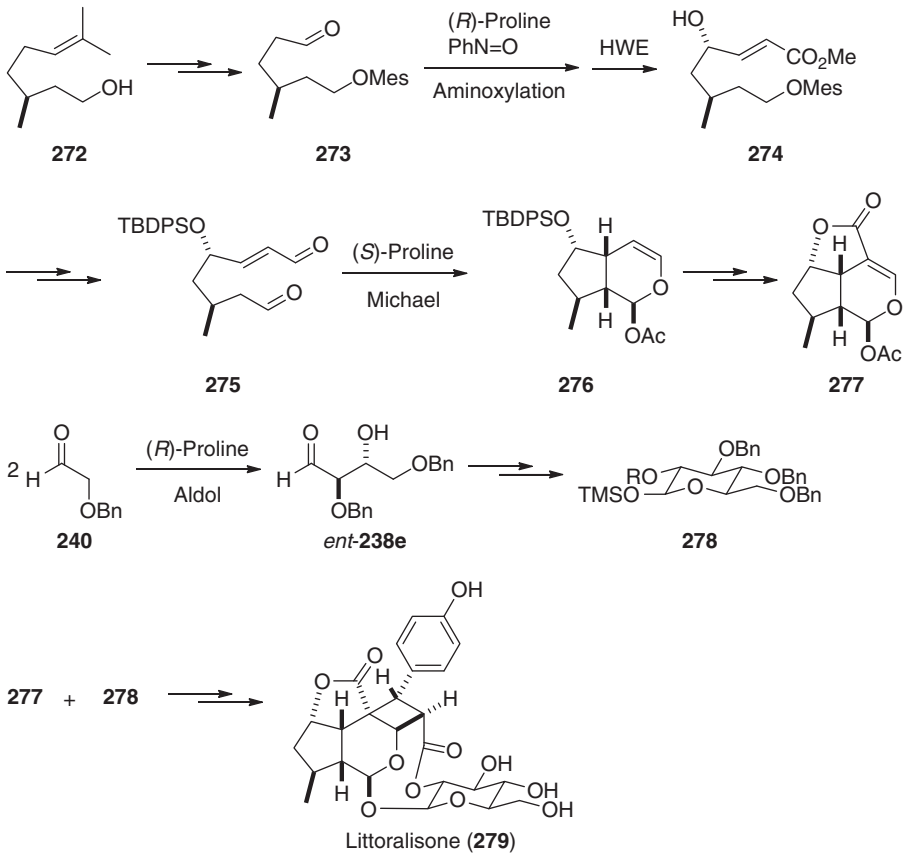
Trifluoromethylacetaldehyde ethyl hemiacetal **270** can also be employed as an electrophilic aldehyde equivalent. Acetal **270** was used directly in the aldol reaction catalyzed by trifluoromethyl-substituted diarylprolinol **262** to afford the aldol product **271** with excellent enantioselectivity (Scheme 55).[130]

An impressive synthesis of natural product using organocatalytic methodology including a proline-catalyzed α-aminoxylation, Michael addition, and aldol reaction is accomplished by the MacMillan group (Scheme 56).[131] Littoralisone (**279**) has a six-membered acetal, an adjacent nine- and five-membered lactones, cyclobutane and cyclopentane rings, and saccharide; in addition, 14 stereocenters including 6 contiguous stereocenters are found. Iridolactone **277** and 2-cinnamoyl saccharide **278** are key



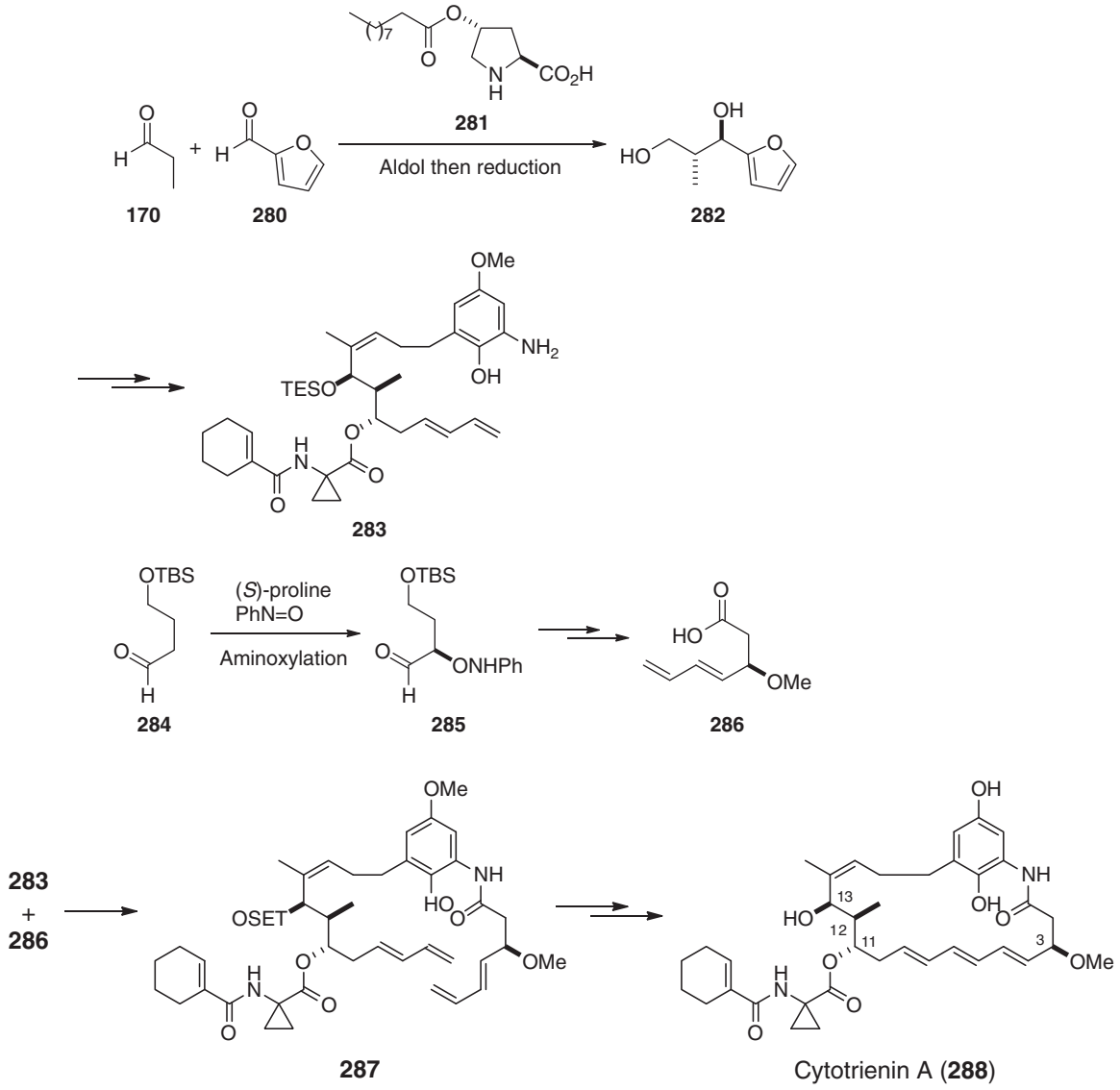
Scheme 55 Diarylprolinol-catalyzed cross-aldol reaction of aldehyde with trifluoromethylacetaldehyde ethyl hemiacetal.

intermediates according to their synthetic strategy. (*S*)-Proline-catalyzed α-aminoxylation of aldehyde **273** derived from readily available (*S*)-citronellol **272** with nitrosobenzene furnishes the corresponding oxyaminoaldehyde. Subsequently, Horner-Wadsworth-Emmons olefination and cleavage of the aminoxy bond afforded the α,β-unsaturated ester **274** in a single operation from **273**. Intramolecular Michael reaction of enal **275** with (*S*)-proline as a catalyst gives the bicyclic product **276**, then further transformation leads the key iridolactone **277**. Another key 2-cinnamoyl saccharide **278** is prepared by (*R*)-proline-catalyzed dimerization of benzyloxyacetaldehyde **240**, followed by Mukaiyama aldol reaction (see Scheme 44). Synthesis of the target littoralisone (**279**) is accomplished by the glycosidic union of **277** and **278**, subsequently intramolecular [2+2] photocycloaddition.



Scheme 56 Littoralisone synthesis through proline-catalyzed α-aminoxylation, Michael addition, and aldol reaction.

Another application of organocatalyst-mediated aldol reaction to total synthesis of natural product is the synthesis of (+)-cytotrienin A (**288**). Cytotrienin A is a microbial antitumor secondary metabolite, isolated from a fermentation broth of *Streptomyces sp.* RK95–74 from soil.[132] It possesses a (*E*,*E*,*E*)-triene within a 21-membered cyclic lactam, which also contains four chiral centers, common structural features of the ansamycin class of natural products. The three contiguous chiral centers have been constructed by the asymmetric aldol reaction as a key step, in which surfactant-proline conjugated catalyst **281** is effective to afford the aldol product **282** with good diastereoselectivity and excellent enantioselectivity in contrast to the low diastereoselectivity in the case of proline-mediated reaction. The chirality at C-3 is controlled by proline-catalyzed α-aminoxylation of aldehyde **284**. Ring-closing metathesis of diene **287** and diene moieties to construct triene moiety afforded the 21-membered macrolactam **288** (Scheme 57).

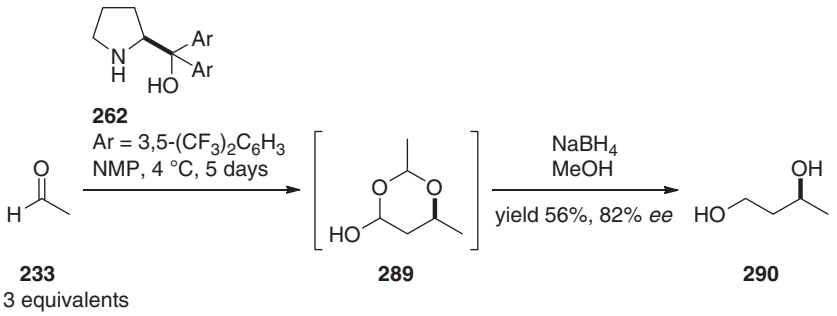


Scheme 57 Asymmetric total synthesis of (+)-cytotrienin A.

2.07.2.2.4.2 Aldol reactions of acetaldehyde nucleophile

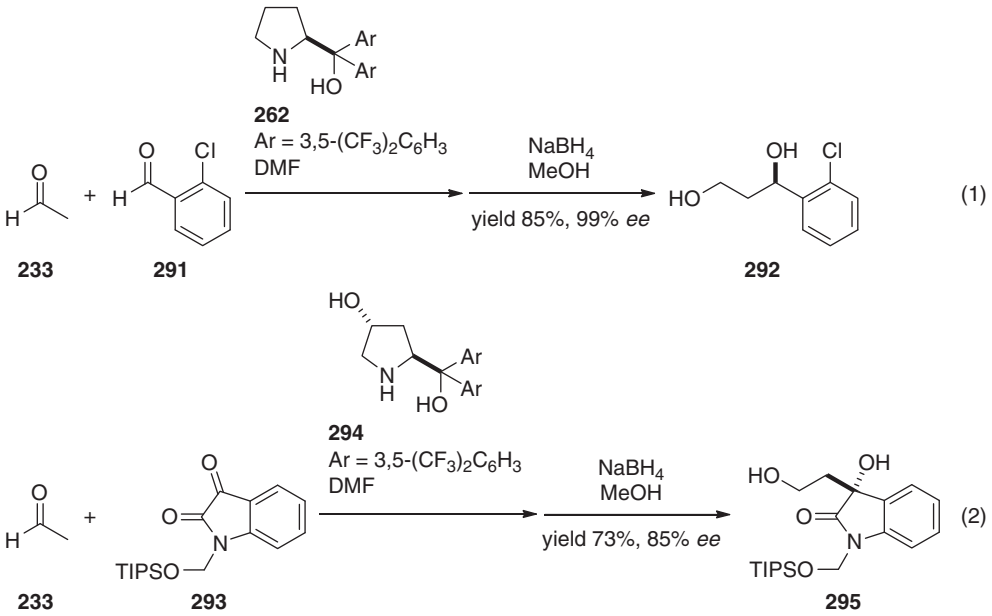
When acetaldehyde **233**, a simple aldehyde that is unsubstituted at the α-position, is employed in an aldol reaction, it is expected to act as both a reactive electrophile and a nucleophile. The aldol product itself is an unhindered nucleophile, and thus suppression of further reaction is a difficult problem. In fact, Barbas and coworkers reported that 5-hydroxy-2-hexenal **235**, a trimerization product of acetaldehyde **233**, was obtained in 10% yield and 90% *ee* when acetaldehyde **233** was treated with (*S*)-proline (Scheme 42).[118] In contrast, Hayashi and coworkers developed a diarylprolinol catalyst **262** that allowed acetaldehyde dimerization (Scheme 58).[72] The aldol product that was generated reacted immediately with another acetaldehyde molecule

through the oxygen atom to generate a cyclic hemiacetal **289**, which suppressed the undesirable overreaction; side reactions, such as dehydration to afford 2-butenal, were not observed.



Scheme 58 Self-aldol reaction of acetaldehyde using diarylprolinol.

When diarylprolinol **262** was employed in the aldol reaction of acetaldehyde **233** with 2-chlorobenzaldehyde **291**, the cross-aldol product **292** was generated in good yield with nearly complete enantioselectivity (Scheme 59–1).[71] The reaction proceeded efficiently with electron-deficient aromatic aldehydes and olefinic aldehydes. Hayashi and coworkers have also developed the asymmetric aldol reaction of acetaldehyde **233** with isatin derivatives **293**, catalyzed by 4-hydroxydiarylprolinol **294**, to afford the desired aldol product **295** in high enantioselectivity (Scheme 59–2).[73] They applied the present method to the short syntheses of *ent*-convolutamydine E and CPC-1, as well as to a route toward madindolines A and B.

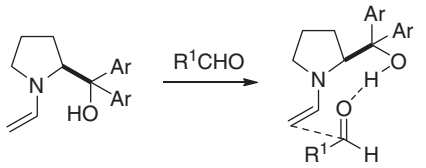


Scheme 59 Diarylprolinol-catalyzed cross-aldol reactions using acetaldehyde as a nucleophile.

The reaction shown in Scheme 59 is thought to proceed as follows: The diarylprolinol catalyst **262** reacts with acetaldehyde **233** to generate the corresponding *anti*-enamine **296**, which then reacts with an electrophilic aldehyde through transition state **297** (Figure 8). The aldehyde is thus activated by coordination to the proton of the hydroxyl group through a hydrogen bond.

2.07.2.3 Aldol Reactions in Water, in the Presence of Water, on Water, and by Water

Reactions in water, in the presence of water, on water, and by water have attracted a great deal of attention because water is an environmentally friendly and safe medium, which avoids the problems of pollution that are inherent to organic solvents.[133–135] Aldol reactions using organocatalysts in the presence of water are not only 'green', but water can also improve reactivity and selectivity in some cases. Water has been known to exhibit special properties when compared with common organic solvents; for



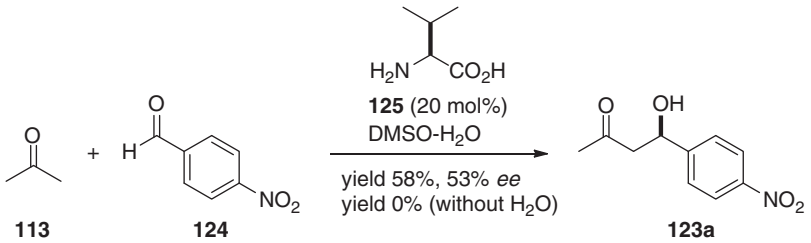
296 297

Figure 8 Enamine intermediate and the transition state model.

instance, Breslow and coworkers reported a rate acceleration of the Diels–Alder reaction 'in water,' wherein the reaction was performed at very high dilution to dissolve all the reactants.[136,137] In contrast, Sharpless and coworkers described 'on water' reaction conditions under which substantial rate acceleration was observed when the organic reactants were insoluble in the aqueous phase.[138] In this section, aldol reactions in water, in the presence of water, on water, and by water using secondary or primary amines are reviewed.[139–142]

2.07.2.3.1 Water as an additive

Water in organocatalytic intermolecular aldol reactions has been investigated by the Barbas group, ever since their seminal full paper in 2001.[57] Therein, it was reported that the reaction of acetone **113** and 4-nitrobenzaldehyde **124** tolerated a small amount of water (<4% v/v) without affecting the enantiomeric excess of the aldol product **123a**. However, increasing the amount of water decreased the enantioselectivity and the rate of formation of the aldol product **123a**. Yamamoto and coworkers subsequently discovered a proline-derived tetrazole species that affects aldol catalysis in the presence of at least 100 mol% water.[68] In their study, only hydrated aldehydes were found to be reactive. Pihko also demonstrated that water has an accelerating effect on proline-catalyzed ketone-aldehyde aldol reactions.[143] Water can also accelerate aldol reactions catalyzed by nonproline amino acids. Amedjkouh reported that valine **125** was able to catalyze the aldol reaction between acetone **113** and 4-nitrobenzaldehyde **124** in good stereoselectivity when employed in aqueous DMSO (equation 15).[144] In contrast, no reaction was observed when reacting in the presence of 20 mol% of **113** in pure DMSO. In an aqueous DMSO reaction medium, good results were also obtained with other amino acids, such as phenylalanine and aspartic acid.



113 124 123a (15)

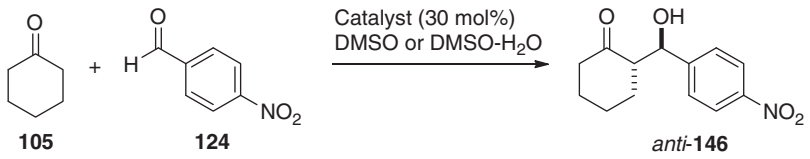
Córdova and coworkers examined the aldol reaction of cyclohexanone **105** and 4-nitrobenzaldehyde **124** using 13 of 20 proteinogenic amino acids and discovered that excellent enantioselectivity was obtained when either valine or isoleucine was used as the catalyst with 10 equivalents of water in DMSO.[102,145,146] They also reported that peptides and peptidic analogs with primary amino acids at their *N*-terminals can be employed as highly stereoselective catalysts.[146] Hayashi and coworkers reported a systematic study of the effectiveness of proteinogenic amino acids in DMSO and aqueous DMSO containing 3 equivalents of water (Table 1).[103] With the exceptions of phenylalanine, lysine, arginine, aspartic acid, and glutamine, in most cases the diastereoselectivity increased when the reaction was performed in aqueous DMSO. A marked increase in the diastereoselectivity was observed when proline was employed: an excellent *de* (82% *de*) was obtained in aqueous DMSO in spite of the low *de* in DMSO (20% *de*). For most of the amino acids employed, the enantioselectivity was the same for the reactions in water-free conditions and those in aqueous DMSO. Water had the positive effect of increasing the enantioselectivity only when proline, serine, and histidine were employed.

Hayashi further investigated aldol reactions of 2-butanone **298** to study the effect of water (Table 2).[103] Two regioisomers **299** and **300** were formed and the effect of water in these two aldol reactions was different. Water had a positive effect when the ethyl side of the ketone reacted, whereas no effect was observed when the methyl side reacted. No effect of water was observed with respect to the regioselectivity of the reaction.

2.07.2.3.2 Water as a solvent

In general, organocatalytic reactions are carried out in a one-pot operation by stirring a carbonyl compound, an amine, and an electrophile in conventional organic solvents, such as DMSO, DMF, or $CHCl_3$, which are toxic, flammable, and volatile. Removal of water is not required for the formation of an enamine intermediate that proceeds to react directly with an electrophile and water tolerance is a desirable characteristic for an organocatalyst. Unlike native aldolases or aldolase antibodies, however, in the presence of bulk water aldolase-type organocatalytic reactions generally result in very poor yield and stereoselectivity.[57,115] It thus seemed

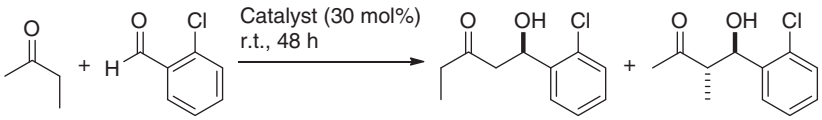
Table 1 Effectiveness of various amino acids in aldol reactions: comparison of DMSO to aqueous DMSO[103]



105 **124** *anti*-**146**

In DMSO					*In DMSO-H_2O*				
Catalyst	*Time (h)*	*Yield (%)*	de *(%)*	ee *(%)*	*Catalyst*	*Time (h)*	*Yield (%)*	de *(%)*	ee *(%)*
Gly	30	73	26	0	Gly	30	75	70	0
Ala	12	74	64	90	Ala	12	72	86	90
Val	6	79	70	93	Val	6	65	88	96
Ile	24	84	69	96	Ile	24	84	86	97
Pro	2	41	20	84	Pro	2	79	82	96
Ser	48	79	29	75	Ser	48	84	68	91
His	24	80	46	59	His	24	82	57	67

Table 2 Effect of Pro, Val, and Ile in aldol reactions of butanone[103]



298 **291** **299** **300**

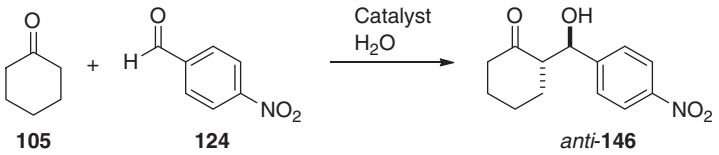
Catalyst	*Solvent*	***299***		***300***		
		Yield (%)	ee *(%)*	*Yield (%)*	de *(%)*	ee *(%)*
Pro	DMSO	45	65	16	44	89
Pro	Aqueous DMSO	46	69	25	>90	98
Val	Aqueous DMSO	9	55	14	47	74
Ile	Aqueous DMSO	11	59	15	49	63

difficult to achieve an asymmetric aldol reaction using water as a solvent, without any organic solvents or additives. It is a common misconception to consider enzymatic reactions as actually taking place 'in water.' An enzyme-catalyzed reaction might more instructively be regarded as taking place in organic solvent wherein the enzyme itself is essentially a water-soluble reaction flask that presents a stereodefined array of organic side chains that affect catalysis. As noted by the Sharpless group, the use of water as the only supporting medium for a reaction provides for ease of product isolation, high specific heat capacity, high specific inductive capacity, unique redox stability, and nonexhaustible resource, even if the rate acceleration is negligible.[138] Developments in aldol reactions catalyzed by enamine-based organocatalysts in aqueous media without addition of organic solvents are highlighted here.[140,141,142]

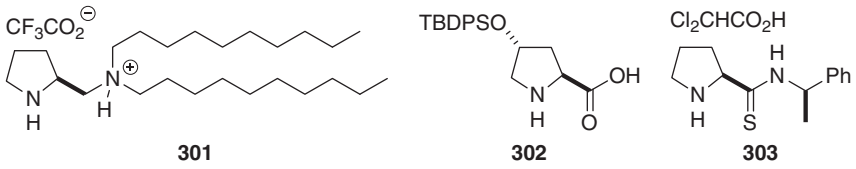
The pioneering work in this field has been independently reported by the Takabe and Barbas group and the Hayashi group based on two distinct strategies. Designed small diamine catalyst **301** (10 mol%) in the presence of trifluoroacetic acid in an emulsion system catalyzes the direct cross-aldol reaction of cyclohexanone (**105**, 2 equivalents) with 4-nitrobenzaldehyde **124** in bulk water (111 equivalents), giving the *anti*-aldol product **146** in quantitative yield with 94% *ee* (**Table 3**, entry 1).[147] A stoichiometric amount of donor **105** was enough to complete the reaction, thereby increasing the economy of the reaction (entry 2). Catalyst loading could also be decreased to 1–0.5 mol% (entries 3 and 4),[140] although no reaction was observed at 1 mol% catalyst loading using DMSO only as solvent.[148] Furthermore, crude aldol products **146** are readily isolated by removal of water using centrifugal separation; no extraction and washing are needed. The recovered catalyst **301** as well as water can be used again. The second strategy employed *trans*-L-siloxyproline **302** as the key catalyst. Using this siloxyproline catalyst **302** under a two-phase system, a marked increase in diastereoselectivity was observed when water was employed as the solvent (entries 5 and 6).[59,60] As these procedures use a small amount of water (3–18 equivalents), these reactions are generally called 'direct aldol reactions in the presence of water.'[149–151] It should be noted, however, that a large excess of water does not disturb the reaction at all. The reaction proceeds smoothly even in the presence of 350 equivalents of water to provide the same excellent selectivity (entries 7 and 8).[60] A great number of direct aldol reactions in aqueous media with no organic solvent have now been reported. Several of these reports are summarized in **Table 3**. On the basis of investigations of different salting-out and salting-in conditions, brine is clearly a

unique aqueous media that accelerates the rate of reaction and affects the stereochemical outcome of the aldol reactions due to hydrophobic aggregation (entries 9 and 10).[152,153] As two electron-withdrawing ester groups strengthen the double hydrogen bonds and the siloxy group increases hydrophobicity, the catalyst **305** is highly reactive (Table 3, entry 11).[154] A combination of fluorous separations with catalysis in water is achieved by the fluorous pyrrolidine sulfonamide **306**, which provides the aldol product **146** in good yield with high stereoselectivity (entry 12).[155] Fluorous extraction allows catalyst recovery and reuse for at least seven cycles. The primary–tertiary diamine **307** in the presence of triflic acid also catalyzes the aldol reaction in water (entry 13).[156]

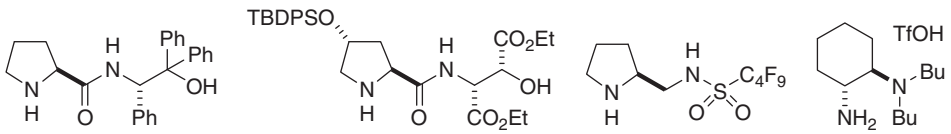
Table 3 Aldol reactions in aqueous media without addition of organic solvents



Catalysts



301 302 303



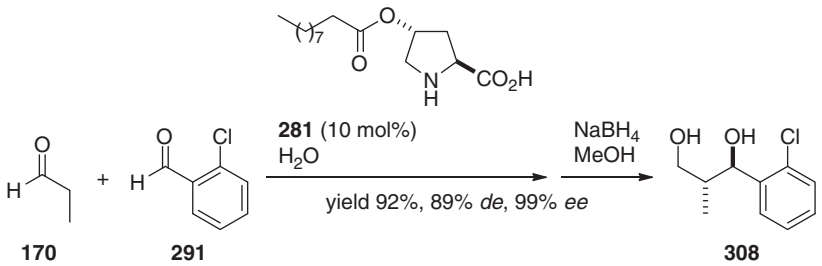
304 305 306 307

Entries	*Catalyst (mol%)*	***105** (equivalents)*	*H_2O (equivalents)*	*Temp (°C)*	*Time (h)*	*Yield (%)*	de *(%)*	ee *(%)*	*References*
1	**301** (10)	2	111	25	24	99	78	94	147
2	**301** (10)	1	111	25	48	98	70	92	147
3	**301** (1)	2	111	25	24	91	62	91	140
4	**301** (0.5)	2	111	25	48	81	62	89	140
5	**302** (10)	5	18	r.t.	5	86	>90	>99	59
6	**302** (1)	2	3	r.t.	42	89	88	97	60
7	**302** (10)	5	100	r.t.	18	84	85	>99	60
8	**302** (10)	5	350	r.t.	18	77	88	>99	60
9	**303** (2.5)	1.2	111[a]	r.t.	28	97	86	93	152
10	**304** (0.5)	4	55[a]	−10	20–48	NI[b]	74	91	153
11	**305** (1)	2	55	25	5	99	>98	94	154
12	**306** (10)	10	111	0	9	92	66	90	155
13	**307** (10)	2	111	r.t.	60	95	90	95[c]	156

[a]Brine was used as aqueous media.
[b]Not indicated in detail.
[c]Enantiomer of **146** was obtained as a major product.

Hayashi developed a direct asymmetric cross-aldol reaction of two different aldehydes in the presence of water, catalyzed by a proline-based surfactant **281** (Scheme 60).[157] Propanal **170** is water soluble, whereas 2-chlorobenzaldehyde **291** is not; thus an emulsion was formed in the reaction mixture and excellent diastereo- and enantioselectivities were attained using the surfactant catalyst **281**, the length of the proline side chain dramatically affected the yield: neither very long nor very short chains were effective, whereas catalyst **281** with a decanoate moiety was found to be the most efficient. Diastereo- and enantioselectivities decreased slightly as the amount of water in the reaction was increased. The aldol reactions also proceeded efficiently under neat reaction conditions, though slight decreases in diastereo- and enantioselectivities were observed. This result provides evidence that the reaction proceeds in the organic phase, and when the reaction is performed in the presence of water, it takes place inside emulsion pockets.

Remarkable temperature-dependent properties were reported for the aqueous aldol reaction using the designed diamine catalyst **301**.[140] When the direct aldol reaction is carried out in DMSO at 10 mol% catalyst loading, enantioselectivity sharply decreases as the temperature is raised (Figure 9). This observation, that *ee* decreases with increasing temperature, is quite general



Scheme 60 Aldehyde–aldehyde cross-aldol reaction catalyzed by a proline-surfactant organocatalyst in the presence of water.

for asymmetric syntheses in organic solvents. However, with water as solvent, the enantioselectivity is only slightly decreased at an elevated temperature and at 10 mol% catalyst loading (94%→90% *ee*). At 0.5 mol%, reactivity improved and enantioselectivity is maintained (yield 52%→86%, *ee* 89%→72%). These results suggest that hydrophobic interactions play an important role in reactivity and enantioselectivity, as increased temperature leads to an increased hydrophobic effect (i.e., the entropy-driven effect).

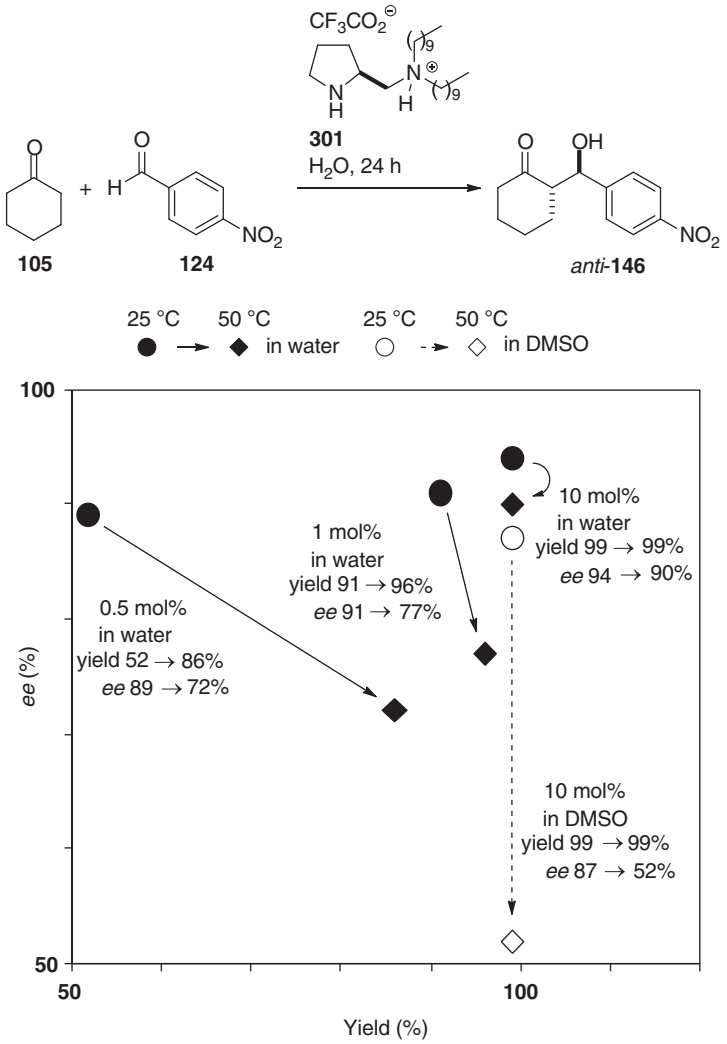


Figure 9 Temperature-dependent properties in aqueous aldol reactions.

The mechanism underlying the rate acceleration and the excellent enantioselectivity of reactions catalyzed by small amines in water is complex; a likely 'in water' mechanism is shown in Figures 10a.[140,148,158] A liquid organic donor assembles in water due to hydrophobic interactions, which forms a metastable micelle with the catalyst. Aggregation of the organic molecules excludes water from the organic phase and drives the equilibrium toward enamine formation. The enamine intermediate, composed of the

carbonyl donor and the catalyst, is more hydrophobic than catalyst alone; therefore, the enamine intermediate moves into the organic phase. It is believed that carbon–carbon bond formation between the enamine intermediate and the aldehyde acceptor occurs quickly in the highly concentrated organic micellar phase through a transition state similar to that observed in organic solvents, and then hydrolysis of the enamine intermediate proceeds. An 'on water' mechanism has also been proposed.[159,160] In this mechanism, a free hydroxy group at the oil–water phase boundary protrudes into the organic phase to catalyze reactions through the formation of hydrogen bonds to a donor, an acceptor, and/or the catalyst (Figure 10b).

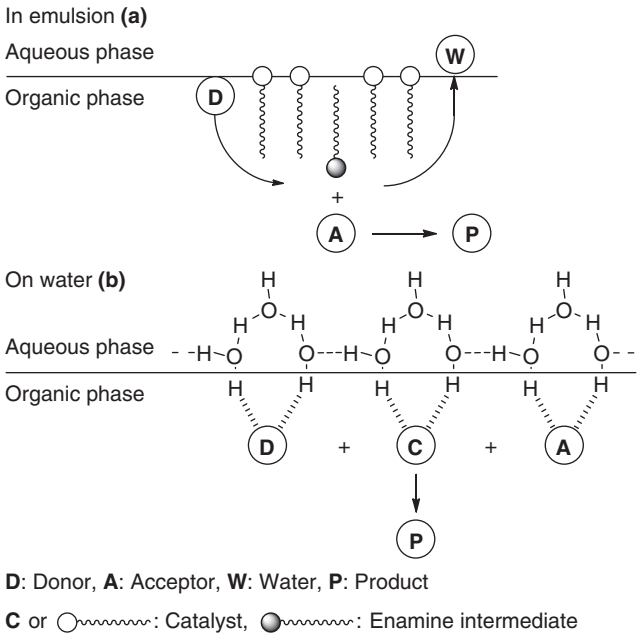
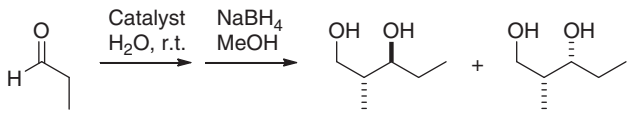


Figure 10 Cartoons of (a) in emulsion and (b) on water catalysis.

As both lipophilic and surfactant organocatalysts can promote asymmetric direct aldol reactions with excellent enantioselectivity in two-phase or emulsion systems, it was previously thought that they proceed in the organic phase at least at its surface. However, aldol reactions in which both the substrate and the catalyst dissolve homogeneously in water have been reported. The Hayashi group reported that some amino acids, dipeptides, and amides derived from amino acids proceed the self-aldol reaction of propanal **170** in water (Table 4).[161] Notable result was obtained when Pro-NH_2 **129** was utilized. A moderate yield was

Table 4 Effect of amino acid, amino amide, or dipeptide as catalysts for the self-aldol reaction of propanal in water[161]



Entries	*Catalyst*	*Time (h)*	*Yield (%)*	dr *(anti/syn)*	ee *(%)*	
					anti	syn
1	Ala	24	<3	ND	ND	ND
2	Pro	24	<3	ND	ND	ND
3	Arg	24	15	64:36	−18	−14
4	Ala-Ala	24	15	50:50	18	3
5	Ala-NH_2	24	18	45:55	28	11
6	Tyr-NH_2	24	41	48:52	−53	−13
7	Thr-NH_2	24	32	40:60	13	9
8	Pro-NH_2	3	41	48:52	78	74

ND, not determined.

obtained in short reaction time with good enantioselectivities (*anti* 78% *ee*, *syn* 74% *ee*). As both propanal and Pro-NH_2 **129** dissolve completely in water, this aldol reaction proceeds 'in water' and not 'in the organic phase,' at least for the first 2.5 h.

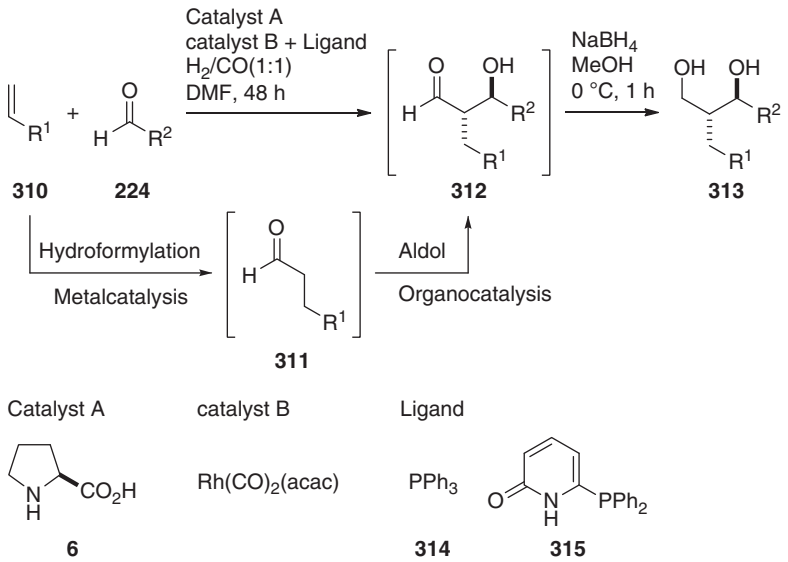
In these reactions catalysed by organocatalysts, there are several discussions and discrepancies about the role of water and the appropriate terminology to use.[149–151] Hayashi proposed to use the term 'in water' when the reactants participating in the reaction are homogeneously dissolved whereas the term 'in the presence of water' should be used for a reaction that proceeds in a concentrated organic phase with water being present as a second phase and influencing the reaction in the organic phase. Although the observed effect for 'on water' reactions is rate acceleration, the observed effect for 'in the presence of water' reaction is an increased enantioselectivity. The reasons behind yield improvement are different in each reaction system. Some case would be effected by 'on water,' or accelerate phase-transfer catalyst. However, it should be noted that there is known organocatalyzed aldol reaction in homogeneous aqueous solution in the case of prolinamide **129**-catalyzed self-aldol reaction of propanal **170** (Table 4). Meanwhile, water improves diastereoselectivities and enantioselectivities by some kind of interaction, the reason behind this influence is still unclear. These reactions may be predisposed to favor transition states that optimize hydrophobic interactions, when highly hydrophobic catalysts are employed in the presence of water.[162,163]

2.07.2.4 Multicatalytic Reaction Sequences

2.07.2.4.1 Metal-catalyzed and organocatalytic reaction sequences

In recent years, combinations of transition metal catalysis and organocatalysis have attracted increasing attention in synthetic organic chemistry. These combinations allow for the regio- and stereoselective synthesis of complex molecule from readily available, simple starting materials.[164–167] A one-pot Rh complex-catalyzed hydroformylation, following (*S*)-proline-catalyzed enantioselective cross-aldol reaction sequence, is one example (Table 5).[168] Simple alkenes **310** are transformed *in situ* to aliphatic aldehydes **311**, giving aldol products **312** in good yields with excellent stereoselectivities in a one-pot operation.

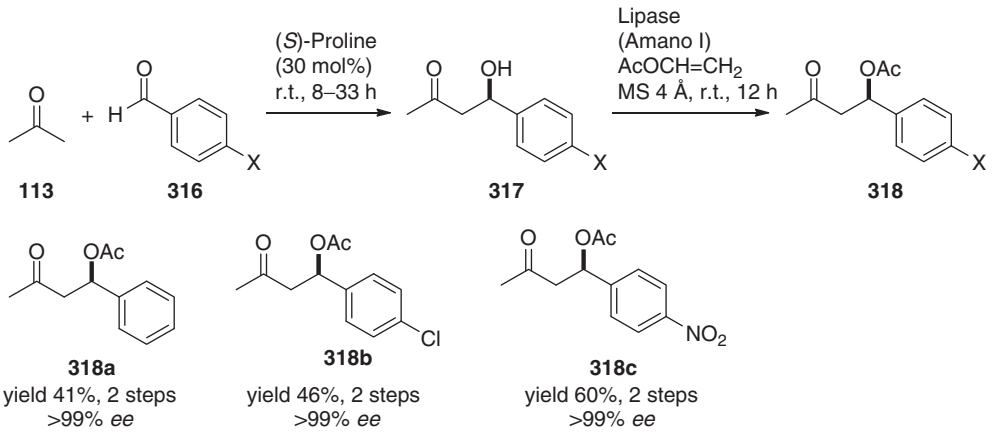
Table 5 Metal-catalyzed and organocatalytic reaction sequence[168]



Entries	R^1	R^2	***6*** *(mol%)*	*[Rh] (mol%)*	*Ligand (mol%)*	*Conditions*	*Yield (%)*	de *(%)*	ee *(%)*
1	H	*i*-Pr	6	0.2	**314** (4.4)	30 bar, 5 °C	76	90	98
2	H	*c*Hex	5	0.25	**314** (5.0)	30 bar, 5 °C	81	86	99
3	H	Ph	5	0.25	**315** (1.0)	30 bar, 5 °C	91	50	94
4	Hex	*i*-Pr	0.15	0.01	**315** (0.1)	20 bar, 15→5 °C	86	90	97

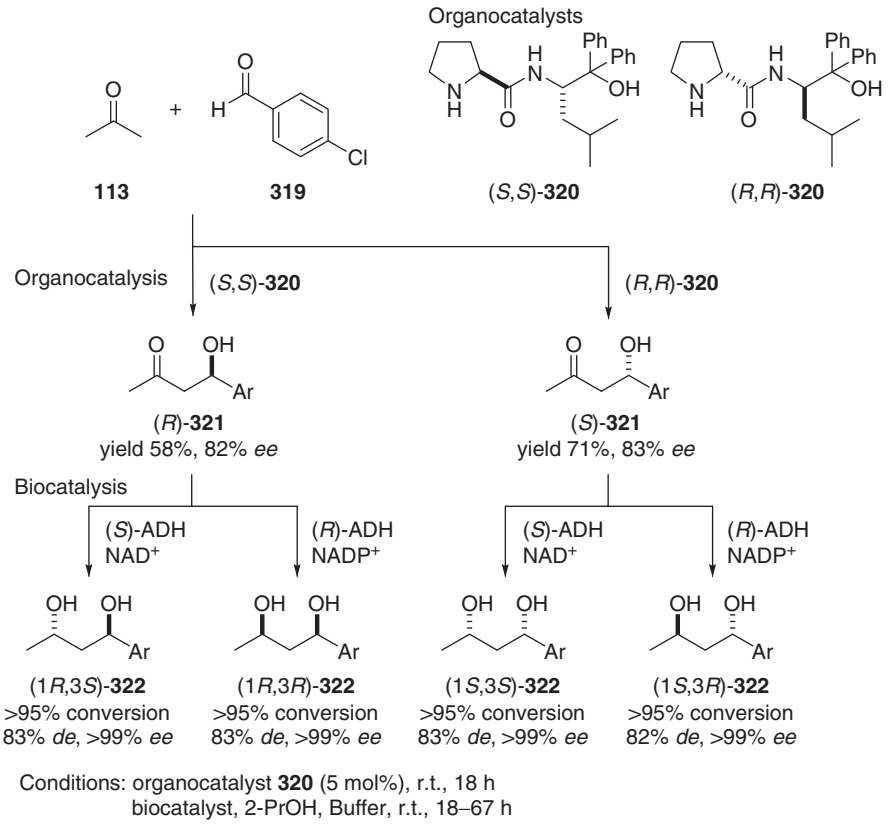
2.07.2.4.2 Organocatalytic and biocatalytic reaction sequences

Like combinations of metalcatalysts and organocatalysts in Table 5, combining biocatalysis and organocatalysis is a powerful strategy to improve the synthetic efficiency. As (*S*)-proline has an insignificant effect on the lipase-catalyzed reaction, the one-pot sequential and/or tandem reactions are investigated by the Córdova group (Scheme 61).[169] Although the first (*S*)-proline-catalyzed aldol reaction provides the desired aldol **317** with less than 80% *ee*, excellent enantioselectivities are achieved after the second lipase-catalyzed kinetic resolution in reasonable chemical yields.



Scheme 61 Sequential direct aldol reactions and lipase-catalyzed kinetic resolutions.

Sequential two-step synthesis based on the organocatalytic aldol reaction and biocatalytic reduction leads to all four possible stereoisomers of 1,3-diols **322** in enantiomerically pure form (Scheme 62).[170] The stereochemistry depends on the combination of the organocatalyst **320** and alcohol dehydrogenase. Furthermore, conversion is improved up to 80% by sequential one-pot synthesis without the workup step after the organocatalytic aldol reaction.

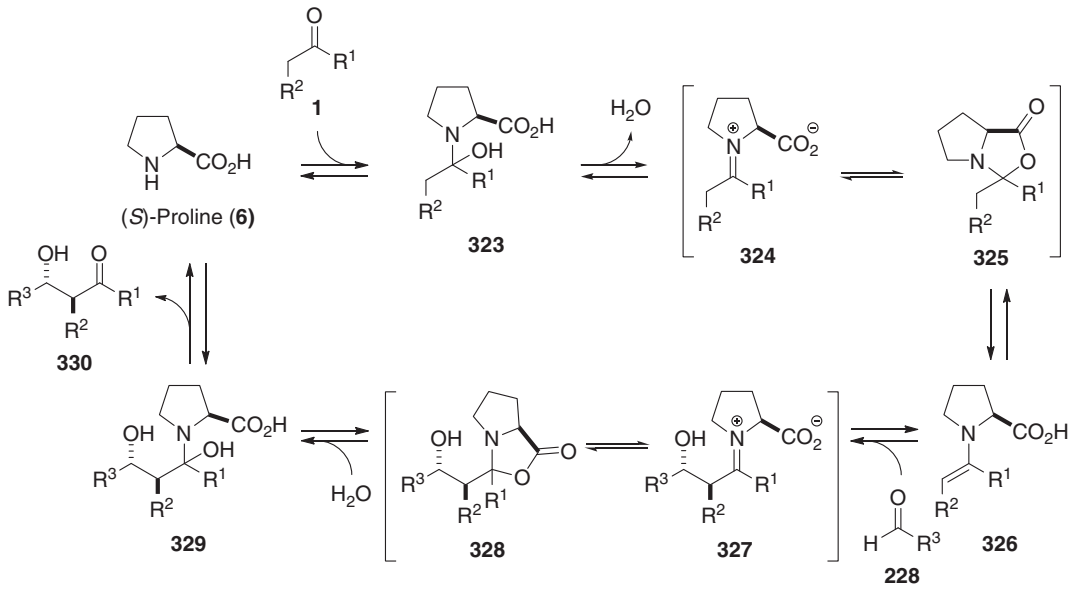


Scheme 62 Organocatalytic and biocatalytic reaction sequence.

2.07.2.5 Mechanistic Studies

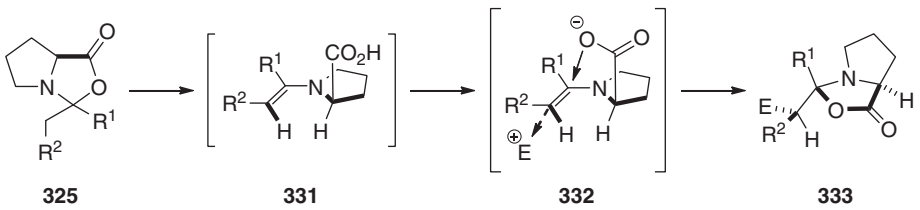
A number of experimental and theoretical studies have been carried out in order to elucidate the mechanism of the (*S*)-proline-catalyzed aldol reaction. The catalytic cycle of (*S*)-proline-catalyzed aldol reactions of nucleophilic aldehydes and ketones with carbonyl electrophiles as shown in Scheme 63 is widely accepted by the organic chemists, in spite of being still under debate.

Nucleophilic attack of the nitrogen atom of (*S*)-proline **6** to the starting carbonyl compound **1** affords an iminium intermediate **324** through dehydration of an aminal intermediate **323**. The iminium **324** and oxazolidinone **325** are the substances at equilibrium. Nucleophilic enamine **326** is formed through deprotonation, making carbon–carbon bond together with the carbonyl compound **228** as an electrophile. This step is the rate-determining step, and possible transition states are given later. The alkylated iminium **327** and/or oxazolidinone **328** are hydrolyzed to give an aminal intermediate **329**. Finally, the desired aldol **330** is released from **329** and (*S*)-proline **6** as a catalyst is regenerated. Overall, this mechanism is similar to the known type I aldolase mechanism as noted in Figure 3.



Scheme 63 Catalytic cycle of aldol reactions with (*S*)-proline.

Seebach and Eschenmoser proposed another mechanism (Scheme 64).[171] Carbonyl compound **1** reacts with (*S*)-proline to afford oxazolidinone **325**, from which enaminocarboxylic acid is generated. From this enamine, with the C=C bond of (*E*)-configuration and the C-atom bearing the COOH group in an *s-cis*-arrangement with the enamino C=C bond, carboxylate anion attacks the double bond of enamine **332**. Next, the generated anion further attacks the electrophile from the opposite side of the carboxyl moiety to afford the oxazolidinone derivative **333**, which is hydrolyzed to provide the desired product **330**.



Scheme 64 Another mechanism proposed by Seebach and Eschenmoser.

The efficiency of aldol reactions is expected to be influenced by the rate of the formation of enamine, the addition step, and stability of catalyst, among other factors. The carbon–carbon bond-forming step has a similar energy barrier as the enamine formation, indicating that under different conditions or with different substrates, the rate-determining step may be this step. In fact, the most recent kinetic evidence obtained by Armstrong and Blackmond indicates that under the reaction conditions studied, the addition step is rate determining.[172] It is believed that four factors control the stereoselectivity of the product (Figure 11): (1) the geometry about the C–N bond of the enamine (**334** vs. **335**); (2) the geometric isomer of the formed enamine (**336** vs. **337**); (3) the enantiotopic face of the enamine for C–C bond formation (**338** vs. **339**); and (4) the enantiotopic face of the electrophile for C–C bond formation (**340** vs. **341**). Several catalysts have been developed to address and to control these issues.

Understanding a reaction mechanism and transition state is very important to realize the whole reaction and stereochemistry. Several reaction intermediates and transition state models are previously accepted in intramolecular aldol reaction (Figure 12). Achiral secondary amines such as pyrrolidine and piperidine have been used as a catalyst for intramolecular aldol reaction since its discovery in 1950 reported by Wieland and Miescher[173]; after a decade and a half, the Spencer group confirmed enamine

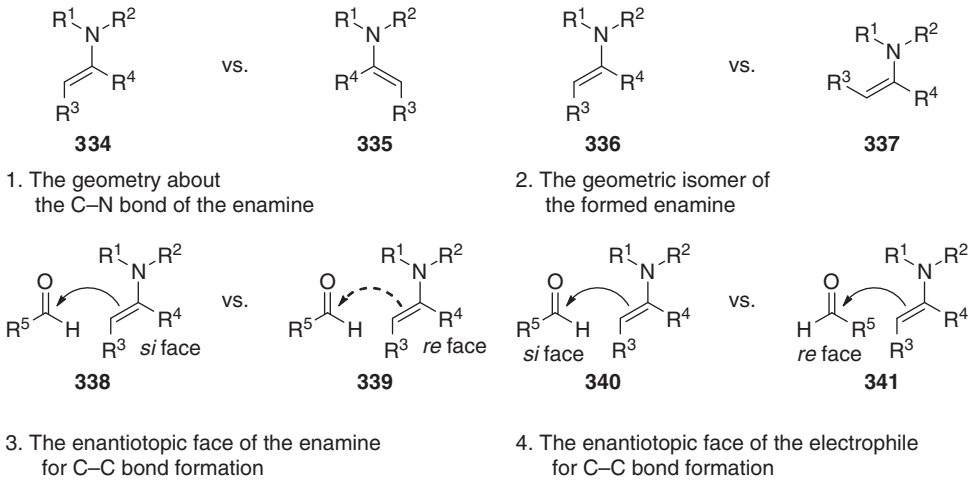


Figure 11 Four factors that affect stereoselectivity in aldol additions.

intermediates **342** through mechanistic studies.[174] The Hajos group showed two possible mechanisms for (*S*)-proline-catalyzed intramolecular aldol reaction in 1974.[5] The first is enamine mechanism **343a** including oxazolidinone mechanism **343b,** which was recently discussed again by the Seebach and Eschenmoser group.[171] However, enamine mechanism **343a** is controverted, because no incorporation of ^{18}O into the aldol product **37** is observed in (*S*)-proline-catalyzed intramolecular aldol reaction of triketone **35** in the presence of ^{18}O-labeled water. Thus, they propose enol mechanism **343c**, which involves the addition of (*S*)-proline in its zwitterionic form to one of the carbonyl groups of the cyclopentanedione ring.

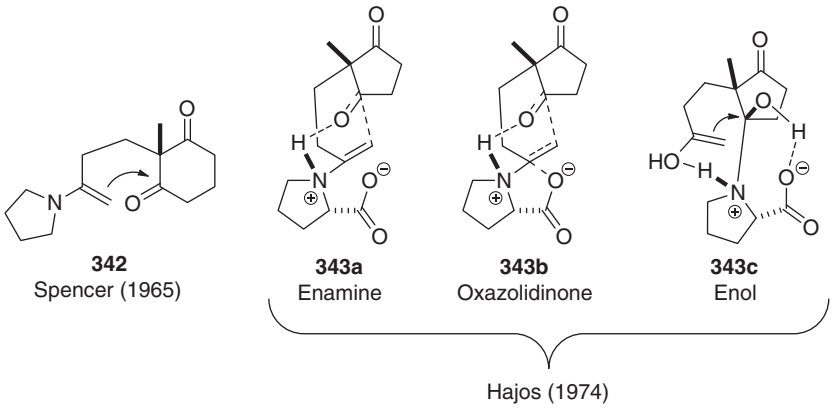
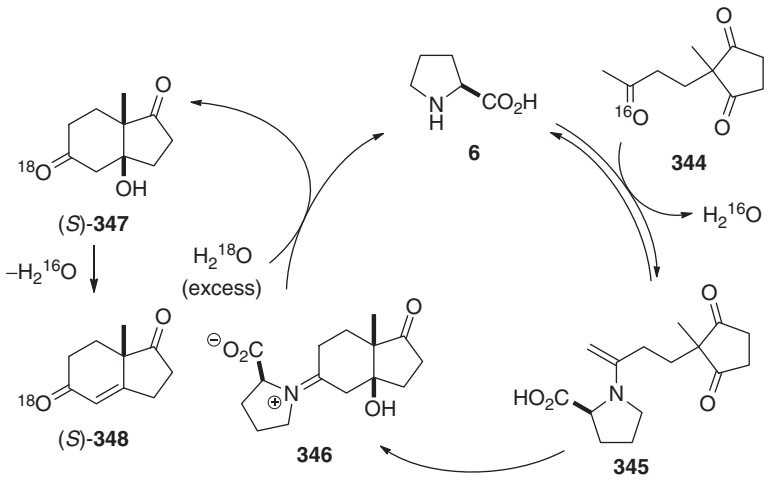


Figure 12 Proposed reaction intermediates and transition state models.

The Hajos group has proposed the enol mechanism according to their ^{18}O-labeled experiments; however, the List group recently reexamined it to prove the enamine mechanism (Scheme 65),[175] though detection of enamines derived from aldehydes or ketones with (*S*)-proline is still difficult to achieve. A high ^{18}O incorporation (>90%) is observed: (1) when the reactions are performed under completely air- and moisture-free conditions; (2) when both the substrate and proline catalyst are carefully dried azeotropically; and (3) when dried solvent (DMSO) is used. These results support that the final hydrolysis step from the iminium **346** to the ketone **347** requires ^{18}O-enriched water, namely, the mechanism of the Hajos–Parrish–Eder–Sauer–Wiechert reaction is confirmed as the enamine mechanism not enol mechanism.

Dilution effect and nonlinear effect indicate that the catalysis for intramolecular aldol reaction needs more than one proline molecule per triketone molecule substrate reported by the Kagan and Agami group (Figure 13, **349**).[176,177] As the computational chemistry is developed, the mechanism for (*S*)-proline-catalyzed aldol reaction is investigated. The Houk group shows evidence for the involvement of only one proline molecule in the transition states of intramolecular aldol reactions, which are based on kinetic measurements and the absence of nonlinear and dilution effects. In addition, these are supported by B3LYP/6-31 G* calculations.[178–182] In the chair transition state model **350a** leading to the corresponding aldol (*S*)-**37**, hydrogen bonding between the carbonyl group of electrophile and the carboxylic acid of (*S*)-proline is formed. The favorable electrostatic interaction of $^{+\delta}$NCH- - O$^{\delta-}$ also contributes to the lower energy of transition state **350a**. Similarly, a Zimmerman–Traxler chair-like model **350b** is also proposed for (*S*)-proline-catalyzed intermolecular aldol reaction. Double activation by (*S*)-proline as a bifunctional



Scheme 65 Proposed enamine catalysis cycle of the Hajos–Parrish–Eder–Sauer–Wiechert reaction.

catalyst is found again, that is, (1) activation of nucleophile through enamine formation with pyrrolidine moiety and (2) activation of electrophile through hydrogen bonding with Brønsted acid moiety.

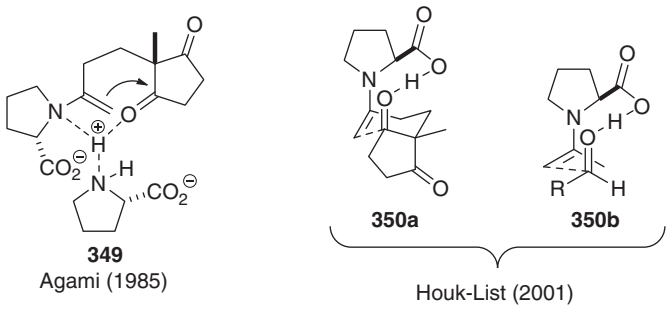


Figure 13 Proposed transition state models.

2.07.3 Brønsted Acid and Hydrogen-Bond Catalysis

Asymmetric reactions catalyzed by chiral Brønsted acids have become the subject of cutting-edge research in synthetic organic chemistry in recent years.[183–187] There are three modes of activation of carbonyl compounds (Figure 14): (1) Brønsted acid catalysis **351**, (2) double hydrogen bonding **352**, and (3) single hydrogen bonding **353**. It is of note, however, that there is no clear distinction between Brønsted acid catalysis and hydrogen-bond catalysis.

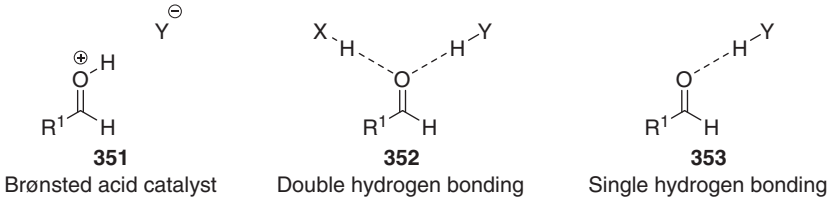


Figure 14 Modes of activation for Brønsted acid and hydrogen-bond catalysis.

In general, the activation of the substrate is enabled through hydrogen bonding or formation of ion pairs, depending on the acidic strength of the catalyst such as phosphoric acids,[188–195] ammonium salts, thioureas,[196] diols,[197] and squaramides.[198] Among the different chiral Brønsted acids (Figure 15), axial chiral phosphoric acid derivatives have shown astonishing versatility.

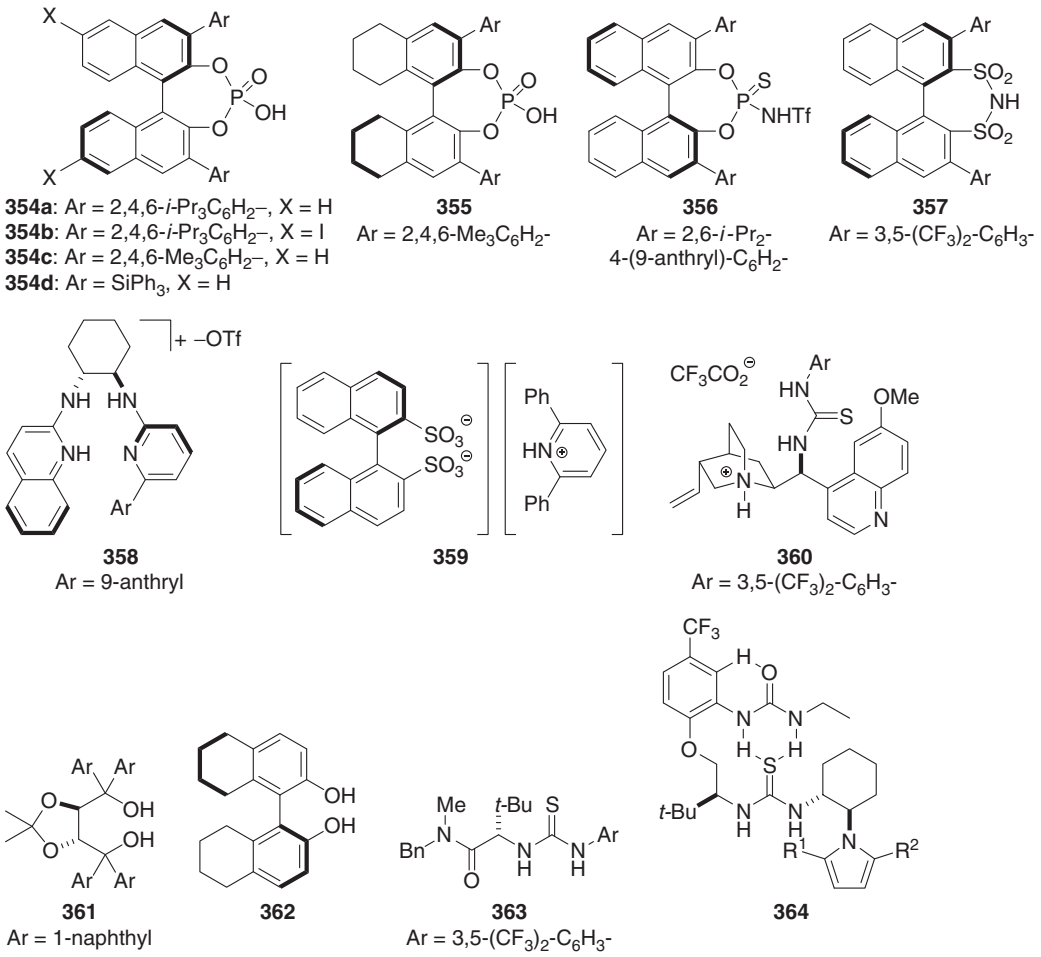
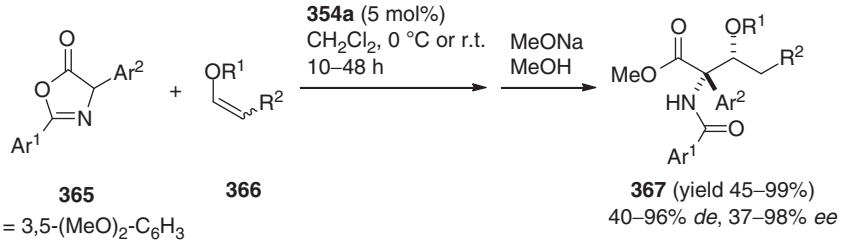


Figure 15 Representative Brønsted acid and hydrogen-bond catalysts.

2.07.3.1 Intermolecular Aldol Reactions in Brønsted Acid and Hydrogen-Bond Catalysis

2.07.3.1.1 Aldol-type reactions of azlactone

The direct aldol-type reaction of azlactone **365** with an oxocarbenium ion through a protonation of vinyl ethers **366** by the chiral phosphoric acid **354a** as a catalyst provides *β*-alkoxy-*α*-amino acid derivatives **367** bearing a quaternary stereogenic center with high diastereo- and enantioselectivity (Scheme 66).[199]



Scheme 66 Direct aldol-type reactions of azlactone.

The ion pairs **368** or **369** likely have a three-dimensionally oriented specific interaction between a chiral conjugate base and an oxocarbenium ion through a C–H···O hydrogen bonding model, controlling enantioselectivity of the transformations (Figure 16).

2.07.3.1.2 Mukaiyama aldol reactions in Brønsted acid catalysis

The Mukaiyama aldol reaction is one of the most synthetically reliable carbon–carbon bond-forming reactions.[3] Although a wide variety of Lewis acid and Lewis base catalysts have been developed for enantioselective Mukaiyama aldol reactions involving silyl

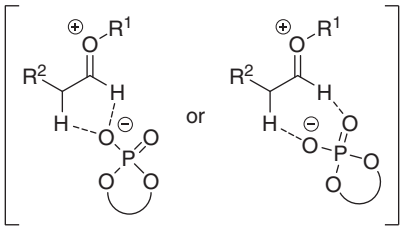
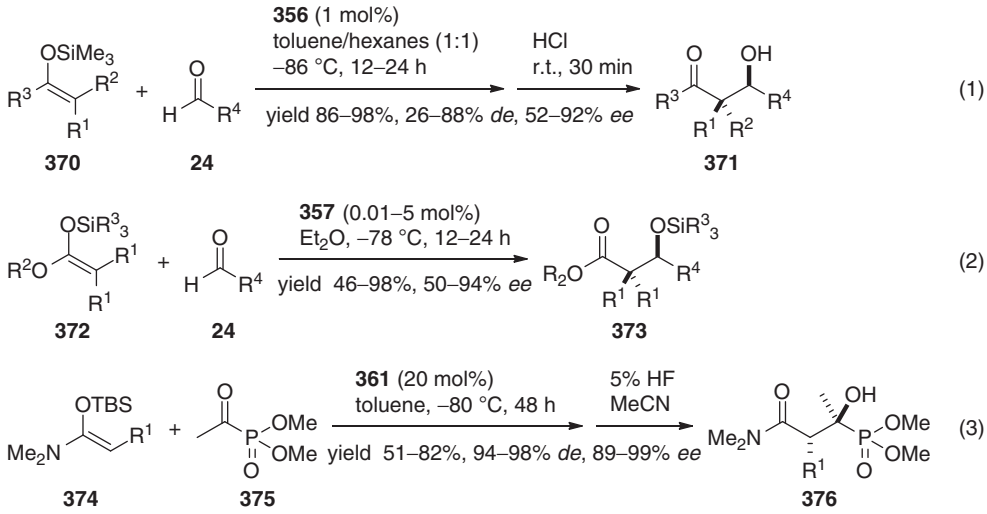


Figure 16 Reactive intermediate in direct aldol-type reactions of azlactone.

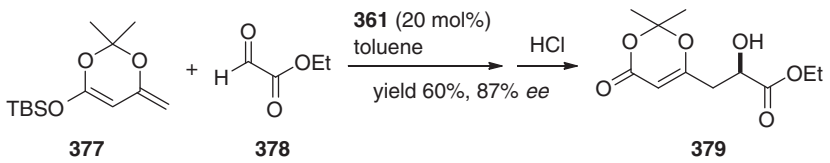
enol ether as a stable enolate component, very few examples of chiral Brønsted acid-catalyzed Mukaiyama aldol reactions were reported before 2006. Catalyst loading (10 mol%) may not be sufficient due to their lower acidities.[200,201] To increase the reactivities of chiral phosphoric acid catalysts, chiral *N*-triflyl thiophosphoramide **356** was developed to catalyze the Mukaiyama aldol reactions of aldehydes **24** using silyl enol ethers of ketones **370** as nucleophiles (Scheme 67–1). From mechanistic studies, the type of catalysis depends on reaction temperature: (1) a Lewis acid pathway associated with the silylated Brønsted acid occurs at room temperature and (2) a Brønsted acid pathway associated with the Brønsted acid itself takes place at a low temperature.[202] A designed chiral disulfonimide **357** was developed as a powerful Brønsted acid for the Mukaiyama aldol reaction of aldehydes **24** using silyl enol ethers of esters **372** as nucleophiles; these reactions provide the desired aldol products **373** with more than 90% *ee* in most cases (Scheme 67–2). The actual catalyst is proposed to be an *in situ* generated *N*-silyl imide.[203] An excellent contribution was made by Rawal and coworkers in 2003 who developed a chiral Brønsted acid catalyst, TADDOL (*α,α,α′,α′*-tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol) in hetero-Diels–Alder reactions.[204] They also developed that a simple chiral diol of the TADDOL **361** catalyzes Mukaiyama aldol reactions between aldehydes and silyl enol ethers of amides **374**.[200,201] In addition, hydrogen-bond activation by the diol catalyst **361** is applicable for the Mukaiyama aldol reactions of acyl phosphonates **375** with silyl enol ethers of amides **374**, giving the aldol product **376** with one tertiary and one quaternary stereocenter with excellent diastereo- and enantioselectivities (Scheme 67–3).[205]



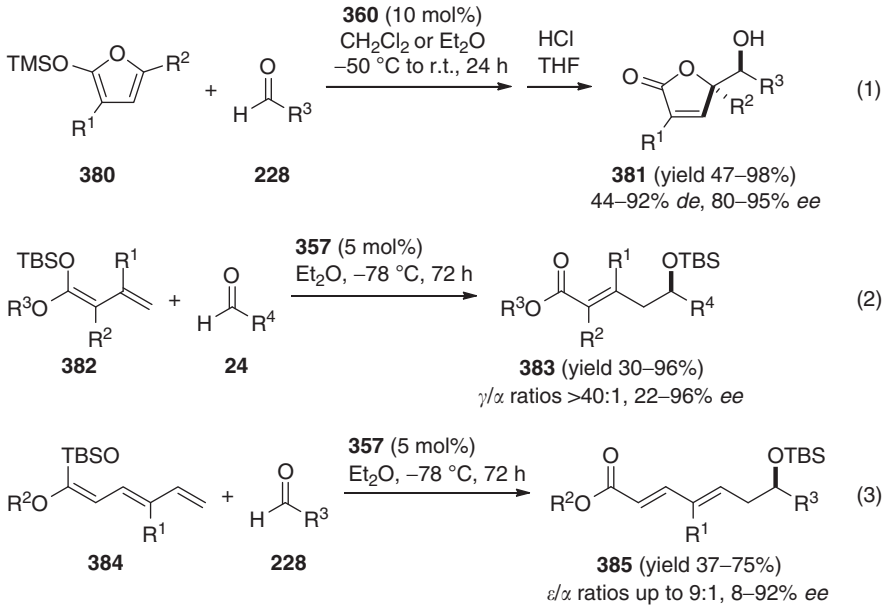
Scheme 67 Mukaiyama aldol reactions.

The applications of aldol reactions with *α,β*-unsaturated carbonyl compounds as nucleophiles, in general, called vinylogous aldol reactions, have attracted much attention.[206] Rawal developed enantioselective vinylogous Mukaiyama aldol reactions of **377** and **378** using **361** in 2005 (Scheme 68).[207] TADDOL catalysts are reliable because they generally exist in a well-defined internally hydrogen-bonded arrangement; furthermore, these catalysts are most effective with reactive aldehydes. In such reactions, the proposed mechanism proceeds through activation of the aldol acceptor **378** by hydrogen bonding.

Organocatalytic approaches using a wide variety of Brønsted acids and hydrogen-bond catalysts have been intensively investigated after 2005.[208] The silyloxy furans **380** are good substrates for the vinylogous Mukaiyama aldol reaction; however, their applications have been limited until recently. Carboxylate-ammonium salt **360** prepared from a cinchona-thiourea and trifluoroacetic acid is an effective catalyst for the vinylogous aldol reaction of the silyloxy furans **380** with aldehydes **228**, producing *anti*-aldol products **381** with high enantiomeric excess (Scheme 69–1).[209] Like the Mukaiyama aldol reaction (Scheme 67–2), the



Scheme 68 TADDOL-catalyzed vinylogous Mukaiyama aldol reaction.

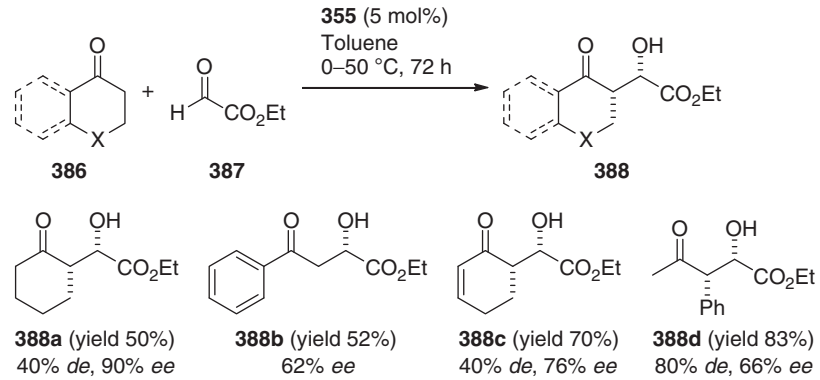


Scheme 69 Vinylogous Mukaiyama aldol reactions.

vinylogous Mukaiyama aldol reactions of crotonic acid-derived nucleophiles **382** with aldehydes **24** are catalyzed by the disulfonimide **357**. Extremely high regioselectivities in γ/α ratios up to $>40{:}1$ and more than 90% enantiomeric excesses are observed in most cases (Scheme 69–2).[210] This methodology was further expanded to ε-selective double vinylogous Mukaiyama aldol reactions (Scheme 69–3).[210] The single-step syntheses of chiral α,β- and $\alpha,\beta,\gamma,\delta$-unsaturated esters **383** and **385** through vinylogous and double vinylogous Mukaiyama aldol reactions would be potentially useful for natural product synthesis.

2.07.3.1.3 Direct aldol reactions in Brønsted acid catalysis

Blanchet reported phosphoric acid-catalyzed direct aldol reactions between ketones **386** and ethyl glyoxylate **387**, which is a reactive electrophile (Scheme 70).[211] Moderate to excellent diastereo- and enantioselectivities have been achieved using H_8-BINOL-derived phosphoric acid **355**. The aldol products **388** have *syn*-configurations; thus, this reaction is complementary to

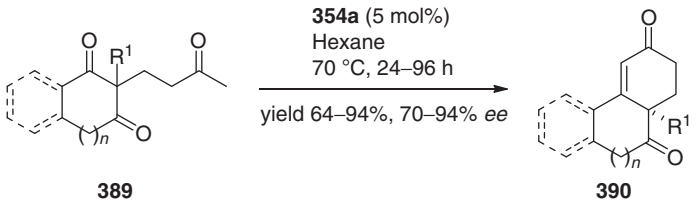


Scheme 70 Phosphoric acid-catalyzed direct aldol reactions.

(*S*)-proline catalysis in Brønsted acids, which in general yields the *anti*-configuration.[9] Furthermore, unreactive substrates in enamine organocatalysis were able to afford the aldol products under these conditions.

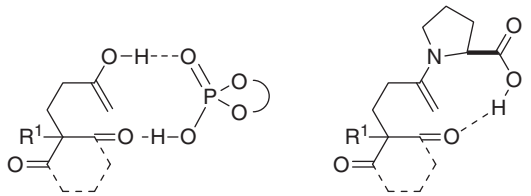
2.07.3.2 Intramolecular Aldol Reactions in Brønsted Acid Catalysis

Significant desymmetrizations of meso-1,3-diones **389** result from intramolecular aldol reactions catalyzed by chiral phosphoric acid **354a**. This method affords a wide variety of chiral cyclohexenones **390** in high yields and with excellent enantioselectivities carried out by the Akiyama group (equation 16).[212]



389 **390** (16)

ONIOM (B3LYP/6-31 G*: HF/3-21 G) calculations suggest the identity of the reaction intermediate and the origin of the enantioselectivity (Figure 17).[212] In the transition state model **391**, the carbonyl and enol groups are activated by chiral phosphoric acid **354a** with Brønsted acidic and Lewis basic sites, respectively. The attack from the *si* face is more favorable than attack from the *re* face and provides the (*R*)-isomer **390** (R^1 = Me). As the (*S*)-isomer is formed in the (*S*)-proline-catalyzed Hajos–Parrish–Eder–Sauer–Wiechert cyclization through transition state **392**,[4–7] Brønsted acid catalysis and enamine catalysis are complementary methodologies.



391 **392**

Figure 17 Proposed intermediates in aldol reactions comparing phosphoric acid catalyst to (*S*)-proline.

2.07.4 Brønsted Base Catalysis Including Bifunctional Catalysis

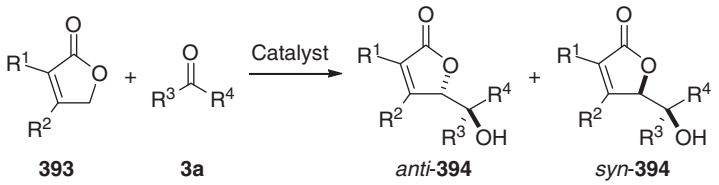
2.07.4.1 Aldol Reactions in Brønsted Base Catalysis Including Bifunctional Catalysis

Organic Brønsted bases have been used to catalyze synthetically valuable carbon–carbon bond-forming reactions of carbonyl and related compounds for decades. With the development of organocatalysis, chiral Brønsted base catalysis has generated significant interest.[213] Nitrogen-containing compounds such as tertiary amines, guanidines,[214,215] amidines, and imidazoles are predominantly used as a chiral Brønsted base catalyst; in particular, the cinchona family is effective due to their extensive versatility, stereochemical diversity, and commercial availability. Bifunctional catalysts such as tertiary amine-thiourea, cinchona-thiourea, and guanidine-thiourea are important in organocatalysis[216,217]; they are included in this section because reactive intermediates in bifunctional catalysis are often onium enolates or enolate-like species, similar to Brønsted base catalysts.

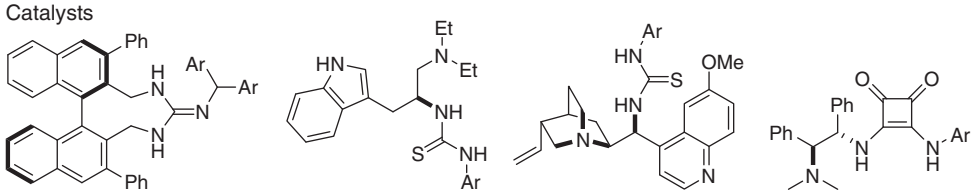
Recently, direct vinylogous aldol reactions of furanones **393** with aldehydes or ketones **3a** have been intensively investigated. These reactions are simple alternatives to the vinylogous Mukaiyama aldol reaction of silyloxy furans discussed in Scheme 69. Highly enantioselective direct vinylogous aldol reactions of dihalogenated furanones **393** ($R^1 = R^2 = Cl$) with aldehydes **3a** ($R^3 = H$) are catalyzed by the axially chiral guanidine **395**. The substituent attached to the guanidine moiety significantly influences the diastereo- and enantioselectivity as well as the catalytic activity. A bis(3,4,5-trimethoxyphenyl)methyl group shows the best results (Table 6, entries 1 and 2).[218] γ-Substituted butenolides **394** containing a tertiary alcohol moiety are provided by the highly *syn*-selective vinylogous aldol reactions between furanones **393** and ketoesters **3a** ($R^3 = Ph$, $R^4 = CO_2tBu$) catalyzed by the bifunctional catalyst **396** containing tertiary amine, thiourea, and tryptophan moieties (entry 3).[219] The *anti*-selective vinylogous aldol reactions of the unactivated furanones **393** ($R^1 = R^2 = H$) with aldehydes **3a** are achieved by the use of cinchona-thiourea bifunctional catalyst **397** under mild conditions (entry 4).[220] Similarly, bifunctional tertiary amine-squaramide **398** enantioselectively catalyzes the vinylogous aldol reaction, but prolonged reaction times are necessary (entry 5).[221]

The proposed transition state **399** in this *syn*-selective vinylogous aldol reaction is shown in Figure 18. A guanidium ion, generated from the deprotonation of the furanone derivative **393** by the guanidine catalyst **395**, would interact not only with the anion but also with aldehyde **3a** through hydrogen-bonding interactions.[218]

Table 6 Direct vinylogous aldol reactions in Brønsted base catalysis



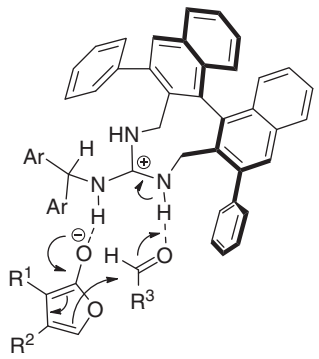
Catalysts



395 Ar = 3,4,5-$(MeO)_3$-C_6H_2 **396** Ar = 3,5-$(CF_3)_2$-C_6H_3- **397** Ar = 3,5-$(CF_3)_2$-C_6H_3- **398** Ar = 3,5-$(CF_3)_2$-C_6H_3-

Entries	R^1	R^2	R^3	R^4	*Catalyst (mol%)*	*Conditions*	*Yield (%)*	dr (anti/syn)	ee *(%)*[a]	*References*
1	Cl	Cl	H	Ph	**395** (5)	THF, –40 °C, 5 h	90	23:77	99	218
2	Br	Br	H	4-MeC_6H_4	**395** (10)	THF, –40 °C, 12 h	95	14:86	99	218
3	Cl	Cl	Ph	CO_2t-Bu	**396** (10)	Acetone/THF (1:1), r.t., 24 h	88	3:97	93	219
4	H	H	H	Ph	**397** (10)	Et_2O, 30 °C, 50 h	87	85:15	82[b]	220
5	H	H	H	2-Naphthyl	**398** (20)	CH_2Cl_2, r.t., 10 days	73	86:14	95[b]	221

[a]The *ee* is indicated for the major product.
[b]Enantiomer ((5*R*,1′*S*)-*ent*-*anti*-**394**) was obtained.



399

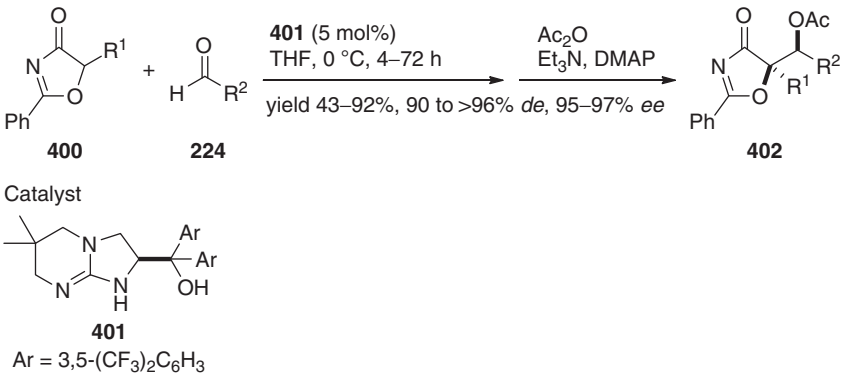
Figure 18 Proposed transition state model in the *syn*-selective vinylogous aldol reaction.

The chiral bicyclic guanidine **401** acts as a Brønsted base catalyst. The hydroxy group controls diastereo- and enantioselectivities in the direct aldol reaction of 5*H*-oxazol-4-ones **400** with aldehydes **224**. The aldol products **402** are easily converted to amides or esters without loss of enantiopurity; thus, this method provides synthetically useful *α*,*β*-dihydroxycarboxylates bearing a chiral quaternary stereogenic center at the *α*-carbon atom (Scheme 71).[222]

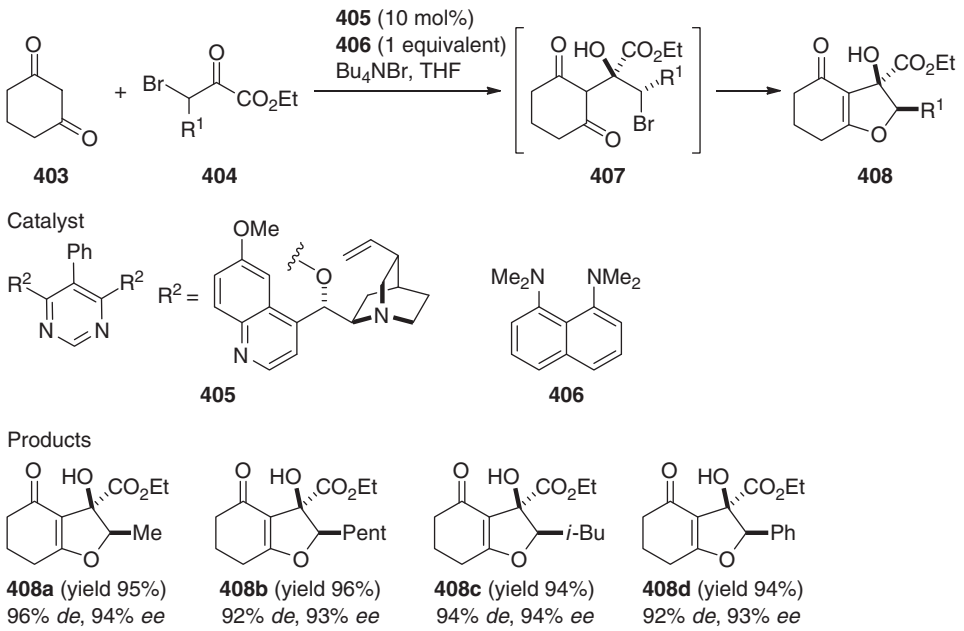
Several groups have suggested that protonated cinchona alkaloids activate electrophiles by hydrogen-bond donation.[223] Among the different cinchona alkaloid derivatives tested, the enantioselective aldol reaction between 1,3-cyclohexanedione **403** and various *α*-bromoketoesters **404** followed by cyclization gave the bicyclic product **408** (Scheme 72).[224] The dimeric catalyst **405** showed the best results when a proton sponge **406** and an ammonium salt were used in the reaction mixture.

The alternative rotamer of the hydrogen-bonded intermediate **410**, which would favor *si* face attack and formation of the opposite enantiomer, is likely to be disfavored by interactions between the bromine of the substrate and the pyrimidine ring of the catalyst (Scheme 73).

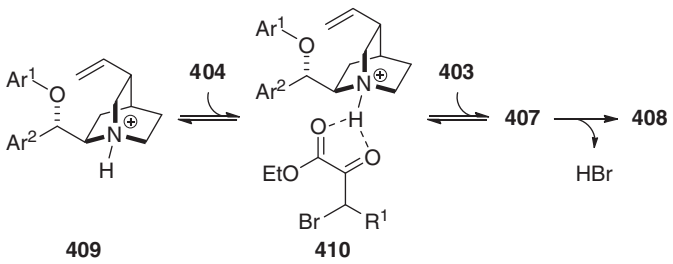
Shibata, Toru, and coworkers reported a cinchona alkaloid-catalyzed aldol reaction of oxindoles **411** with trifluoropyruvate **412** (Scheme 74).[225] $(DHQD)_2PHAL$ **413** and $(DHQ)_2PHAL$ afforded the best results. By employing suitable cinchona alkaloids as



Scheme 71 Guanidine base-catalyzed aldol reaction of 5*H*-oxazol-4-ones.



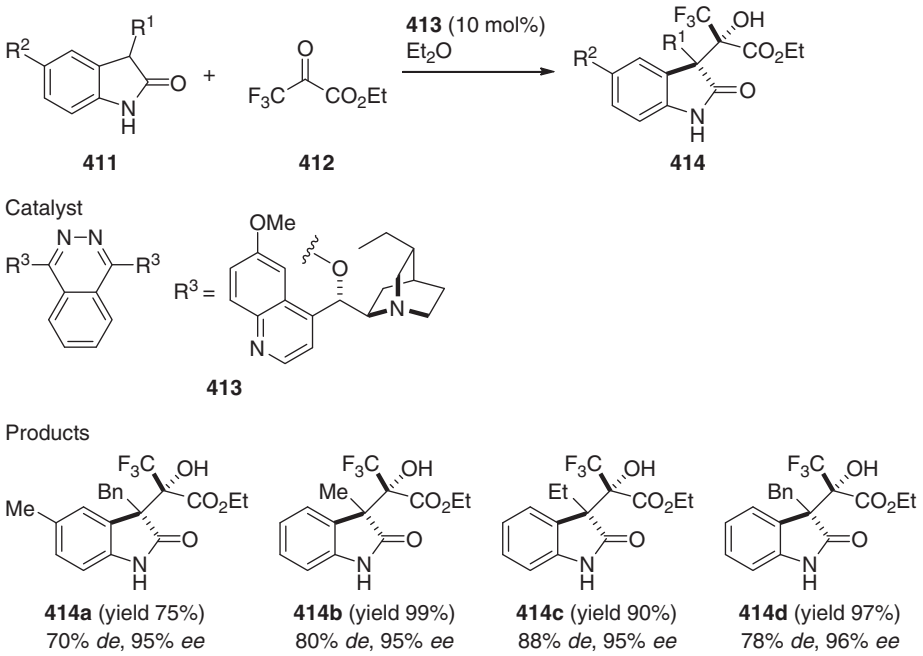
Scheme 72 Cinchona alkaloid-catalyzed aldol/cyclization.



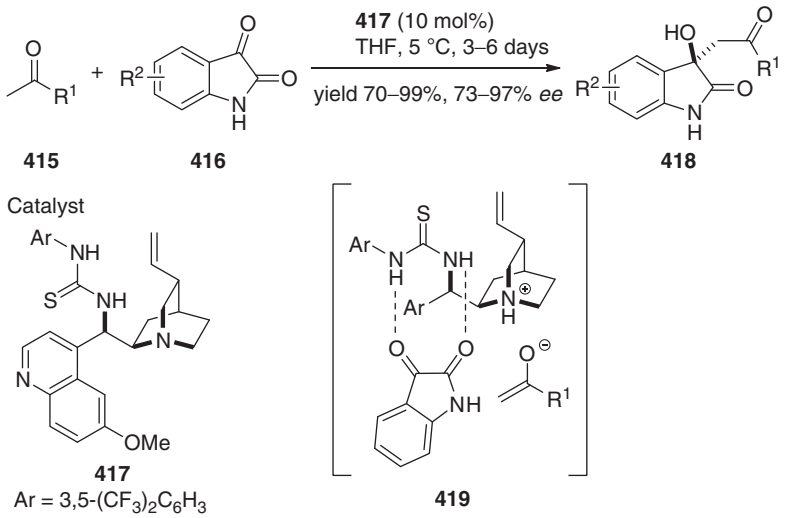
Scheme 73 Mechanism of a cinchona alkaloid-catalyzed aldol reaction process.

catalysts, both enantiomers **414** with two contiguous asymmetric quaternary carbon centers can be obtained. The CF_3 group of the pyruvate is essential for success of this type of aldol reaction.

Aldol reactions of unactivated ketones **415** with isatins **416** are catalyzed by the quinidine-thiourea bifunctional catalyst **417** through an ammonium enolate mechanism. The enolate of ketone **415** closely associates with the catalyst **417** through ionic interactions; in addition, two carbonyl groups of isatin **416** are activated by two hydrogen bonds with the thiourea moiety of catalyst **417** as shown in the transition state model **419** (Scheme 75).[226] The reaction results in high yields and enantioselectivities.



Scheme 74 Cinchona alkaloid-catalyzed aldol reactions of oxindole with ethyl trifluoropyruvate.



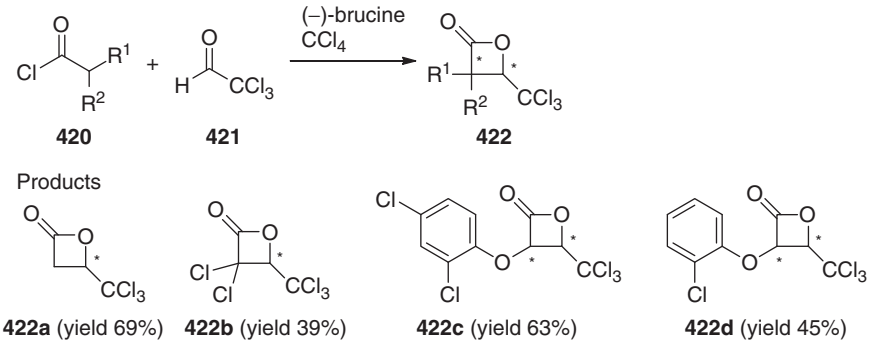
Scheme 75 Cinchona-thiourea-catalyzed aldol reactions of isatins.

2.07.4.2 Aldol-Lactonization Reactions in Nucleophilic Base Catalysis

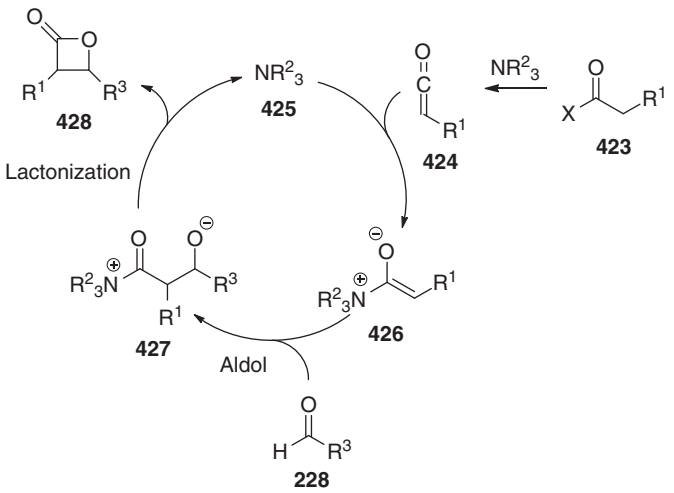
β-Lactones are important molecules that are integral structural features of many pharmacologically active compounds, and these are very useful for synthetic intermediates.[227] In 1966, Borrmann and Wegler first synthesized optically active lactones **422** through formal [2+2] cycloaddition processes, consisting of α-chlorinated aldehydes **421** such as chloral, (−)-brucine, and acyl halides **420**, through the intermediary of an *in situ* generated ketene (Scheme 76).[228–230] These lactones **422** were isolated in good yields with up to 72% *ee*.

The proposed mechanism for the reaction above involves an aldol-lactonization process (Scheme 77). The chiral tertiary amine attacks ketene **424**, the resulting zwitterionic ammonium enolate **426** attacks aldehyde **228**, and then cyclization of the newly formed alkoxide onto the acyl ammonium species **427** forms the β-lactone **428**. In Section 2.07.4.2, formal [2+2] sequences that involve ammonium enolates in intramolecular aldol-lactonization reactions will be discussed.[227]

The Wynberg β-lactone synthesis was one of the first practical, catalytic, asymmetric reactions,[231,232] in which quinidine and quinine were found to be good catalysts for the formal [2+2] cycloaddition of ketene **429** and chloral **430** (Scheme 78).

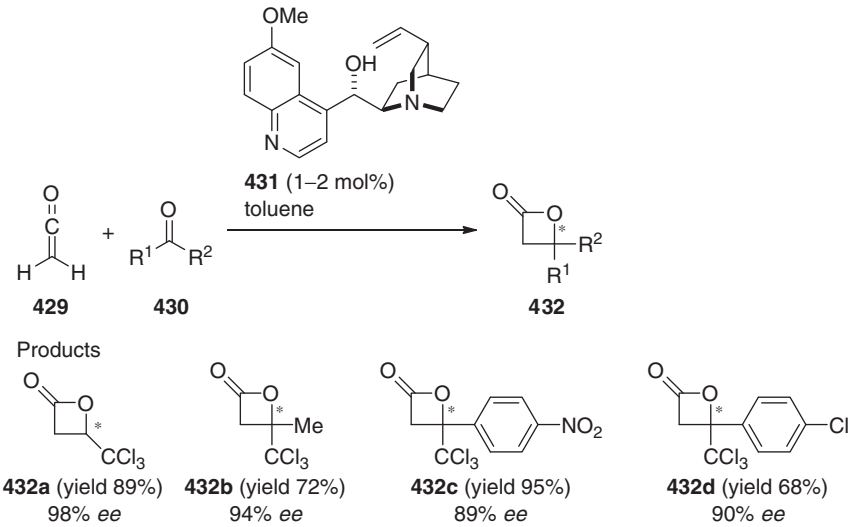


Scheme 76 The first example of an organocatalytic aldol-lactonization reaction.



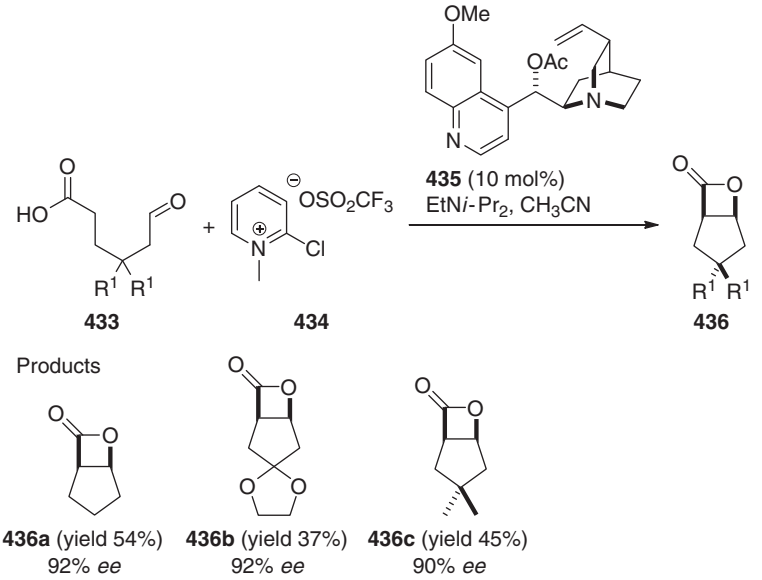
Scheme 77 Proposed mechanism in the Borrmann and Wegler example involves an aldol-lactonization process.

The resulting β-(trichloromethyl)-β-propiolactone **432** was obtained in good yield and excellent enantioselectivity. Wynberg's procedure for the asymmetric synthesis of β-lactones was then extended by the Romo group to involve an *in situ* generated ketene with dichlorinated aldehydes.[233] The use of toluene as the solvent to precipitate the hydrochloride salt of Hunig's base, generating the nucleophilic free base catalyst, was crucial for the success of this reaction.



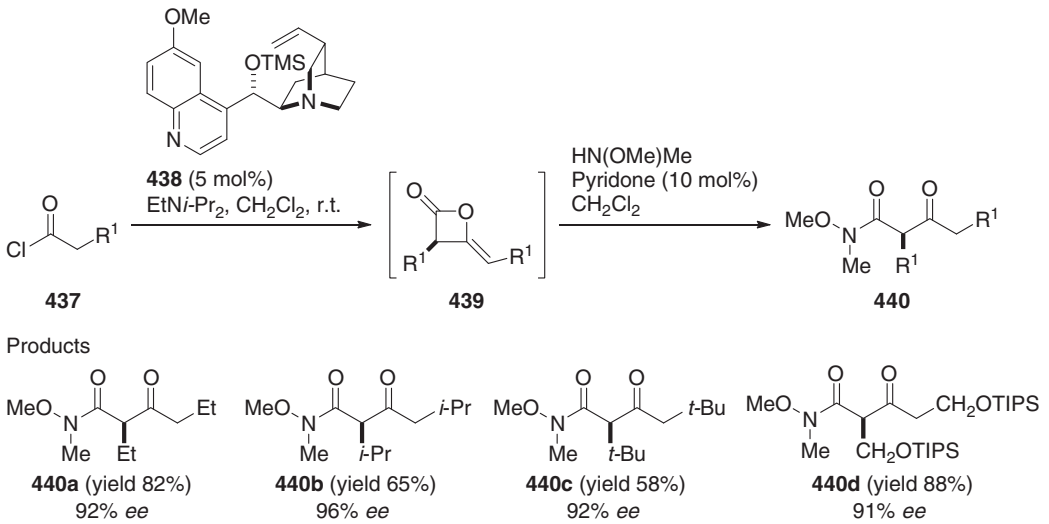
Scheme 78 Quinidine-catalyzed aldol-lactonization reactions of ketenes.

Intramolecular aldol-lactonization reactions of the aldehyde–carboxylic acid **433** catalyzed by *O*-acetylquinidine **435** have been developed (Scheme 79).[234] Aldehyde-acid substrates **433** in conjunction with Mukaiyama's reagent **434** as carboxylate activators, as well as catalytic amounts of the cinchona alkaloid derivative **435**, delivered bicyclic *β*-lactones **436** with high enantiomeric excess and in good yield.



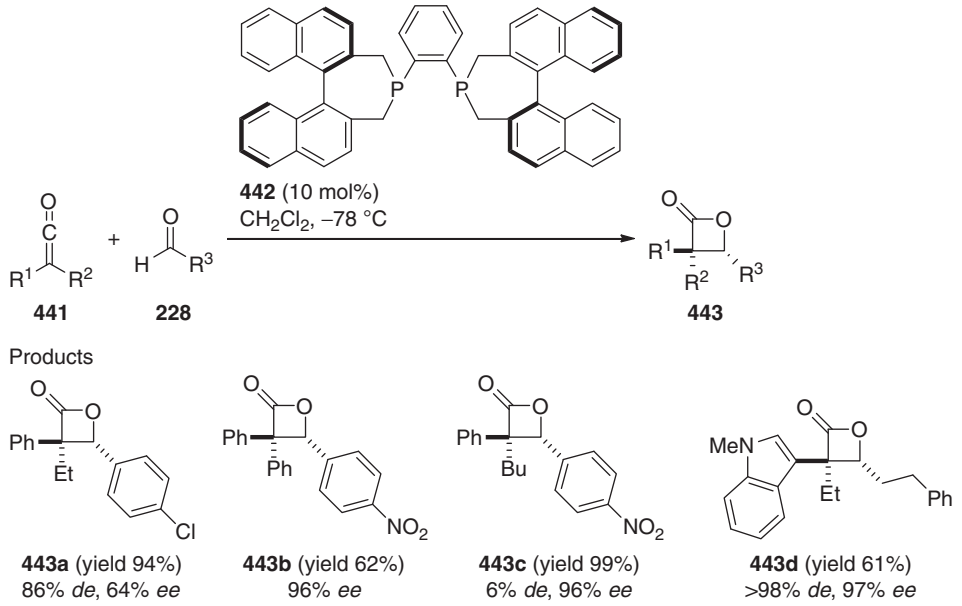
Scheme 79 *O*-acetylquinidine-catalyzed aldol-lactonization reactions.

The Calter group reported that trimethylsilylquinine **438** catalyzed the dimerization of monosubstituted ketenes generated *in situ* from the reaction of acid chlorides **437** and diisopropylethylamine yields ketene dimers **439** in high yields and enantioselectivities (Scheme 80).[235] For determining yield and enantiomeric purity, the researchers immediately converted the volatile and unstable methylketene dimers into *β*-ketoamides **440**. Kinetic studies suggested that the rate-determining step for the reaction is the deprotonation of the acid chloride by the tertiary amine to form the ketene.



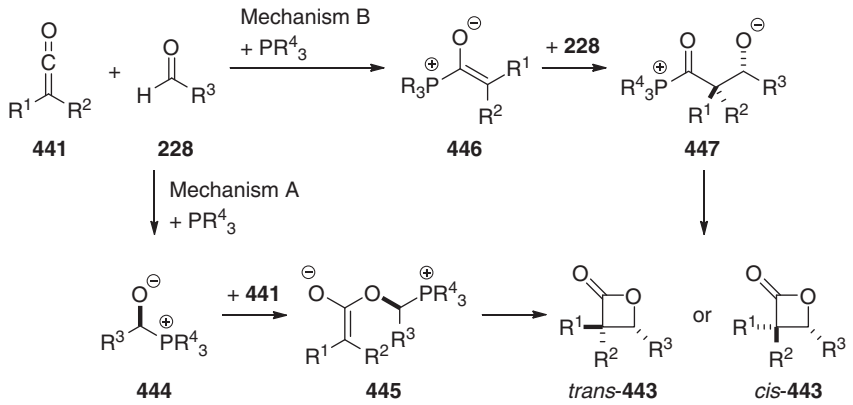
Scheme 80 Trimethylsilylquinine-catalyzed dimerization of monosubstituted ketenes.

Deviating slightly from tertiary amine systems, chiral phosphine-catalyzed formal [2+2] cycloadditions of ketenes **441** and aldehyde **228** have also been reported (Scheme 81).[236] The BINAPHANE **442** catalytic system displayed excellent enantioselectivity and high diastereoselectivity in generating *trans*-isomer **443**.



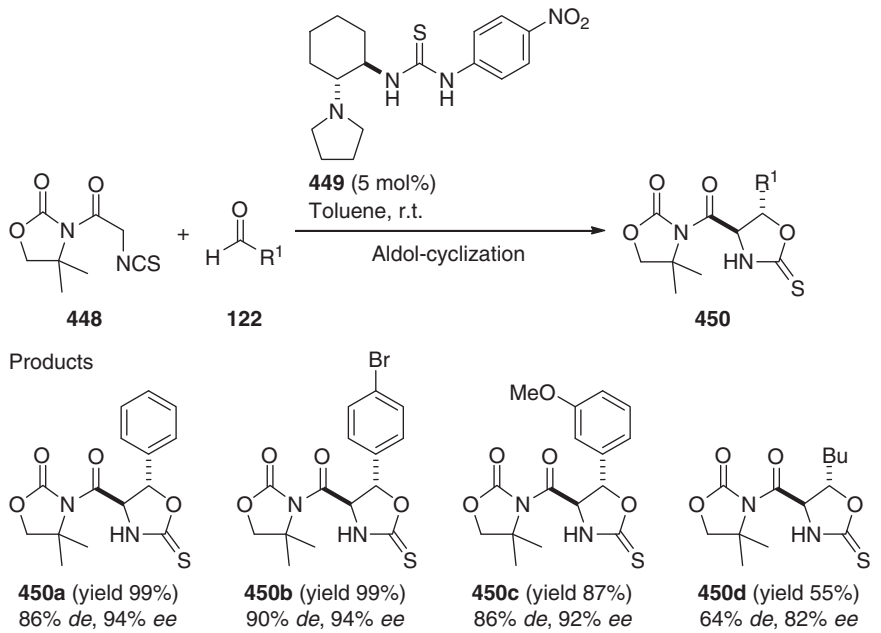
Scheme 81 Phosphine-catalyzed formal [2+2] cycloadditions.

Two mechanisms have been suggested to rationalize the observed stereoselectivity (Scheme 82).[236] The first mechanism A involves an attack of BINAPHANE **442** to aldehyde **228** to give phosphonium alkoxide **444**, which would then add to ketene **441** to generate enolate **445**. Intramolecular S_N2 displacement would provide *trans* β-lactone **443** as the major product. The other mechanism B involves a BINAPHANE **442** attack on ketene **441** first, to generate enolate **446**, which would then add to aldehyde **228** and go on to product **443**. Although the more commonly encountered mechanism B cannot be ruled out, Kerrigan and coworkers speculate that the mechanism for the formation of *trans*-**443** involves initial attack of BINAPHANE **442** on aldehyde **228** to give phosphonium alkoxide **444** through mechanism A. There is precedence for such a mode of addition in the work of Fu on the synthesis of *trans*-β-lactams from ketoketenes and *N*-triflyl imines.[237] Fu group provided both ^{1}H NMR and X-ray crystallographic evidence that the nucleophilic catalyst, a chiral 4-(pyrrolidino)pyridine derivative, attacks first the *N*-triflylimine rather than the ketene.



Scheme 82 Proposed mechanisms for phosphine-catalyzed formal [2+2] cycloaddition.

Curran and coworkers used urea derivatives as aldol catalysts,[238] whereas Jacobsen and coworkers described a parallel library approach to the discovery of urea catalyst derivatives.[239] The Takemoto group developed a novel bifunctional thiourea catalyst bearing a tertiary amine moiety.[240] Ever since these seminal reports, chiral thiourea catalysis has been one of the growing fields in hydrogen bond catalysis. Seidel and coworkers reported aldol reactions of α-isothiocyanatoimides **448** to aldehydes **122** using bifunctional thiourea catalyst **449**.[241] The catalyst loading can be even reduced to 5 mol%. Several electron-rich and poor aromatic aldehydes **122** with different substitution patterns gave rise to products **450** that were generally obtained in good yields, and with high diastereo- and enantioselectivities. The obtained products **450** are synthetic equivalents of *syn*-β-hydroxy-α-amino acids, which are useful intermediates for the synthesis of various natural products (Scheme 83).



Scheme 83 Bifunctional amine-thiourea-catalyzed aldol-cyclization reactions.

2.07.5 Phase-Transfer Catalysis

Phase-transfer catalysis is critical not only to industrial manufacturing of high-performance chemical products in low-cost processes but also to academic research on various asymmetric bond formation reactions under mild conditions. For example, phase-transfer catalysis has been used to catalyze epoxidations, Darzens condensations, Michael reactions, Robinson annulations, and alkylations. Beneficial properties of phase-transfer catalysis such as simple operation, mild conditions, inexpensive reagents and solvents, and large-quantity preparations could open the way to a seamless development of synthetic methods from academia to industry.[242–248]

2.07.5.1 Aldol Reactions in Phase-Transfer Catalysis

In 1984, the first efficient chiral phase-transfer catalyst, *N*-(4-(trifluoromethyl)benzyl)cinchonidium bromide, was developed by the Merck group for asymmetric methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone, providing the desired product in 92% *ee*.[249] The reaction of glycine derivatives with various aldehydes using cinchonidium salt as a catalyst was the first example of aldol reaction in phase-transfer catalysis. The generated products, *β*-hydroxy *α*-amino acid derivatives, are constituents of many bioactive peptide natural products. In 1991, Miller reported low diastereoselectivities and very low enantioselectivities in aldol reactions using cinchonidium salt **451** as a catalyst (46–92% yield, 0–56% *de*, 3–12% *ee*, Figure 19).[250] The reaction mechanism of this quaternary ammonium salt-catalyzed process is thought to proceed through an ion-pair mechanism (Figures 1, 10b). Since then, several catalysts have been reported for this reaction, but the enantioselectivities of these processes remain low. For example, cinchonidium salts **452** gave moderate results (34–78% yield, 0–14% *de*, 52–83% *ee*, Figure 19).[251]

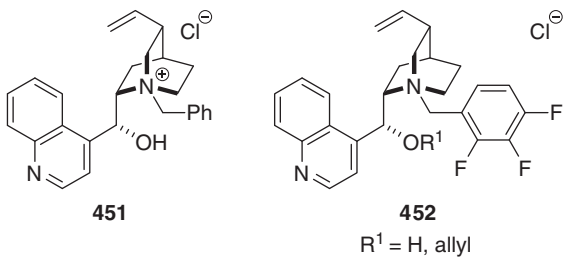
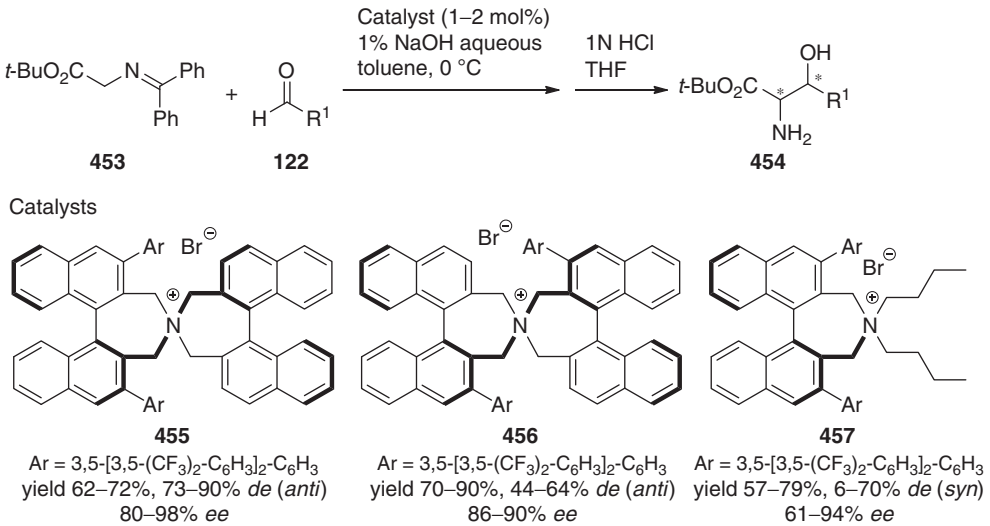


Figure 19 Types of cinchonidium salt catalysts.

A significant improvement in quaternary ammonium salt-catalyzed aldol reactions was reported by Maruoka and coworkers. Highly enantioselective and *anti*-selective aldol reactions could be performed in the presence of 2 mol% of chiral C_2-symmetric

quaternary salt catalyst **455** along with NaOH and toluene (Scheme 84).[252] Mechanistic investigations revealed the intervention of an unfavorable yet inevitable retro-aldol process involving the chiral catalyst. On the basis of this information, a reliable procedure has been established; the use of 1% NaOH (aqueous) and ammonium chloride **455**. Furthermore, the spiro-type phase-transfer catalyst (**456**, Ar=H) possessing a C_2-symmetry axis provides a single type of asymmetric environment; in contrast, a newly designed spiro-type phase-transfer catalyst (**456**, Ar≠H) has two different asymmetric environments. The substituents of the binaphthyl subunits affect enantioselectivity, and the 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl group is the best substituent of those evaluated in the *anti*-selective aldol reactions of glycine Schiff base **453** with aldehydes **122** (Scheme 84).[253] Similarly, simplified chiral phase-transfer catalyst **457** bearing the 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl substituent, which is prepared in a combinatorial approach from the readily available (*S*)-1,1′-binaphthyl-2,2′-dicarboxylic acid, effectively catalyzes *syn*-selective aldol reactions (Scheme 84).[254,255]



Scheme 84 Quaternary ammonium salt-catalyzed aldol reactions.

Maruoka suggested that the observed *anti*-selectivity may be partially attributed to the selective formation of the (*E*)-enolate. This stereochemistry could be explained by the huge steric repulsion caused by the chiral quaternary ammonium cation, overcoming the gauche interactions between the aldehyde substituent (R^1) with both the 2-imino moiety and the *tert*-butoxy group (Figure 20, **458a** vs. **458b**). On the basis of the product configuration, the *re* face of the enolate should be shielded effectively by the chiral ammonium cation, and the aldehyde can only approach from the *si* face.

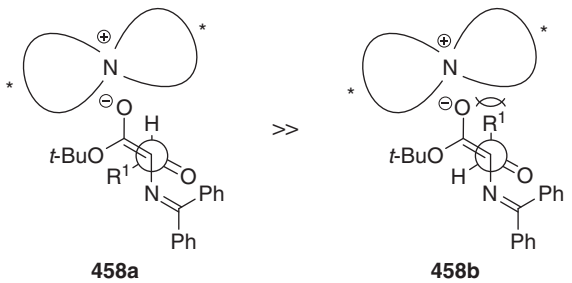
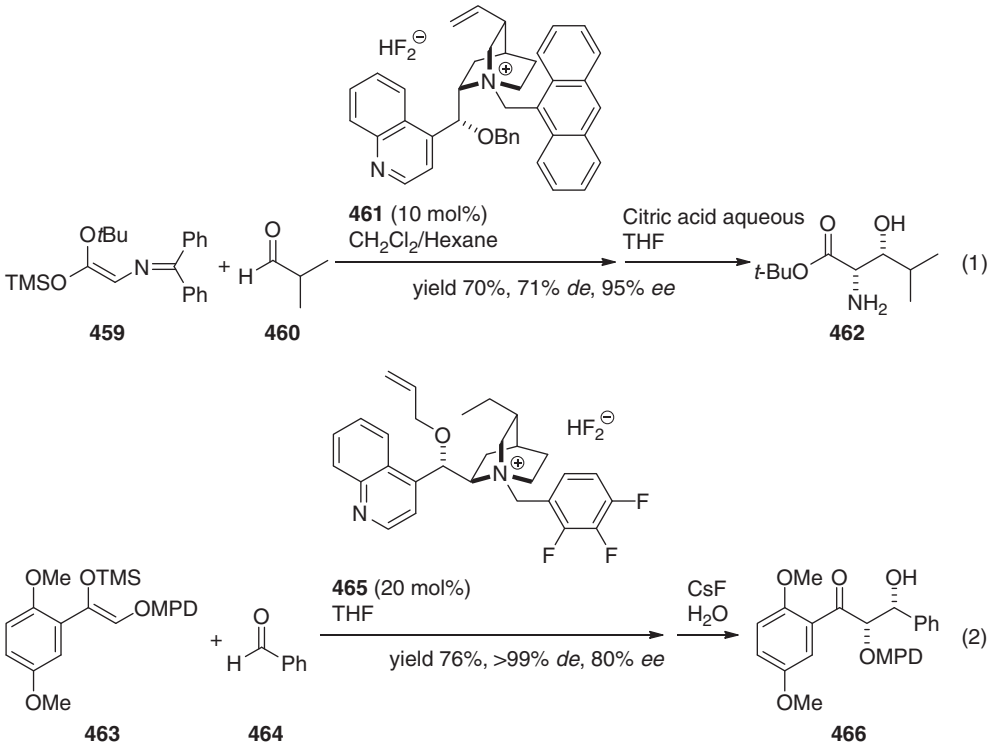


Figure 20 Proposed transition state models for aldol reactions catalyzed by Maruoka's quaternary ammonium salt.

Corey and coworkers reported a Mukaiyama-type aldol reaction of ketene silyl acetal (Scheme 85–1).[256] This reaction, catalyzed by a cinchonidine-derived ammonium bifluoride **461**, gave mostly *syn*-*β*-hydroxy-*α*-amino ester **462** as the major diastereomer with good enantiomeric excess. After 6 years, the Andrus group reported catalyst **465** in the aldol reaction between *α*-alkoxyacetophenone derivatives **463** and benzaldehyde **464** to give the single *syn*-product **466** in 76% yield and 80% *ee* (Scheme 85–2).[257]

2.07.6 Supported Organocatalysis

In general, reaction efficiency, regiochemistry, and stereochemistry can be better predicted in homogeneous catalysis than in heterogeneous catalysis; however, there are limitations to applications of homogeneous systems in the chemical industry.



Scheme 85 Corey's and Andrus' asymmetric aldol reaction.

For example, (1) high-cost chemicals including chiral ligands and noble metals, (2) toxic metal contamination, (3) lability against air, moisture, and heat, and (4) difficulty in catalyst recovering. On the other hand, heterogeneous catalysis is beneficial as the catalysts can be readily separated from the products and reused. Supported organocatalysts are classified as (i) covalently supported catalysts, (ii) noncovalently supported catalysts, and (iii) biphasic or multiphasic systems (Figure 21). Some excellent examples of supported organocatalysts are introduced in this section.[258,259]

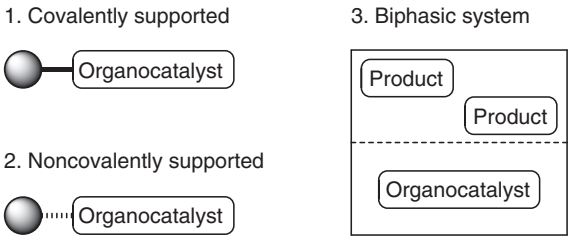


Figure 21 Categories of supported organocatalysts.

2.07.6.1 Covalently Supported Organocatalysts

(*S*)-proline including its derivatives is covalently anchored to an insoluble or soluble support. Polymer and silica are often used as a support due to easy availability, robustness, and wide variety of functional groups. In 1985, the first polystyrene-supported (*S*)-proline catalyst **467** was reported by the Takemoto group (Figure 22–1).[260] Incorporation of a spacer for binding the (*S*)-proline moiety onto a polymer support is found to improve the enantiomeric excess ($n=1$, 18% *ee*; $n=7$, 39% *ee*).

Intermolecular aldol reaction in water is performed by the Pericàs group, and supported catalyst **468** is prepared by binding reaction of 4-hydroxyproline with a polystyrene resin through click chemistry. The high hydrophobicity of the resin and the presence of water are key to ensuring high stereoselectivity, whereas yield can be increased by using catalytic amounts of water-soluble DiMePEG (Figure 22–2).[261] The soluble poly(ethylene glycol) (PEG)-supported catalyst **469** shows excellent stereoselectivities as similar as that with the nonsupported catalyst reported by the Benaglia and Cozzi group. The soluble PEG-supported catalyst **469** is precipitated, when Et_2O is added to the reaction mixture. Simple filtration recovers catalyst **469**,

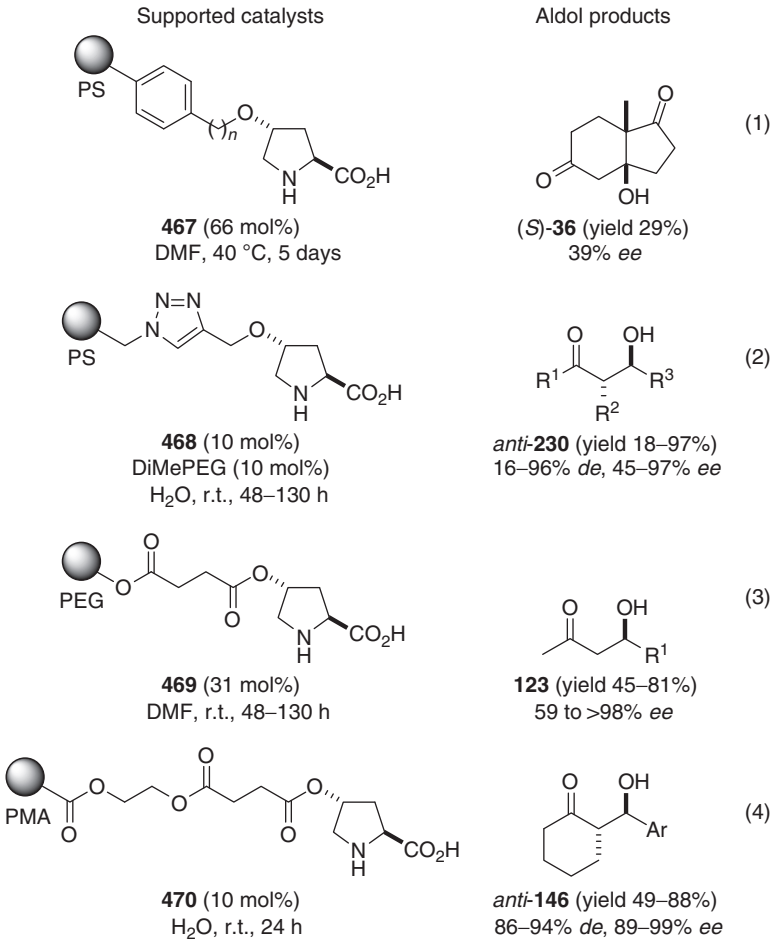


Figure 22 Polymer-supported organocatalyst in aldol reactions.

which is then used for the next reaction (Figure 22–3).[262] A postmodification of polymer beads with catalyst precursors is traditionally employed in the preparation of supported catalysts including organocatalysts. The Hansen group reported an alternative and more scalable approach for polymer-supported organocatalysts. Copolymerization of functional methacrylic monomers affords the desired supported catalyst **470** on multigram scale, which catalyzes the aldol reaction in water to give aldols **146** in excellent yield and enantiomeric excess (Figure 22–4).[263]

Mobile crystalline material 41 (MCM-41), which has a larger specific surface area than other mesoporous silicas, is modified for supported organocatalysts by the Fernández-Mayoralas group (Figure 23).[264,265] MCM-41-supported catalyst **471** provides aldols **158** or **163** in good to excellent yields, even when the reaction is carried out in nonpolar solvent such as toluene, where the use of (*S*)-proline is hampered by insolubility problems.

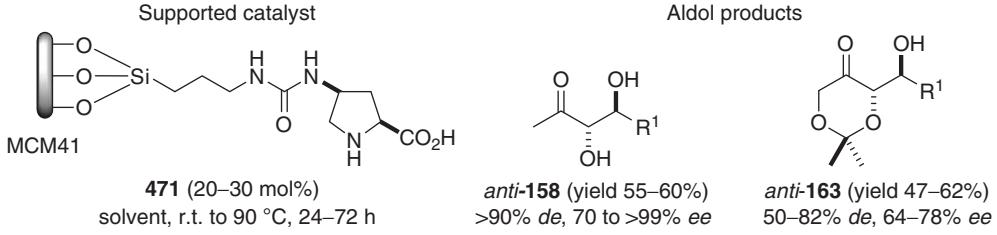


Figure 23 MCM-41-supported organocatalyst in aldol reactions.

Dendrimers are spheroid or globular nanostructures, the size, shape, and reactivity of which are dependent on generation and chemical composition of the core, interior branching, and surface functionalities.

(*S*)-proline catalyst supported on surface-functionalized diaminobutane poly(propyleneimine) dendrimers $DAB(AM)_8$ is evaluated as catalysts for asymmetric aldol reactions reported by the Kokotos group (Figure 24).[266] Using 6.5 mol% of the second

generation modified dendrimer catalyst **472**, aldols **123** are obtained in good yield and *ee* comparable to those observed using (*S*)-proline itself. Reaction time with catalyst **472** is shorter than that with (*S*)-proline, as the reaction occurs in complete homogeneous solution due to the increased solubility of dendrimer catalyst **472** in organic solvents. The Portnoy group described the importance of characteristic features to the dendritic architecture on asymmetric aldol reaction (Figure 24).[267] In the aldol reaction with catalyst **473**, the proximity of the two proline units is crucial for achieving higher yield and enantioselectivity.

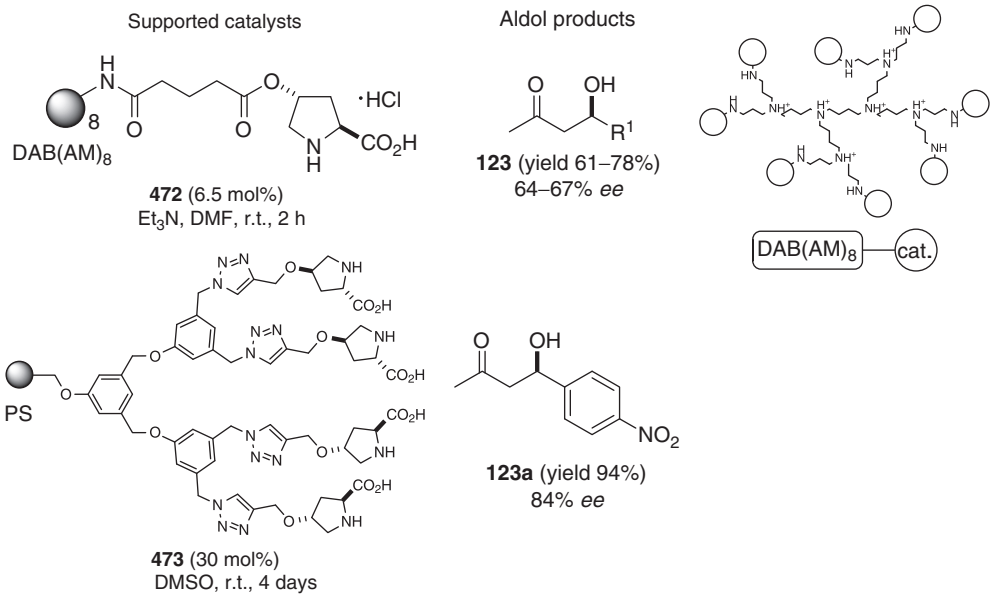
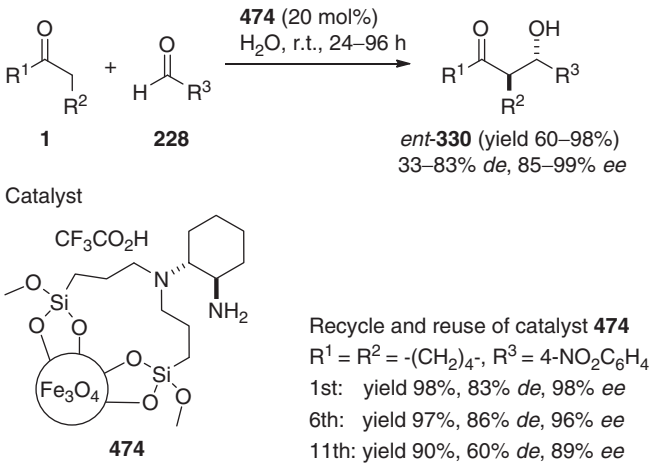


Figure 24 Dendrimer-supported organocatalyst in aldol reactions.

Although nanoscale catalyst recovery is difficult with conventional filtration, very small particles of the supported catalyst would be advantageous because of a large surface-to-volume ratio relative to bulk materials. Recently, the isolation and separation of nanosize catalysts have been achieved using magnetically separable nanoparticles.[268,269] Magnetic nanoparticle-supported chiral primary amine **474** efficiently and stereoselectively catalyzed aldol reactions under on-water conditions. Catalyst **474** can be recycled magnetically and reused up to 11 times with no significant loss of activity or stereoselectivity (Scheme 86).[270]



Scheme 86 Magnetically supported amine-catalyzed aldol reactions.

2.07.6.2 Noncovalently Supported Organocatalysts

Organocatalysts are often noncovalently anchored to an insoluble support such as montmorillonite and β-cyclodextrin. Although bond strength in noncovalently supported catalyst is weak, the catalyst itself is directly used for immobilization without need for

modification or synthetic steps required for covalent attachment to support.[271] Inclusion of (*S*)-proline derivatives with β-cyclodextrin is a useful method for noncovalently supported organocatalyst (Figure 25). The Zhang group demonstrated that the β-cyclodextrin-immobilized catalyst **475** is prepared conveniently by simply heating (4*S*)-phenoxy-(*S*)-proline and β-cyclodextrin in ethanol water and by removal of the solvent.[272] Direct asymmetric aldol reactions with the supported catalyst **475** proceeds in good yields and stereoselectivities, and the catalyst **475** can be recycled four times without loss of enantioselectivity. (4*S*)-*tert*-Butylphenoxy-(*S*)-proline binding a sulfated β-cyclodextrin **477** catalyzes the aldol reaction in water reported by the Armstrong group.[273] Enantio- and diastereoselectivities up to >99% are achieved for stoichiometric amounts of cyclohexanone and aryl aldehydes with this system.

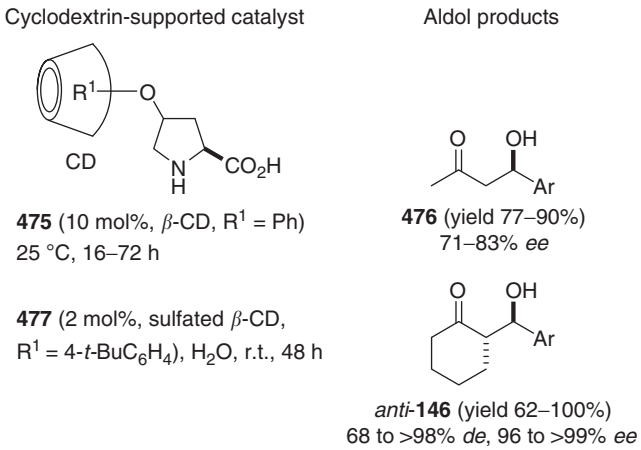
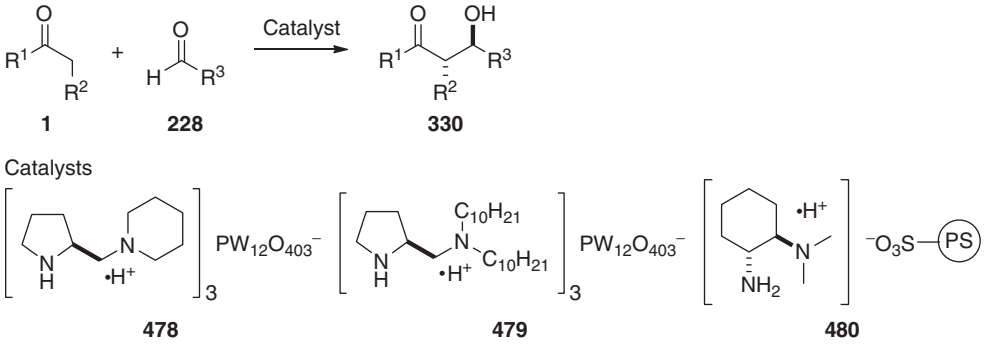


Figure 25 β-Cyclodextrin-supported organocatalysts.

Polyoxometalates (POMs) are transition metal oxygen clusters with well-defined atomic coordination structures. POMs are used as functional nanocolloidal materials and as supports for catalysts through ion-pair interactions due to their acidic properties. Combinations of chiral diamines and POM **478** effectively catalyze enamine-based aldol reactions. Less than 1 mol% of chiral amine loading is sufficient to catalyze the reaction (Table 7, entries 1 and 2).[274] Highly diastereo- and enantioselective cross-aldol reactions of aldehydes are accomplished using chiral diamine-POM **479** under emulsion condition (entries 3 and 4).[275]

Table 7 Polyoxometalate-supported diamine-catalyzed aldol reactions

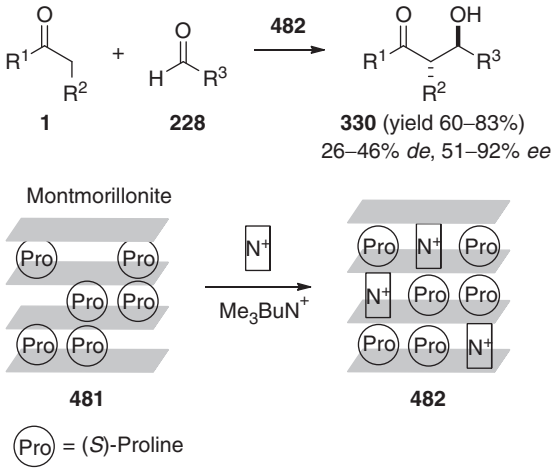


Entries	R^1	R^2	R^3	*Catalyst (mol%)*	*Conditions*	*Yield (%)*	dr (anti/syn)	ee *(%)*[a]	*References*
1	$-(CH_2)_4-$		4-$NO_2C_6H_4$	**478** (0.33)	r.t., 16 h	99	87:13	99	274
2	Me	Me	4-$NO_2C_6H_4$	**478** (0.33)	r.t., 19 h	59	90:10	98	274
3	H	Me	4-$NO_2C_6H_4$	**479** (2.5)	H_2O, 0 °C, 24 h	92	>95:<5	99	275
4	H	Me	Ph	**479** (2.5)	H_2O, 0 °C, 80 h	80	>95:<5	99	275
5	$-(CH_2)_4-$		4-$NO_2C_6H_4$	**480** (10)	CH_2Cl_2, r.t., 16 h	97	91:9	97[b]	276
6[c]	$-(CH_2)_4-$		4-$NO_2C_6H_4$	**480** (10)	CH_2Cl_2, r.t., 34 h	95	92:8	96[b]	276

[a]Enantiomeric excess for the *anti*-diastereomer.
[b]Enantiomer of **330** was obtained as a major product.
[c]After four cycles.

Sulfonated polystyrene or fluoropolymer nafion® NR50 is also a good support for the immobilization of primary diamines. The catalyst **480** can be recovered by filtration and reused for at least four cycles with no loss of stereoselectivity (entries 5 and 6).[276,277]

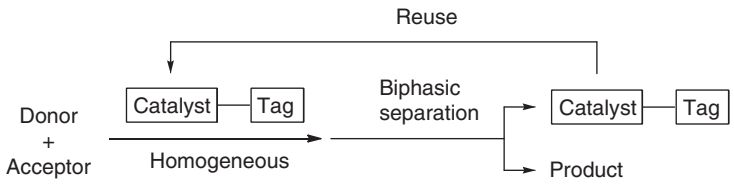
Clays are abundant and available substances that promote a variety of chemical reactions. The characteristic layered structure of clays attracted the attention of synthetic chemists who have used it as a support material.[278] For example, chiral organic–inorganic hybrid materials **482** based on (*S*)-proline-exchanged clay such as montmorillonite are used for heterogeneous aldol reactions (Scheme 87). Coinclusion of ammonium cations within the layers enhances yields and stereoselectivities. Upon recycling catalyst **482** showed no decrease in enantioselectivity or conversion after 10 cycles.[279]



Scheme 87 Clay-supported (*S*)-proline-catalyzed aldol reactions.

2.07.6.3 Supported Organocatalysts in Multiphasic Systems

Despite the advantage of easy separation in solid-phase synthesis, the use of insoluble solid-supported catalysts sometimes requires long reaction times, low chemical yields, and low stereoselectivity. Liquid-phase syntheses using soluble linear polymers as catalyst supports have been developed to improve the chemical reactivities.[280] In addition, ionic or fluorous tags have been employed in organocatalytic transformations in recent years (Scheme 88).[281–287]

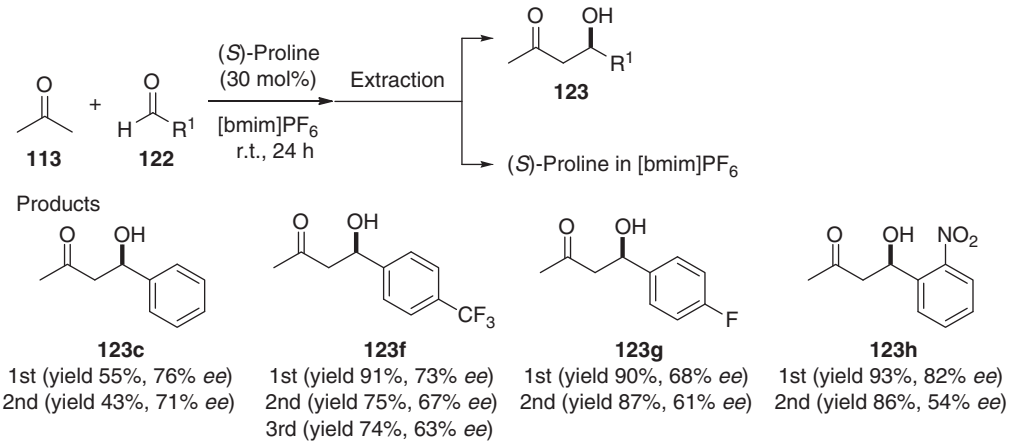


Scheme 88 Tagged organocatalysts.

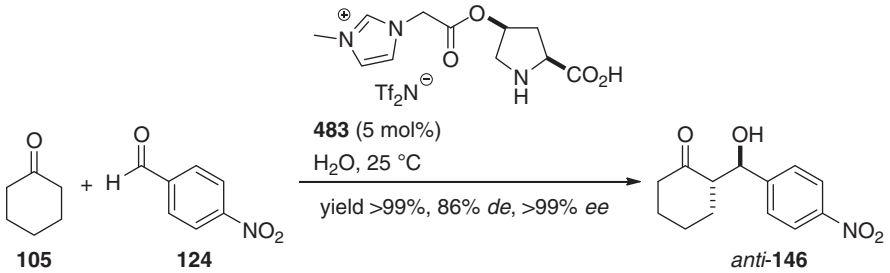
Polar organocatalysts such as amino acids and peptides are almost insoluble in conventional organic solvents, but they are soluble in ionic liquids. Owing to these physical properties, asymmetric syntheses in ionic liquids under biphasic condition have been reported.[288,289] The Toma group reported that (*S*)-proline-catalyzed direct aldol reaction of acetone **113** with arylaldehyde **122** in ionic liquid such as 1- butyl-3-methylimidazolium hexafluorophosphate (Scheme 89).[290] Good yields with reasonable enantioselectivities are achieved, even when just 1–5% of (*S*)-proline is used. Immobilization of the catalyst in an ionic liquid phase offers simple product isolation, that is, product **123** could be extracted using an immiscible solvent against ionic liquid, and reuse of the catalytic system in subsequent reactions.

The introduction of an imidazolium tag through acetate connection at the C-4 position of *cis*-4-hydroxy-l-proline **483** provides a highly efficient catalyst for the direct asymmetric aldol reaction that works in a remarkably low catalyst loading (0.1 mol%) with *ee* up to >99% (Scheme 90).[291]

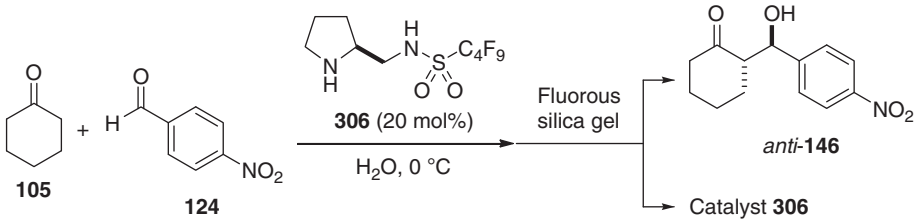
Similar to biphasic system with ionic liquid, fluorous system is also a powerful methodology in organic synthesis. Catalyst **306**, fluorous (*S*)-pyrrolidine sulfonamide, is shown to be a very effective catalyst in the direct aldol reaction in water providing aldol **146** in good yields with high diastereo- and enantioselectivities as reported by the Wang group (Scheme 91).[155] Fluorous separation allows catalyst recovery and reuse for seven cycles without a significant loss of catalytic activity and stereoselectivity.



Scheme 89 Reuse of (*S*)-proline in aldol reaction in ionic liquids.



Scheme 90 Aldol reaction using ionic tag.



1st : (6 h, yield 90%, 67% *de*, 90% *ee*)
2nd : (7 h, yield 92%, 67% *de*, 90% *ee*)
3rd : (12 h, yield 90%, 67% *de*, 90% *ee*)
4th : (13 h, yield 90%, 67% *de*, 90% *ee*)
5th : (19 h, yield 91%, 67% *de*, 89% *ee*)
6th : (24 h, yield 92%, 67% *de*, 87% *ee*)
7th : (40 h, yield 88%, 67% *de*, 87% *ee*)

Scheme 91 Recovery of the fluorous catalyst.

Recently, combinations of solid catalysts and ionic liquids have been intensively studied. The supported ionic liquid phase catalyst is a new generation of the supported liquid-phase catalyst.[292]

Polar molecules such as (*S*)-proline are absorbed onto the monolayer surface of silica gel covalently attached to ionic liquid with additional ionic liquid reported by the Gruttadauria group (Figure 26).[293] These layers serve as the reaction phase as well as the supported homogeneous catalyst phase. Good yields and enantiomeric excess comparable to those obtained with (*S*)-proline itself are observed; in addition, the supported catalyst **484** shows high reusability. Polar ionic-liquid-supported catalysts are precipitated through biphasic separation by adding a less polar solvent into the reaction mixture, and the recovered catalyst can be reused. Polyelectrolytes are also a good support for (*S*)-proline. The (*S*)-proline/poly(diallyldimethylammonium) hexafluorophosphate combination as a supported catalyst **485** is developed by the Zlotin group.[294] Recycling of catalyst **485** is possible at least six times without loss of activity and enantioselectivity in asymmetric aldol reaction.

The supported ionic liquid phase catalyst **486** is readily prepared by adsorption of (*S*)-proline **6** or peptide **487** onto the surface of silica gels covalently functionalized with an ionic monolayer. These supported catalysts catalyze the aldol reaction between

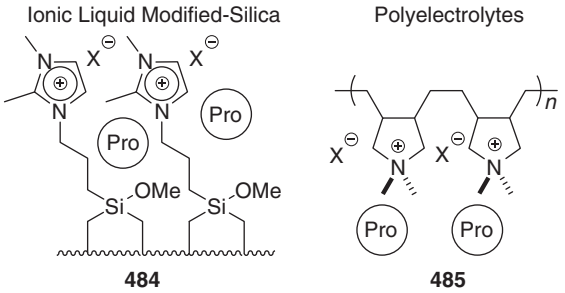
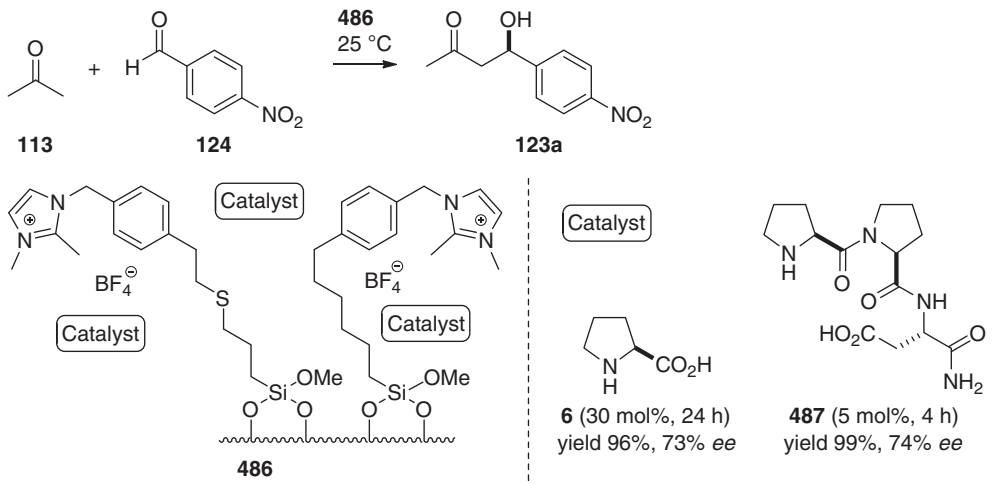


Figure 26 Proline catalyst in multiphase.

acetone **113** and aldehyde **124** to give the desired product **123a** in high yields. The supported catalyst **486** is easily recovered by filtration and can be used several times without loss of either conversion or selectivity (Scheme 92).[295]



Scheme 92 Supported ionic liquid phase catalyst.

2.07.7 Conclusions

The past two decades have been an age of exploration and discovery in organocatalysis, and new and powerful synthetic tools have been developed. The catalytic asymmetric assembly of readily available precursor molecules gives rise to complex products with extremely high stereoselectivities under operationally simple and, in some cases, environmentally friendly experimental conditions. Until now, organocatalysis has been developing at a remarkable pace, but there is still room for improvement, as the generality scope is not yet determined; diastereoselectivities and enantioselectivities are still low in some cases, and high catalyst loadings are still required. It is believed that this rapidly growing field will rise to meet these challenges in the near future.

For related chapters in this Comprehensive, you can refer to – Chapters 2.11, 4.03, 2.08, 2.09, 2.10, 2.13, and 2.12.

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2.08 The Aldol Reaction: Group I and Group II Enolates

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2.08.1 Introduction

Traditionally, aldol reactions were carried out under protic conditions, such that the enolate was formed reversibly. An added measure of control is possible if one uses a sufficiently strong base that the enolate may be quantitatively formed prior to addition of the electrophile. The renaissance that has occurred in the aldol reaction in the last two decades has been mainly due to the development of methods for the formation and use of preformed enolates. The simplest enolates to prepare are those associated with lithium and magnesium, and there now exists a considerable literature documenting certain aspects of lithium and magnesium enolate aldol chemistry. This chapter summarizes the aldol chemistry of preformed enolates of these Group I and Group II metals. Other chapters in this volume deal with boron enolates, zinc enolates, transition metal enolates and the related chemistry of silyl and stannyl enol ethers.

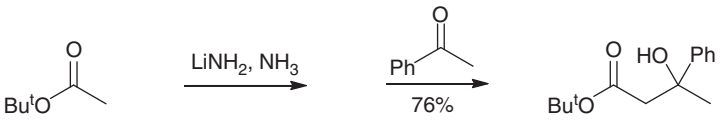
2.08.2 Formation and Aldol Reactions of Regio-Defined Enolates

The great power of the aldol addition reaction lies in the ability to generate and use structurally defined enolates. In this section, the emphasis is on the formation of regio-defined enolates, and the aldol reactions of these enolates. Stereochemical issues are dealt with in Sections 2.08.2–2.08.4.

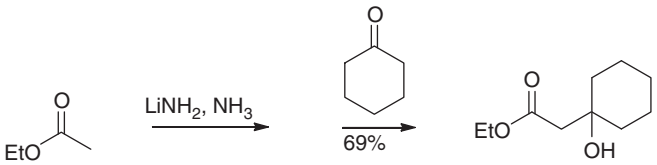
2.08.2.1 Stoichiometric Deprotonation of Carbonyl Compounds

The first use of preformed enolates for synthesis appears to have been by Hauser and coworkers, who converted *t*-butyl and ethyl acetate into the lithium enolates by reaction with $LiNH_2$ in liquid ammonia; the resulting enolates were found to react with aldehydes and ketones to give β-hydroxy esters (equations 1 and 2).[1]

 doi:10.1016/B978-0-08-097742-3.00209-3



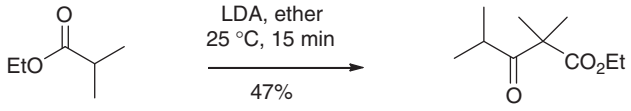
(1)



(2)

It was later found that dialkyl- and disilyl-amides have several attractive advantages, relative to the unsubstituted amides. Firstly, because they are relatively hydrophobic, these bases dissolve readily in organic solvents such as ether, tetrahydrofuran (THF), benzene and toluene. Secondly, the steric hindrance of the nitrogen atom reduces the nucleophilicity of the amide, thus ameliorating one of the principal side reactions of $LiNH_2$ and $NaNH_2$ with esters.[2]

One of these important bases, diisopropylaminomagnesium bromide, was first introduced by Frostick and Hauser in 1949 as a catalyst for the Claisen condensation.[3] However, the most generally useful base has turned out to be lithium diisopropylamide (LDA), which was first used by Hamell and Levine for the same purpose in 1950 (equation 3).[4] After the introduction of LDA, it was more than 10 years before it was used by Wittig for the stoichiometric deprotonation of aldimines in what has come to be known as the 'Wittig directed aldol condensation.'[5] In a seminal paper in 1970, Rathke reported that the lithium enolate of ethyl acetate is formed by reaction of the ester with lithium hexamethyldisilazane in THF.[6,7] Rathke found that THF solutions of the lithium enolate are stable indefinitely at −78 °C, and that the enolate reacts smoothly with aldehydes and ketones to give *β*-hydroxy esters (equation 4).



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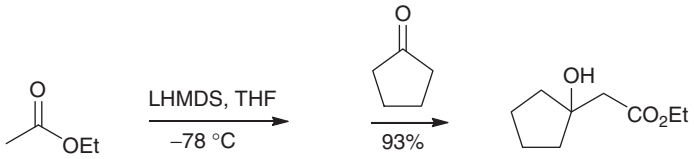


(4)

In a 1971 paper, Rathke and Lindert reported that lithium *N*-isopropylcyclohexylamide (LICA) is a superior reagent for the generation of ester enolates.[8] Subsequent workers, however, have found that LDA works just as well.[9] This base has the added virtue of being derived from a relatively volatile amine (the b.p. of diisopropylamine is 84 °C).

Lithium 2,2,6,6-tetramethylpiperidide (LITMP) was introduced by Olofson and Dougherty in 1973.[10] This base appears to be significantly more hindered than LDA, and is useful for regioselective enolate formation in cases where a very bulky base is desirable.[9c] Another very hindered base is lithium *t*-butyl-*t*-octylamide, introduced by Corey and Gross.[11]

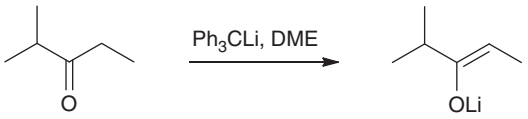
Lithium, sodium and potassium hexamethyldisilazanes are available from the corresponding amine, bis(trimethylsilyl)amine. (This amine has a multitude of traditional common names, the most common of which are 'hexamethyldisilazine' and 'hexamethyldisilazane.' Its conjugate base has been called 'hexamethyldisilazide' and 'hexamethyldisilazane,' among other things. Although these names are somewhat confusing to the uninitiated, they are firmly entrenched in the literature. In this volume, we will use hexamethyldisilazane, abbreviated HMDS.) The lithium base may be formed by treatment of the amine with an alkyllithium in an ether solvent;[12] the sodium and potassium bases are produced by reaction of the amine with $NaNH_2$ or KNH_2.[7,13] All three of the hexamethyldisilazanes are also commercially available.

Triphenylmethylpotassium[14] and triphenylmethyllithium[15,16] were once used for stoichiometric deprotonation of ketones, but these bases offer no significant advantages over the foregoing amide bases, and they are rarely used now.

2.08.2.2 Regioselective Deprotonation of Ketones

The introduction of the foregoing bases opened the way for the preparation of structurally defined enolates; examples are seen in equations (5–7).[16,17] The first examples of the use of these regio-defined enolates in crossed aldol reactions were reported by Stork, Kraus and Garcia in 1974; representative examples are shown in equations 8 and 9.[18,19]

An application of this process is seen in the synthesis of (±)-[6]-gingerol (**1**; equation 10).[20] In this example, the regioselectivity of deprotonation is 92% at C-1 and 8% at C-3. With the weaker base lithium hexamethyldisilazane, the C-1:C-3 ratio is only 3:1. The method has also been used to prepare nine other (±)-gingerols.



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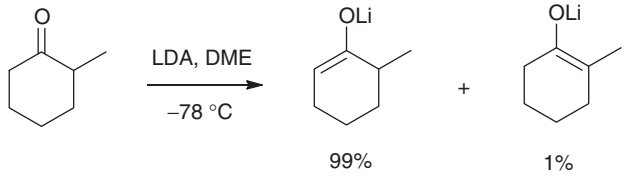

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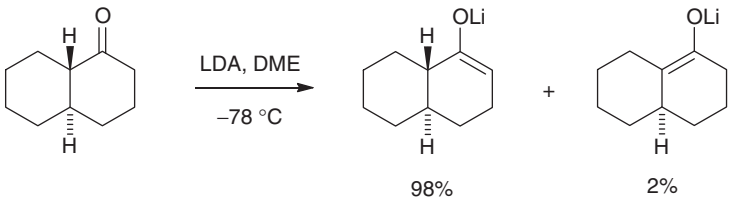

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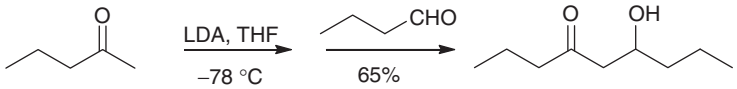

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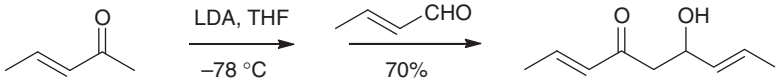

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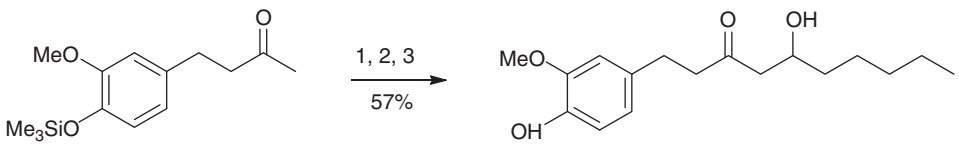
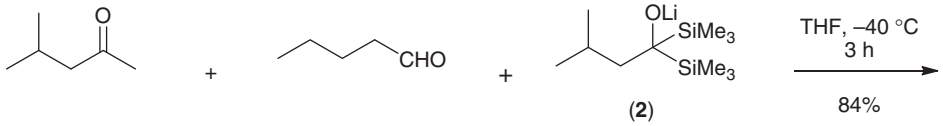


(**1**)

(10)

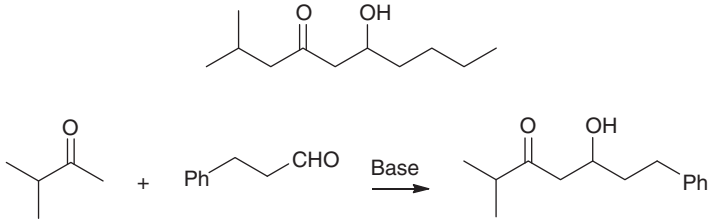
1. LDA, DME, –78 °C; 2. $Me(CH_2)_4CHO$; 3. H_3O^+

Kuwajima and coworkers used very hindered bases such as (**2**) to deprotonate methyl alkyl ketones regioselectively *in the presence of enolizable aldehydes.*[21] One example of this amazing process is shown in equation 11; the reaction is reported to work equally well with other methyl ketones, including 2-pentanone. The process was also demonstrated with other bases in the reaction of 3-methyl-2-butanone with dihydrocinnamaldehyde (equation 12). Among the bases that are effective are LDA, lithium hexamethyldisilazane, lithium *t*-butoxide and even lithium ethoxide. However, base (**2**) is superior, giving the aldol in 83% yield.



(**2**)

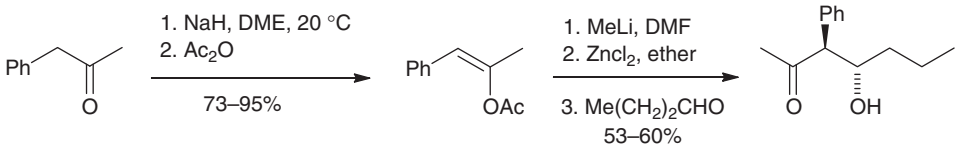
(11)



(12)

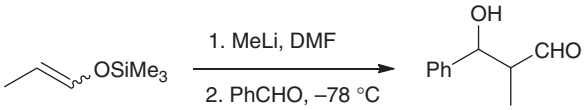
2.08.2.3 Enolates from Enol Esters and Silyl Enol Ethers

Enolates can also be prepared by reaction of enol esters[16,22,23] or silyl enol ethers[16,24] with alkyllithium reagents. House has worked out a protocol wherein these enolates are allowed to react with aldehydes to give the corresponding aldols.[25] Higher yields of aldol products are obtained when the lithium enolate is generated in ether or 1,2-dimethoxyethane (DME) by reaction of an enol acetate with methyllithium. Lower yields are obtained if the enolate is produced by reaction of a silyl enol ether with methyllithium. For the aldol reaction, ether or mixtures of ether and DME are superior to THF. Acceptable yields of aldol adducts are obtained in ether at low temperatures (−20 to −50 °C). In the more polar solvents DME or THF, the addition of anhydrous $ZnCl_2$ or $MgBr_2$ results in higher yields. An example is seen in equation 13.[25b] The stereochemistry of this process is discussed in Section 2.08.5.



(13)

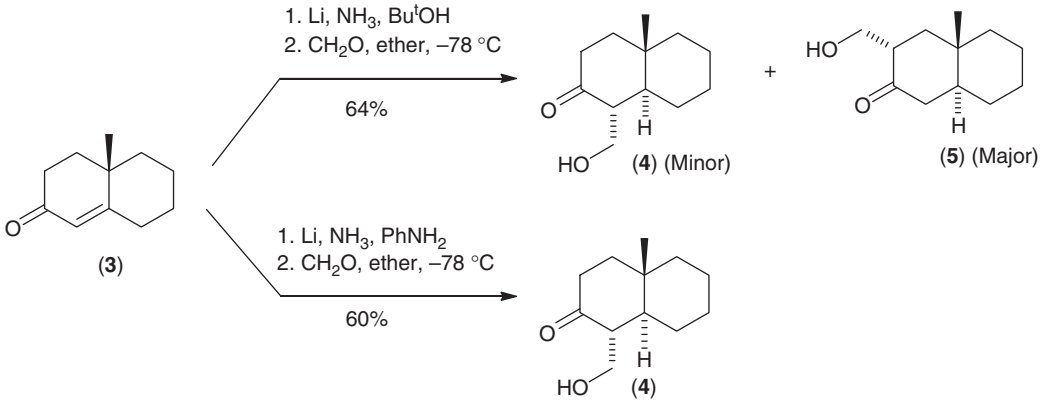
The enol ester or silyl enol ether route to enolates has advantages over direct deprotonation in certain cases. If direct deprotonation provides a mixture of regio- or stereo-isomers, it is often possible to trap the enolate mixture by esterification or silylation, separate the desired enol ester or silyl enol ether and regenerate the enolate by reaction with methyllithium. It is also useful for preparation of enolates from substances that are so electrophilic that direct deprotonation is complicated by self-aldolization. For example, aldehyde enolates have been prepared in this manner (equation 14).[9c]



(14)

2.08.2.4 Enolates from Conjugate Additions to α,β-Unsaturated Carbonyl Compounds

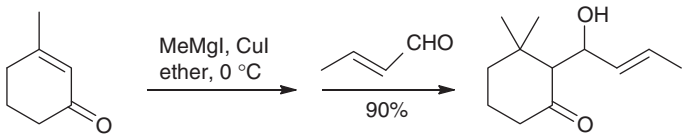
A classic method for generating regio-defined enolates is metal-ammonia reduction of an enone.[26] Stork and d'Angelo found that the enolate resulting from lithium-ammonia-*t*-butyl alcohol reduction of octalone (**3**), followed by evaporation of ammonia, suspension of the enolate in ether and treatment with gaseous formaldehyde, provides a mixture of hydroxy ketones (**4**) and (**5**), with the latter predominating (equation 15).[27] Enolate equilibration can be suppressed by use of aniline, rather than *t*-butyl alcohol, as the proton source in the reduction step (equation 15). However, the yield of hydroxymethyl ketone is only 60%. A much better overall yield (90%) is realized by trapping the original enolate as the trimethylsilyl enol ether and regenerating the enolate in the absence of any proton donors (*vide infra*).



(15)

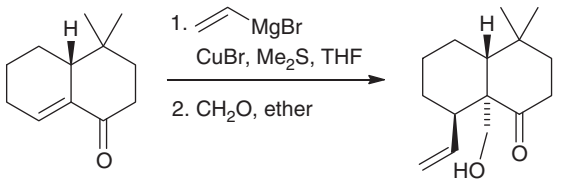
As shown in equation 15, the necessary presence of a proton source in the reaction medium that is used to generate specific enolates by metal-ammonia reduction limits the use of these enolates for regiodefined aldol reactions. The enolates resulting from conjugate additions of Grignard reagents or Gilman reagents to *α,β*-unsaturated carbonyl compounds do not suffer from this limitation, and have frequently been employed for aldol reactions.

Two papers that appeared in 1974 were the first to demonstrate the preparation and aldol reaction of a regio-defined magnesium enolate from copper(I)-mediated conjugate addition of a Grignard reagent to an enone.[27,28] As shown in equation 16, 3-methylcyclohexenone reacts with methylmagnesium iodide to give an enolate that reacts smoothly with crotonaldehyde, producing an aldol as a mixture of diastereomers in excellent yield.



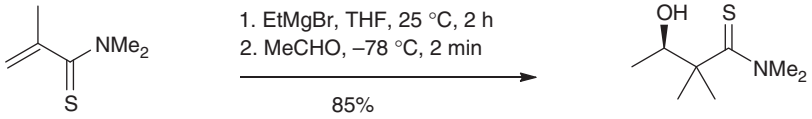
(16)

A nice example of the foregoing stratagem is seen in equation 17; enone (**6**) undergoes copper(I)-catalyzed reaction with vinylmagnesium bromide from its less-hindered face to give an enolate that reacts with formaldehyde from the opposite face to provide decalone (**7**), an intermediate in the synthesis of insect antifeedants.[29] Yoshida and coworkers have used this method for the stereospecific generation of tetrasubstituted thioamide enolates, which undergo remarkably stereoselective aldol reactions (equation 18).[30] The stereochemistry of this process is discussed in Section 2.08.3.6.



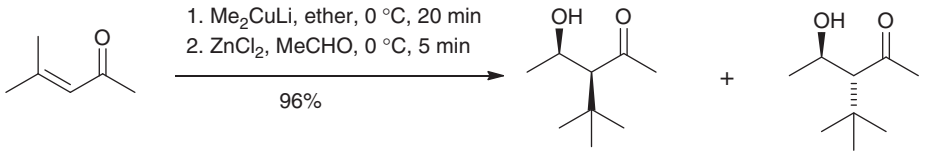
(**6**) (**7**)

(17)



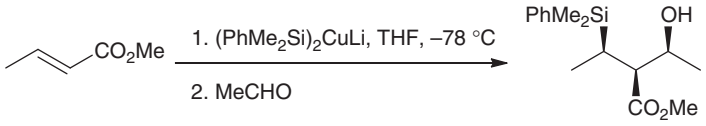
(18)

Heng and Smith found that the regio-defined enolates resulting from conjugate addition of lithium dialkylcuprates to enones undergo acceptable aldol additions under the House conditions.[31] One of the many examples reported in this investigation is shown in equation 19. The stereochemistry of these reactions is discussed in Section 2.08.3.2.



(19)

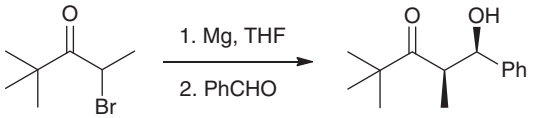
Fleming has generated enolates by conjugate addition of lithium bis(phenyldimethylsilyl)cuprate to α,β-unsaturated esters.[32] The intermediate (*Z*)-enolates undergo stereoselective aldol addition, providing adducts having three contiguous stereocenters; one example of this process is seen in equation 20.[33]



(20)

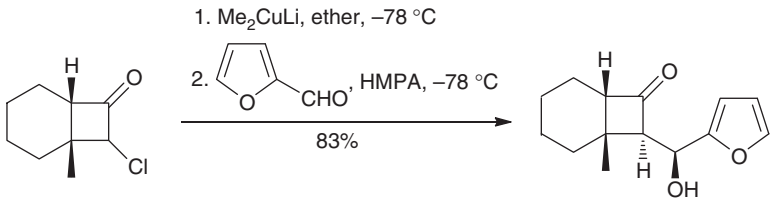
2.08.2.5 Enolates from Reduction of α-Heteroatom-substituted Carbonyl Compounds

Several workers have observed aldol reactions with enolates prepared by reductive removal of an α-heteroatom from a carbonyl compound. The classic example is the Reformatsky reaction, which is reviewed in Volume 2, Chapter 1.8. Dubois and coworkers have employed this method for the preparation of magnesium enolates.[34] An important example from this study, which stimulated much of the subsequent work on aldol stereoselectivity, is shown in equation 21.



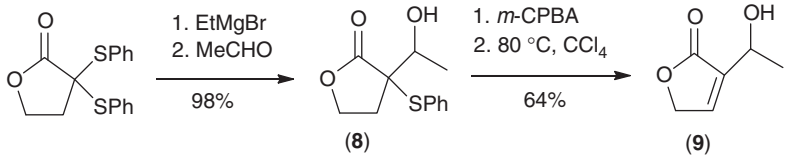
(21)

Clark and coworkers have used a similar process for generation and aldol reactions of a cyclobutanone enolate; one example from many is illustrated in equation 22.[35] Direct formation of the enolate in this case gives aldols in low yield.



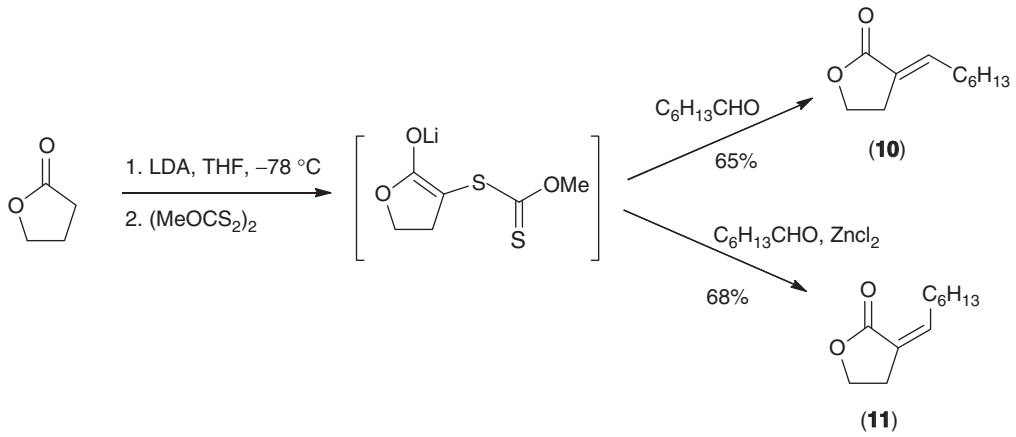
(22)

Trost has used α,α-disulfenylated lactones as enolate precursors.[36] As shown in equation 23, α,α-di-(phenylthio)-γ-butyrolactone is treated sequentially with ethylmagnesium bromide and acetaldehyde to obtain β-hydroxy lactone (**8**) in virtually quantitative yield. Oxidation of the phenylthio group and subsequent elimination of the resulting sulfoxide provides the unsaturated hydroxy lactone (**9**). The process was employed with more complex lactones in a total synthesis of iridoids. The method fails with α,α-disulfenylated ketones unless a catalytic amount of copper(I) bromide is included in the reaction mixture.



(23)

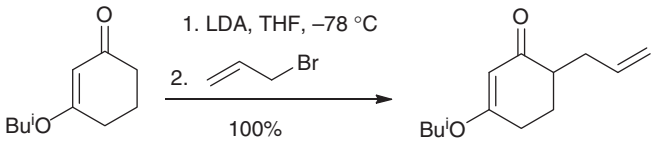
Reaction of γ-butyrolactone with LDA and bis[methoxy(thiocarbonyl)] disulfide in THF at −78 °C provides an enolate that reacts with heptanal to give the (*E*)-α-heptylidine-γ-butyrolactone (**10**), contaminated by only 4% of the (*Z*)-isomer (**11**; equation 24).[37] If the aldol step is carried out in the presence of $ZnCl_2$, compounds (**11**) and (**10**) are formed in a ratio of 85:15. The reaction apparently proceeds through an intermediate episulfide, and the double-bond geometry is a function of the initial aldol stereochemistry. The process illustrated in equation 24 seems to be quite general; the original reference should be consulted for numerous other examples.



(24)

2.08.2.6 Enolates of α,β-Unsaturated Carbonyl Compounds

α,β-Unsaturated carbonyl compounds can present two regiochemical problems. With ketones that have hydrogens at the γ- and α'-position, there is a regiochemical issue in the deprotonation reaction itself. Stork and Danheiser have shown that α'-deprotonation is favored over γ-deprotonation, and that the resulting enolates may be alkylated without the complication of proton transfer (equation 25).[38] Stork and Kraus extended this method to aldol reactions, as shown in equation 26.[39,40] Although the original aldol reaction occurs exclusively at the α'-position of the vinylogous ester, the product after reduction and acid hydrolysis of the initial aldol is the one that would result from aldol reaction at the γ-position of 3-penten-2-one.



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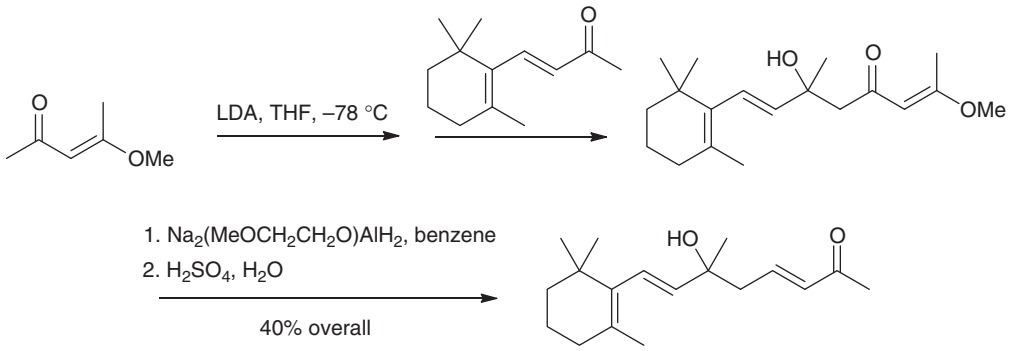
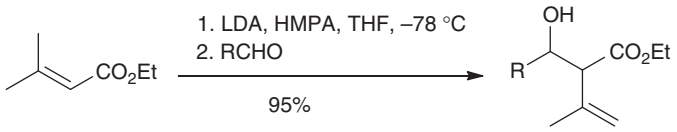


(26)

α,β-Unsaturated carbonyl compounds that do not have enolizable hydrogens at the α'-position give ambident enolates that can react with electrophiles at two sites – α or γ.[41] Reaction at either position has been observed. Instructive examples are seen in the different behaviors of ethyl 3-methylcrotonate and ethyl 2-methylcrotonate (equations 27 and 28).[42,43] Control experiments showed that both enolates undergo alkylation exclusively at the α-position. It is likely that both also undergo kinetic aldol addition at this position, but that the more substituted α-substituted aldolate from ethyl 2-methylcrotonate equilibrates with the less-congested γ-substituted isomer.



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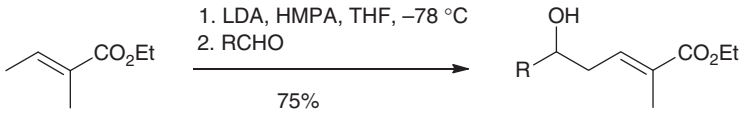
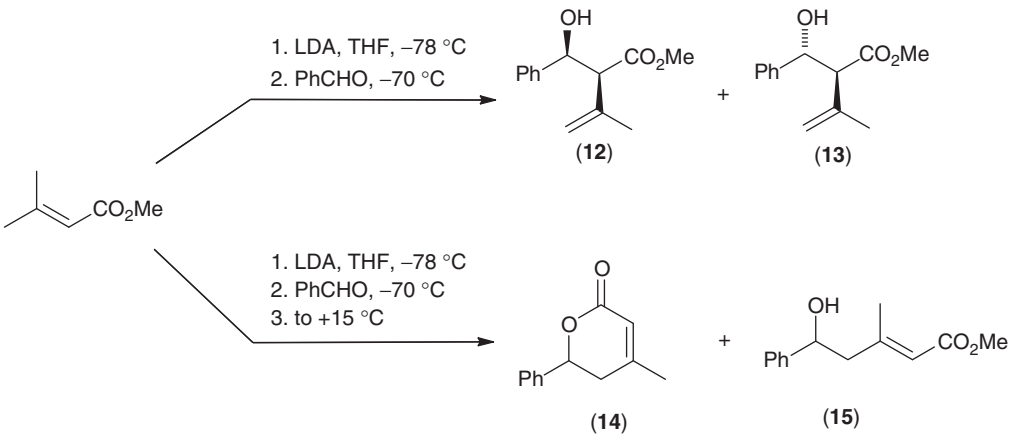


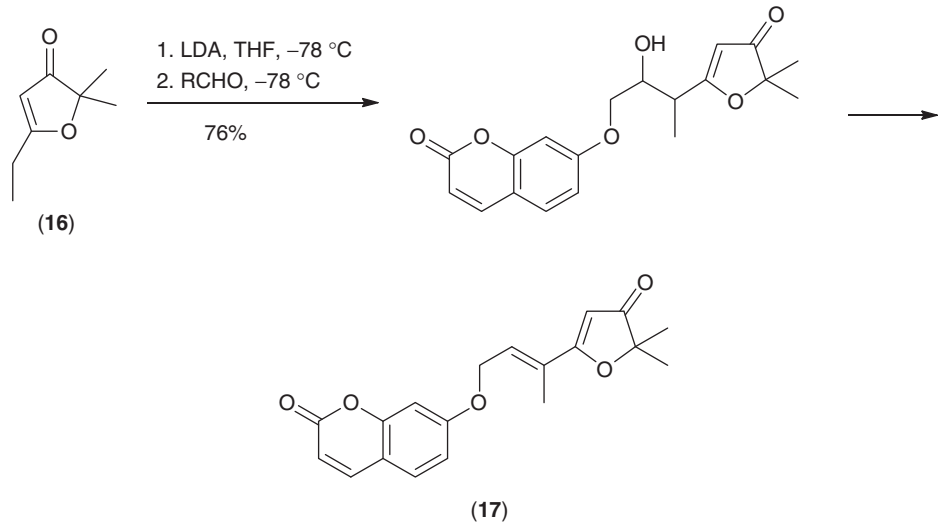
(28)

Heathcock and Dugger examined the enolate derived from methyl 3-methylcrotonate (equation 29).[44] When the aldol reaction with benzaldehyde is carried out at −70 °C and quenched at this temperature, diastereomeric aldols (**12**) and (**13**) are formed in a ratio of 3:2. However, if the aldolate is warmed to 15 °C prior to work-up, lactone (**14**; 80%) and hydroxy ester (**15**; 12%) are produced. These results conclusively demonstrate that such dienolates react kinetically at the α-position, and that the initial aldolate isomerizes to the more stable γ-substituted isomer at elevated temperatures.



(29)

3(2*H*)-Furanone (**16**) gives a dienolate that shows a proclivity for reaction with electrophiles at the exocyclic γ-position (equation 30).[45] Dehydration of the mixture of diastereomeric aldols gives a 1:1 mixture of geiparvarin (**17**) and its geometric isomer.

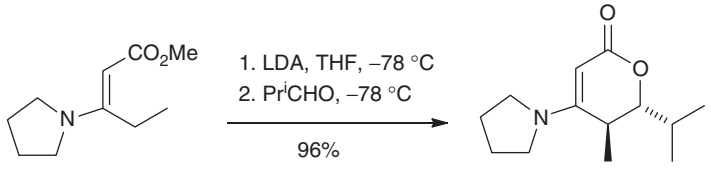


(16)

(17)

(30)

Schlessinger and coworkers have studied the aldol reactions of the dienolates derived from the vinylogous carbamate (**18**); in all cases, reaction occurs solely at the γ-position, as shown in equation 31.[46] Various evidence has been adduced that (**18**) reacts kinetically at the γ-position, in contrast to the behavior of crotonate enolates (*vide supra*). The process has been used to synthesize the Prelog-Djerassi lactonic acid and a chiral version of (**18**) has been used to synthesize a fragment of the antibiotic virginiamycin M_2 (*vide infra*).[47]

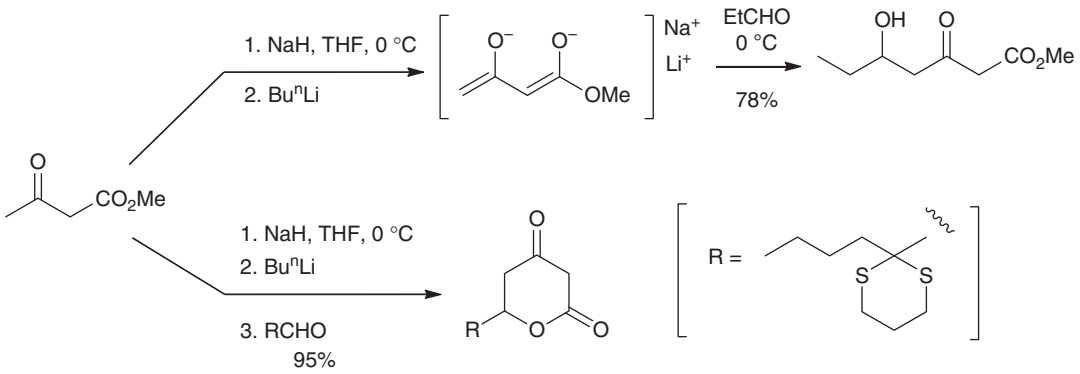


(18)

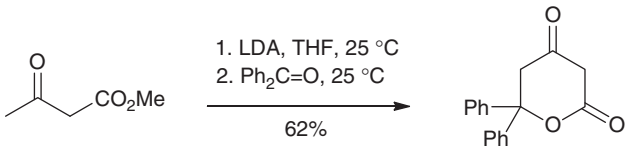
(31)

2.08.2.7 Dianions of Diketones and Keto Esters

β-Dicarbonyl compounds may be converted into dianions, which react with electrophiles at the more basic site.[48] Huckin and Weiler found that β-keto ester dianions undergo aldol addition reactions at the more basic methyl position (equation 32).[49] The lithium/sodium dianion shows surprisingly weak reactivity, giving the aldol in only 11% yield after 1 h at −78 °C! In contrast, the lithium enolates of simple ketones and esters, which should be much less basic than the β-keto ester dianion, react with aldehydes to give nearly quantitative yields of aldols in THF in seconds at −78 °C. (See, inter alia, ref. 9c.) Seebach and Meyer also studied this reaction, and obtained the oxolactone (equation 33).[50] Simple diastereoselection in the reaction of β-keto ester dianions has also been studied (*vide infra*).

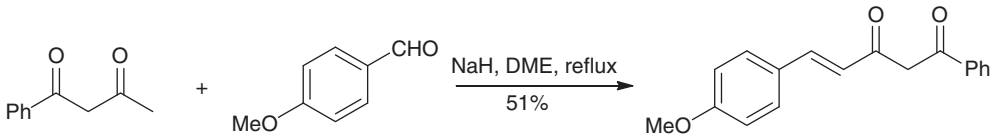


(32)

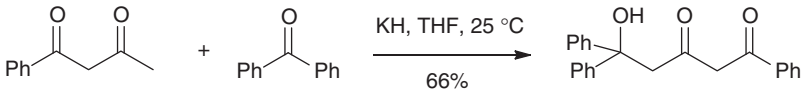


(33)

Hauser and coworkers have extensively developed the chemistry of 1,3-diketone dianions.[51] In a 1965 paper, it was reported that treatment of a refluxing DME solution of benzoylacetone with NaH and various aromatic aldehydes and ketones gives unsaturated *β*-diketones in fair yield (equation 34).[52] Although this result suggests the intermediacy of the dianion, control experiments showed that benzoylacetone is converted only into the monoanion under the reaction conditions. Wolfe and coworkers reexamined this reaction with KH and found that, indeed, treatment of a THF solution of benzoylacetone with 4 equivalents of KH at 25 °C gives only 1.1 equivalents of hydrogen, corresponding to the formation of only 10% dianion. However, upon addition of benzophenone to the reaction mixture, the remaining 0.9 equivalent of hydrogen is rapidly evolved. Upon work-up, the aldol is obtained in 66% yield (equation 35).[53] The reason for this unusual behavior is still not clear.

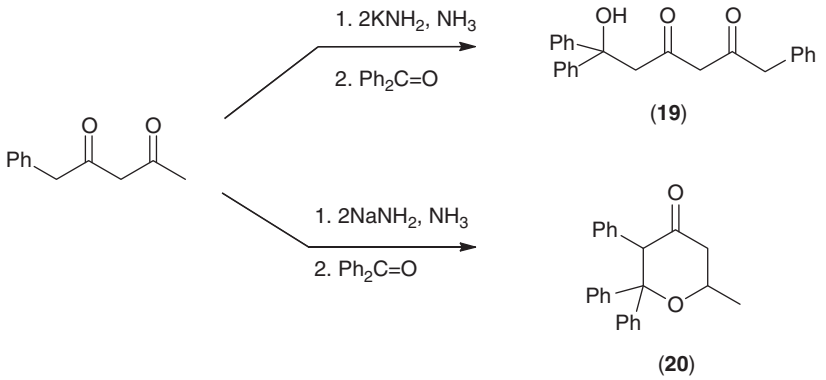


(34)



(35)

When 1-phenyl-2,4-pentanedione is doubly deprotonated with potassium amide in ammonia, the ensuing aldol reaction with benzophenone gives the expected aldol (**19**).[54] However, if sodium amide is employed to generate the dianion, the reaction product with benzophenone is the dihydro-*γ*-pyrone (**20**; equation 36).[55] This result suggests the intermediacy in the latter reaction of a dianion involving the benzylic position. Further study of this interesting reaction is warranted.

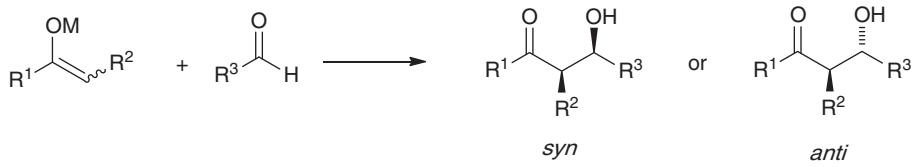


(36)

2.08.3 Simple Diastereoselection

2.08.3.1 General Overview

The principal factor that was responsible for the rebirth of the venerable aldol reaction as a modem method of synthesis was the discovery that its stereochemistry can be controlled quite effectively through the use of preformed enolates.[56] In this section is discussed 'simple diastereoselection' reactions between prochiral enolates and prochiral aldehydes (equation 37); the *syn*/*anti* stereochemical notation is employed. (For a discussion of stereostructural notations that have been used for aldols, see ref. 57d, p. 112.)

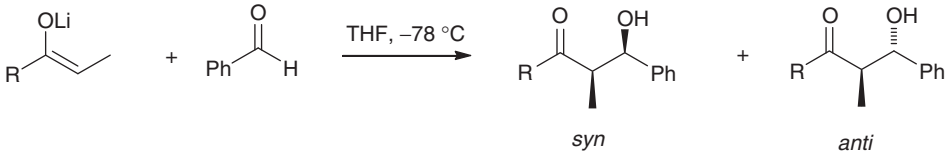


(37)

Before commencing this discussion, it is appropriate to consider briefly the issue of kinetic versus thermodynamic control in the reactions of preformed Group I and Group II enolates and to summarize the structure-stereoselectivity generalizations that have emerged to date. It is now well established that preformed lithium, sodium, potassium and magnesium enolates react with aldehydes in ethereal solvents at low temperatures (typically −78 °C) with a very low activation barrier. For example, reactions can often be quenched within seconds of the addition of an aldehyde to a solution of a lithium enolate.[9c]

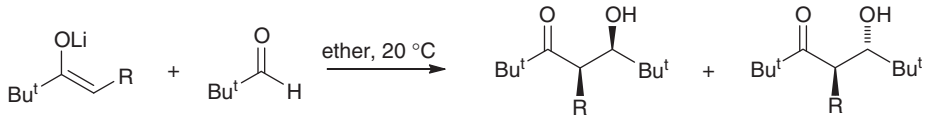
The kinetic stereoselectivity of the aldol is a function of the enolate stereochemistry *and* its structure. One often reads the over-generalization that '(*Z*)-enolates gives *syn* aldols and (*E*)-enolates give *anti* aldols.' However, the situation is much more complex than this; in addition to enolate geometry, several variables are involved. The following generalizations may be made at this time (refer to equation 37 for definition of R^1, R^2 and R^3).

(Z)-Enolates. If R^1 is large, (*Z*)-enolates give *syn* aldols; for moderate R^1, (*Z*)-enolates are still fairly *syn* selective; but for very small R^1, they are stereorandom. Examples are shown in equation 38.[9c] Another apparent structural effect is the size of R^2 (equation 37). As this is increased in size, there is a greater propensity for formation of the *anti* aldol; examples are seen in equation 39.[57]



(38)

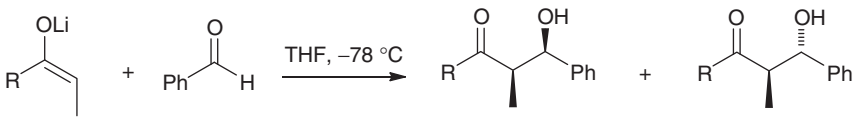
R	*syn:anti*	R	*syn:anti*
Bu^t	98.7:1.3	Et	90:10
Pr^i	90:10	H	50:50



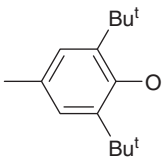
(39)

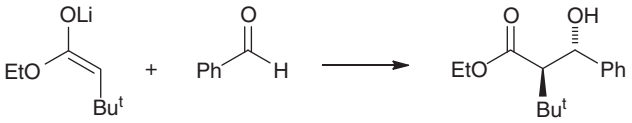
R	*syn:anti*	R	*syn:anti*
Me	100:0	Bu^i	97:3
Et	100:0	Pr^i	29:71
Pr^n	98:2	Bu^t	0:100

(E)-Enolates. For large R^1, high *anti* selectivity is seen but (*E*)-enolates with medium-sized and small R^1 groups are stereo-random (equation 40).[9c] The effect of the size of R^2 on (*E*)-enolate stereoselectivity has been investigated. If one extrapolates from the behavior of (*Z*)-enolates, it is likely that the (*E*)-enolate of an ester like ethyl 3,3-dimethylbutanoate might react with aldehydes to give rather high *anti* selectivity (equation 41).



(40)

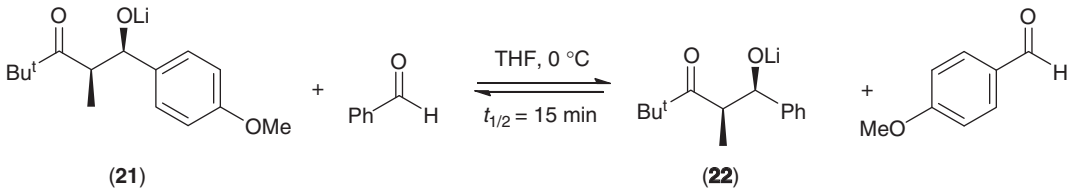
R	*anti:syn*	R	*anti:syn*
	>98:2	MeO	60:40
		Et	60:40
		Pr^i	50:50
		H	60:40



(41)

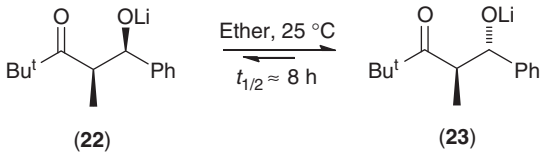
In addition to the foregoing structural effects, it is clear that the nature of the enolate cation affects aldol stereoselectivity. Since the kinetic stereoselectivity of the aldol reaction seems to result from a rather tightly organized, six-center transition state (for a complete discussion of transition state hypotheses, see ref. 57d, p. 154), cations that are effectively chelated tend to give higher stereoselectivity. Although the question has not yet been carefully investigated, magnesium enolates appear to give somewhat higher stereoselectivity than comparable lithium enolates. Boron enolates give even higher simple diastereoselection.

Although most aldol reactions of preformed Group I and Group II enolates are quite rapid, even at −78 °C, the ΔG° of reaction is not normally very negative. Thus, aldol reversal is possible under relatively mild conditions. In such cases, the observed stereochemistry is governed partially or fully by the thermodynamic properties of the diastereomeric aldolates. For the purpose of the following discussion, the most important factor is the basicity of the enolate. In general, the more basic the enolate, the less likely is aldol reversal. Amide and ester aldolates show little tendency toward reversal, whereas ketone aldolates often undergo reversal under very mild conditions. Of course, the occurrence of a retroaldol process need not be reflected in rapid erosion of stereochemical homogeneity. For example, the *syn* aldolate (**21**) derived from ethyl *t*-butyl ketone and *p*-anisaldehyde reacts with benzaldehyde to give aldolate (**22**) with a half-life of only 15 min at 0 °C (equation 42). However, aldolate (**22**) equilibrates to its *anti* diastereomer (**23**) in ether with a half-life of approximately 8 h at 25 °C (equation 43).[9c] The reason for this discrepancy is that the (*Z*)-enolate that results from the retroaldol reaction of (**21**) or (**22**) shows a very high kinetic stereoselectivity (*ca.* 80:1). Thus, on average, aldol reversal must occur 80 times in order for one molecule of (**22**) to be converted into one molecule of (**23**).



(**21**) (**22**)

(42)

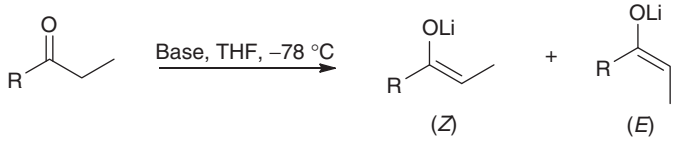


(**22**) (**23**)

(43)

2.08.3.2 Ketone Enolates

Enolates of acyclic ketones can be prepared stereoselectively with a fair amount of control by varying the base that is used for deprotonation. Some representative data are shown in equation 44 and **Table 1**.[9c] In discussing the stereochemistry of enolates, the (*E*)/(*Z*) notational format suggested by Evans (ref. 2c) is followed. Thus, in naming an enolate derived from an ester $R^2CH_2CO_2R^1$, OM is assigned higher priority than OR^1, regardless of the metal. It is clear from this table that there is an intrinsic preference for esters and ketones with small R groups to give the (*E*)-enolate, regardless of base. As R is increased in size an increasing amount of (*Z*)-enolate results. On the other hand, a more bulky base gives relatively more of the (*E*)-enolate (i.e., LITMP vs. LDA).



(*Z*) (*E*)

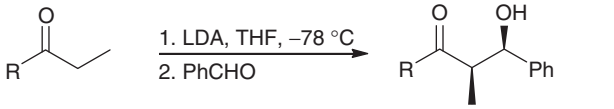
(44)

Masamune and coworkers studied the deprotonation of 3-pentanone and ethyl cyclohexyl ketone with various bases.[58] These workers confirmed that lithium hexamethyldisilazane gives more (*Z*)-isomer than does LDA and found that other bis(trialkylsilyl) amides are even more (*Z*)-selective. The best base studied was lithium hexamethyldisilazane, which gives >99% (*Z*)-isomer with both ketones.

Table 1 Enolate stereochemistry (equation 44)

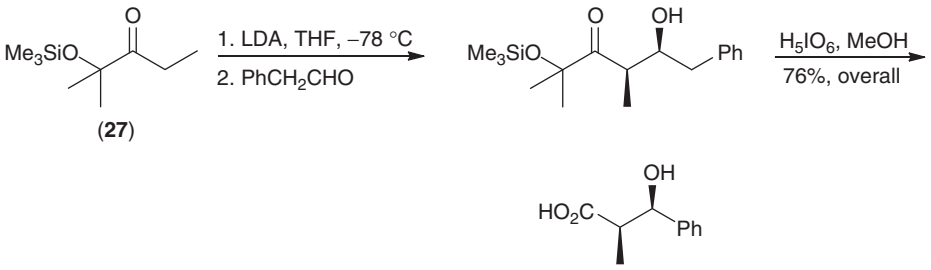
R	*LITMP*	*(Z)-Isomer (%)* *LDA*	*LHMDS*
MeO	–	5	–
2,4,6-$Me_3C_6H_2$	4	8	87
Et	16	30	66
Pr^i	32	56	>97
Pr^i_2N	52	81	–
Ph	>97	>97	>97
Bu^t	>97	>97	>97

Certain (*Z*)-ketone enolates react with aldehydes to give *syn* aldols with excellent stereoselectivity. As shown in equation 45, the (*Z*)-enolates of ethyl *t*-butyl ketone, ethyl 1-adamantyl ketone and ethyl mesityl ketone all react with benzaldehyde to give *syn:anti* ratios of >50:1.[9c,59] The bulky *t*-butyl, adamantyl and mesityl groups assure that (*Z*)-enolates are formed with high selectivity and organize the transition state so as to maximize formation of the *syn* aldol. To capitalize on this discovery, various ketone reagents have been devised that have bulky alkyl groups that can be removed oxidatively or reductively. One such reagent is the α-trimethylsilyloxy ketone (**27**; equation 46).[9c,60] A related reagent, compound (**28**), also gives high *syn* selectivity in its aldol reactions. The resulting β-hydroxy ketone may be reduced to a diol that is oxidatively cleaved by lead tetraacetate to an aldehyde (equation 47).[61] Trityl ketone (**29**) functions predictably, giving *syn* aldol with excellent stereoselectivity and in high yield (equation 48).[62] These aldols may be reductively cleaved with lithium triethylborohydride, after protection of the secondary alcohol. The (*Z*)-lithium enolate of ketone (**30**), formed with lithium hexamethyl-disilazane, gives *syn* aldols with several aldehydes. Flash vacuum pyrolysis of the aldol silyl ether expels cyclopentadiene by a retro-Diels–Alder reaction, providing the *syn* aldol of an α,β-unsaturated ketone (equation 49).[63]



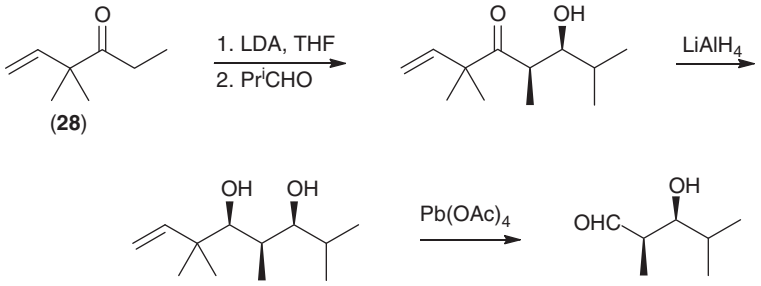
(**24**) R = Bu^t
(**25**) R = 1-adamantyl
(**26**) R = 2,4,6-$Me_3C_6H_2$

(45)



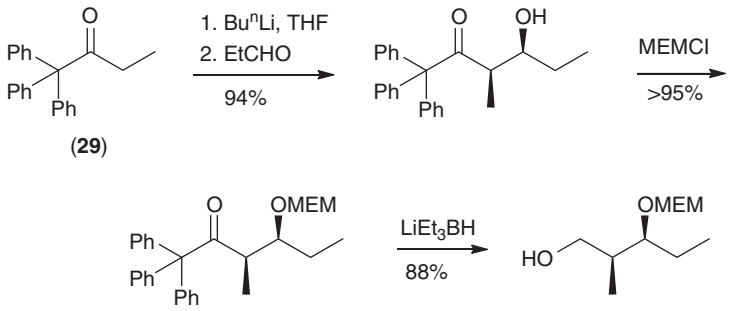
(**27**)

(46)



(**28**)

(47)



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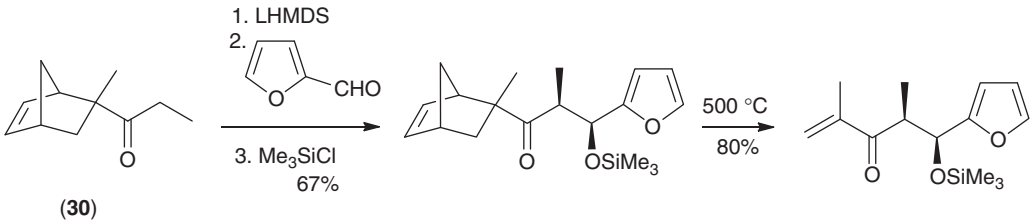
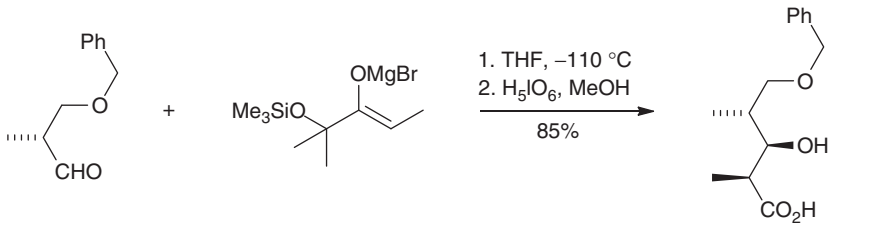


(49)

Ketone (**27**) and reagents related to it have been used in synthesis. In equation 50 is shown an application of the magnesium enolate in Still's synthesis of monensin; the facial selectivity in this case is 5:1 and the reaction proceeds in 85% yield.[64] The lithium enolate of (**27**) has been employed in a synthesis of the C-1,C-7 segment of erythronolide A (equation 51); the facial selectivity in this case is 6:1.[65] Ketone (**31**) was used in a synthesis of the basic nucleus of crassin acetate (equation 52).[66] The aldol reaction of (**31**) with (**32**), derived from geraniol, occurs in 58% yield to give only one isomer. Four further steps converted the aldol into the 14-membered crassin ring. (±)-Ristosamine was synthesized starting with ketone (**33**), which adds to (S)-*O*-benzyllactaldehyde to give the *syn* aldol (**34**; equation 53); the facial selectivity in this reaction is 4:1 and the total yield is 97%.[67] Ketone (**27**) has been used in a similar manner to prepare the C-29,C-37 fragment of amphotericin B and nyastatin (equation 54).[68]



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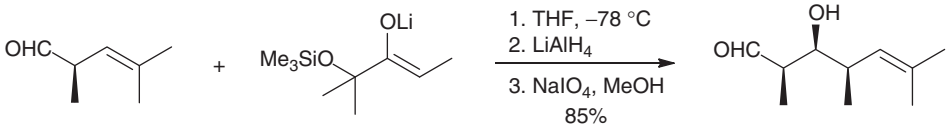

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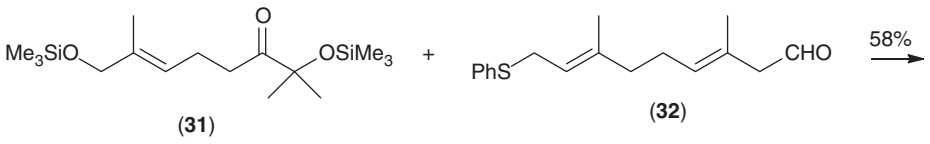

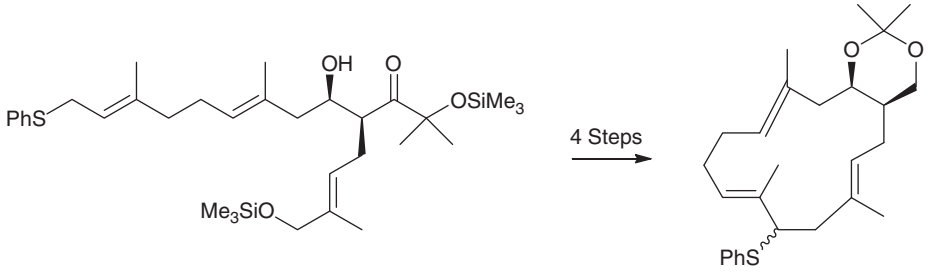

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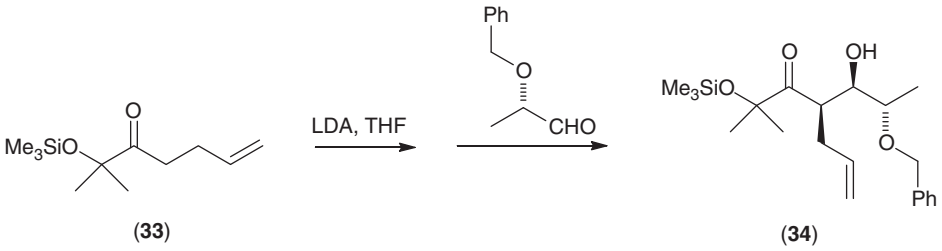
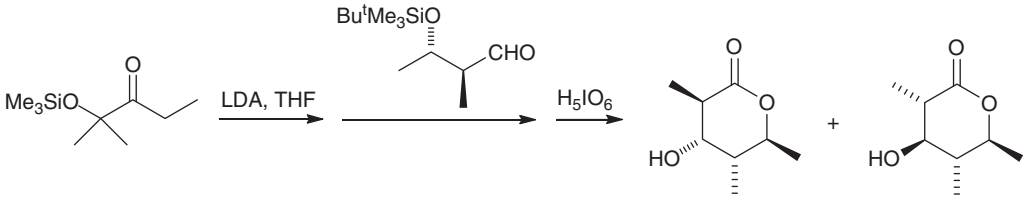
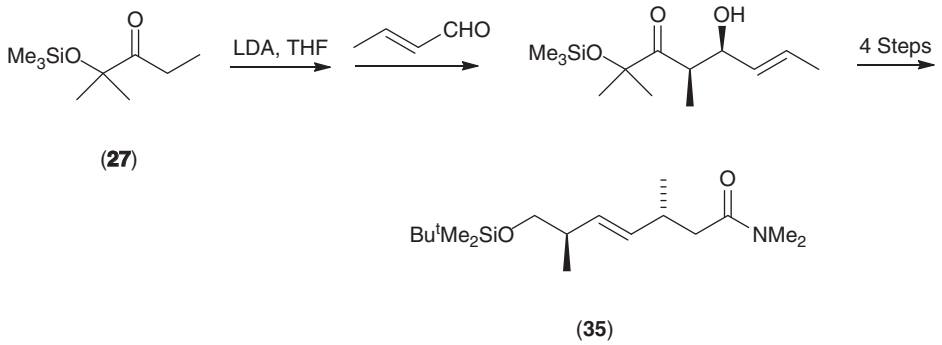


(33) (34) (53)

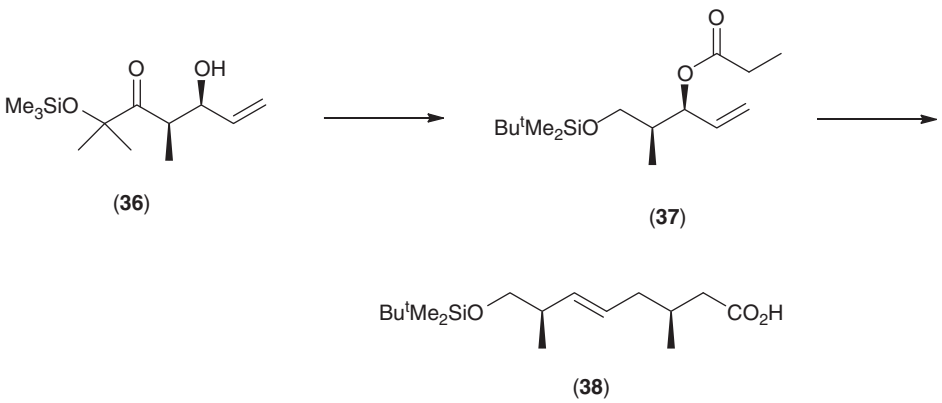


(27) 40% 15% (54)

Reaction of reagent (27) with crotonaldehyde provides a *syn* aldol, which is transformed by a four-step sequence including a Claisen rearrangement into (35) (equation 55).[69] Aldol (36), obtained from (27) and acrolein, was converted via propionate (37) into (38), a building block for the vitamin E side chain (equation 56).[69b,70] The strategy of parlaying the 1,2 relative stereochemistry obtainable from the aldol reaction into 1,5 relative stereochemistry by use of a Claisen rearrangement has also been used to prepare the C_{40} archaebacterial diol and one of its stereoisomers.[69b,71]



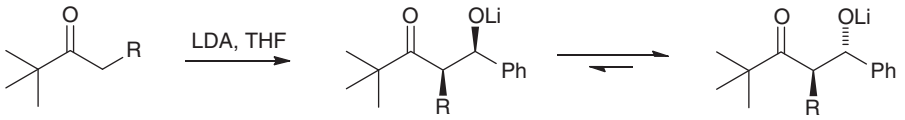
(27) (35) (55)



(36) (37) (38) (56)

A study of ethyl *t*-butyl ketone (39) and its homologs (40) to (42) (equation 57) revealed several interesting differences.[72] Firstly, there is a significant steric effect on the rate of deprotonation in this series. Whereas ketone (39) (0.2 M in THF) is deprotonated completely by LDA in 20 min at −20 °C, ketone (42) requires 4 h for deprotonation at this temperature. Aldol reactions of (39) to (42) with benzaldehyde were compared in THF and in pentane. All four ketones give exclusively the *syn* aldol in THF at −78 °C. In pentane, (40) to (42) give some *anti* aldol under the normal reaction conditions, with the amount of *anti*

product being greater with increasing size of R. With ketone (**42**), reaction for 30 min at room temperature provides aldols with an *anti:syn* ratio of >50:1. The formation of *anti* aldols in pentane solution was shown to result from equilibration of the kinetic *syn* product to the more stable *anti* aldolate. Whereas the equilibration of *syn* aldolate (**43**) to *anti* aldolate (**44**) has a half-life in ether solution at 25 °C of approximately 8 h (*vide supra*), this reaction has a half-life in pentane at 25 °C of only 45 min. As expected, steric bulk in the aldolate promotes the retroaldol reaction; the half-life for equilibration of (**45**) to (**46**) in pentane at 25 °C is only 7 min; the *n*-propyl and *n*-butyl aldolates undergo *syn* to *anti* equilibration under the same conditions with a half-life of less than 4 min.



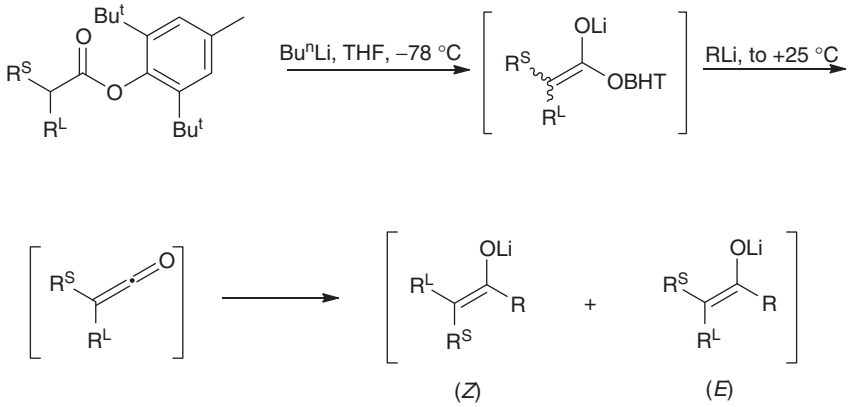
(57)

(**39**) R = me
(**40**) R = Et
(**41**) R = Pr^n
(**42**) R = Bu^n

(**43**) R = Me
(**45**) R = Et

(**44**) R = Me
(**46**) R = Et

Although a considerable amount of data exists pertaining to simple diastereoselection with trisubstituted enolates, very little is known about reactions of fully substituted enolates, principally because of a dearth of methods for the stereospecific generation of such enolates. (Ester enolates that are substituted at the α-position by heteroatoms constitute a special exception to this generalization; these fully substituted enolates are discussed in Section 2.08.3.3.) Two research groups have recently reported an interesting approach to the generation of such enolates, which is summarized in equation 58.[73] The method is based on the discovery that amine-free enolates of 2,6-di-*t*-butyl-4-methylphenol ('butylated hydroxytoluene', or BHT) decompose by ejection of phenoxide upon being warmed from −78 °C to room temperature (the onset of decomposition is believed to be at about −20 °C). If this decomposition occurs in the presence of an alkyllithium species, the ketene produced is trapped to give a regiodefined enolate. If the ester has two α-substituents of differing size, the enolate produced is also stereochemically defined because the alkyllithium reagent attacks the ketene preferentially *syn* to R^S, the smaller of the two substituent groups. Consequently, a (*Z*)-ketone enolate is generated preferentially, the stereoselectivity of the process depending upon the difference in size between R^S and R^L. The enolate mixture so generated may be trapped with trimethylsilyl chloride to give a mixture of stereoisomeric silyl enol ethers, which reflects the stereoselectivity of enolate formation; data for three different esters are summarized in **Table 2**. As is shown in the table, there is a little stereoselectivity in enolate formation when R^S and R^L are Me and Et, moderate stereoselectivity when the two groups are Me and Pr^i, and excellent stereoselectivity with Me and Bu^t.



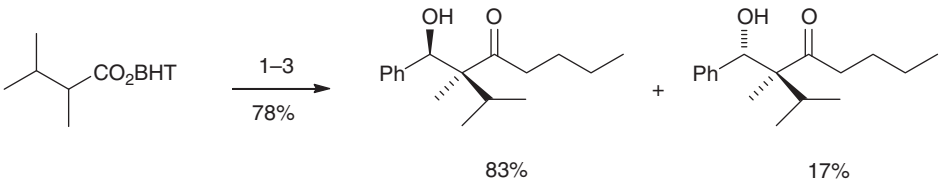
(58)

Table 2 Enolate stereochemistry (equation 58)

R^S	R^L	R	Yield (%)[a]	(Z):(E)
Me	Et	Me		1.7:1
Me	Pr^i	Me		7:1
Me	Bu^t	Me		>99:1
Et	Me_3Si	Bu^n	77	>99:1
Me	Ph	Bu^n	50	>99:1
Et	Ph	Bu^n	76	>99:1
H	Bu^t	Bu^t	62	>99:1

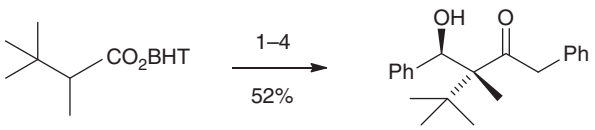
[a]Yield of the trimethylsilyl enol ether.

The substituted enolates produced in the foregoing manner may be trapped with aldehydes; one example is shown in equation 59. In this case, the aldol ratio, assigned as shown without rigorous proof, corresponds closely to the enolate ratio (Table 2). A related enolate, in which R^S and R^L are Me and Bu^t gives a sole aldol (equation 60); this aldol was found to have the indicated structure by X-ray analysis.[74] This result is understood in terms of the Zimmerman-Traxler transition state, if one assumes that the *gauche* interaction between the phenyl of the aldehyde and the bulky *t*-butyl group strongly destabilizes the normal chair-like transition state with phenyl equatorial. (For a discussion of the stereochemistry in terms of the Zimmerman-Traxler hypothesis, see ref. 57d, p. 154.) (The stereochemical outcome of this reaction is also in accord with the results of Dubois and Fellmann on 2-*t*-butyl-5,5-dimethylcyclopentanone (*vide infra*, equation 67).) In the light of this result, the stereochemical assignment of the aldols shown in equation 59 should probably be regarded as tentative.



(59)

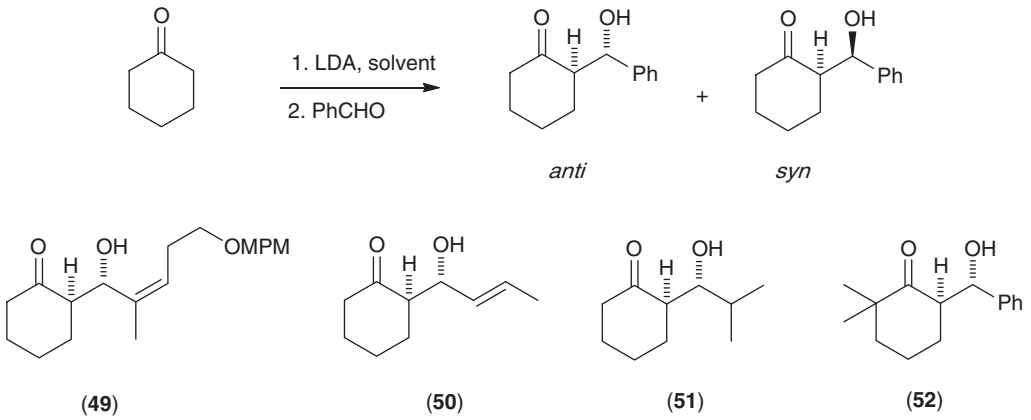
1. 2 equivalents Bu^nLi, THF, −78 °C; 2. warm to +25 °C; 3. PhCHO



(60)

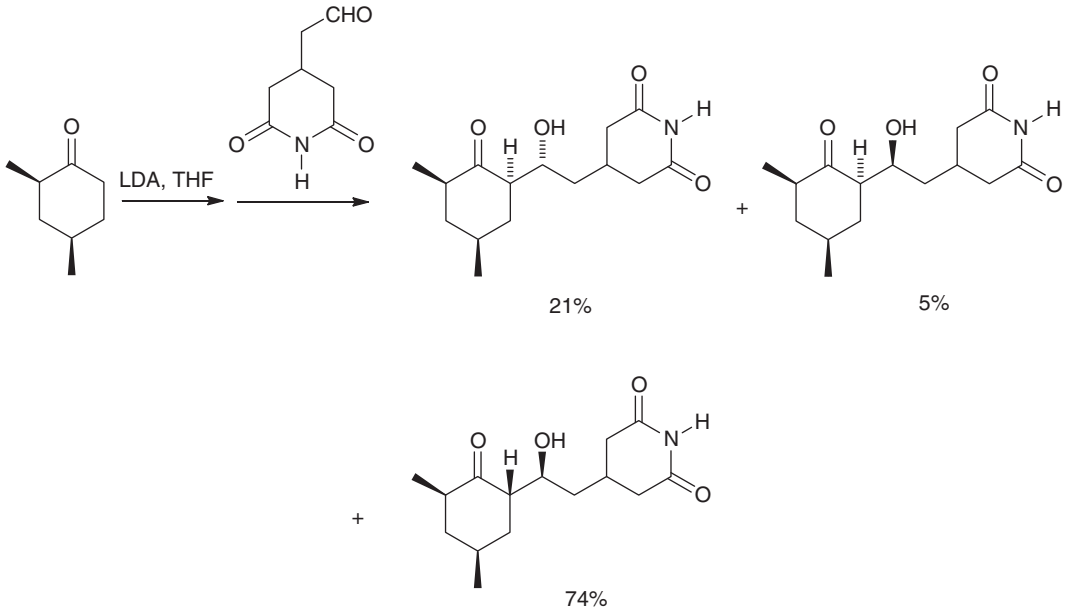
1. Bu^nLi, THF, −78 °C; 2. $PhCH_2Li$; 3. Warm to +25 °C; 4. PhCHO

The degree of stereoselectivity of aldol reactions of simple cyclohexanone enolates has been a subject of some confusion. For cyclohexanone itself, it has been reported that reaction of the lithium enolate with benzaldehyde gives the two isomeric aldols (Scheme 1) in ratios of 52:48 in THF at −78 °C[9c] and 50:50 in dimethoxyethane at −20 °C.[75] On the other hand, Seebach reports ratios of 79:21 at −78 °C and 85:15 at −150 °C.[76] Hirama and coworkers reinvestigated the reaction of the lithium enolate of cyclohexanone with benzaldehyde (Scheme 1) and found *anti*:*syn* ratios of about 82:18 at −78 °C.[77] The ratio is also 82:18 at −50 °C if the reaction is worked up after 3 s, but falls to 60:40 if worked up after 5 min. Careful temperature monitoring showed that there is a significant rise (up to 5 °C) at the moment of addition of benzaldehyde to the enolate solution, even if the aldehyde is precooled. Hirama and coworkers also observed high *anti* selectivity in the preparation from cyclohexanone of aldols (**49**; 100% *anti*),[78] (**50**; 88% *anti*) and (**51**; 96% *anti*). The lithium enolate of 2,2-dimethylcyclohexanone reacts with benzaldehyde to produce aldol (**52**; 88% *anti*).[9c,79]



Scheme 1

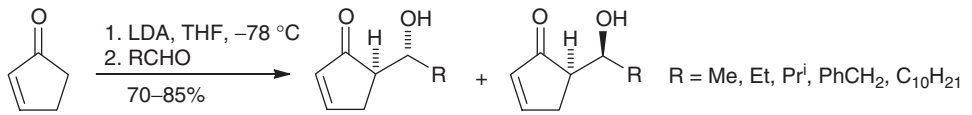
The lithium enolate of (2*R*,4*R*)-2,4-dimethylcyclohexanone has been condensed with an appropriate aldehyde to prepare several isomers of the antibiotic cycloheximide (equation 61).[80] The major isomer results from reaction on the unsubstituted face of the cyclohexanone ring, and has the same relative stereochemistry at the two new stereocenters as the major isomer in Scheme 1. The second most abundant isomer is also a *syn* aldol, and results from attack on the more-substituted face of the dimethylcyclohexanone.



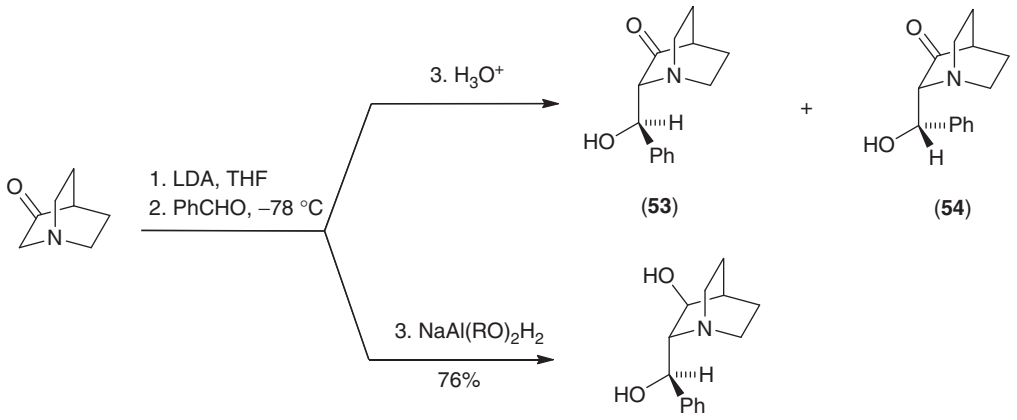
(61)

The α'-enolate of cyclopentenone reacts with aldehydes to give *anti* and *syn* aldols in ratios of 70:30 to 95:5, with the degree of stereoselectivity being related to the size of R (equation 62).[81] Similar yields, with reversed diastereoselectivity, are observed with the corresponding zirconium enolates.

Stotter has reported a study to suggest that the low stereoselectivity sometimes observed in aldol reactions of cyclohexanones results from significant aldolate equilibration.[82] As shown in equation 63, the lithium enolate of 1-azabicyclo[2.2.2]octan-3-one reacts with benzaldehyde to give, after normal work-up, aldols (**53**) and (**54**) in a ratio of about 90:10. Aldol (**53**) was found to be exceedingly sensitive with respect to conversion to (**54**), particularly in solution. If the initial aldolate was reduced prior to work-up, a single diol was obtained, suggesting that the aldol reaction itself proceeds with nearly 100% diastereoselectivity.



(62)

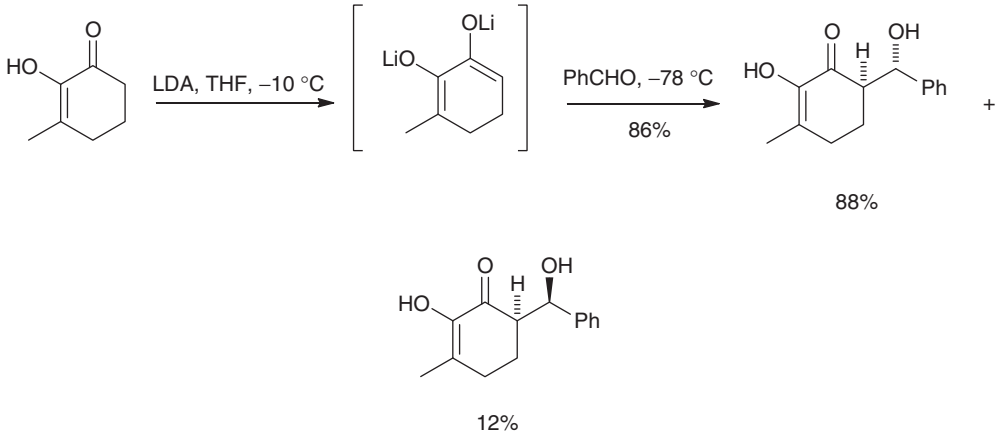


(63)

Dianions derived from 1,2-cyclohexanediones react with aldehydes rather stereoselectively, as shown in equation 64.[83] The *anti: syn* ratio of about 8:1 was shown to be kinetic rather than thermodynamic in nature, and was found to be independent of the alkyl group at C-3. The *anti* stereoselectivity is even higher with a-branched aldehydes (e.g., >99:1 with isobutyraldehyde).

Dubois and Fellmann have carried out a careful investigation of the reaction of magnesium enolates of substituted cyclopentanones with various aldehydes (**Scheme 2**).[57] Data from this important study are summarized in **Table 3**. As shown in entries 1–6, the a-unsubstituted cyclopentanone enolate shows *anti* selectivity, with the magnitude of stereoselectivity increasing with the degree of branching at the α-position of the aldehyde; branching at the β-position of the aldehyde has essentially no effect.

Substitution at the enolate carbon has an interesting effect, *reducing the amount of* anti *diastereomer as the size of* R^1 *increases* (Table 3, entries 7–11). This study also revealed that the magnesium enolate is somewhat more stereoselective than the corresponding lithium enolate. With the lithium enolate only minor medium-effects are observed.



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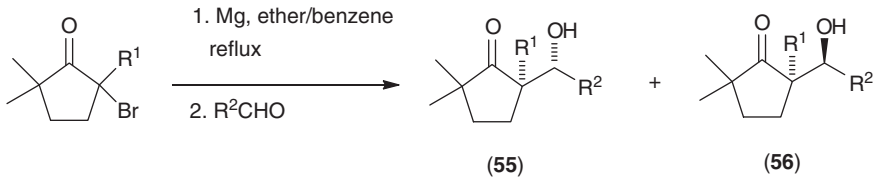
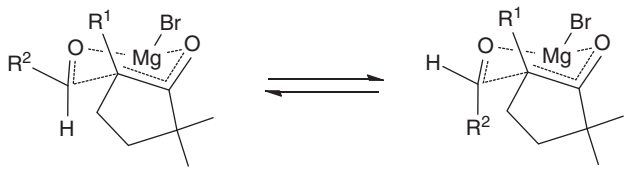




(**A**) (**B**)

(**55**) (**56**)

Scheme 2

Table 3 Aldol stereochemistry (Scheme 2)

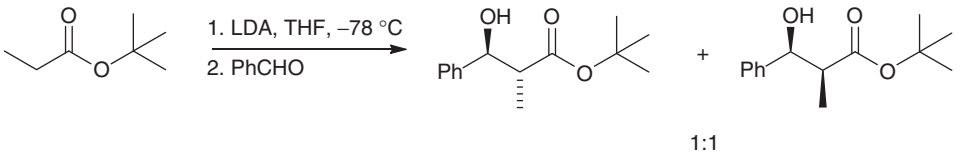
Entry	R^1	R^2	(**55**):(**56**)
1	H	Me	93.5:6.5
2	H	Et	94:6
3	H	Bu^i	93.5:6.5
4	H	neo-Pe[a]	94:6
5	H	Pr^i	97:3
6	H	Bu^t	>99:1
7	Me	Me	93.5:6.5
8	Et	Me	87.5:12.5
9	Bu^i	Me	80:20
10	Pr^i	Me	46:54
11	Bu^t	Me	29:71

[a]neo-Pe = neopentyl.

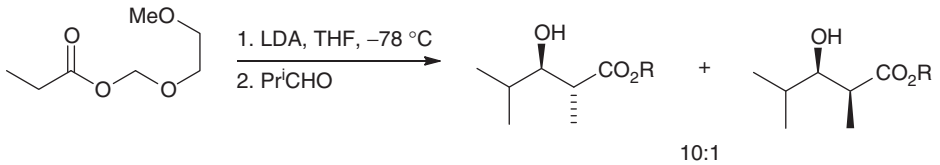
The foregoing results are in accord with the transition state structures depicted in Scheme 2. The usual Zimmerman–Traxler chelates (**A**) and (**B**) lead to aldols (**55** and **56**), respectively. With small R^1, (**A**) is favored over (**B**), because the latter transition state brings group R^2 into interaction with the cyclopentane ring; this interaction is more serious with larger R^2 groups. If group R^1 is larger, the *gauche* R^1:R^2 interaction disfavors (**A**) and leads to more reaction through transition state (**B**). Note that these results are precisely in accord with the observations by Seebach and coworkers with an acyclic (*Z*)-tetrasubstituted enolate (*vide supra*, equation 60).

2.08.3.3 Ester and Lactone Enolates

Deprotonation of esters with lithium dialkylamides gives rise to (*E*)-enolates.[9c,84] However, with normal alkyl propionates there is little or no stereoselectivity in additions to aldehydes (equation 65).[9c] It was found by Meyers and Reider that certain esters that contain additional ether oxygens in the alcohol moiety give reasonably high *anti* selectivity (equation 66).[85] This high selectivity is not general, as is shown by the example in equation 67.[9c]



(65)



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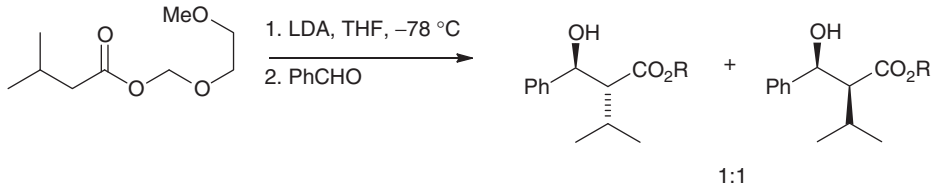


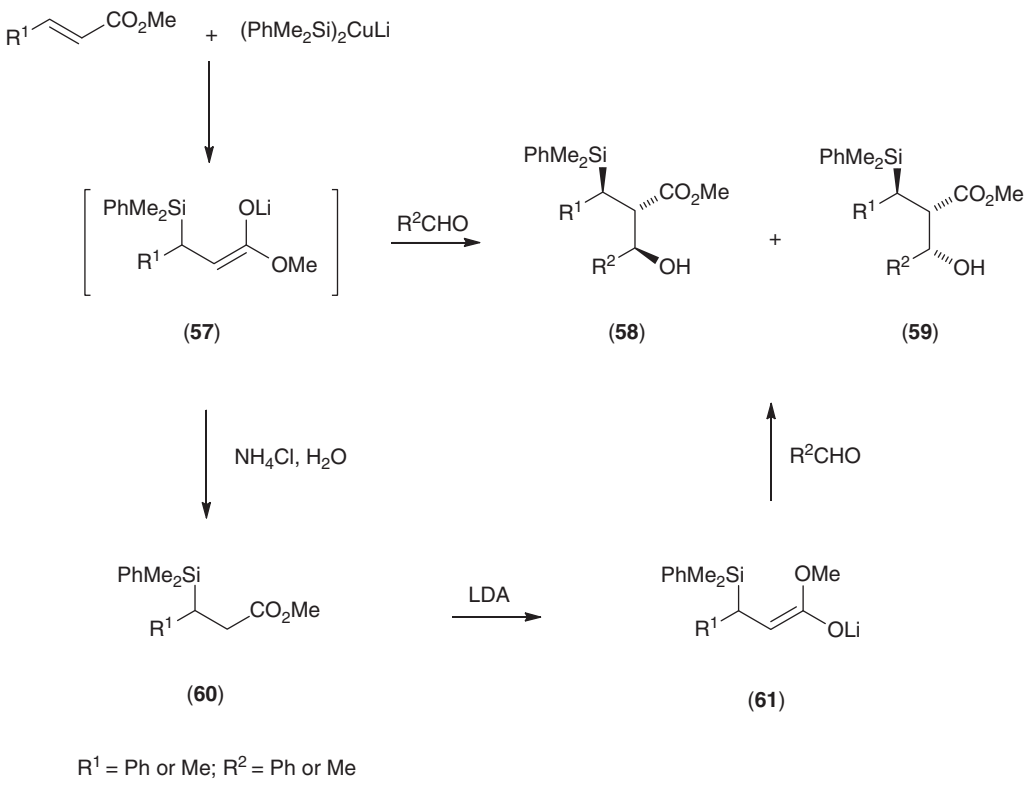
(67)

As shown in Scheme 3, (*Z*)-enolate (**57**), prepared by conjugate addition of lithium bis(phenyldimethylsilyl)cuprate to methyl crotonate or methyl cinnamate, reacts with acetaldehyde or benzaldehyde to give a mixture of two diastereomeric aldols, (**58**) and (**59**), with excellent diastereomeric excess favoring (**58**) (ratios of 85:15 to 94:6).[33] On the other hand, deprotonation of ester (**60**) by LDA provides the (*E*)-enolate (**61**), which reacts with the same two aldehydes to give the aldol (**59**) as the major product (ratios of 89:11 to 94:6). Enolates (**57**) and (**61**) both show exceptional diastereofacial preferences, in the same sense.

If one assumes enolate homogeneity, the simple diastereoselection observed (6:1 to 16:1) is remarkable. The sense of simple diastereoselection is the same as is observed for other stereoselective enolates [(*Z*)-enolate (**57**) gives the 2,3-*anti* aldol and (*E*)-enolate (**61**) gives the 2,3-*syn* aldol]. This process has been used in a synthesis of the antibiotic thienamycin.[86]

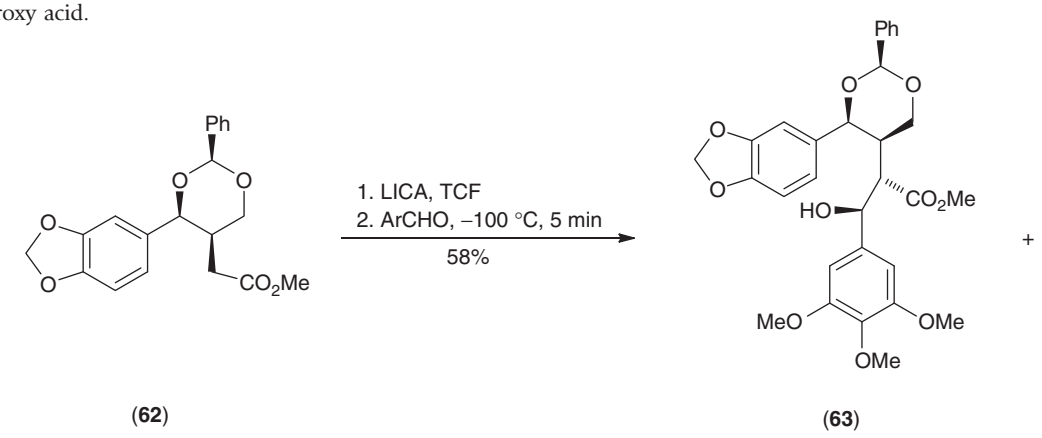
In connection with the synthesis of podophyllum lignans, ester (**62**) was deprotonated and the resulting enolate condensed with 3,4,5-trimethoxybenzaldehyde to give a 1:1 mixture of diastereomeric aldols (equation 68).[87] The structure of (**63**) was established by X-ray analysis; the other diastereomer was assigned the 2,3-*anti* relative stereochemistry (**64**) on circumstantial evidence. It was suggested that the 1:1 mixture of isomeric products results from a 1:1 mixture of the (*E*)- and (*Z*)-enolate, each of which shows complete simple and diastereofacial selectivity in its reactions with 3,4,5-trimethoxybenzaldehyde. For this to be true, it is also necessary that the (*E*)-enolate reacts through a 'non-Zimmerman', boat-like transition state, whereas the (*Z*)-enolate reacts through the normal chair-like transition state.

The hindered aryl esters (**65**) to (**71**) (Scheme 4) have been shown to be effective reagents for the preparation of 2,3-*anti* aldols.[88] Aldol additions with the enolates of these esters give predominantly 2,3-*anti* aldols (Table 4). The DMP esters (**65**), (**66**) and (**67**) give *anti*:*syn* ratios of 6:1 to 10:1 with aromatic aldehydes and α-unbranched aliphatic aldehydes (Table 4, entries 1, 2, **7** and 8) and pure *anti* products with α-branched aliphatic aldehydes (entries 3–6, 9). The BHT and DBHA esters (**68**) to (**71**) give only *anti* aldols with all aldehydes (Table 4, entries 10–20). The DMP, BHT and DBHA esters are conveniently prepared from commercially available phenols. The DMP aldols may be hydrolyzed to obtain the corresponding β-hydroxy acids. The DMP reagents are limited, however, since high stereoselectivity is only observed with β-branched aldehydes. The BHT reagents do not have this limitation, and have the added virtue that the product aldols are often nicely crystalline solids. However, the BHT aldols may not be hydrolyzed, because of the severe steric hindrance of the carbonyl group. The DBHA reagents show the same high



Scheme 3

stereoselectivity as their BHT analogs. With this reagent, the DBHA moiety may be removed oxidatively, thus permitting access to the β-hydroxy acid.



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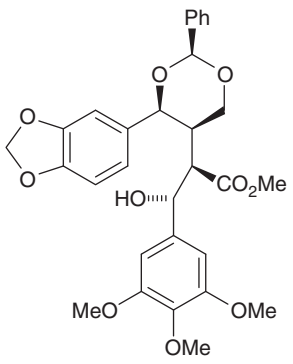

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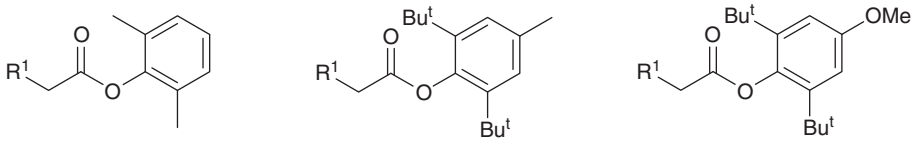
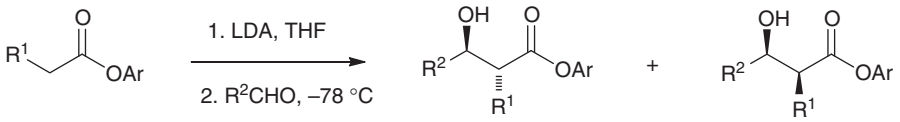


(**65**) R^1 = Me
(**66**) R^1 = Et
(**67**) R^1 = H_2C=$CHCH_2$

(**68**) R^1 = Me
(**69**) R^1 = H_2C=$CHCH_2$

(**70**) R^1 = Me
(**71**) R^1 = Et



anti *syn*

Scheme 4

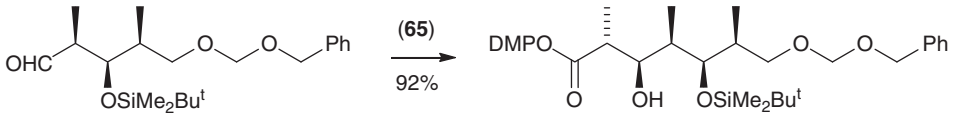
Table 4 Aldol stereochemistry (**Scheme 4**)

Entry	*Ester*	*Aldehyde*	*Yield (%)*	Anti:syn
1	(**65**)	PhCHO	72	88:12
2	(**65**)	n-C_5H_{11}CHO	70	86:14
3	(**65**)	Pr^iCHO	78	>98:2
4	(**65**)	Bu^tCHO	82	>98:2
5	(**65**)	Ph(Me)CHCHO	81	>98:2[a]
6	(**66**)	Pr^iCHO	93	>98:2
7	(**67**)	PhCHO	87	91:9
8	(**67**)	EtCHO	67	84:16
9	(**67**)	Pr^iCHO	77	>98:2
10	(**68**)	PhCHO	96	>98:2
11	(**68**)	Pr^iCHO	100	>98:2
12	(**68**)	Ph(Me)CHCHO	100	>98:2[a]
13	(**69**)	PhCHO	76	>94:6
14	(**69**)	EtCHO	81	>98:2
15	(**69**)	Pr^iCHO	60	>96:4
16	(**70**)	EtCHO	75	>98:2
17	(**70**)	n-C_5H_{11}CHO	70	>98:2
18	(**70**)	Pr^iCHO	79	>98:2
19	(**70**)	Bu^tCHO	77	>98:2
20	(**71**)	Pr^iCHO	68	>98:2

[a]4:1 mixture of C-3,C-4 diastereomers.

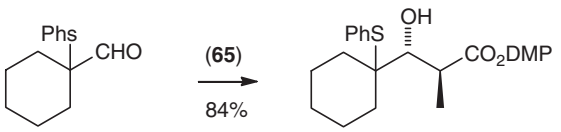
The foregoing *anti* selective aldol reagents have been employed for several synthetic purposes. Paterson used reagent (**65**) to convert aldehyde (**72**) into *β*-hydroxy ester (**73**); the yield in this reaction is 92% and the diastereomer ratio at −100 °C is 13:1 (equation 69).[89] Aggarwal and Warren employed (**65**) to convert aldehyde (**74**) into aldol (**75**) (equation 70, stereoselectivity=95:5) and the related acyclic aldehyde (**76**) into aldol (**77**) (equation 71).[90] In the latter example, the aldol stereoselectivity (C-2,C-3) is complete and the diastereofacial selectivity (C-3,C-4) is 10:1.

In the course of a synthesis of davanone, Bartlett and Holmes utilized ester (**68**) to convert aldehyde (**78**) into aldol (**79**); the stereochemical purity of the product is 97.6% (equation 72).[91] Sato and co-workers added (**68**) to the *β*,*γ*-unsaturated aldehyde (**80**) to obtain aldol (**81**), of at least 97% stereochemical purity (equation 73).[92]

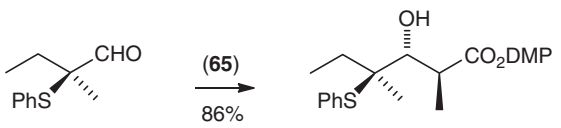


(69)

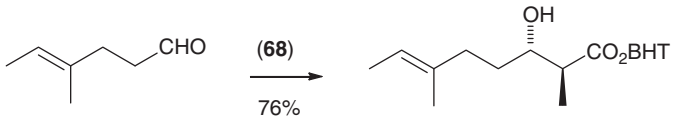
(**72**) (**73**)



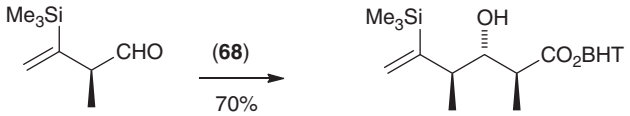
(74) (75) (70)



(76) (77) (71)

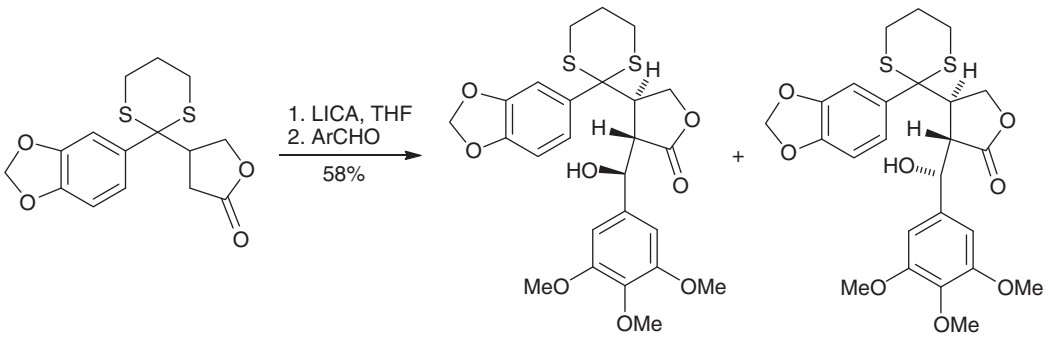


(78) (79) (72)



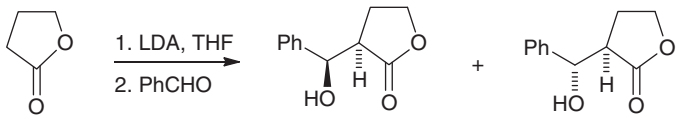
(80) (81) (73)

Lactone enolates typically show poor simple diastereoselection. For example, in connection with a synthesis of (±)-podorhizol, Ziegler and Schwartz added the lithium enolate of butyrolactone (**82**) to 3,4,5-trimethoxybenzaldehyde (equation 74). Although the diastereofacial selectivity of the chiral enolate is complete, aldols (**83**) and (**84**) are formed in a ratio of 50:50 in THF and 25:75 in an equimolar mixture of dimethoxyethane and ether.[93]



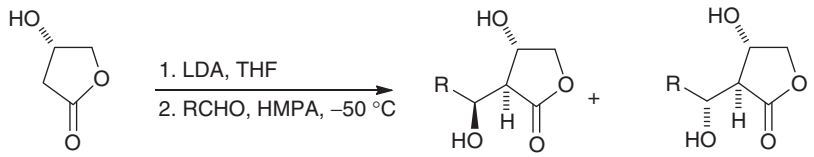
(82) (83) (84) (74)

Widdowson and coworkers investigated aldol reactions of butyrolactone itself with benzaldehyde (equation 75).[94] The lithium enolate gives diastereomers (**85**) and (**86**) in a ratio of 40:60 to 30:70, depending upon reaction temperature. If 0.5 mol equivalent $ZnCl_2$ is added to the reaction mixture prior to enolate formation, the (**85**):(**86**) ratio is 56:44 to 70:30, depending upon reaction temperature.



(85) (86) (75)

The dianion of the hydroxybutyrolactone (**87**) reacts with aldehydes with high diastereofacial selectivity to give mixtures of dihydroxy lactones (**88**) and (**89**) (equation 76; Table 5).[95] The lithium enolate shows little simple stereoselection with the sterically undemanding aldehydes phenylacetaldehyde and tetradecanal. Significant stereoselectivity is seen in the reaction with benzaldehyde, and pivalaldehyde gives only a single product. Because the aldol relative stereochemistry in the reactions with benzaldehyde and pivalaldehyde is different from that normally observed with (*E*)-enolates, the authors postulate an open transition state to explain the results. As in the previous example, the stereoselectivity is not very much affected by the addition of $ZnCl_2$, although yields are improved significantly.



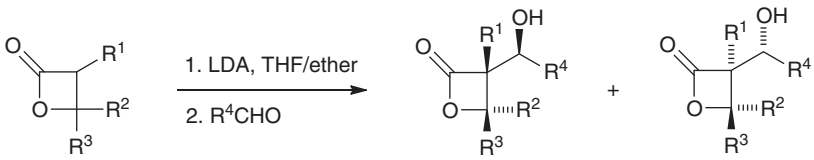
(76)

(**87**) (**88**) (**89**)

Table 5 Aldol stereochemistry (equation 76)

R	*Without $ZnCl_2$*		*With $ZnCl_2$*	
	(88):(89)	*Yield (%)*	***(88):(89)***	*Yield (%)*
Ph	90:10	43	80:20	85
$PhCH_2$	57:43	45	42:58	89
Bu^t	>100:1	34	>100:1	48
n-$C_{13}H_{27}$	50:50	48	45:55	60

β-Propiolactone enolates that are substituted at C-2 show excellent simple and diastereofacial selectivity in their reactions with aldehydes.[96] As shown in equation 77 and Table 6, the reaction is quite general; yields are in the range 85–95%. In only one case (Table 6, entry 2) is an isomer detected; in this case the (**90**):(**91**) ratio is 85:15. (The data in Table 6 are taken from the preliminary communication (ref. 101a). In this publication, structures (**90**) and (**91**) were tentatively advanced. In ref. 101b, it is reported that the structure of the major product (**90**) had been determined by X-ray crystallography. This was presumably done on the major product of Table 6, entry 1, although this is not clear from ref. 96b. In addition, in ref. 101b, it is stated that the reactions in equation 77 all proceed with >88% enantioselectivity, presumably referring to the degree of simple diastereoselection. No experimental details for the preparation of aldol (**90**) were given in this full paper.)



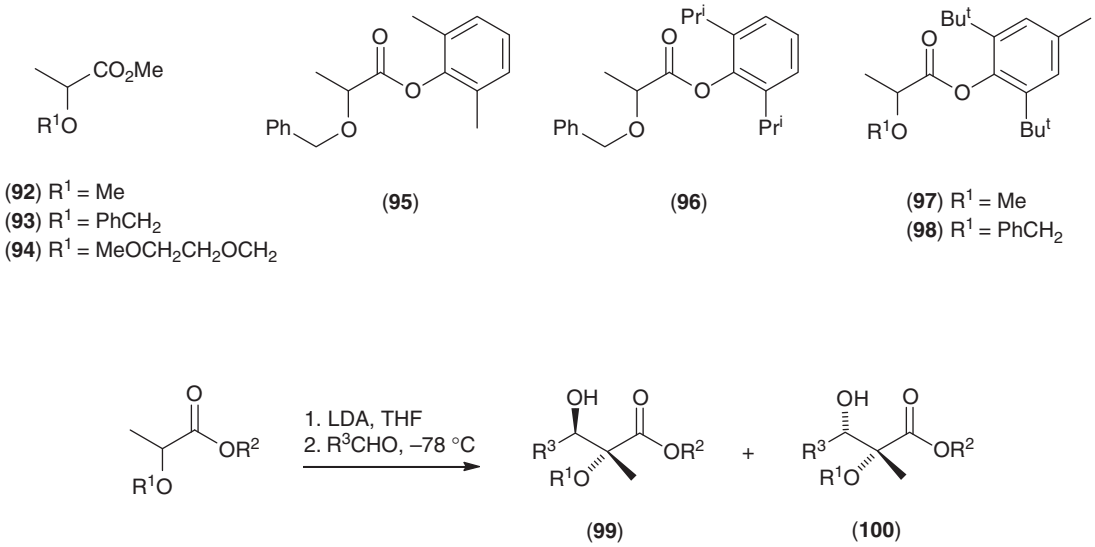
(77)

(**90**) (**91**)

Table 6 Aldol stereochemistry (equation 77)

Entry	*R^1*	*R^2*	*R^3*	*R^4*	*Isomer ratio*
1	Bu^t	H	Ph	Ph	Only one
2	Bu^t	H	Ph	Me	85:15
3	Bu^t	H	Ph	H	Only one
4	Pr^i	H	Ph	Ph	Only one
5	Pr^i	H	Ph	Me	Only one
6	Pr^i	H	Ph	H	Only one
7	Pr^i	H	H	H	Only one
8		$(CH_2)_4$	Ph	Ph	Only one
9		$(CH_2)_4$	Ph	Me	Only one
10	Bu^t	H	Me	Ph	Only one

An extensive study of the aldol reactions of α-alkoxypropionate esters has been carried out.[97] The results of this investigation are summarized in Scheme 5 and Table 7. The trend that emerges from an examination of the data in Table 7 is that aldols of structure (**99**) are favored by small R^2, while aldols of structure (**100**) are favored by large R^2. The size of R^3, the aldehyde ligand, is also important; the larger this group, the more aldol of structure (**100**) is produced (compare entries 13–17, 18–19 and 20–23, Table 7). The ethers of methyl lactate (**92**) to (**94**) show only modest preferences for aldol structure (**99**). An exception to this generalization is seen in the reaction of methyl *O*-methyllactate (**92**), which gives a single isomer in its reactions with α-branched aliphatic aldehydes (Table 7, entries 2 and 3). The excellent complementary stereoselectivity observed with this reagent and the



Scheme 5

Table 7 Aldol stereochemistry (Scheme 5)

Entry	*Ester*	*Aldehyde*	*Yield (%)*	*(**99**):(**100**)*
1	(**92**)	EtCHO	99	70:30
2	(**92**)	Pr^iCHO	98	>97:3
3	(**92**)	Bu^tCHO	84	>97:3
4	(**92**)	PhCHO	85	>75:25
5	(**93**)	EtCHO	87	70:30
6	(**93**)	Pr^iCHO	85	70:30
7	(**93**)	Bu^tCHO	80	70:30
8	(**93**)	PhCHO	100	70:30
9	(**94**)	EtCHO	60	82:18
10	(**94**)	Pr^iCHO	83	85:15
11	(**94**)	Bu^tCHO	73	88:12
12	(**94**)	PhCHO	95	85:15
13	(**95**)	$CH_2{=}CHCHO$	65	64:36
14	(**95**)	EtCHO	50	78:22
15	(**95**)	Pr^iCHO	77	83:17
16	(**95**)	Bu^tCHO	30	<3:97
17	(**95**)	PhCHO	65	25:75
18	(**96**)	Pr^iCHO	73	33:67
19	(**96**)	PhCHO	73	10:90
20	(**98**)	EtCHO	57	17:83
21	(**98**)	Pr^iCHO	89	<3:97
22	(**98**)	Bu^tCHO	0	–
23	(**98**)	PhCHO	62	<3:97
24	(**97**)	Pr^iCHO	84	<3:97
25	(**97**)	PhCHO	91	<3:97
26	(**97**)	Ph(Me)CHCHO	59	<3:97[a]

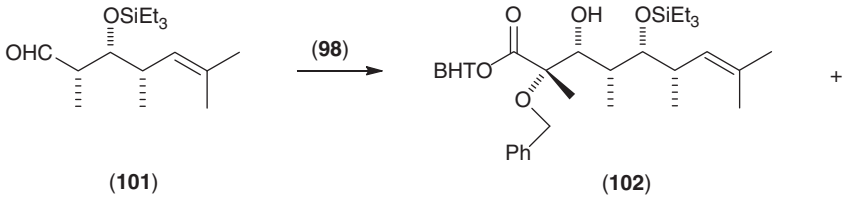
[a]A single diastereofacial isomer is produced in this reaction.

corresponding BHT ester (**97**) is striking (entries 24–26). It is also noteworthy that 2-phenylpropanal shows perfect diastereofacial selectivity in its reaction with the latter reagent.

Reagent (**98**) has been employed in syntheses of the C-l,C-7 and C-8,C-15 segments of erythronolide A.[65,98] Reaction of the lithium enolate of (**98**) with aldehyde (**101**) provides aldols (**102**) and (**103**) in a ratio of 85:15 (equation 78).[65] With the *β,γ*-unsaturated aldehyde (**104**), ester (**98**) gives a single aldol (equation 79).[98]

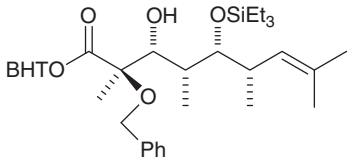
The enolate of *α,β*-dialkoxy ester (**105**) reacts with acetone to give (**106**) in good yield (equation 80); the product has been converted into (+)-viridifloric acid.[99]

The enolates of dioxolanones (**107**) react with aldehydes to give aldols (**108**) and (**109**) with, at most, a 3:1 preference for the former (equation 81).[97b] This modest preference is of the same magnitude, and in the same sense, as the preference seen with the lithium enolate of butyrolactone (equation 75, *vide supra*). However, Seebach and coworkers have carried out aldol reactions with chiral dioxolanone (**110**) and have observed high diastereofacial preference, as well as high simple diastereoselection in some cases (equation 82, **Table 8**).[100] The enolate of (**110**) also adds, in excellent yield and with essentially perfect diastereofacial selectivity, to ketones (cyclohexanone, acetone, acetophenone and benzophe-none).

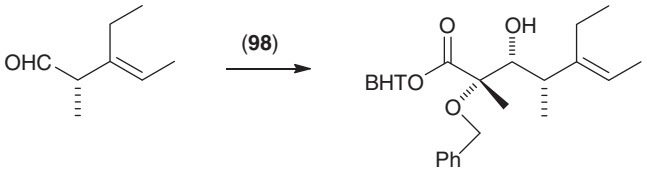


(**101**) (**102**)

(78)

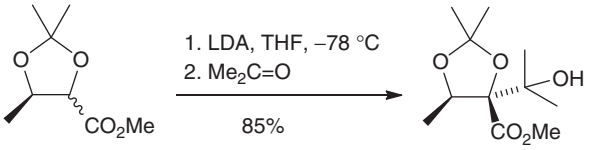


(**103**)



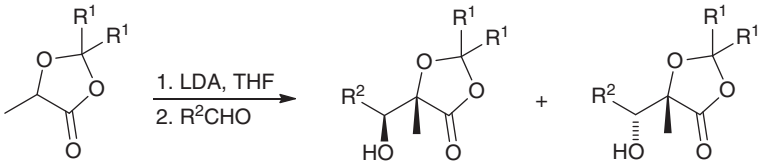
(**104**)

(79)



(**105**) (**106**)

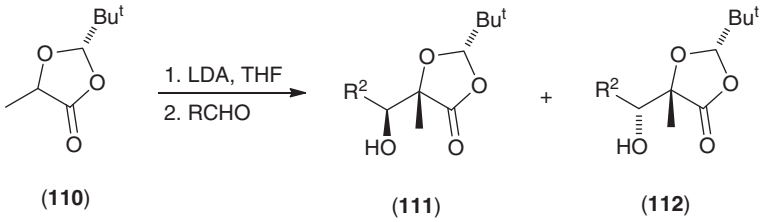
(80)



(**107**) (**108**) (**109**)

(81)

R^1 = H, Me; R^2 = Et, Pr^i, Bu^t, Ph

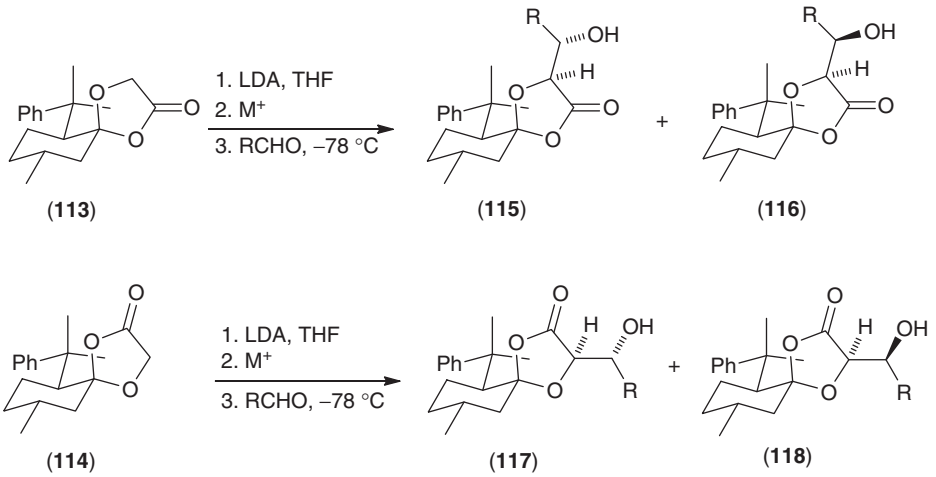


(82)

Table 8 Aldol stereochemistry (equation 82)

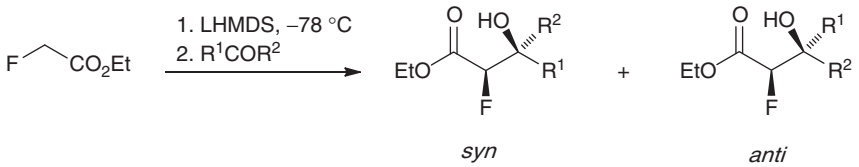
Entry	*R*	*Yield (%)*	***(111)*:*(112)***
1	Me	84	82:18
2	Et	80	85:15
3	Bu^t	83	53:47
4	Ph	85	84:16
5	2,4,6-$Me_3C_6H_2$	65	78:22
6	CH═CHPh	66	64:40

Aldol reactions of chiral dioxolanones (**113**) and (**114**) are summarized in Scheme 6 and Table 9.[101] With both (**113**) and (**114**), essentially perfect diasterofacial selectivity is observed. The simple diastereoselection is modest to good, and is dependent on the enolate counterion. For the lithium and magnesium enolates, the sense of simple diastereoselection is the same as is observed with the achiral dioxolanone (**107**) and the chiral dioxolanone (**110**). Use of the zirconium enolate generally reverses the sense of simple diastereoselection, although the isomer ratios are not very high in some cases.



Scheme 6

Ethyl fluoroacetate gives a 1:1 mixture of the (*E*)- and (*Z*)-enolates, which reacts with aldehydes and ketones to give mixtures of *syn* and *anti* aldols (equation 83).[102] Stereoselectivity is generally low, the *syn:anti* ratio ranging from 50:50 for 2-butanone to 4:1 for ethyl *t*-butyl ketone. However, since a mixture of enolates was employed in this study, there remains the possibility that one of the enolates is highly stereoselective, whereas the other one is stereorandom.



(83)

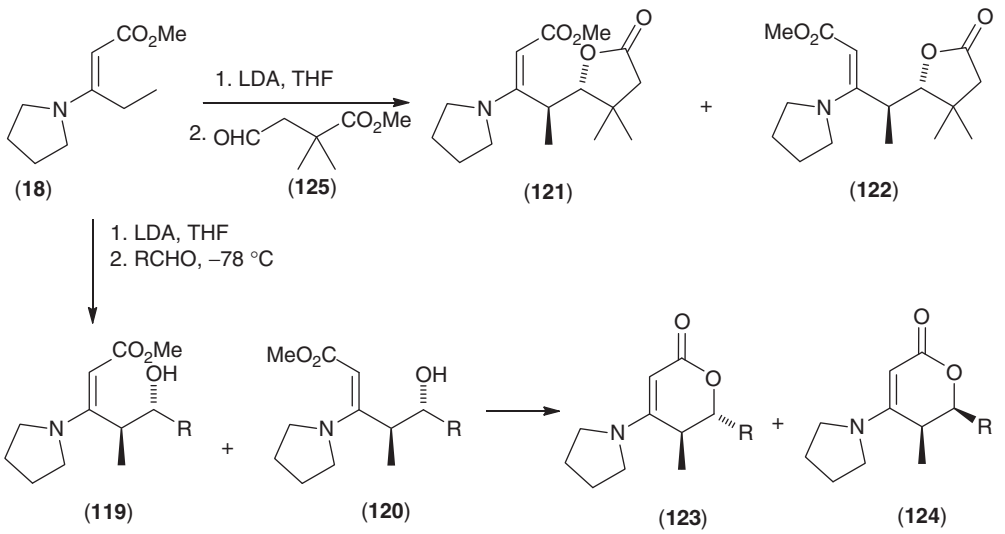
Table 9 Aldol stereochemistry (Scheme 6)

Entry	*Dioxolanone*	*M*$^{+}$[a]	*R*	*Yield (%)*	*(**115**):(**116**)*	*(**117**):(**118**)*
1	(**113**)	Li^{+}	Ph	92	68:32	–
2	(**113**)	Mg^{2+}	Ph	92	83:17	–
3	(**113**)	Zr^{4+}	Ph	95	19:81	–
4	(**113**)	Li^{+}	Pr^{n}	93	96:4	–
5	(**113**)	Mg^{2+}	Pr^{n}	86	90:10	–
6	(**113**)	Zr^{4+}	Pr^{n}	97	45:55	–
7	(**113**)	Li^{+}	Pr^{i}	85	90:10	–
8	(**113**)	Mg^{2+}	Pr^{i}	86	73:27	–
9	(**113**)	Zr^{4+}	Pr^{i}	91	24:76	–
10	(**114**)	Li^{+}	Ph	99	–	68:32
11	(**114**)	Mg^{2+}	Ph	89	–	75:25
12	(**114**)	Zr^{4+}	Ph	91	–	18:82
13	(**114**)	Li^{+}	Pr^{n}	96	–	88:12
14	(**114**)	Mg^{2+}	Pr^{n}	92	–	74:26
15	(**114**)	Zr^{4+}	Pr^{n}	91	–	37:63
16	(**114**)	Li^{+}	Pr^{i}	86	–	96:4
17	(**114**)	Mg^{2+}	Pr^{i}	89	–	89:11
18	(**114**)	Zr^{4+}	Pr^{i}	89	–	17:83

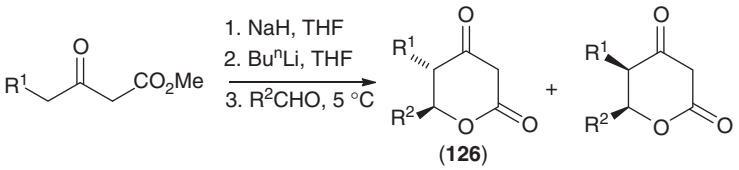
[a]For $M^{+}=Li^{+}$, no extra salt was used; for $M^{+}=Mg^{2+}$or Zr^{4+}, 1.0 equivalent of $MgBr_2$ or CP_2ZrCl_2 was added.

Schlessinger and coworkers have investigated vinylogous ester enolates derived from enamino ester (**18**).[46] As shown in Scheme 7, the lithium enolate of (**18**) reacts with isobutyraldehyde or pivalaldehyde at −78 °C to give two adducts, (**119**) and (**120**), that both have the *anti* relative configuration at the new stereocenters. If the initial aldolate solution from the reaction of (**18**) with isobutyraldehyde is kept for an extended period of time at −78 °C, or warmed to 0 °C for 5 min, cyclization occurs, providing lactones (**123**) and (**124**) in a ratio of 20:1 under both conditions. However, the pivalaldehyde adduct gives (**123**) and (**124**) in a ratio of 18:1 at −78 °C or 7.8:1 at 0 °C. If the enolate of (**18**) is treated with aldehyde (**125**), the only products obtained are lactones (**121**) and (**122**), both having the *anti* relative configuretion at the new stereocenters. The foregoing evidence is taken to indicate that the enolate of (**18**) reacts kinetically at C-4, in contrast to simple crotonate esters, which undergo aldolization at C-2. Cyclization of the original aldolate must involve geometric isomerization of the double bond, and may be complicated by reverse aldolization, particularly with the pivalaldehyde adduct at 0 °C.

The foregoing reactions bear a resemblance to the reactions of *β*-keto ester dianions (*vide supra*, equation 32), in that reaction occurs at C-4 instead of C-2. The only study of simple diastereoselection in the aldol reactions of *β*-keto ester dianions shows a stereochemical similarity as well. As shown in equation 84, the dianions of a series of *β*-keto esters react with aldehydes to give largely the *trans* lactone (**126**); data are summarized in Table 10.[103]



Scheme 7



(84)

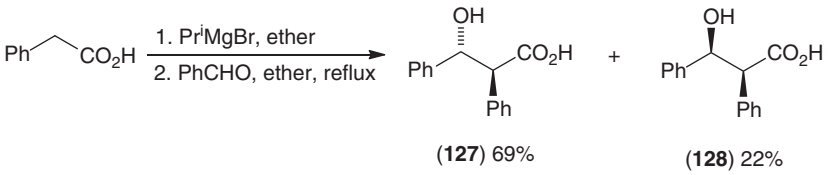
Table 10 Aldol stereochemistry (equation 84)

Entry	R^1	R^{2a}	*Yield (%)*	***(125):(126)***
1	$PhCH_2$	Me	94	100:0[b]
2	$PhCH_2$	n-C_3H_7	96	100:0[b]
3	$PhCH_2$	n-C_7H_{15}	82	100:0
4	$PhCH_2$	c-C_6H_{11}	91	100:0
5	$PhCH_2$	c-C_8H_{15}	85	89:11
6	$PhCH_2$	Ph	78	87:13
7	*m*-$MeOC_6H_4CH_2$	c-C_6H_{11}	21	100:0
8	*p*-$MeC_6H_4CH_2$	n-C_3H_7	26	100:0[b]
9	$CH_2{=}CHCH_2$	c-C_6H_{11}	84	79:21
10	$CH_2{=}C(CH_3)CH_2$	c-C_6H_{11}	94	100:0[b]
11	Bu	Ph	83	63:37

[a]c-C_6H_{11} = cyclohexyl; c-C_8H_{15} = cyclooctyl.
[b]Although a single diastereomer was obtained, the NMR spectra did not allow definite stereochemical assignment.

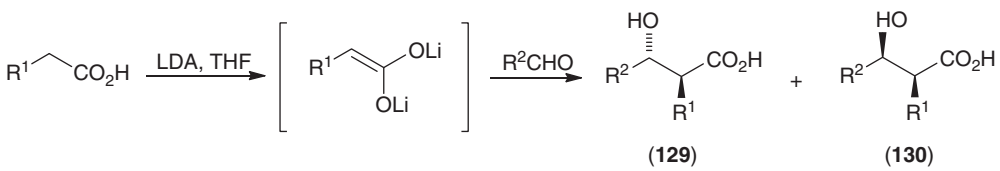
2.08.3.4 Carboxylic Acid Dianions (Ivanov Reaction)

The Ivanov reaction is the preparation of *α,β*-hydroxy acid by reaction of the magnesium dianion of a carboxylic acid with an aldehyde or ketone.[104] In a seminal paper, Zimmerman and Traxler investigated the Ivanov reaction of phenylacetic acid and benzaldehyde and obtained *anti* and *syn β*-hydroxy acids (**127**) and (**128**) in 69% and 22% yields, respectively (equation 85).[105] The observed stereochemistry was rationalized with a cyclic, chair-like transition state in which a magnesium cation is chelated by one oxygen each of the carboxylate enolate and the aldehyde (the 'Zimmerman–Traxler transition state'). Blagoy et al. examined the effect of the counterion on the stereochemistry of this reaction.[106] With the bis(bromomagnesium) salt, a (**127**):(**128**) ratio of about 60:40, similar to that observed by Zimmerman and Traxler, is obtained. With the disodium salt, the sole isomer obtained (in 40% yield) is (**127**).



(85)

Mulzer and coworkers have examined the reactions of dilithium salts of carboxylic acids (equation 86, Table 11).[107] Products were assayed under kinetic conditions (10 min at −50 °C), and after 3 d at 50 °C. The compounds studied fall into two categories. For one set of reactions (e.g., Table 11, entries 1–4), the diastereomer ratios under the two conditions are essentially the same, showing that there is no equilibrtion after prolonged reaction time at elevated temperature. On the other hand, if the combined steric bulk of R^1 and R^2 is great enough, there is significant equilibration to isomer (**129**) under the more vigorous reaction conditions (e.g., Table 11, entries 7–15).



(86)

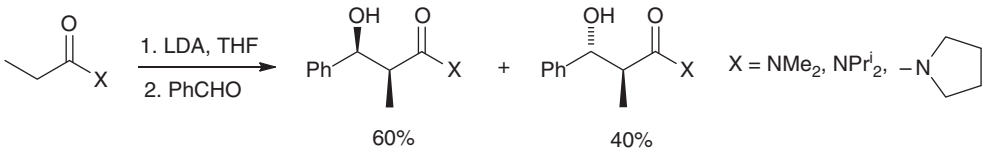
Table 11 Aldol stereochemistry (equation 86)

Entry	R^1	R^2	*Method A*[a]		*Method B*[b]	
			Yield (%)	***(129):(130)***	*Yield (%)*	***(129):(130)***
1	Me	Bu^t	70	50:50	68	50:50
2	Me	Ph	75	55:45	75	55:45
3	Et	Ph	73	52:48	75	55:45
4	Pr^i	Ph	80	55:45	73	58:42
5	Bu^t	Pr^i	78	79:21	75	90:10
6	Bu^t	$PhCH_2CH_2$	70	67:33	65	67:33
7	Bu^t	Bu^t	85	80:20	83	>98:2
8	Bu^t	Ph	73	60:40	70	88:12
9	Ph	Ph	88	71:29	90	92:8
10	Ph	1-Naphthyl	85	73:27	80	92:8
11	Ph	2-Thienyl	75	70:30	68	91:9
12	Ph	2-Furyl	68	71:29	60	92:8
13	Ph	PhCH=CH	88	71:29	79	92:8
14	Bu^t	Mesityl	68	64:36	60	93:7
15	Mesityl	Mesityl	95	91:9	85	>98:2
16	1-Adamantyl	Bu^t	80	>95:5	77	>95:5
17	Ph	Bu^t	95	66:34	90	>98:2
18	Ph	Pr^i	83	66:34	77	93:7
19	Ph	Et	70	58:42	77	64:36
20	Ph	Me	65	58:42	60	64:36

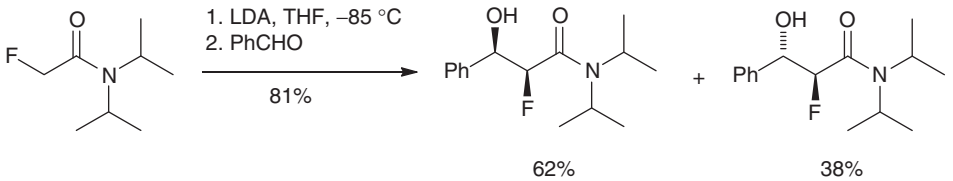
[a]Method A: –50 °C, 10 min.
[b]Method B: 50 °C, 3 days.

2.08.3.5 Amide and Lactam Enolates

Simple amide enolates give poor stereoselection as shown by the examples in equation 87.[9c,108,109] This low degree of simple stereoselection appears to result from differences in the diastereomeric transition states, since *N*-propionylpyrrolidine gives a single enolate.[108] Welch found that the lithium enolates of fluoroacetamides give mixtures of *syn* and *anti* aldols, and that the lack of stereoselectivity is due to the fact that enolate mixtures are obtained; a typical example is shown in equation 88.[110] On the other hand, *N*-acyl derivatives of 2,3-dihydro-4*H*-1,4-benzothiazine and phenothiazine react with a variety of aldehydes to give *syn*-*β*-hydroxy amides (equations 89–90).[111]



(87)



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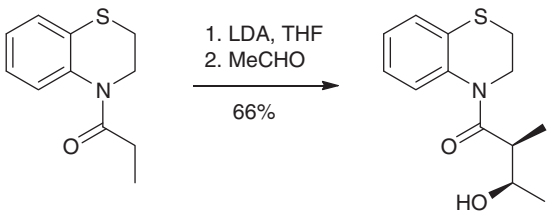
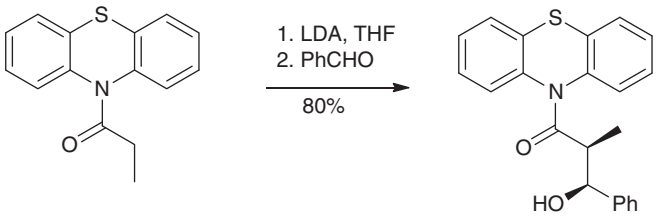


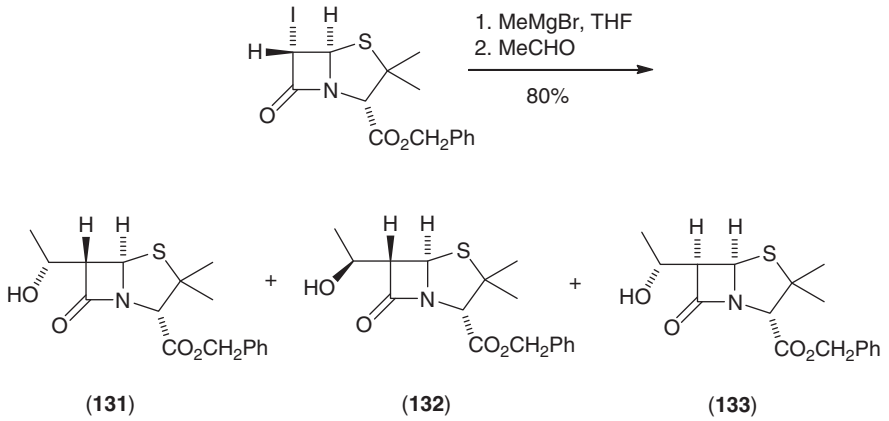
(89)



(90)

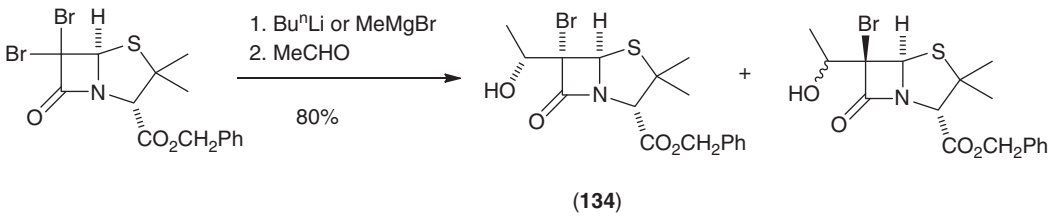
The antibiotic thienamycin has stimulated considerable interest in aldol reactions of β-lactams. In one of the first papers on this subject, DiNinno and coworkers examined various versions of this aldol reaction, one of which is shown in equation 91.[118] The magnesium enolate of the β-lactam, prepared by metallation of the 6-iodo derivative in THF, gives isomers (**131**) to (**133**) in a ratio of 24:49:27. In this reaction, the facial preference of the chiral β-lactam and the simple diastereoselection (*anti:syn*) are both modest (3:1). If metallation is carried out with *n*-butyllithium in ether, the ratio of the three isomers is 47:35:18, corresponding to a facial preference of 4:1 and an *anti:syn* ratio of 1:1. The stereochemistry of aldol reactions of the 6-bromopenam enolate derived from metallation of 6,6-dibromopenams has also been studied.[112,113] If the metallation is carried out in THF, either with *n*-butyllithium or methylmagnesium bromide, there is a surprising preference for reaction on the more congested concave face of the β-lactam; with the magnesium enolate, aldol (**134**) is isolated in 67% yield (equation 92). Metallation of the dibromo-β-lactam (**135**) with methylmagnesium bromide, followed by reaction of the magnesium enolate with acetaldehyde, gives aldol (**136**) as a single isomer in excellent yield (equation 93).[114] Again, the aldehyde attacks the concave face of the bicyclic system.

Several groups have studied aldol reactions of simpler β-lactam enolates. Diarylazetidinones such as (**137**) react as their lithium enolates to give completely or largely one of the four possible stereoisomers (**138**); a typical reaction is shown in equation 94.[115] (The interpretation of this paper is complicated by an error in nomenclature; product (92) and a number of structural analogs are incorrectly designated as (α*S**,3*S**,4*R**), rather than as (α*R**,3*S**,4*S**) or (α*S**,3*R**,4*R**).) The aldol product has the *anti* configuration at the two new stereocenters, as expected for an (*E*)-enolate. In a few cases, minor amounts of the *syn* product were isolated.



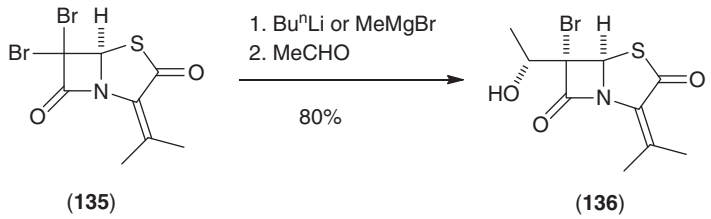
(**131**) (**132**) (**133**)

(91)



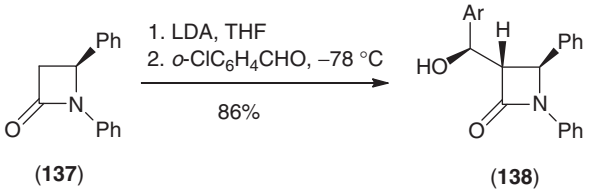
(**134**)

(92)



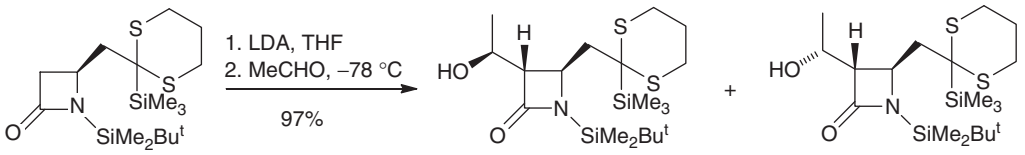
(**135**) (**136**)

(93)

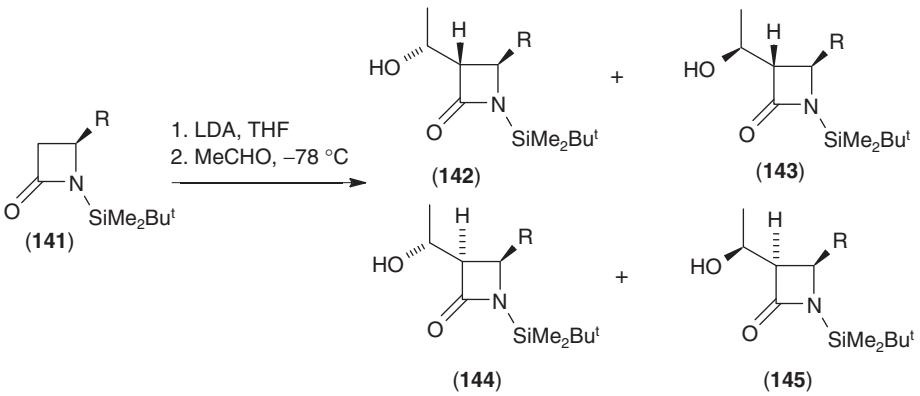


(137) (138) (94)

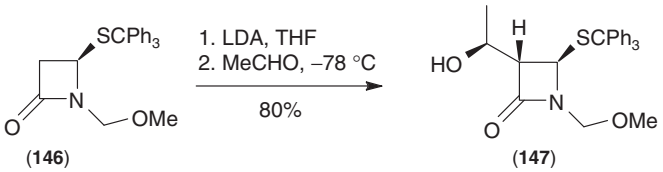
On the other hand, it has been found that β-lactams having other substituents at C-l and C-4 give complex isomer mixtures.[116–118] A typical example is shown in equation 95; *anti* and *syn* aldols (**139**) and (**140**) are formed in excellent yield, but in a ratio of 1:1.[116] Another example is seen in the reaction of β-lactam (**141**; R=SPh); aldols (**142**) to (**145**) are produced in a ratio of 34:27:11:23 (equation 96).[119] Similar results are obtained with the 4-trityl derivative (**141**; R=CPh_3); aldols (**142**) to (**145**) are formed in a ratio of 32:39:12:17.[120] However, the lithium enolate of β-lactam (**146**) reacts with acetaldehyde to give a single aldol (**147**) in 80% yield (equation 97)! The implication from these results is that the methoxymethyl group in (**146**) effects the stereoselectivity, both facial and simple, by coordination of the lithium cation. Again, (**147**) has *anti* aldol stereochemistry, as is expected for an (*E*)-enolate.



(139) (140) (95)

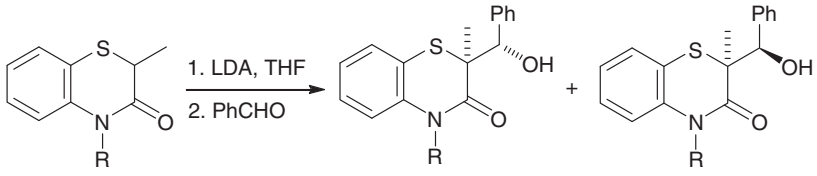


(141) (142) (143) (144) (145) (96)



(146) (147) (97)

The lithium enolate of lactam (**148**; R=Me) reacts with aromatic aldehydes to give the diastereomeric aldols (**149**) and (**150**) in ratios of 6:1 to 9:1 (equation 98); stereoselectivity is reduced with (**148**; R=H), and with aliphatic aldehydes.[121]

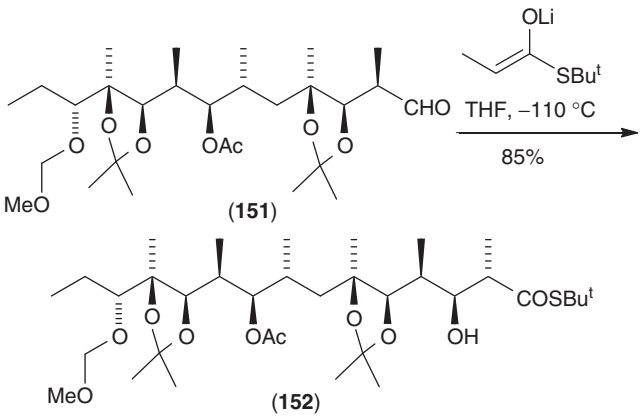


(148) (149) (150) (98)

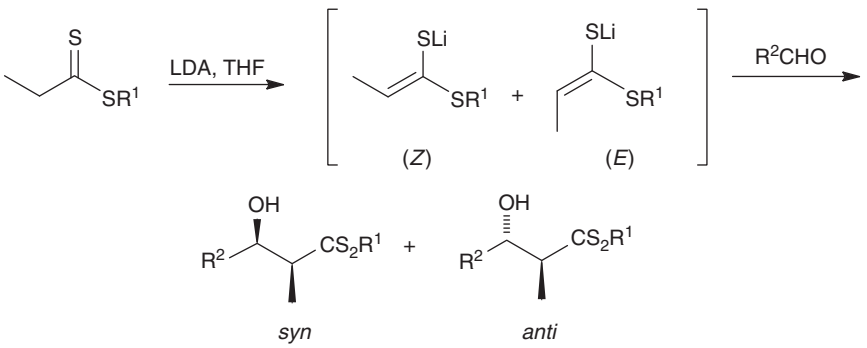
2.08.3.6 Thioester and Thioamide Enolates

In the Woodward erythromycin synthesis, the lithium enolate of *t*-butyl thiopropionate[122] was added to aldehyde (**151**); aldol (**152**) was obtained in 85% yield (equation 99).[123] The remarkable diastereofacial selectivity observed in this reaction may be a general property of thioester enolates (*vide infra*).

Dithiopropionate esters are deprotonated by LDA in THF to give mixtures of the (*Z*)- and (*E*)-enolate, favoring the former.[124] (As with ester enolates, the Evans (*E*)/(*Z*) notational format (ref. 2c) is followed. Thus, in naming an enolate derived from a dithioester $R^2CH_2CS_2R^1$, SM is assigned higher priority than SR^1, regardless of the metal.) The reactions of these enolate mixtures with aldehydes have been studied (equation 100; Table 12).[125,126] The data in Table 12 suggest a relationship between enolate geometry and aldol stereochemistry, at least for (*Z*)-enolates of dithioesters with moderately large R^1 groups. The simple diastereoselection seen with the sterically encumbered aldehydes 2-phenylpropanal and 2-cyclohexylpropanal (Table 12, entries 3 and 4) is exceptional in light of the fact that the enolate ratio is probably of the order of 75:25. This high stereoselectivity, apparently independent of enolate geometry, has been interpreted by Meyers and Walkup as indicative of an open transition state.

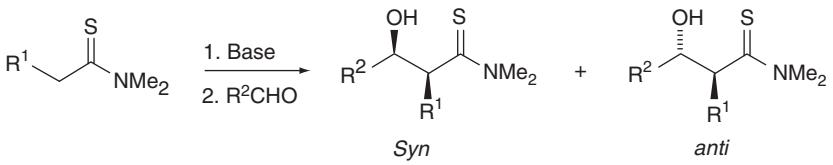


(99)



(100)

Thioamides of secondary amines give (*Z*)-enolates that react with aldehydes to give *syn* aldols with good stereoselectivity (equation 101; Table 13).[109,127] The stereoselectivity is slightly greater with the magnesium enolate than with the lithium enolate (Table 13, entries 2 and 3) and is strongly influenced by conditions (entries 6 and 7). The poor stereoselectivity observed with the thioamide of valeric acid (Table 13, entries 10 and 11) is attributed to the formation of a mixture of enolate geometric isomers.



(101)

Thioamides of primary amines react with two equivalents of *n*-butyllithium or isopropylmagnesium bromide to give dianions that have been shown to have the (*Z*)-configuration. These species react with aldehydes to afford predominantly *anti* aldols (equation 102; Table 14).[128] Again, the magnesium dianions generally show superior stereoselectivity. In certain cases, the degree of stereoselectivity is excellent. This procedure provides a convenient complement to the *syn* selectivity obtained with thioamides of secondary amines.

Table 12 Aldol stereochemistry (equation 100)

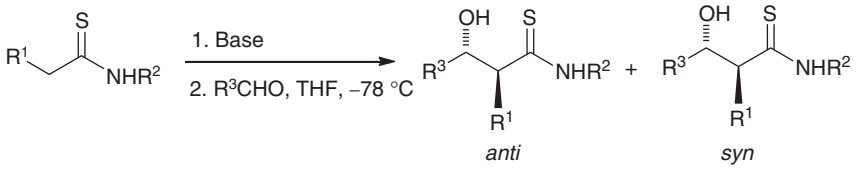
Entry	R^1	*(Z):(E)*[a]	R^2	*Temperature (°C)*	*Yield (%)*[d]	Syn:anti	*References*
1	Me	75:25	Ph	−78	84	57:43	125
2	Et	[b]	Ph	−120	50–60	46:54	126
3	Et	[b]	Ph(Me)CH	−120	50–60	95:5	126
4	Et	[b]	c-C_6H_{13}(Me)CH	−120	50–60	84:16	126
5	Pr^i	81:19	Et	−78	85[e]	82:18	125
6	Pr^i	81:19	Pr^i	−78	50[f]	83:17	125
7	Bu^t	84:16	Ph	−78	40	77:23	125
8	Bu^t	84:16	Et	−78	60	76:24	125
9	CH_2OMe	86:14	Et	−78	50	77:23	125
10	Ph	87:13	Ph	−78	35	74:26	125
11	Ph	87:13	Et	−78	15[f]	81:19	125
12	Pr^i	44:56[c]	Ph	−78	60	64:36	125

[a]Enolate ratio obtained with LDA in THF at −78 °C.
[b]The enolate ratio was not determined in this study.
[c]Enolate ratio obtained with LHMDS or LITMP.
[d]Yield after 10 s reaction time, unless stated.
[e]Reaction time 30 s; yield after 10 s was 47%.
[f]Reaction time 2 min.

Table 13 Aldol stereochemistry (equation 101)

Entry	R^1	R^2	*Base*	*Temperature (°C)*	*Time (min)*	Syn:anti[a]	*References*
1	Me	Pr^i	Pr^iMgBr	−78	30	95:5	109
2	Me	Ph	Pr^iMgBr	−78	2	93:7	109
3	Me	Ph	Bu^nLi	−78	2	87:13	109
4	Me	Et	Bu^nLi	−78	10	90:10	109
5	Me	$CH_2{=}CH$	Pr^iMgBr	−78	30	89:11	109
6	Ph	Pr^i	Pr^iMgBr	−78	2	72:28	109
7	Ph	Pr^i	Pr^iMgBr	+25	60	3:97	109
8	Ph	$CH_2{=}CMe$	Pr^iMgBr	−78	10	73:27	109
9	PhS	Pr^i	Pr^iMgBr	−78	10	66:34	109
10	Pr^i	Ph	Pr^iMgBr	−78	2	34:66	127
11	Pr^i	$PhCH_2CH_2$	Bu^nLi	−78	2	32:68	127

[a]Combined isolated yields = 85–100%.



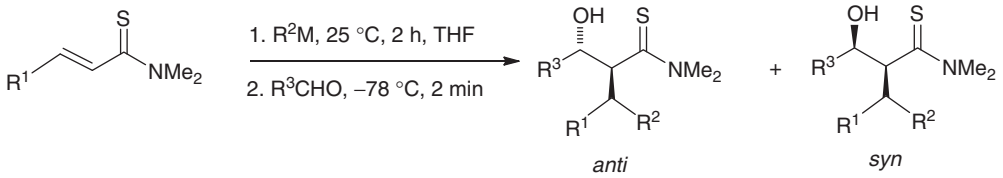
(102)

Table 14 Aldol stereochemistry (equation 102)

Entry	R^1	R^2	R^3	*Base*	*Anti:syn*[a]
1	Me	Ph	Me	Bu^nLi	69:31
2	Me	Ph	Pr^i	Bu^nLi	88:12
3	Me	Ph	Ph	Bu^nLi	62:38
4	Pr^i	Ph	Pr^i	Bu^nLi	93:7
5	Pr^i	Ph	Ph	Bu^nLi	69:31
6	Ph	Me	Pr^i	Bu^nLi	78:22
7	Ph	Me	Pr^i	Pr^iMgBr	98:2
8	Ph	Me	Ph	Bu^nLi	71:29
9	Ph	Me	Ph	Pr^iMgBr	94:6
10	Ph	CH_2CH_2OMe	Ph	Bu^nLi	94:6
11	Ph	CH_2CH_2OMe	Ph	Pr^iMgBr	97:3

[a]Combined isolated yields = 75–99%.

Thioamide enolates may be prepared by conjugate addition of organometallics to α,β-unsaturated thioamides. Reaction of these enolates with aldehydes affords *anti* aldols, often in excellent diastereomeric excess (equation 103; **Table 15**).[127] It is believed that the conjugate addition reactions provide (*Z*)-enolates, via a cyclic, six-centered transition state.[129] The *anti* stereochemistry observed in the aldol reactions of these (*Z*)-enolates would result from a boat-like, chelated transition state. The transition state has boat-like character to avoid a serious *gauche* interaction between R^3 and the bulky secondary alkyl group in the thioamide enolate. Several of the intermediate enolates in this study (e.g., **Table 15**, entries 5–8, 12–14) are chiral. However, no information pertaining to the diastereofacial selectivity, if any, has been provided.



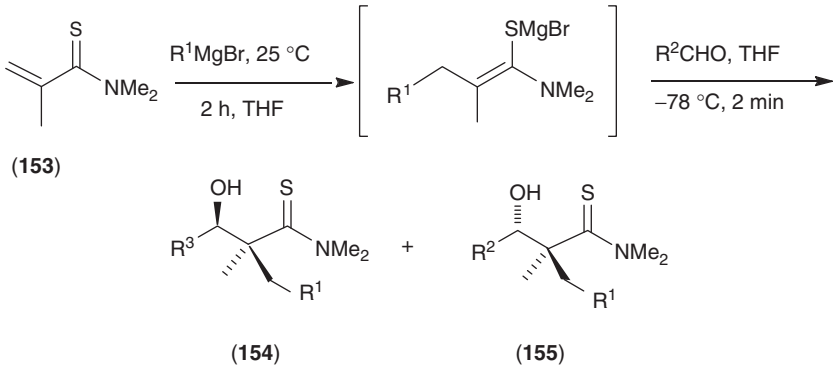
(103)

Table 15 Aldol stereochemistry (equation 103)

Entry	R^1	R^2-*Metal*	R^3	Anti:syn[a]
1	Me	MeMgI	Me	96:4
2	Me	MeLi	Me	90:10
3	Me	MeMgI	Pr^i	>99:1
4	Me	MeMgI	Ph	94:6
5	Me	EtMgBr	Ph	85:15
6	Me	Bu^nLi	Ph	87:13
7	Me	Pr^iMgBr	Me	74:26
8	Me	Pr^iMgBr	Pr^i	>99:1
9	MeCH=CH	MeMgI	Pr^i	>99:1
12	MeCH=CH	Pr^iMgBr	Me	89:11
13	MeCH=CH	Pr^iMgBr	Pr^i	>99:1
14	Ph	Pr^iMgBr	Me	82:18

[a]Combined isolated yields = 70–88%.

Conjugate addition to thioamide (**153**) gives tetrasubstituted enolates, presumably having the (*Z*)-configuration.[30] Reaction of these enolates with aliphatic aldehydes gives aldols of high stereochemical purity (equation 104; **Table 16**).[127] This is a relatively uncommon example of a stereoselective aldol reaction involving a tetrasubstituted enolate. Note that the use of benzaldehyde as the electrophile leads to stereochemical reversal, which is strongest under conditions of thermodynamic control (**Table 16**, entries 8–11).



(104)

2.08.4 Diastereofacial Selectivity

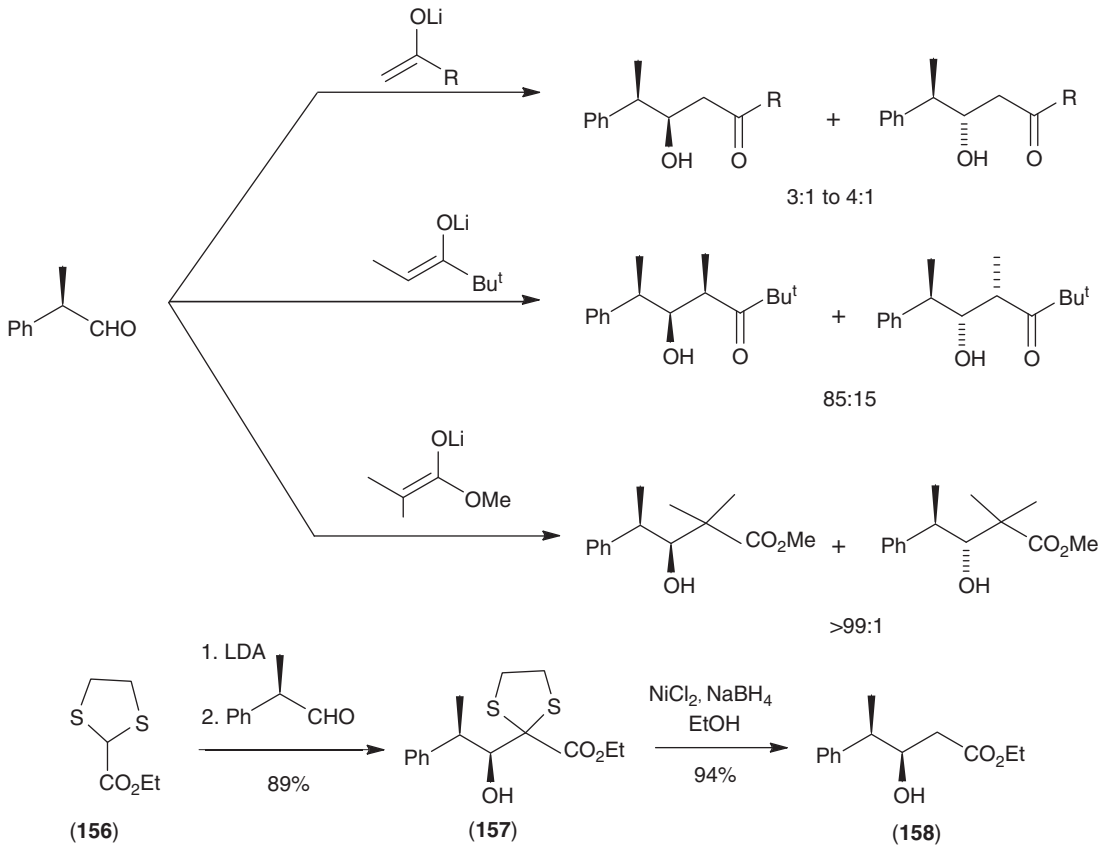
In this section are treated aldol reactions of preformed lithium and magnesium enolates in which one or both of the reaction partners are chiral.

Table 16 Aldol stereochemistry (equation 104)

Entry	R^1	R^2	*Temperature (°C)*	*Time (min)*	***(154):(155)***	*Yield (%)*
1	Et	Me	−78	2	>99:1	85
2	Et	Pr^i	−78	2	>99:1	86
3	Pr^i	Me	−78	2	>99:1	95
4	Pr^i	Et	−78	2	>99:1	86
5	Ph	Me	−78	2	>99:1	24
6	Ph	MeCH=CH	−78	2	>99:1	25
7	Ph	PhCH=CH	−78	2	>99:1	48
8	Et	Ph	−78	2	41:59	80
9	Et	Ph	+25	1080	8:92	80
10	Pr^i	Ph	−78	2	33:67	83
11	Ph	Ph	−78	2	17:83	81

2.08.4.1 Chiral Substrates

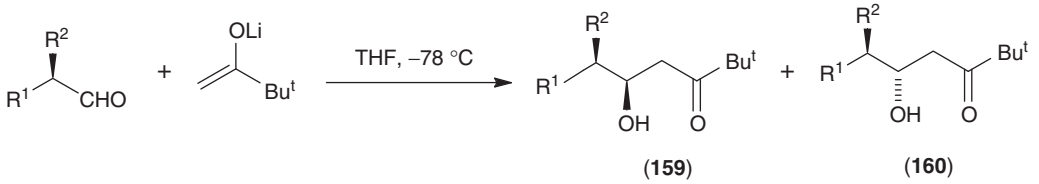
The two faces of a chiral aldehyde are diastereotopic, and reaction with an achiral enolate can therefore give two diastereomeric products. Qualitatively, the major and minor products of such a reaction are determined by the intrinsic diastereofacial preference of the chiral aldehyde, which may be evaluated by the use of Cram's rule or one of its more modern derivatives.[130] Quantitatively, the diastereomeric ratio in such a reaction is a function of the enolate. An example is seen in Scheme 8. 2-Phenylpropanal reacts with the lithium enolates of acetone, pinacolone, methyl acetate and *N*,*N*-dimethylacetamide to give 3,4-*syn* and 3,4-*anti* diastereomers in ratios of 3:1 to 4:1.[131] With ethyl ketones and propionate esters, the diastereofacial ratio is approximately 6:1,[9c] and with methyl isobutyrate only a single isomeric product is produced.[132] This tendency of more bulky nucleophiles to give higher diastereofacial ratios in reactions with chiral aldehydes has been exploited as shown in Scheme 8; addition



Scheme 8

of the enolate of ester (**156**) to 2-phenylpropanal gives a single adduct (**157**), which is desulfurized to obtain β-hydroxy ester (**158**).[133]

Data for the addition of the lithium enolate of pinacolone to a variety of α-chiral aldehydes are presented in equation 105 and Table 17.[134] The results in the table show that the diastereofacial preference of a chiral aldehyde is a function of the steric bulk and the electronic nature of the groups attached to the stereocenter. In a purely empirical manner, the major isomer may be correctly predicted by the Felkin model for asymmetric induction if one uses the order of ligand preferences for the *anti* position: MeO > Bu^t > Ph > Pr^i > Et > Me > H. Note that the major isomers produced in reactions of the α-methoxy aldehydes (Table 17, entries 5–9) are not those expected from a chelation-controlled process.



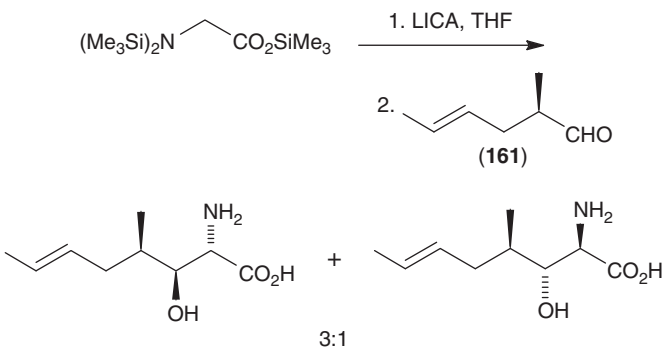
(**159**) (**160**) (105)

Table 17 Aldol stereochemistry (equation 105)

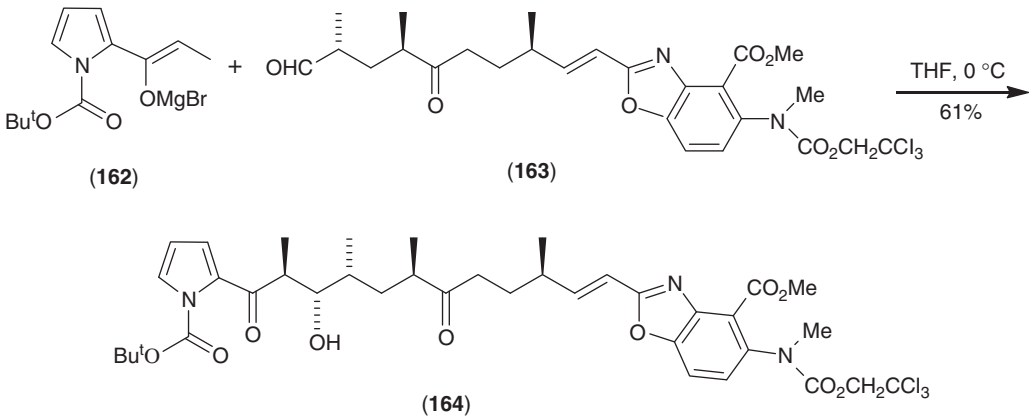
Entry	R^1	R^2	(**159**):(**160**)[a]
1	Ph	Me	78:22
2	Ph	Et	86:14
3	Ph	Pr^i	70:30
4	Ph	Bu^t	37:63
5	Ph	OMe	17:83
6	Me	OMe	42:58
7	Et	OMe	24:76
8	Pr^i	OMe	8:92
9	Bu^t	OMe	7:93

[a]Each ratio is the average of three independent determinations.

It is often necessary in a synthetic project to carry out an aldol addition on a chiral aldehyde in which the α-ligands are hydrogen, methyl and an alkyl group. In the synthesis of MeBMT, the characteristic amino acid of the antibiotic cyclosporin, the lithium enolate of *N*,*N*,*O*-tris(trimethylsilyl)glycine is added to aldehyde (**161**) to give, after deprotection, two hydroxy amino acids in a ratio of 3:1 (equation 106).[135] One step in a total synthesis of the polyether antibiotic A23187 (calcimycin) is the aldol reaction of the magnesium enolate (**162**) with aldehyde (**163**); β-hydroxy ketone (**164**) is obtained in 61% yield, along with 16% of a stereoisomer (equation 107).[136] For other examples of such reactions, see equations (50 and 51), (69), (73) and (78) and (79).

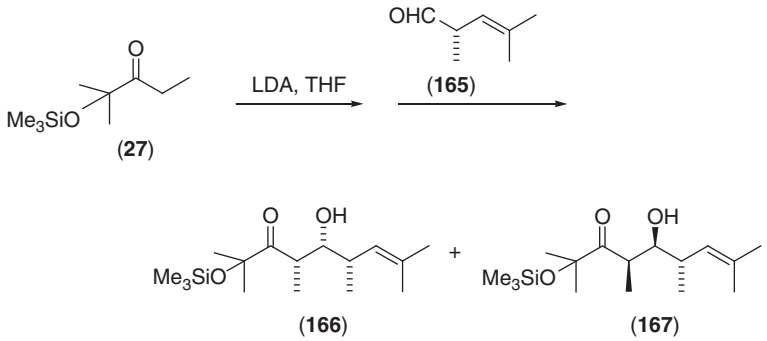


(106)



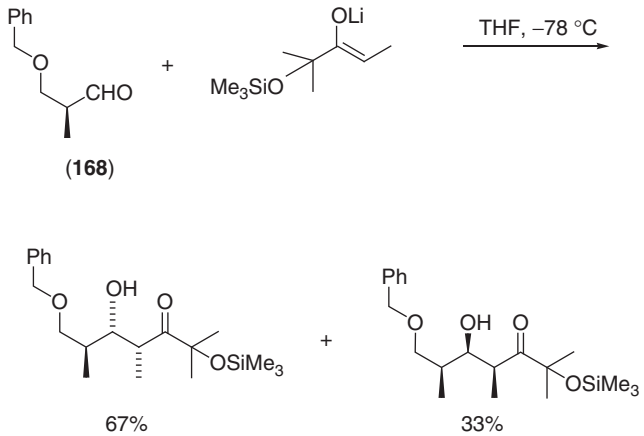
(107)

Reagent (**27**) has been used in a synthesis of the C-l,C-7 segment of erythronolide A, as shown in equation 108.[137] Addition of the lithium enolate of (**27**) to chiral aldehyde (**165**) provides aldols (**166**) and (**167**) in a ratio of approximately 6:1. (The initial report that this aldol reaction gives a stereoisomer ratio of approximately 15:1 was subsequently found to be in error (ref. 144b).)



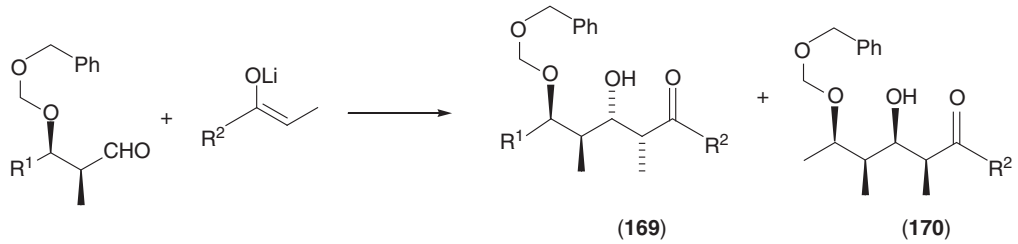
(108)

The major and minor products obtained in aldol reactions of chiral aldehyde (**168**; equation 109) are not those predicted by Cram's rule, presumably because the lithium cation is chelated by the alkoxy and aldehyde oxygens, leading to a rigid six-membered intermediate that undergoes attack primarily from its unsubstituted face.[65] Similar behavior, with somewhat higher diastereofacial selectivity (5:1), is seen with the magnesium enolate (equation 50).



(109)

Masamune and coworkers have examined the facial selectivity of the (*Z*)-lithium enolates of 3-pentanone and ethyl cyclohexyl ketone with a series of *β*-alkoxy aldehydes having stereocenters at both the *α*- and *β*-position (equation 110; **Table 18**).[58] In the six-membered chelate, the methyl and R^1 groups are on the same side of the ring, and it may be seen from the data in **Table 18** that the nature of R^1 influences the facial preference of the chiral aldehyde. Another example of this effect is seen in equation 54.



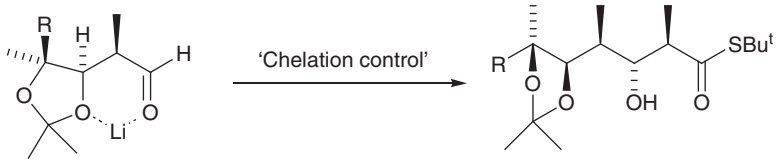
(110)

Table 18 Aldol stereochemistry (equation 110)

R^1	R^2	(**169**):(**170**)	Yield (%)
H	Et	80:20	87
H	Cy[a]	78:22	79
Et	Et	83:17	81
Et	Cy	90:10	79
$PhCD_2$	Et	85:15	71
$PhCD_2$	Cy	90:10	70
Pr^i	Et	87:13	75
Pr^i	Cy	92:8	68
$Bu^tMe_2SiOCH_2CH_2$	Et	93:7	82
$Bu^tMe_2SiOCH_2CH_2$	Cy	95:5	79

[a]Cy = cyclohexyl.

However, such chelation effects are not always observed. For example, in the Woodward erythromycin A synthesis (equation 99), the facial preference of aldehyde (**151**) is that predicted by application of Cram's rule, even though there is an alkoxy group at the *β*-position. Addition to a chelated carbonyl group in this case would amount to a choice between addition to the convex or concave face of a bicyclo[4.3.0]nonane structure (equation 111).



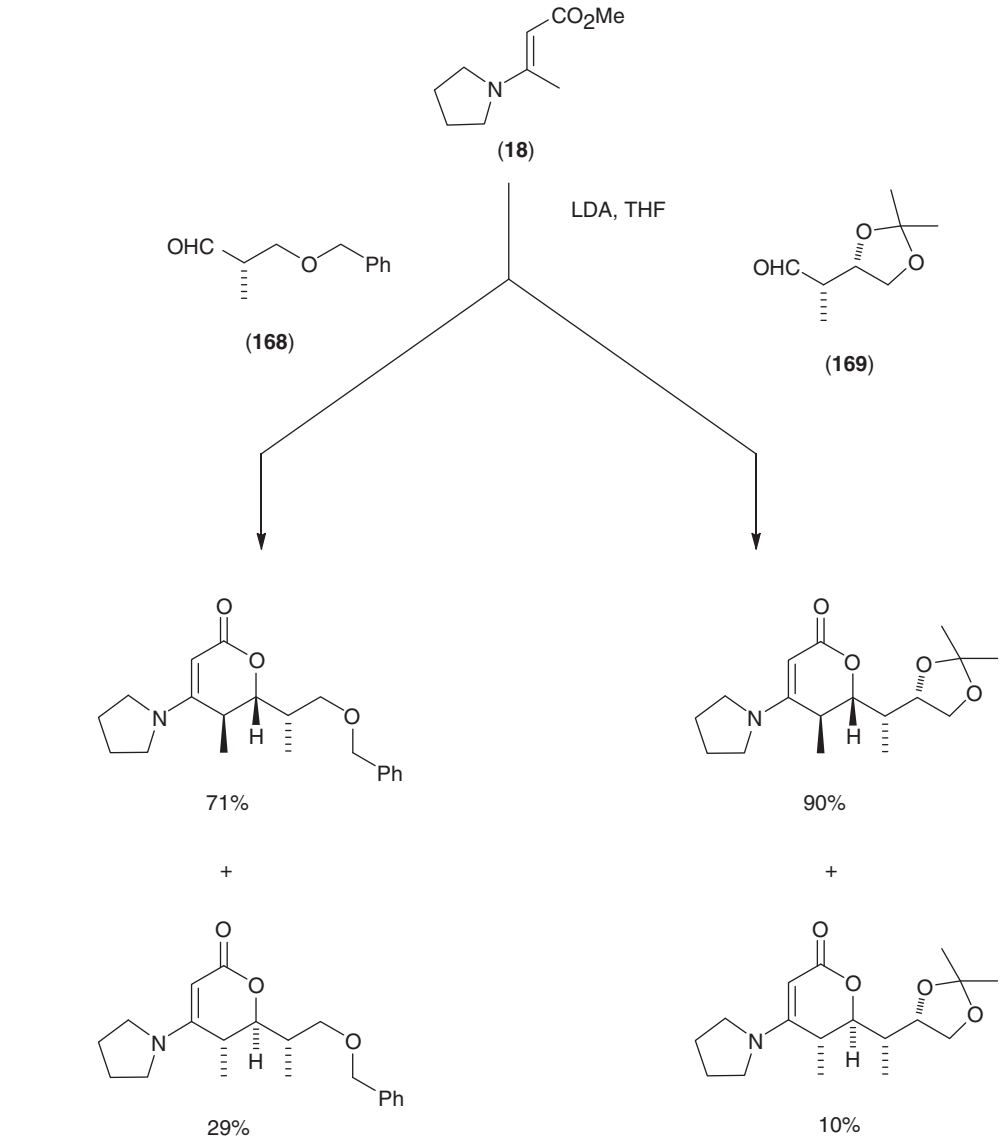
(**151**)

(111)

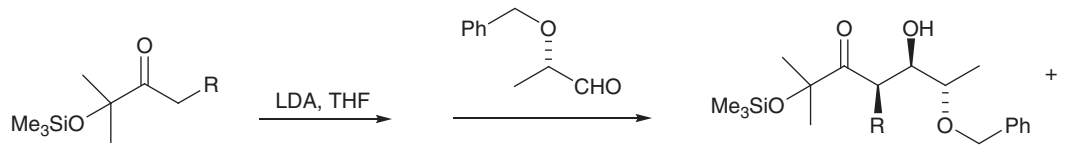
Other cases in which chelation control is not involved in addition to a chiral *β*-alkoxy aldehyde are shown in equations 69 and 78; in these cases, it might be argued that the *t*-butyldimethylsilyloxy and triethylsilyloxy groups are not good ligands for steric reasons. Yet other examples are seen in the two reactions summarized in **Scheme 9**.[46a] Here, the lithium enolate of the vinylogous ester (**18**) adds to aldehyde (**168**) to give predominantly the Cram-predicted isomer; with aldehyde (**169**), the Cram diastereofacial preference is even greater.

Additions to chiral aldehydes in which the stereocenter ligands are H, methyl and alkoxy are also relatively common. With lithium enolates, these aldehydes show diastereofacial preferences that suggest that the major product does not involve addition to an intermediate chelate (*vide supra*). However, diastereomer ratios are often rather low. For example, in equation 112 the diastereofacial preference with reagent (**27**) is 65:35,[138] and that with reagent (**33**) is 78:22.[67]

A detailed study has been carried out with the lithium enolates of methyl and *t*-butyl *N*,*N*-dimethylglycinate (equation 113).[139] Selected data from this study are presented in **Table 19**. The data show that the size of R^1 has a significant effect, whereas that of R^2 or R^3 is not very important. The solvent, temperature and period of metallation strongly affect the diastereomer ratio, suggesting that enolate equilibration may be occurring. This was confirmed by trapping the enolate as its *t*-butyldimethylsilyl enol ether. Deprotonation at −78 °C with LDA in THF gives two enolates in a ratio of 67:33, whereas the use of LDA in ether at 0 °C for 4 h leads to a ratio of 14:86.

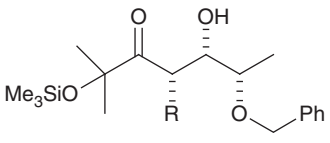


Scheme 9



(**27**) R = Me
(**33**) R = H_2C=$CHCH_2$

(112)



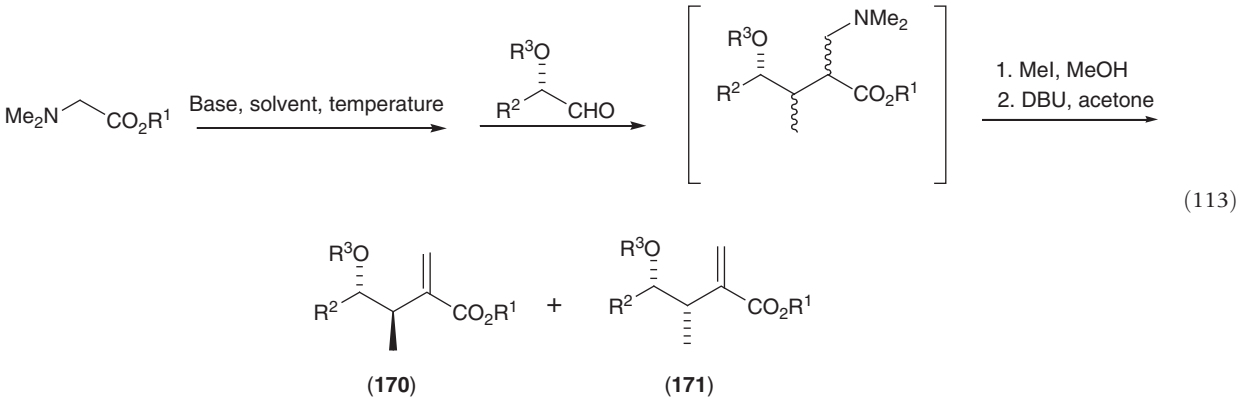


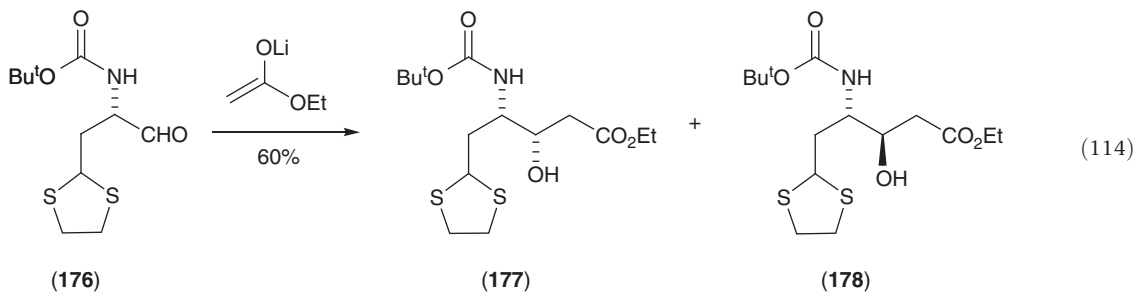
Table 19 Aldol stereochemistry (equation 113)

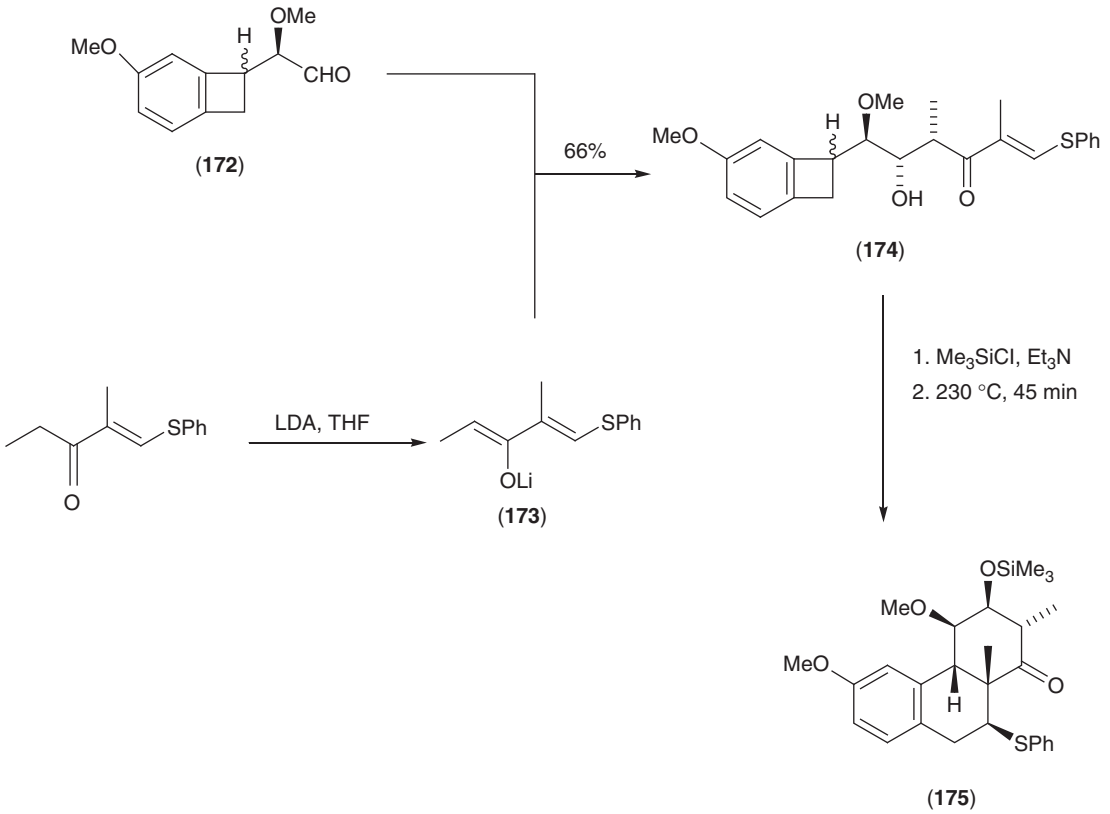
Entry	R^1	R^2	R^3	*Solvent*	*Metallation temperature (°C)*[a]	*Yield (%)*	Anti:syn
1	Me	Me	$PhCH_2OCH_2$	THF	–78	55	65:35
2	Bu^t	Me	$PhCH_2OCH_2$	THF	–78	68	80:20
3	Me	Me	$MeOCH_2$	THF	–78	42	77:23
4	Bu^t	Me	$MeOCH_2$	THF	–78	47	83:17
5	Me	Me	$MeOCH_2CH_2OCH_2$	THF	–78	52	65:35
6	Bu^t	n-C_6H_{13}	$PhCH_2OCH_2$	THF	–78	72	79:21
7	Me	n-C_6H_{13}	$MeOCH_2$	THF	–78	60	73:27
8	Bu^t	n-C_6H_{13}	$MeOCH_2$	THF	–78	69	82:18
9	Bu^t	n-C_6H_{13}	$MeOCH_2$	THF/HMPA	–78	–[c]	63:37
10	Bu^t	n-C_6H_{13}	Me	THF	–78	71	80:20
11	Bu^t	n-C_6H_{13}	Me	THF	–30	–[c]	87:13
12	Bu^t	n-C_6H_{13}	Me	THF	0	–[c]	88:12
13	Bu^t	n-C_6H_{13}	Me	Ether	–30	–[c]	92:8
14	Bu^t	n-C_6H_{13}	Me	Ether	0	–[c]	93:7
15	Bu^t	n-C_6H_{13}	Me	Ether	0[b]	–[c]	96:4

[a]Metallation was carried out at the indicated temperature for 1 h, unless otherwise noted.
[b]Metallation was carried out for 4 h in this case.
[c]Yields were not given for these cases.

Scheme 10 summarizes what appears to be a highly stereoselective addition to an α-methoxy aldehyde.[140] The (*Z*)-lithium enolate (**173**), formed from the enone by reaction with lithium hexamethyldi-silazane, reacts with benzaldehyde to give *syn* and *anti* aldols in a ratio of 8:1. Reaction of (**173**) with aldehyde (**172**), a diastereomeric mixture, gives diastereomeric aldols (**174**). These isomers must have the same relative stereochemistry at C_α, C_β and C_γ because the intramolecular Diels–Alder reaction that occurs upon heating the trimethylsilyl ethers of (**174**) gives a single product, (**175**).

Much less is known about aldol additions to chiral aldehydes that have heteroatoms other than oxygen at the α-stereocenter. In connection with a synthesis of statine analogs, α-amino aldehyde (**176**) was allowed to react with ethyl lithioacetate to obtain (**177**) and (**178**) in a ratio of 60:40 (equation 114).[141]



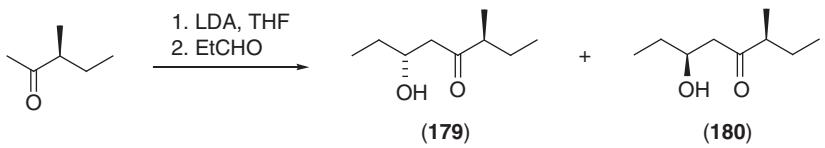


Scheme 10

2.08.4.2 Chiral Enolates

In this section are discussed aldol reactions of achiral aldehydes with chiral enolates. In previous sections, many such examples have already been given for enolates derived from rigid cyclic ketones, lactones and lactams. The emphasis here is on reactions of the enolates of conformationally flexible, achiral ketones, esters and amides.

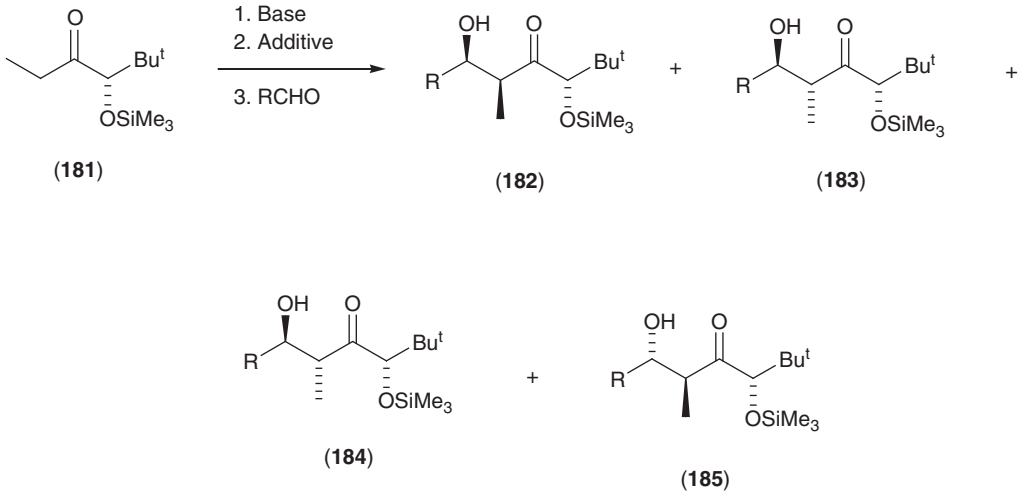
In one of the first such examples, the lithium enolate of (*S*)-3-methyl-2-pentanone was allowed to react with several aldehydes; in the case of propanal, the two products are formed in 15% diastereomeric excess, favoring (**179**; equation 115).[142] The di-*n*-butylboron enolate of this ketone has been studied and found to give (**179**) and (**180**) in a ratio of 63:37 in CH_2Cl_2 and 64:36 in pentane.[143]



(115)

In the interest of asymmetric synthesis, there has been a considerable effort to develop chiral ketones, esters and amides that will undergo aldol reactions with high diastereofacial preference. One such reagent is ketone (**181**), available in three steps from (*S*)-*t*-butylglycine.[144] (For a discussion of the use of the racemic version of ketone (**181**) for aldol reactions, see ref. 56d, pp. 181–184.) Aldol reactions of several different enolates of (**181**) have been studied with benzaldehyde (**Scheme 11**; **Table 20**).[15c,d] The lithium and di-*n*-butylboron enolates both have the (*Z*)-configuration. However, they have opposite diastereofacial preferences because lithium can be coordinated by three oxygens in the aldol transition state, whereas boron cannot. Deprotonation of (**181**) with bromomagnesium diisopropylamide gives the (*E*)-enolate, which has the same diastereofacial preference as the lithium enolate. Finally, treatment of the (*E*)-bromomagnesium enolate with tris(isopropoxy)titanium chloride[145] affords the (*E*)-titanium enolate, which reacts with the same diastereofacial preference as does the (*Z*)-boron enolate, leading predominantly to isomer (**185**). Thus, by appropriate choice of reaction conditions, all four stereoisomeric aldols can be obtained from the same chiral reactant.

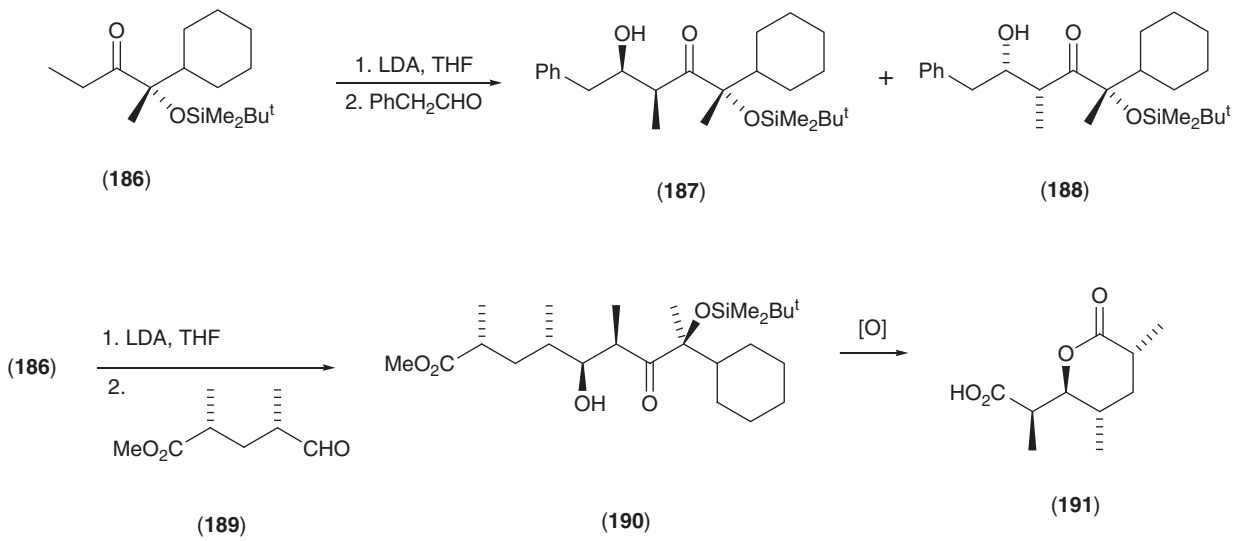
A related reagent (**186**) is prepared in three steps from (*S*)-atrolactic acid.[146] The lithium enolate of (**186**) reacts with phenylacetaldehyde to give two aldols in a ratio of 94:6 (**Scheme 12**). (The full relative stereochemistry of aldols (**187**) and (**188**) was not rigorously determined, but may be deduced from the stereochemistry of (**190**). It is surprising that the lithium enolate of



Scheme 11

Table 20 Aldol stereochemistry (**Scheme 11**)

Entry	*Enolization Conditions*	*Enolate (Z):(E)*	*R*	***(182)***	***(183)***	***(184)***	***(185)***	*Yield (%)*
1	LDA, THF, −78 °C	>98:2	Ph	>95	<5	0	0	80
2	LDA, THF, −78 °C	>98:2	Pr^i	>95	<5	0	0	70
3	Bu_2BOTf, R_3N, CH_2Cl_2	>98:2	Ph	<5	>95	0	0	85
4	Bu_2BOTf, R_3N, CH_2Cl_2	>98:2	Pr^i	<5	>95	0	0	70
5	Pr^i_2NMgBr, THF, −78 °C	<4:96	Ph	0	0	95	5	80
6	Pr^i_2NMgBr, THF, −78 °C	<4:96	Pr	0	0	95	5	75
7	i, Pr^i_2NMgBr, THF, −78 °C, ii, $(Pr^iO)_3TiCl$, sonicate	<4:96	Ph	0	0	20	80	80
8	i, Pr^i_2NMgBr, THF, −78 °C, ii, $(Pr^iO)_3TiCl$, sonicate	<4:96	Ph	0	0	<5	>95	80

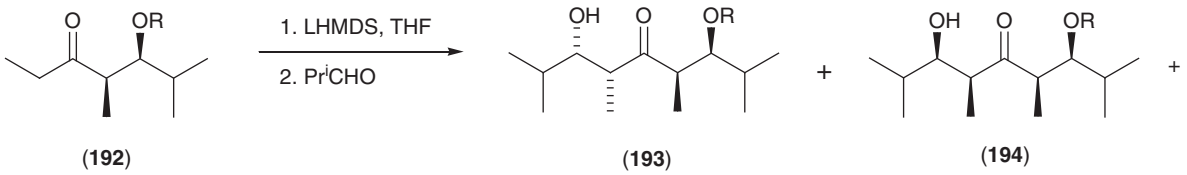


Scheme 12

(**186**) has a diastereofacial preference that is *opposite* that of the related ketone (**181**).) Compound (**186**) has been used in a synthesis of the Prelog–Djerassi lactonic acid (**191**), as shown in **Scheme 12**. Reagents related to (**181**) and (**186**) have been used as their boron enolates for other synthetic purposes (*see* Chapter 1.05, this volume).

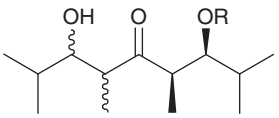
The diastereofacial preferences of keto ethers (**192**) are summarized in equation 116 and **Table 21**. The (*Z*)-lithium enolate of (**192**), prepared by reaction of the keto ether with lithium hexamethyldisilazane, reacts with isobutyraldehyde to give *syn* aldols

(**193**) and (**194**), along with small amounts of an *anti* aldol of undefined stereochemistry (**195**).[147] The results of this investigation demonstrate that the facial preference of a chiral β-hydroxy ketone can be affected to some extent by the hydroxy-protecting group.



(**192**) (**193**) (**194**)

(116)

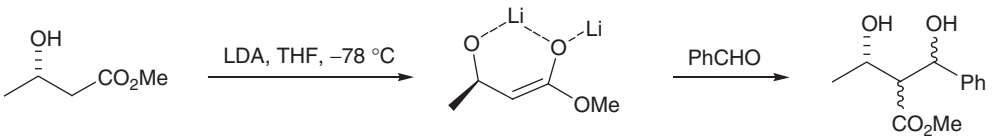


(**195**) (unknown *anti*)

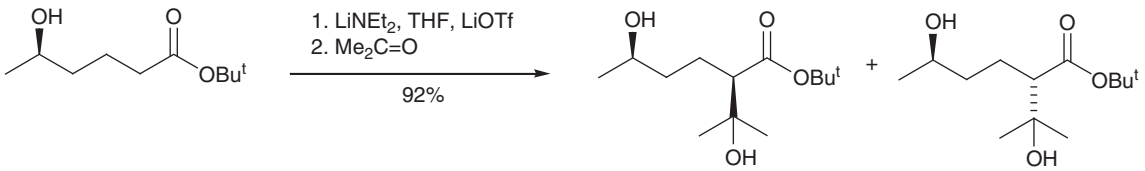
Table 21 Aldol stereochemistry (equation 116)

Entry	*R*	*(**193**)*	*(**194**)*	*(**195**)*	*Yield (%)*
1	H	26	54	20	75
2	$PhCH_2$	52	48	0	79
3	$MeOCH_2CH_2OCH_2$	56	40	4	73
4	$PhCH_2OCH_2$	63	31	6	81
5	Bu^tMe_2Si	76	17	7	85
6	Me_3Si	78	13	9	66
7	Et_3Si	78	12	10	74

Although alkylation of β-hydroxy ester dianions occurs with high diastereofacial selectivity, the aldol reaction of the dianion obtained from methyl 3-hydroxybutanoate with benzaldehyde gives all four diastereomeric aldols in a ratio of 43:34:14:9 (equation 117).[148] On the other hand, dianions of δ-hydroxy esters show rather good diastereofacial preferences under the proper conditions. Deprotonation of *t*-butyl-5-hydroxyhexanoate with lithium diethylamide in the presence of lithium triflate gives an enolate that reacts with benzaldehyde to give aldols (**196**) and (**197**) in a ratio of 91:9 (equation 118).[149] Use of the *t*-butyldimethylsilyl ether instead of the alcohol resulted in no facial preference.



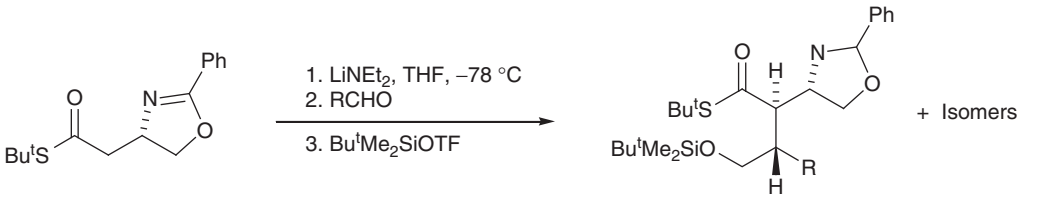
(117)



(**196**) (**197**)

(118)

The chiral β-amino thiol ester (**198**) gives a lithium enolate that shows excellent diastereofacial preference in its reactions with α,β-unsaturated and aryl aldehydes (equation 119; Table 22).[147] The stereochemistry of the major isomer (**199**) is consistent with attack of the aldehyde on a relatively rigid enolate chelate.



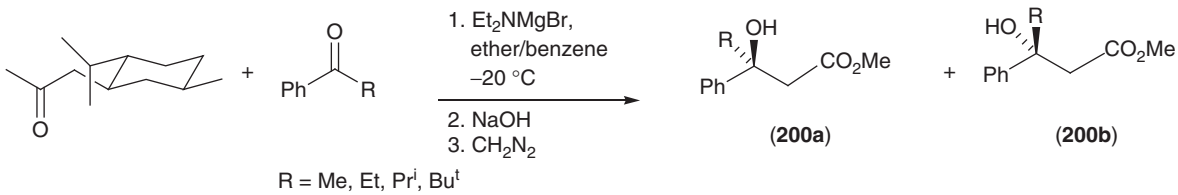
(198) (199) (119)

Table 22 Aldol stereochemistry (equation 119)

Entry	*RCHO*	*Yield (%)*	(***199***):(isomers)[a]
1	EtCHO	70	77:(18:5)
2	Bu^{t}Me$_2$SiOCH$_2$CH$_2$CHO	67	79:(21)
3	PhCHO	89	>50:(1)
4	3,4,5-(MeO)$_3$C$_6$H$_2$CHO	99	87:(13)
5	4-NO$_2$C$_6$H$_4$CHO	92	95:(3:1:1)
6	CH$_2$=CHCHO	95	>50:(1)
7	(*E*)-PhSCH=CHCHO	>40	84:(13:3)
8	(*E*)-Me$_3$SiCH=CHCHO	91	20:(1)

[a]Ratio of isomer (**199**) and other detectable isomers.

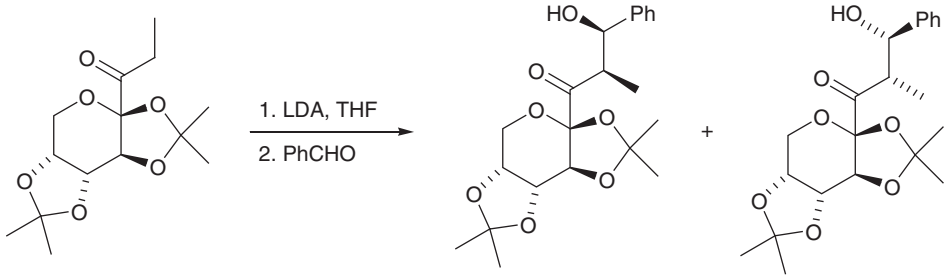
In an early attempt to achieve useful levels of asymmetric induction in aldol reactions of chiral esters, Solladie and coworkers examined the reaction of menthyl acetate with several aryl ketones in the presence of bromomagnesium diethylamide (equation 120).[150] After hydrolytic removal of the chiral auxiliary and methylation of the resulting β-hydroxy acid, the β-hydroxy esters are obtained in 48–58% enantiomeric excess, favoring enantiomer (**200a**).



R = Me, Et, Pr^i, Bu^t

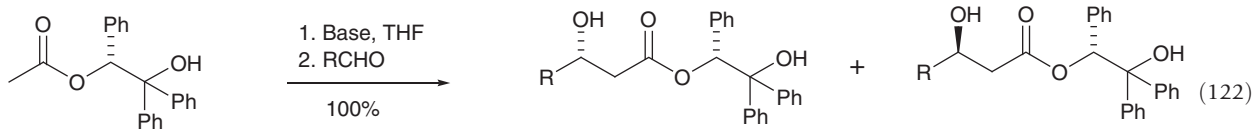
(200a) (200b) (120)

A number of ethyl ketones and propionate esters derived from carbohydrates have been investigated in the aldol reaction.[151] None of the compounds studied give useful levels of stereoselection. The most selective compound from this study is ketone (**201**; equation 121); *syn* aldols (**202**) and (**203**) are produced in a ratio of 79:21.



(201) (202) (203) (121)

Chiral acetate (**204**) shows excellent diastereofacial selectivity and has obvious utility as a reagent for asymmetric aldol reactions.[152] As shown in equation 122, reaction of (**204**) with benzaldehyde provides diastereomers (**205**) and (**206**). As shown in Table 23, entry 1, the diastereoselectivity is 83% if the lithium enolate is formed in the conventional manner and the aldol reaction is carried out in THF at −78 °C. A significant improvement is obtained by using the magnesium enolate (Table 23, entry 5), and diastereoselectivity of up to 98% is obtained by the use of very low reaction temperatures (Table 23, entries 10–13).

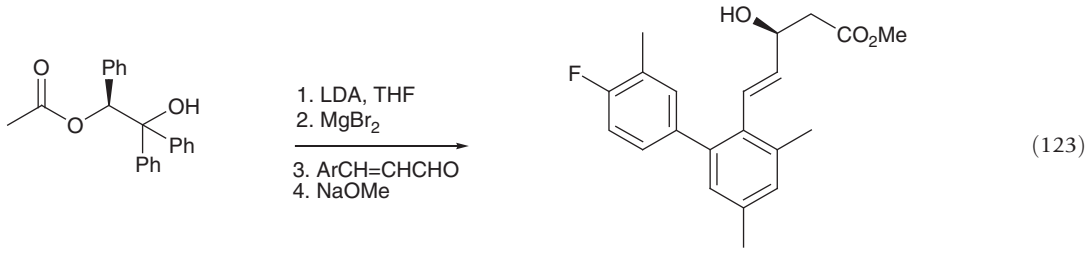


(204) (205) (206) (122)

Table 23 Aldol stereochemistry (equation 122)

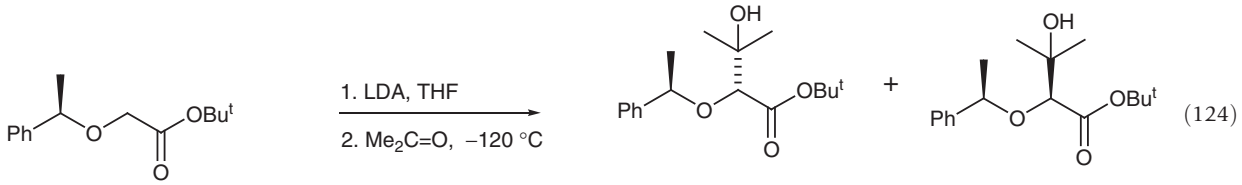
Entry	*Temperature (°C)*	*Solvent*	*Base*	*Additive*	*(**205**):(**206**)*
1	−78	THF	LDA	None	83:17
2	−78	THF	Me_3SiCH_2K	None	59:41
3	0	THF	LDA	$ZnCl_2$	60:40
4	−78	THF	LDA	$(Pr^iO)_3TiCl$	85:15
5	−78	THF	LDA	$MgBr_2$	88:12
6	−78	DME	LDA	$MgBr_2$	84:16
7	−78	Ether	LDA	$MgBr_2$	59:41
8	−150	2-MeTHF	LDA	$MgBr_2$	55:45
9	−78	THF	Pr^i_2NMgBr	None	60:40
10	−135	THF/Me_2O	LDA	$MgCl_2$	94:6
11	−135	THF/Me_2O	LDA	$MgCl_2$	96:4
12	−130	THF/2-methylbutane	LDA	$MgBr_2$	97:3
13	−135	THF/Me_2O	LDA	MgI_2	98:2

One of the virtues of the Braun reagent is that both enantiomers are available, since the chiral diol is made by reaction of phenylmagnesium bromide with (*R*)- or (*S*)-methylmandelate. An application of the (*S*)-enantiomer is shown in equation 123.[153] The initial aldol reaction was carried out with the magnesium enolate in THF at −78 °C to give the diastereomeric aldols in a ratio of 97:3. Transesterification with methanol gives 0-hydroxy ester (**207**) in 94% enantiomeric excess.



(207) (123)

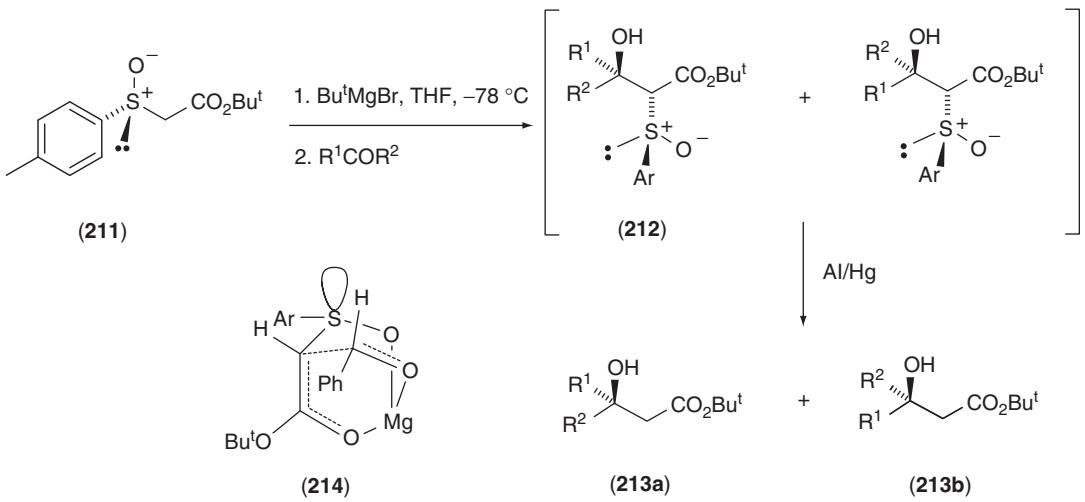
Aldol reactions of the lithium enolates of chiral α-alkoxy esters have also been studied. Ester (**208**) reacts with acetone to give diastereomers (**209**) and (**210**) in a ratio of 85:15 in THF at −120 °C (equation 124); the ratio is only 64:36 in THF at −78 °C.[154] Even higher facial selectivity is obtained with the mesityl analog of (208); the lithium enolate of this ester reacts with acetone in THF at −120 °C to give the aldols corresponding to (**209**) and (**210**) in a ratio of 94:6. The Seebach and Pearson methods to accomplish this same goal have already been discussed (*vide supra*, Schemes 6 and 7).



(208) (209) (210) (124)

Solladié has introduced α-sulfinyl acetates as reagents for asymmetric aldol reactions.[155] Compound (**211**) is prepared in good optical purity from the menthyl ester of *p*-tolylsulfinic acid. The magnesium enolate of (**211**), prepared by reaction of the sulfinyl

ester with *t*-butylmagnesium bromide, reacts with aldehydes and ketones to give diastereomeric mixtures of *α*-sulfinyl-*β*-hydroxy esters (Scheme 13). No condensation results if *t*-butyllithium or sodium hydride is used as the base for formation of the enolate ion. Reductive removal of the chiral auxiliary provides the corresponding *β*-hydroxy esters (**213a**) and (**213b**): data are summarized in Table 24. The diastereofacial selectivity is excellent with aldehydes and with some ketones. The full stereochemistry of the intermediate *α*-sulfinyl-*β*-hydroxy ester was found to be as shown in (**212**) for the reaction with benzaldehyde. A transition state (**214**) in which the magnesium cation is chelated by three oxygens was invoked to explain the observed facial and simple stereoselectivity. Several applications of the Solladié reagent in synthesis have been reported.[156,157]

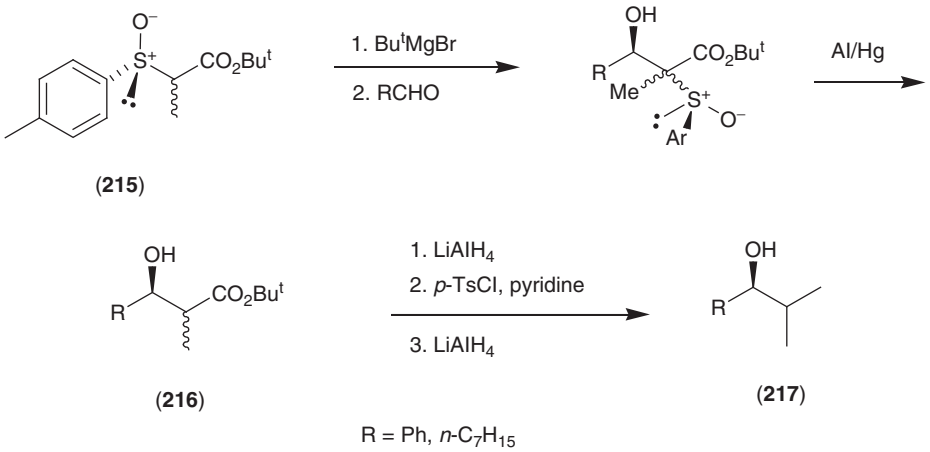


Scheme 13

Table 24 Aldol stereochemistry (Scheme 13)

Entry	R^1	R^2	*Yield (%)*	***(213a):(213b)***
1	Ph	H	85	95:5
2	Ph	Me	75	84:16
3	Ph	CF_3	75	64:40
4	n-C_7H_{15}	H	80	93:7
5	$Pr^nCH{=}CH$	H	65	85:15
6	n-$C_{11}H_{23}$	H	74	90:10
7	n-C_8H_{17}	H	80	92:8
8	c-C_6H_{11}	Me	88	98:2
9	CO_2Et	Me	80	54:46
10	$CH(OMe)_2$	Me	80	55:45
11	$CH_2CH(OMe)_2$	Me	57	54:46
12	CH_2CH_2OAc	Me	90	(70:30)
13	$CH_2CH_2CO_2Me$	Me	63	75:25
14	$CH_2CH_2CH_2CO_2Me$	H	76	80:20
15	CH_2NMe_2	Me	0	–
16	$PhC{=}C$	H	75	>95:5
17	$Pr^nC{=}C$	H	73	95:5
18	n-$C_6H_{13}C{=}C$	H	53	95:5
19	$Bu^tC{=}C$	H	64	92:8

Attempts to extend this methodology to *α*-sulfinyl derivatives of other esters have been only moderately successful.[158] As shown in Scheme 14, ester (**215**) may be deprotonated by *t*-butylmagnesium bromide and added to aldehydes, although not to ketones. The intermediate *β*-hydroxy-*α*-sulfinyl esters, in each case a mixture of diastereomers, are reduced to obtain diastereomeric mixtures of *β*-hydroxy esters. The diastereomeric ratio of these materials does not reveal the degree of asymmetric induction in the original aldol reactions, because of the unknown stereochemistry of the desulfurization step. Aldols (**216**) were converted by a three-step process into secondary alcohols (**217**), which were found to have isomeric purities of 33.5% enantiomeric excess for R=Ph and 80% enantiomeric excess for R=*n*-heptyl.



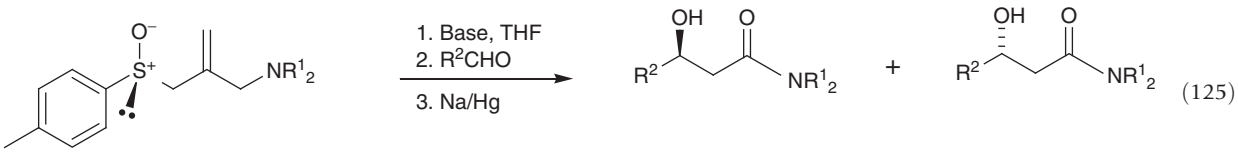
(**215**)

(**216**)

(**217**)

Scheme 14

The Solladié method has been extended to *N*,*N*-dimethylacetamide derivatives with good success (equation 125; Table 25).[159,160] The lithium enolate of (**218**) gives low overall stereoselectivity (Table 25, entries 1–9). The stereoisomer ratios observed seem to be kinetic, rather than thermodynamic, since the same yield and enantiomeric excess are observed at reaction times of 3 or 60 min (Table 25, entries 3 and 4). Stereoselectivity decreases as the size of R^2 increases (entries 1, 2, 3 and 6). Addition of HMPA has a deleterious effect on stereoselectivity. The magnesium enolate shows excellent diastereoselectivity. Again, stereoselectivity diminishes as the size of R^2 increases (Table 25, entries 10, 11, 14 and 16) and HMPA has a detrimental effect (entry 18). The analogous thioamide was prepared and studied, but it appears to offer no advantage over the oxoamide.[161]



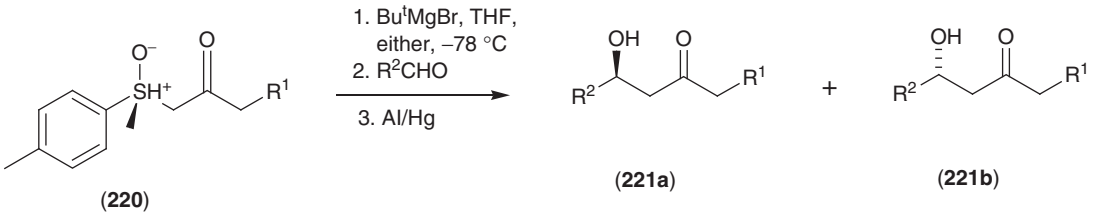
(**218**) (**219a**) (**219b**) (125)

Table 25 Aldol stereochemistry (equation 125)

Entry	*R^1*	*Base, mol equivalent*	*Reaction time (min)*	*R^2*	*Yield (%)*	*(**219a**):(**219b**)*
1	Me	Bu^nLi, 1.1	3	Me	65	74:26
2	Me	Bu^nLi, 1.1	3	Bu^i	77	73:27
3	Me	Bu^nLi, 1.1	3	pr^i	77	67:33
4	Me	Bu^nLi, 1.1	60	Pr^i	78	66:34
5	Me	Bu^nLi, 2.0	3	Pr^i	40	59:41
6	Me	Bu^nLi, 1.1	3	Bu^t	20	54:26
7	Me	Bu^nLi, 1.1	3	Pr^i	78	60:40[a]
8	Me	Bu^nLi, 0.55	60	Pr^i	74	64:36
9	Me	LDA, 1.1	60	Pr^i	70	67:33
10	Me	Bu^tMgBr, 0.55	60	Me	68	>99:1
11	Me	Bu^tMgBr, 0.55	60	Bu^i	71	99:1
12	Me	Bu^tMgBr, 1.1	3	Bu^i	73	95:5
13	Me	Bu^tMgBr, 0.55	3	Pr^i	62	93:7
14	Me	Bu^tMgBr, 0.55	60	Pr^i	66	98:2
15	Me	Bu^tMgBr, 1.1	3	Pr^i	63	85:15
16	Me	Bu^tMgBr, 0.55	60	Bu^t	56	95:5
17	Me	Bu^tMgBr, 0.1	60	Pr^i	31	64:40
18	Me	Bu^tMgBr, 0.55	60	Pr^i	31	76:24[a]

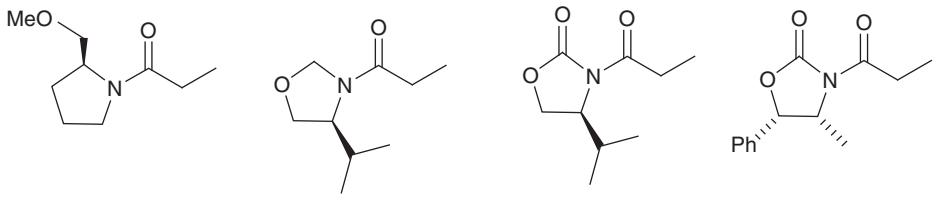
[a]In the presence of 3 mol equivalents of HMPA.

Schneider and Simon prepared the α-sulfinyl ketones (**220**) and studied their aldol reactions with several aldehydes (equation 126).[162] In seven cases examined, the chiral secondary alcohols (**221**) were obtained in reasonable overall yield (40–67%), but with only modest stereoselectivity (54–78% *ee*).



(220) (221a) (221b)

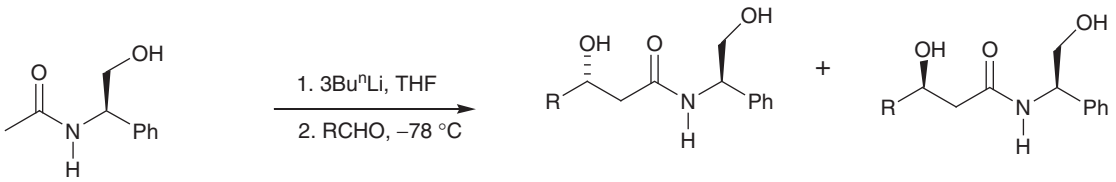
R^1 = H, Me; R^2 = Et, c-C_6H_{11}, Ph, $PhCH_2CH_2$ (126)



(222) (223) (224) (225)

Chiral amides (222) and (223) and imides (224) and (225) have also been studied as reagents for asymmetric aldol reactions. These reagents show excellent diastereofacial preferences as their boron and zirconium enolates, but generally show poor selectivity as their lithium enolates. The reader is referred to other chapters in this volume for a discussion of these and related reagents.

The lithium enolate of amide (226) shows reasonable diastereofacial selectivity in its reactions with several aldehydes (equation 127; Table 26).[163] The hydroxymethyl group is important, as *N*-acetylphenethylamine has almost no diastereofacial preference.[164]



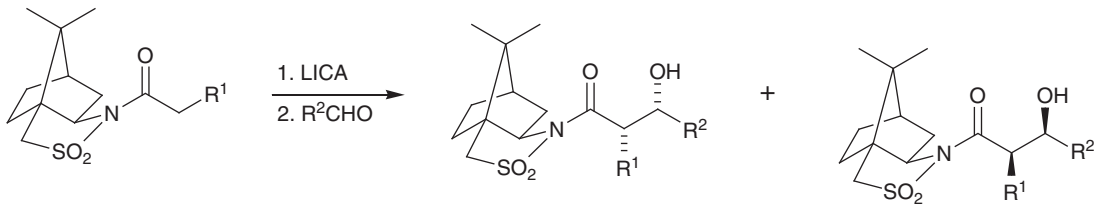
(226) (227) (228) (127)

Table 26 Aldol stereochemistry (equation 127)

Entry	*R*	*Yield (%)*	*(**227**):(**228**)*	*Yield (%)*[a]
1	Ph	96	80:20	43
2	Bu^t	98	85:15	35
3	Pr^i	82	77:23	24
4	Pr^n	93	78:22	25

[a]Yield of pure (**227**) after recrystallization.

One of the more useful chiral auxiliaries that has been developed is illustrated in equation 128.[165] The lithium enolates of imides (229) react with aldehydes to give mainly the *syn* diastereomer (230), along with (231) and an *anti* isomer (Table 27). After purification, the major *syn* isomer is obtained in good yield and in good stereochemical purity. The results shown in Table 27 nicely complement the results obtained using the boron enolate. In this case, no *anti* products are observed and the (231):(230) ratio is >95:5 in all cases. Thus, acylsultam (229), like α-alkoxy ketone (181; Scheme 11), has opposite diastereofacial preference as its lithium and boron enolates.



(229) (230) (231) (128)

Table 27 Aldol stereochemistry (equation 128)

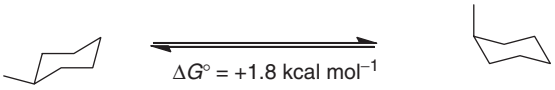
Entry	R^1	R^2	***(230)*:(*231*):*other***	*Major product*[a]	
				Yield (%)	de *(%)*
1	Me	Ph	8:85:(7)	72	>99
2	Me	Pr^i	6:86:(8)	70	>95
3	Et	Ph	9:88:(3)	51	>95
4	Me	Bu^t	7:88:(5)	51	>95

[a]Yield and purity of (**231**) after recrystallization or chromatography.

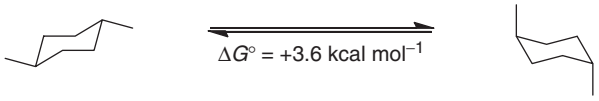
2.08.4.3 Double Diastereoselection

In this section is discussed the phenomenon of double diastereoselection (double asymmetric synthesis). If both partners in a reaction are chiral, each has its own intrinsic diastereofacial preference. New stereocenters that are created in such a process are, therefore, formed under the influence of both chiral reactants.[166–170] To a first approximation, one can think of the effects of the two stereodifferentiating reactants as being additive.[145,150,171] For example, as shown in equation 121 (*vide supra*), chiral ketone (**201**) reacts with benzaldehyde, a representative achiral aldehyde, to give aldols (**202**) and (**203**) in a ratio of 4:1. As shown in **Scheme 15**, chiral aldehyde (*S*)-(**234**) reacts with achiral ketone (**27**) to give aldols (**232**) and (**233**) in a ratio of 4.3:1. The two double stereodifferentiation experiments are also shown in **Scheme 15**. Reaction of ketone (**201**) with (*S*)-(**234**) gives a single aldol (**235**), whereas reaction of (**201**) with (*R*)-(**234**) gives *syn* aldols (**236**) and (**237**) and an *anti* aldol in a ratio of 5.5:2.5:1.[150] Similar experiments have been reported by several other workers.[145,162a,172] Double stereodifferentiation experiments such as those illustrated in **Scheme 15** have been referred to as 'consonant' and 'dissonant' and as 'matched' and 'mismatched' pairs. If one of the reactants has an exceedingly high diastereofacial preference, it will totally dominate the situation and solely determine the stereochemistry at the new stereocenters.[173]

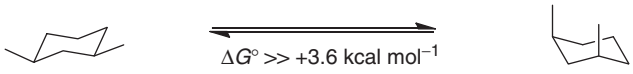
However, one should not always expect to see additivity in such double stereodifferentiation experiments, as is illustrated by the following logic.[174] For equation 129, $\Delta G^\circ = +1.8$ kcal mol^{-1} (1 cal = 4.18 J); that is, an axial methyl group disfavors the conformation on the right by 1.8 kcal mol^{-1}. In equation 130, the effects of two axial methyl groups are additive, and $\Delta G^\circ =$ 3.6 kcal mol^{-1}. However, in equation 131, the effects of the two axial methyl groups are not additive, and $\Delta G^\circ > 3.6$ kcal mol^{-1}. Thus, we should expect that there will be cases in which the ideas of 'consonant' and 'dissonant' double stereodifferentiation will break down.[169,175]



(129)



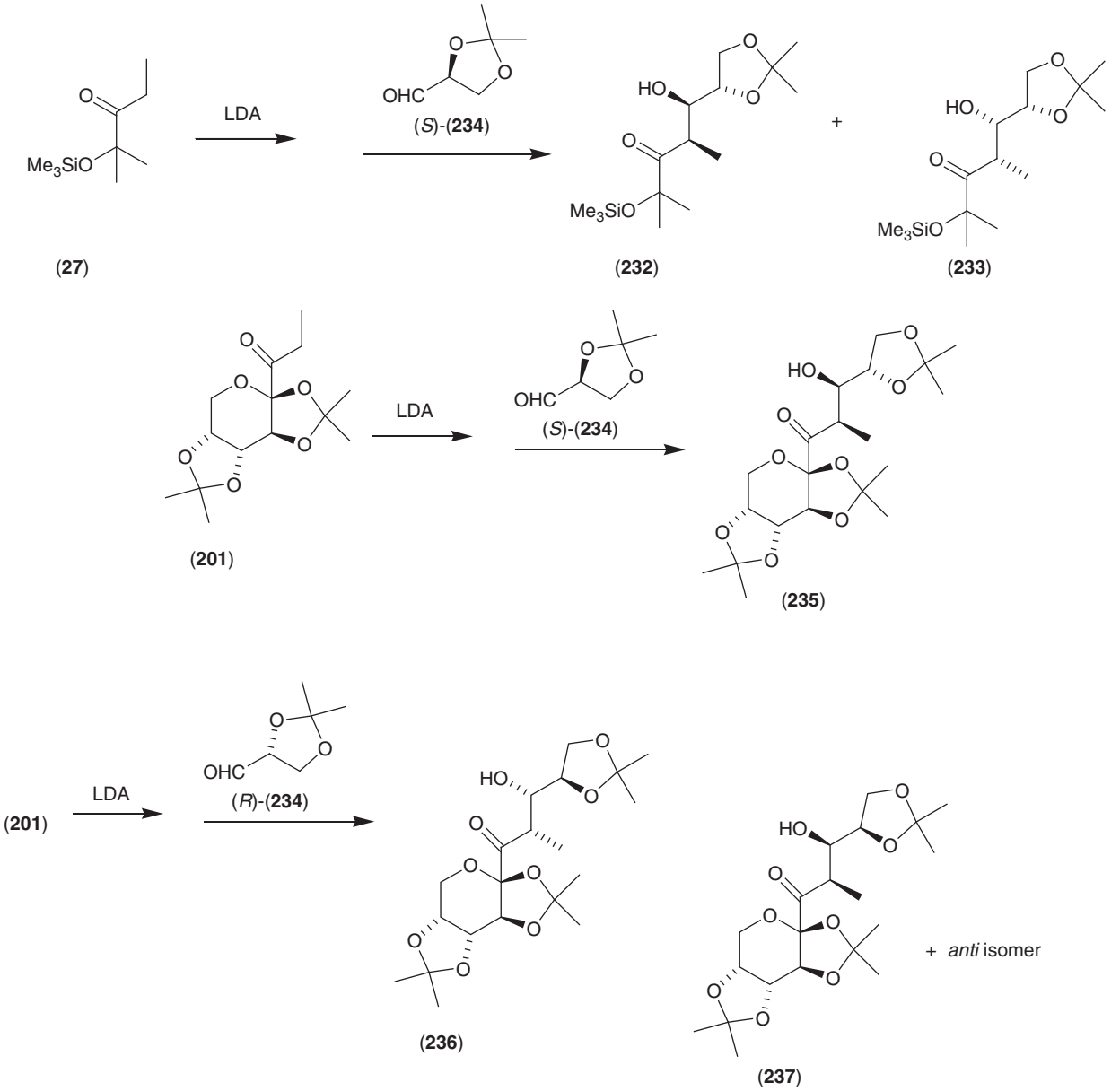
(130)



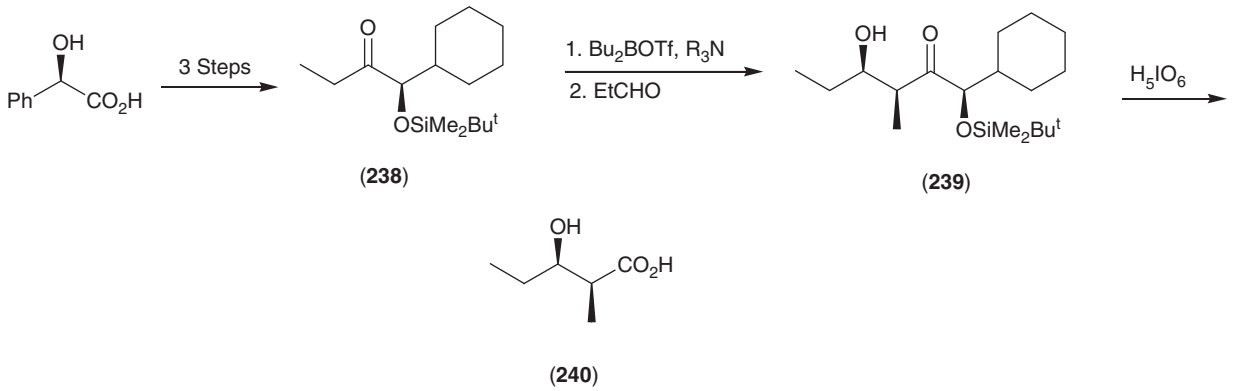
(131)

2.08.4.4 Chiral Auxiliaries

Some of the chiral reagents discussed in earlier sections have proven useful for preparation of enantiomerically pure aldols. From a practical viewpoint, the first level of asymmetric induction is that in which the chiral auxiliary is stoichiometrically consumed in the overall process. An example of this kind of 'first order' asymmetric induction is illustrated in equation 132.[176] Mandelic acid is converted by a three-step procedure into the enantiomerically homogeneous α-silyloxy ketone (**238**). The boron enolate of the latter substance shows excellent diastereofacial preference in reactions with aldehydes, giving aldol (**239**) in high purity (diastereoselectivity = 100:1). Desilylation of (**239**) and periodic acid cleavage of the resulting α,β-dihydroxy ketone provides the corresponding β-hydroxy acid (**240**) and cyclohexanecarbaldehyde. In this process, the chiral auxiliary is mandelic acid and at least 1 mol of this material is expended for each mole of hydroxy acid prepared. Other examples of this kind of 'immolative' process are the Solladié reagent (**211**) and the related amide (**218**) (*vide supra*).



Scheme 15

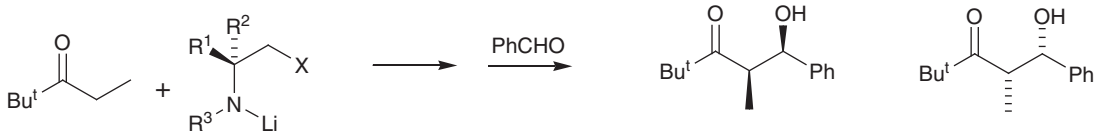


(132)

A more efficient process is one in which the chiral auxiliary, although still used stoichiometrically, can be recovered and reused. A notable example of a 'second order' chiral reagent is ester (**204**; equation 122). In this process, methyl mandelate is converted into chiral ester (**204**). After the aldol reaction, the product (**205**) is saponified and the chiral auxiliary may, in principle, be fully recovered and recycled. However, in practice, yields are never quantitative and the overall efficiency of auxiliary recovery is usually of the order of 50%.

The most efficient kind of asymmetric induction is one in which the chiral auxiliary is used catalytically. An outstanding example of such a process is the Monsanto procedure for enantioselective catalytic hydrogenation of dehydro amino acids.[177] So far, there has been no report of a highly efficient catalytic asymmetric aldol reaction of Group I or Group II enolates. There is one report of good asymmetric induction involving a noncovalently bound chiral auxiliary in an aldol reaction of a tin(II) enolate.[178] However, there is to date only one example of a truly *catalytic* asymmetric aldol addition reaction, the Ito–Hiyashi carbomethoxyisoxazoline synthesis, which proceeds through a gold(I) enolate.[179]

A number of chiral amines, diamines and amino ethers have been investigated, but only low degrees of asymmetric induction have been observed with lithium or magnesium enolates.[180] (See ref. 57d, p. 203.) Recently, however, progress has been made.[181] The aldol reaction employed in this study was that between the lithium enolate of ethyl *t*-butyl ketone and benzaldehyde (equation 133); *syn* aldols (**242a**) and (**242b**) are produced in various ratios if the enolate is formed with a lithium amide derived from the chiral secondary amine (**241**). One of these amines ($R^1 = Pr^i$, $R^2 = H$, $R^3 = Me$ and X = OMe) was utilized to optimize the reaction conditions; results are presented in Table 28. The data reveal a pronounced effect on stereoselectivity of the *amount of base*. Thus, when 1.2 equivalents of base are employed, the aldol yield is excellent, but the product is obtained in only 18% *ee* (Table 28, entry 2). If more base is used, enantioselectivity improves at the expense of yield (entries 3–4). These results suggest that the lithium amide derived from (**241**) is a more effective chiral auxiliary than the amine itself. In fact, if the reaction is carried out with excess *n*-butyllithium, along with a corresponding amount of the achiral diisopropylamine, the yield is excellent and the diastereomeric excess is a very respectable 68% (Table 28, entry 6). It is interesting to observe that the stereoselectivity diminishes, both at higher and lower temperatures (entries 5 and 8).



(**241**) (**242a**) (**242b**) (133)

Table 28 Aldol stereochemistry (equation 133)

Entry	*Ketone*	*Reagent ratios*		Pr^i_2NH	*Temperature (°C)*	*Yield (%)*	***(242a)*:*(242b)***
		(241)	Bu^nLi				
1	1.0	1.2	0.6		−10	89	49:51
2	1.0	1.2	1.2		−10	90	59:41
3	1.0	1.2	1.8		−10	52	79:21
4	1.0	1.2	2.2		−10	29	86:14
5	1.0	1.2	2.2	1.2	25	92	74:26
6	1.0	1.2	2.4	1.2	−10	93	84:16
7	1.0	1.2	2.4	1.2	−40	91	84:16
8	1.0	1.2	2.4	1.2	−70	88	67:33

Using the optimum conditions (Table 28, entry 6), a variety of chiral secondary amines have been investigated. The results are shown in Table 29. The most effective auxiliary for preparation of the enantiomeric aldol (**242b**) is the phenylglycine-derived amine (Table 29, entry 8).

The foregoing results clearly constitute an encouraging lead, and represent the best that has yet been done with chiral auxiliaries for lithium enolate aldol reactions. Although the chiral auxiliary is not covalently attached to either reactant, it is still used stoichiometrically. Furthermore, the process has only been demonstrated with the aldol reaction in equation 133. It will be interesting to see if the efficacy of this method will extend to other enolates and aldehydes.

2.08.5 Equilibration; Thermodynamic Control

The bulk of this chapter has dealt with kinetically controlled aldol addition processes. However, one of the characteristics of aldol reactions involving Group I and Group II enolates is that they are frequently subject to ready reversibility. Under appropriate

Table 29 Aldol stereochemistry (equation 133)

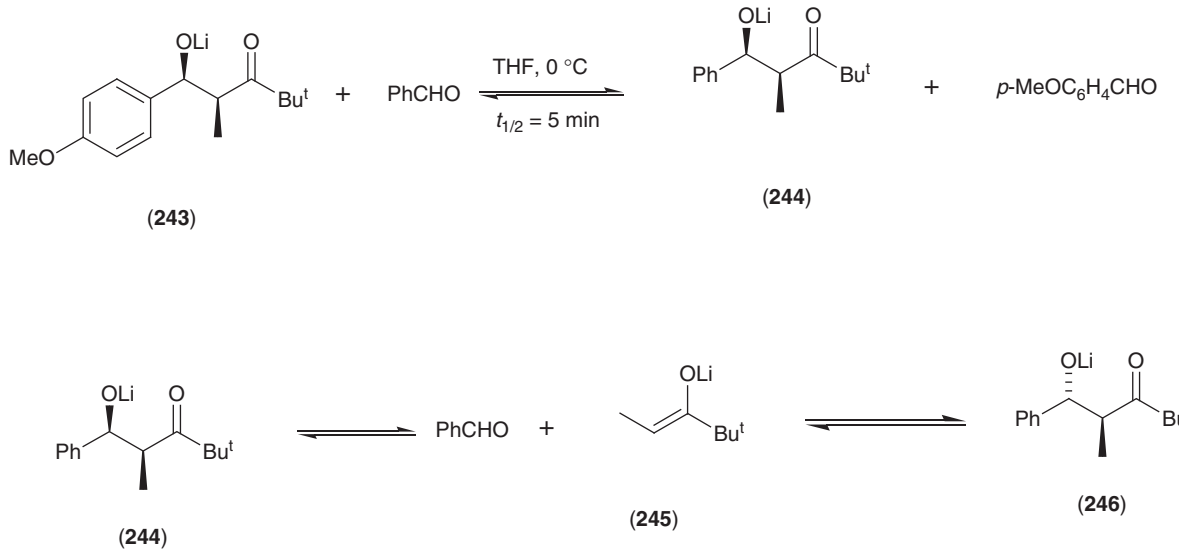
Entry	R^1	R^2	R^3	*X*	*Yield (%)*	***(242a):(242b)***
1	Me	H	Pr^i	MeO	85	73:27
2	Pr^i	H	Me	MeO	77	53:47
3	Pr^i	H	Pr^i	MeO	93	84:16
4	Pr^i	H	Et_2CH	MeO	90	68:32
5	Pr^i	H	c-C_6H_{11}	MeO	89	79:21
6	Pr^i	H	Bu^tCH_2	MeO	93	56:44
7	H	Ph	Pr^i	H	80	17:83
8	H	Ph	Pr^i	MeO	92	16:84
9	H	Ph	Pr^i	Bu^tO	85	23:77
10	H	Ph	Pr^i	Me_2N	87	36:64
11	H	Ph	Pr^i	$(CH_2)_5N$	84	35:65
12	$PhCH_2$	H	Pr^i	MeO	80	72:28

conditions, aldol reactions can be carried out under thermodynamic control. Furthermore, it is usually found that the stereoisomer ratio formed under equilibrating conditions is quite different from the kinetic isomer mixture.

In most cases, aldolate equilibration is to be avoided, since the result is usually to degrade the kinetically established stereoisomer ratio. A good example is seen in the reaction of the lithium enolate of cyclohexanone with benzaldehyde (**Scheme 1**, *vide supra*). If this reaction is carried out at −50 °C and worked up after 3 s, the diastereomer ratio is 82:18. If the reaction mixture is worked up after 5 min, the ratio is only 60:40.

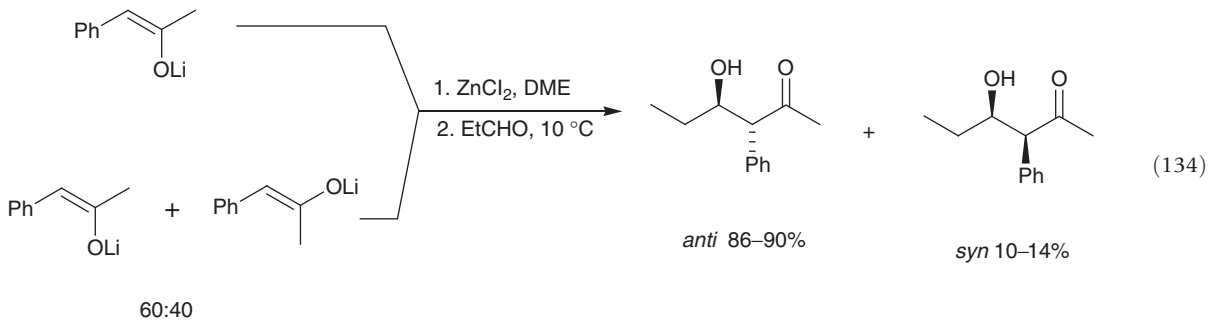
In some cases, however, there is a significant bias in favor of the more stable aldolate. For example, the kinetic product mixture in the reaction of the bromomagnesium enolate of ethyl *t*-butyl ketone and benzaldehyde is *syn:anti* >95:5 (equation 21, *vide supra*).[34] However, under conditions of thermodynamic control the *anti:syn* ratio is >95:5.

Even when the retroaldol reaction is fairly facile, stereoisomer equilibration can be slow.[9c] This phenomenon is illustrated in **Scheme 16**. A solution of the lithium aldolate (**243**) and benzaldehyde equilibrates to (**244**) and *p*-anisaldehyde with a half-life of 15 min at 0 °C. However, the *syn* lithium aldolate (**244**) equilibrates with its *anti* diastereomer (**246**) with a half-life of approximately 8 h at room temperature. The reason for this apparent dichotomy is that enolate (**245**) is so stereoselective in its reactions with aldehydes. Since the kinetic *syn:anti* ratio is 98.7:1.3,[9c] the *syn* aldolate must dissociate approximately 75 times in order for one *syn* aldolate molecule to be converted into one *anti* aldolate molecule. Of course, for less stereoselective enolates, such as the cyclohexanone enolate referred to above, stereochemical isomerization will more nearly parallel the rate of actual aldol reversal.



Scheme 16

The classic case of effective stereocontrol under equilibrating conditions is the House method, wherein the aldol reaction of the preformed lithium enolate is carried out in the presence of coordinating divalent metal ions, such as magnesium and zinc.[182] An example is seen in equation 134. The enolate of phenylacetone reacts with propionaldehyde to give 86–90% *anti* aldol, regardless of the original enolate geometry. Further discussion on zinc endates is found in Volume 2, Chapter 1.8.



(134)

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2.09 The Aldol Reaction: Group IV Enolates (Mukaiyama, Enol Ethers)

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Glossary

Aldol reaction The aldol reaction is a carbon–carbon bond-forming reaction between a carbonyl group and the α-position of another carbonyl compound to form a β-hydroxycarbonyl compound.

Amplification of enantioselectivity Amplification of enantioselectivity is a phenomenon in which higher enantioselectivity of a product is obtained even when a chiral auxiliary with low optical purity is used in asymmetric synthesis.

Closed, cyclic transition state and open, extended transition state For the aldol-type reaction, a closed, cyclic transition state is when the carbonyl group is coordinated to the metal component of the enolate to form a closed, six-membered ring transition state. The diastereomeric outcome of the aldol reaction is dependent on the geometric structure of the enolate. An open, extended transition state is when the carbonyl group is not coordinated to the metal component of the enolate and the diastereomeric outcome is independent on the geometric structure of the enolate. The Mukaiyama aldol reaction often proceeds through an open transition state.

Hypervalency Hypervalency, in chemistry, is a property conferred on molecules that can expand its valence shell beyond the limits of the Lewis octet rule (i.e., more than eight electrons in their valence shells).

Lewis acid-surfactant combined catalyst Lewis acid-surfactant combined catalyst (LASC) acts both as a Lewis acid to activate the reactants and as a surfactant to form stable colloidal dispersions in water. It is often used to perform several organic reactions in water.

Mukaiyama aldol reaction Mukaiyama aldol reaction is a method to perform cross-aldol reaction selectively by using a preformed, less-reactive silicon enolate and a Lewis acid activator.

Single electron transfer Single electron transfer (SET) is a process in which a single electron transfers from one species to another.

Transmetallation Transmetallation is an organometallic reaction in which ligand exchange between two different metal centers occurs.

Water exchange rate constant Water exchange rate constant (WERC) is defined as the exchange rate constant for the substitution of inner-sphere water ligands ('coordinated water').

 doi:10.1016/B978-0-08-097742-3.00210-X

2.09.1 Introduction

Aldol reactions are among the most important carbon–carbon bond-forming reactions. Historically, aldol reactions were performed under basic conditions. Although potential utility of this reaction is very high, several side reactions such as self-condensations, overreactions, and dehydrations of products, took place and regio- and stereoselectivities were generally low. In conventional aldol reactions, lithium, sodium, potassium, and magnesium enolates were used (*see* Chapter 2.08). Compared with these enolates, enolates based on group IV elements, such as silicon and tin, are relatively stable. For example, silicon and tin(IV) enolates are stable at high temperature, and even isolation and purification by distillation are possible in many cases. These isolable enolates are called as preformed (metal) enolates, whereas many other enolates are prepared *in situ* and regarded as intermediates. Stability and reactivity are often a trade-off, and indeed, most silicon and tin(IV) enolates are stable but do not react with aldehydes spontaneously.

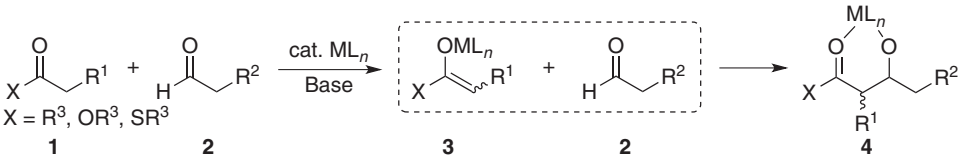
Silicon enolates are the most popular and have been well investigated. Silicon enolates are sometimes called as silyl enol ethers (silicon enolates derived from ketones) and ketene silyl acetals (silicon enolates derived from esters). They react with aldehydes to afford aldol adducts in the presence of Lewis acids or fluoride anions. Different from conventional aldol reactions under basic conditions, the Lewis acid-mediated aldol reactions of silicon enolates with aldehydes (Mukaiyama aldol reactions) proceed under acidic conditions and solved many problems of aldol reactions under basic conditions. For example, silicon enolates were preformed and thus cross-aldol reactions are conducted smoothly. No isomerization and epimerization occurs under acidic conditions.

Another important aspect of silicon enolates and Mukaiyama aldol reactions in organic chemistry and organic synthesis is development of chiral Lewis acids. After discovery of Mukaiyama aldol reactions and due to increasing demand of asymmetric reactions, many chiral Lewis acids for Mukaiyama aldol reactions were developed. Here, chiral Lewis acids work as a catalyst, and thus catalytic asymmetric aldol reactions are attained.

This chapter covers aldol reactions using group IV enolates. Most parts are devoted to silicon enolates, which is one of the most popular enolates. Many chiral Lewis acids and their use in asymmetric aldol reactions are discussed. Tin(IV) and tin(II) enolates are the next major topics. Finally, Ge and Pb enolates in aldol reactions are described.

2.09.2 General Background

Cross-aldol reactions based on the use of preformed metal enolates have played an important role in placing the aldol reaction as an important and reliable method for the stereoselective construction of β-hydroxycarbonyl compounds. In particular, the Lewis acid-promoted cross-aldol reactions of group IV enolates (silicon and tin) reported by Mukaiyama opened the door for the use of stable, isolatable enolates as substrates for highly diastereo- and enantioselective aldol reactions under chiral Lewis acidic conditions.[1] Typically, group IV enolates derived from ketones, esters, and thioester are unresponsive toward aldehydes at ambient conditions and requires the aid of Lewis acids to facilitate the cross-aldol reactions with aldehydes. The power of this approach is clearly illustrated when compared to the challenges associated with metal catalysis with direct aldol reactions (Scheme 1).



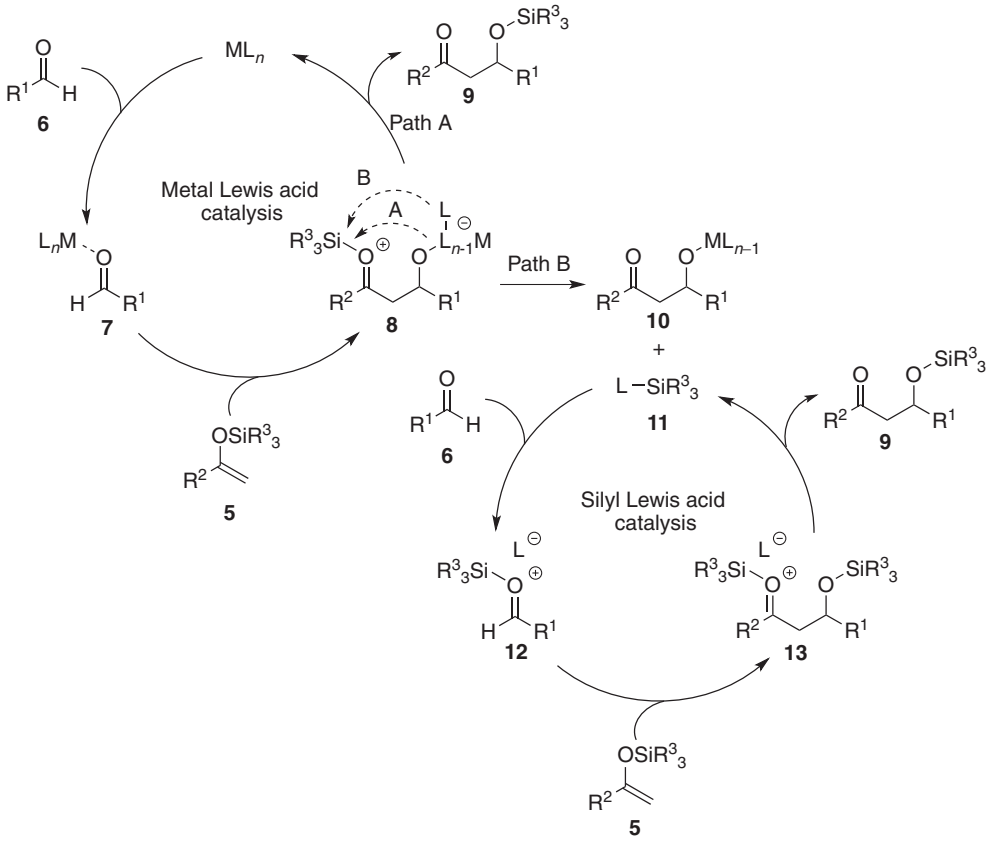
Scheme 1 Metal-catalyzed aldol reaction.

The use of metals as catalyst for the direct cross-aldol reaction suffers with issues concerning chemoselectivity since the aldehyde aldol acceptor **2** possess a more acidic α-proton and may undergo unproductive homo-aldol reactions. In addition, the resulting β-hydroxycarbonyl **4** is more basic than the starting substrates and thus limit catalyst turnover. However, the Mukaiyama aldol reaction overcomes these limitations since the addition of the preformed group IV enolates under mild acidic conditions would prevent dimerization of aldehydes, whereas the resulting silylated aldol product would allow for catalyst turnover. In addition, asymmetric catalysis would be possible through the use of chiral metal–ligand complexes as catalysts.

2.09.2.1 General Mechanistic Considerations

The working hypothesis by Mukaiyama for the $TiCl_4$-mediated cross-aldol reaction with silicon enolates **5** and aldehydes **6** was that the weakly nucleophilic group IV silicon enolate could be incorporated to the carbonyl moiety through the electrophilic activation by the Lewis acidic $TiCl_4$.[2] Although it is plausible that a titanium enolate could be generated *in situ*, the absence of such an intermediate was determined through spectroscopic studies.[3] In addition, preformed α-substituted titanium enolates were

found to react with aldehydes in a *syn*-selective fashion, whereas the $TiCl_4$-mediated aldol reaction proceeded in an *anti*-selective manner. Mechanistic investigations have been performed and focused on the silylation of the metal aldolate intermediate and the nature of the real active catalyst (Scheme 2).[4]



Scheme 2 Catalytic cycles of Mukaiyama aldol reaction using metal Lewis acid.

The nucleophilic addition of silicon enolate **5** to an activated carbonyl complex **7** leads to the formation of silyloxycarbenium intermediate **8**. The key atom transfer step occurs through an intramolecular silyl transfer process to afford silylated aldol product **9** and regenerate the Lewis acid catalyst (path A). Alternatively, intermolecular transfer of the silyl group through a ligand-assisted process generates metalated aldol adduct **10** and a silyl Lewis acid **11** (path B). The production of a powerful silyl Lewis acid **11** leads to an alternative catalytic cycle and can be problematic when it competes with chiral Lewis acids for asymmetric Mukaiyama aldol reactions.

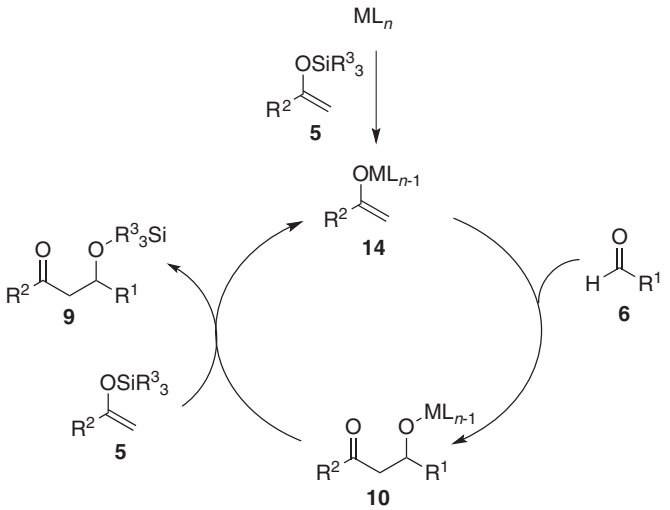
Although the use of Lewis acids can facilitate the Mukaiyama aldol reaction through the electrophilic activation of the aldol acceptor, an alternative mode of activation can be envisioned through a transmetallation pathway in which the weakly nucleophilic silicon enolate **5** is activated by metal complexes to generate more reactive metal enolate **14** for the cross-aldol reaction (Scheme 3).[5]

Although advancement in metal-catalyzed Mukaiyama aldol reactions have been focused on the activation of the electrophilic partner, the alternative mechanism based on metalation of **14** serves as a means to construct new catalytic systems that may offer unique reactivities or selectivities.

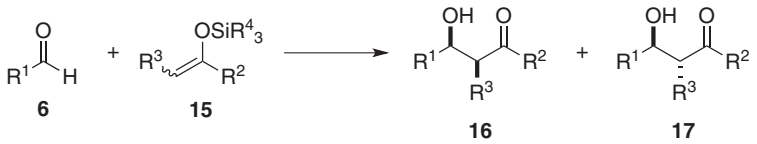
2.09.2.2 Diastereoselection in Mukaiyama Aldol Reactions

Cross-aldol reactions of α-substituted preformed silicon enolate **15** with aldehyde **6** can furnish 1,2-*syn***16** and 1,2-*anti***17** diastereomeric aldol adducts (Scheme 4).

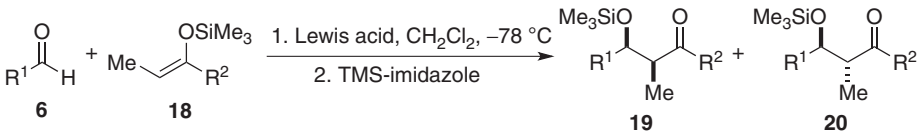
The correlation of the enolate geometry and the diastereoselection is greatly dependent on the mechanism of the aldol reaction and the structure of the transition state. The proposed models to rationalize the diastereomeric outcome of the Mukaiyama aldol reactions are: (1) open, extended transition state and (2) closed, cyclic transition state. In the seminar work by Heathcock et al., the Lewis acid-mediated intermolecular Mukaiyama aldol reaction of aldehydes was examined with various silicon enolates **18** (Scheme 5).[6]



Scheme 3 Catalytic Mukaiyama aldol reaction via transmetallation mechanism.

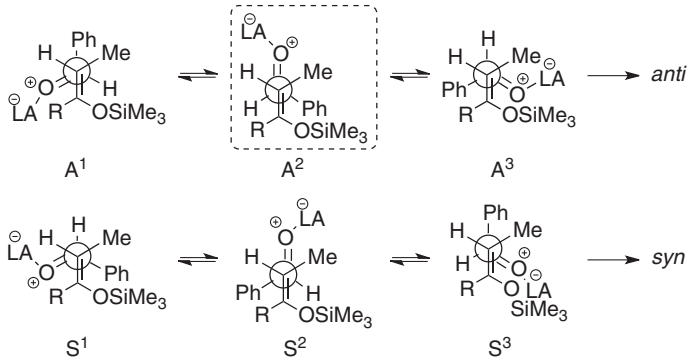


Scheme 4 Mukaiyama aldol reaction with *syn*- and *anti*-selectivity.



Scheme 5 Lewis acid-mediated Mukaiyama aldol reaction.

Although modest diastereoselectivities were observed in most cases under Lewis acidic conditions (*syn*:*anti* = 70:30 to 28:72), significantly high *anti*-selectivity was achieved with (*Z*)-silyl enol ether **18** derived from ethyl *tert*-butyl ketone ($R^2 = {}^tBu$) as the aldol donor (*syn*:*anti* = < 5:95). The dependency of the bulkiness of **18** for the observed diastereoselectivity was explained by examining the staggered transition states for the reaction of enol silane **18** with benzaldehyde (Scheme 6).



Scheme 6 *anti*- and *syn*-Selectivities via open, extended transition state.

Under the assumption that the coordinated Lewis acid adopts a *cis* conformation, six open-state transition models were proposed to account for either the *anti*- or *syn*-aldol products. Conformers $\mathbf{A^3}$ and $\mathbf{S^3}$ were deemed unfavorable due to the destabilizing dipole–dipole interaction between the two carbon–oxygen bond. In addition, the steric interaction between R and Ph would cause further destabilization of the transition state. Similar unfavorable steric interactions would be operational with $\mathbf{A^1}$ (between R and the Lewis acid) and $\mathbf{S^2}$ (between OTMS and Ph). Thus, Heathcock concluded that the *anti*-selectivity arose from transition state $\mathbf{A^2}$. If the bulky *tert*-butyl group was replaced with smaller substituents, the expected stereoselectivity would be diminished since other conformers ($\mathbf{A^1}$, $\mathbf{S^1}$, and $\mathbf{S^2}$) would be energetically viable intermediates. Closed transition-state structures were not considered since the lithium enolate derived from ethyl *tert*-butyl ketone underwent the aldol reaction with *syn*-selectivity and similar diastereoselection was observed with different Lewis acids. This implied that there appears to be little to no interaction between the Lewis acid and the silyl group in the transition-state structures.

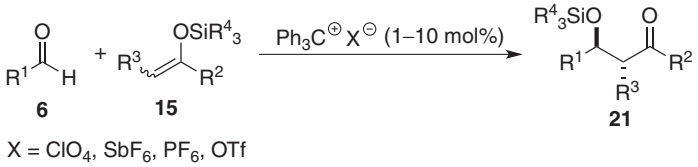
2.09.3 Silicon Enolate

2.09.3.1 Lewis Acid-Catalyzed Mukaiyama Aldol Reactions

2.09.3.1.1 Addition to aldehydes and ketones

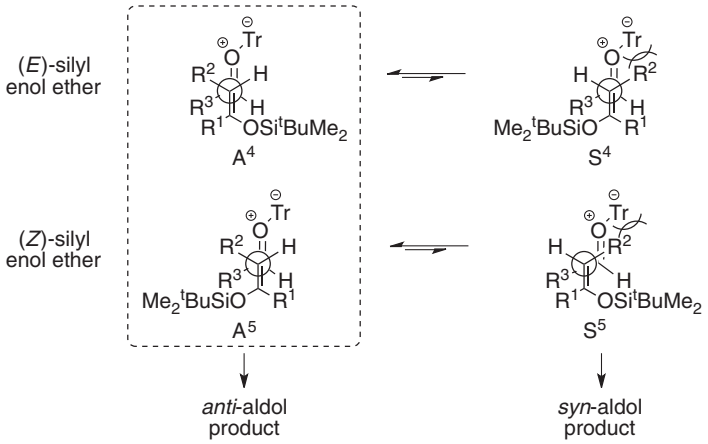
2.09.3.1.1.1 Achiral Lewis acid-catalyzed reactions

After the initial report on the $TiCl_4$-mediated aldol reactions of silicon enolates with aldehydes, the development of catalytic variants of the Mukaiyama aldol reactions have emerged. The first example of a catalytic system was reported by Mukaiyama and involved the use of trityl cationic species as Lewis acids (Scheme 7).[7]



Scheme 7 Mukaiyama aldol reaction using trityl cationic species as Lewis acids.

Interestingly, the trityl-catalyzed Mukaiyama aldol reaction exhibited stereochemical convergence to the *anti*-aldol adduct regardless of the geometry of the silyl enol ethers. Mukaiyama forwarded an open-state transition model to rationalize the observed stereoselectivity (Scheme 8).

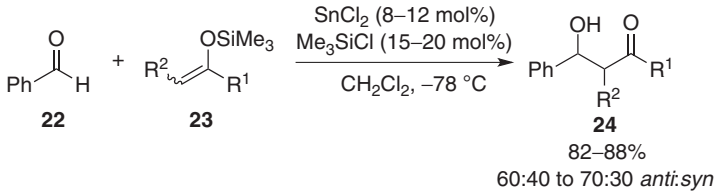


Scheme 8 Mechanism of trityl-catalyzed Mukaiyama aldol reaction.

For the (*E*)-silicon enolate, the proposed open transition state $\mathbf{A^4}$ is believed to be the most stable conformation in which the steric hindrance between the trityl cation, R^2, and the bulky silyloxy group is minimized. Although there is some steric interaction between R^2 and R^3 in $\mathbf{S^4}$, Mukaiyama believed that the trityl-R^2 steric repulsion is greater than that of the R^2–R^3 steric interaction. The predominant steric interaction of trityl cation and R^2 is the basis to rationalize the *anti*-selectivity observed in the Mukaiyama aldol reactions with (*Z*)-enol ethers. The true nature of the catalytic species was examined by Denmark and Chen through crossover experiments with doubly labeled silicon enolates, kinetic and stereochemical studies.[4b] Although TBSOTf could act as a catalyst, Denmark and Chen were able to distinguish the trityl catalysis from the silyl-mediated pathway.

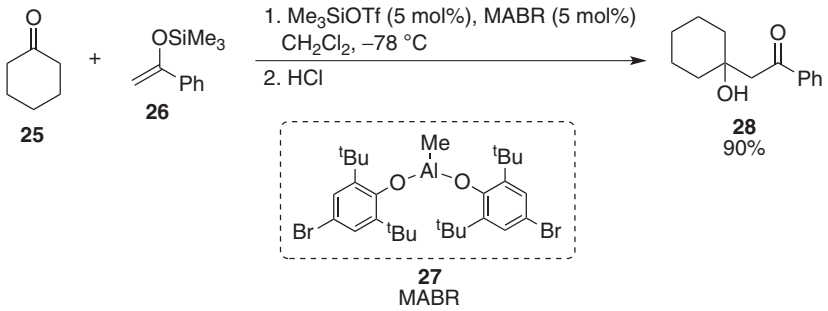
The *in situ* generation of active silyl Lewis acidic species has been reported as an effective means of catalyzing the Mukaiyama aldol reaction. The combination of $SnCl_2$ and TMSCl was found to efficiently catalyze the Mukaiyama aldol reaction (Scheme 9).[8]

Control studies by Mukaiyama revealed that either TMSCl or $SnCl_2$ by itself can act as a catalyst or mediator for the aldol reaction and the proposed active catalyst was believed to be a cationic silicon species derived from the coordination of the chloride of TMSCl by the tin catalyst. Such activated cationic silicon catalyst is reasonable given that TMSOTf itself can be used as a catalyst for the Mukaiyama aldol reaction.



Scheme 9 Catalytic Mukaiyama aldol reaction using $SnCl_2$ and TMSCl.

In order to develop more efficient catalysts for the Mukaiyama aldol reaction, preparation of more active silylium ion catalyst has been explored. Applying a similar strategy employed by Mukaiyama, Davis and Plunkett reported the combination of trialkylsilyl triflates and chlorides with $B(OTf)_3$ to generate supersilylating agents *in situ* for the cross-aldol reaction with silicon enolates.[9] Yamamoto demonstrated a remarkable enhancement to the catalytic activity of TMSOTf for the Mukaiyama aldol reaction by introducing bulky organoaluminum reagents to generate more cationic silylium ions.[10] Ketones, which are notoriously poor reagents for the Mukaiyama aldol reaction, were viable substrates and could deliver the aldol adducts without the formation of a dehydrated byproduct (Scheme 10).



Scheme 10 Catalytic Mukaiyama aldol reaction using TMSOTf and MABR.

Yamamoto also examined the use of Lewis acids derived from superacid bis(trifluoromethylsulfonyl)amine (Tf_2NH) as highly efficient catalysts for a variety of carbon–carbon bond formation reactions, including the Mukaiyama aldol reaction.[11] Mechanistic studies suggested that the trialkylsilyl triflimide-catalyzed Mukaiyama aldol reaction did not conform to the well-established reaction mechanism for the Lewis acid-catalyzed reaction (Scheme 2) due to the inherent low nucleophilicity of the triflimide anion. Yamamoto proposed that the real active species for the silyl triflimide-catalyzed reaction are silyloxycarbenium cation intermediates **12** or **13** (Figure 1).[12]

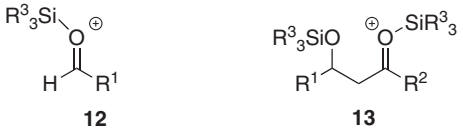
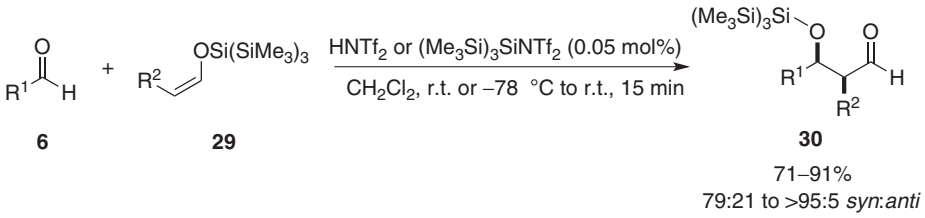


Figure 1 Silyloxycarbenium cation intermediates.

Yamamoto further advanced the chemistry of the Mukaiyama aldol reaction by introducing the use of silicon enolates **29** derived from tris(trimethylsilyl)silyl (TTMSS or super silyl) as reagents for cross-aldol reactions with aldehydes and ketones.[13] The synthetic utility of these unique reagents was demonstrated by performing a highly diastereoselective Mukaiyama aldehyde cross-aldol reaction (Scheme 11).

The extremely large steric bulk of the TTMSS group endowed these silicon enolates to possess unprecedented reactivity and selectivity. Although open transition-state Mukaiyama aldol reactions demonstrate *anti*-selectivity, silicon enolates with TTMSS



Scheme 11 Mukaiyama aldol reaction using TTMSS enol ether.

groups are highly diastereoselective for the *syn*-adduct. This unexpected selectivity was rationalized through an open transition-state intermediate with unfavorable steric interactions with the TTMSS Lewis acid and the carbonyl group with the R substituent of the aldehyde for the *anti*-adduct (Figure 2).

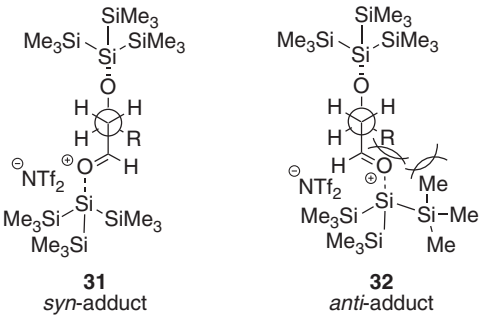
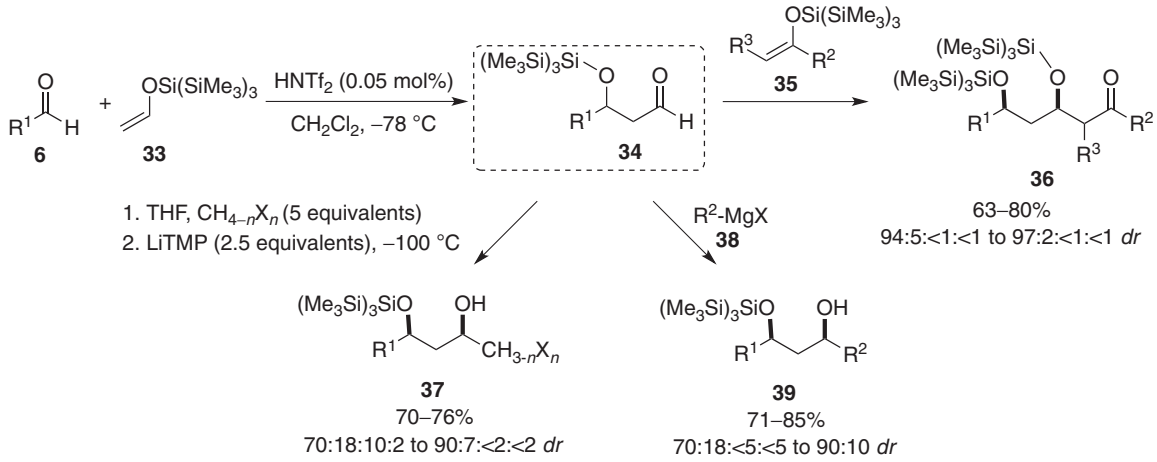


Figure 2 Effect of TTMSS group in open transition state.

The steric bulkiness of the TTMSS group was also invoked to rationalize the high selectivity for the 1:1 aldol adduct. In principle, the *β*-alkoxy aldehydes **30** can undergo a second Mukaiyama aldol reaction. However, the steric bulkiness of the TTMSS group lowers the reactivity of **30** such that high selectivity for the 1:1 adduct is observed.

The presence of a Si–Si bond of TTMSS also is responsible for its unique chemical characteristics. The silicon Lewis acidity of $TTMSSNTf_2$ was found to be more acidic when compared to TMS and $TBSNTf_2$ by ^{29}Si NMR studies. In addition, the unique property of the Si–Si bond renders it UV active and allows for the selective deprotection of the TTMSS group by irradiation with UV lamps.

Although the $HNTf_2$-catalyzed aldol reaction with super silyl enolates provides exclusively the 1:1 aldol adduct, a second highly diastereoselective Mukaiyama reaction occurs when excess of the silyl nucleophile (2.2 equivalents) is utilized to provide 2:1 ratio of the aldol adducts **36**. Yamamoto imagined *β*-alkoxy aldehyde **34** could serve as a valuable intermediate for one-pot sequential reactions in which the diastereoselectivity of the second addition step would be governed by the bulky TTMSS group (Scheme 12).[13,14]



Scheme 12 Stereoselective aldol reactions using TTMSS enol ether.

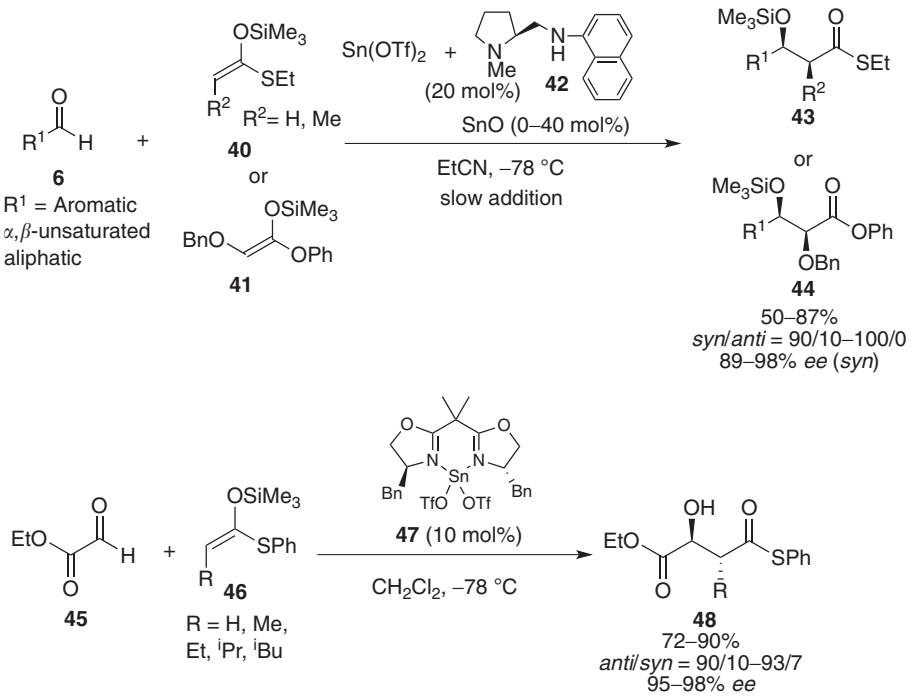
Due to the low catalyst loading of the acid catalyst, Yamamoto believed that the sequential reactions could occur even with strong and basic organometallics like polyhalomethyllithiums and Grignard reagents to furnish 1,3-*syn*-diols **37** and **39**, respectively, in good yields and diastereoselectivity.

Despite the extensive work on the use of silicon-based Lewis acids, other high-valent metals are known to serve as catalysts for the Mukaiyama aldol reaction. Of particular significance is the use of lanthanide triflates as excellent catalysts for the aldol reaction with silicon enolates.[15] Originally developed as water-stable Lewis acids, lanthanides have been applied to other alternative and environmentally benign solvents such as ionic liquids[16] and supercritical carbon dioxide.[17] In addition, immobilization of lanthanide salts to heterogeneous supports has been developed and the overall greenness of the Mukaiyama aldol reaction has been improved.[18]

2.09.3.1.1.2 Chiral Lewis acid-catalyzed reactions

Asymmetric carbon–carbon bond-forming reaction is one of the most powerful and useful methods for the synthesis of optically active and highly functionalized complex molecules such as biologically active compounds. In the past three decades, the concept of asymmetric synthesis has matured dramatically from diastereoselective synthesis using optically active natural compounds (chiral pool method) to enantioselective synthesis using optically active catalysts. In aldol reactions, the development of asymmetric synthesis has been intensively investigated, with the use of chiral boron activators or enolate precursors with chiral auxiliaries as the most successful examples. However, catalytic asymmetric aldol reactions have been recognized as a more advanced methodology to obtain enantiomerically pure *β*-hydroxy ketones. In the chemistry of enolates derived from carbonyl compounds, highly reactive alkaline metal enolates, such as lithium enolates, were often employed as a nucleophilic species in stereoselective synthesis. However, their highly reactive nature makes them difficult to control in the presence of a catalyst for catalytic asymmetric synthesis. However, the use of less-reactive preformed enolates in the presence of a Lewis acid activator has been recognized as a promising method for catalytic asymmetric synthesis, since the reactivity of the preformed enolates can be controlled by the Lewis acids. Therefore, several highly functionalized Lewis acid catalysts have been developed for catalytic asymmetric Mukaiyama aldol reactions.[19]

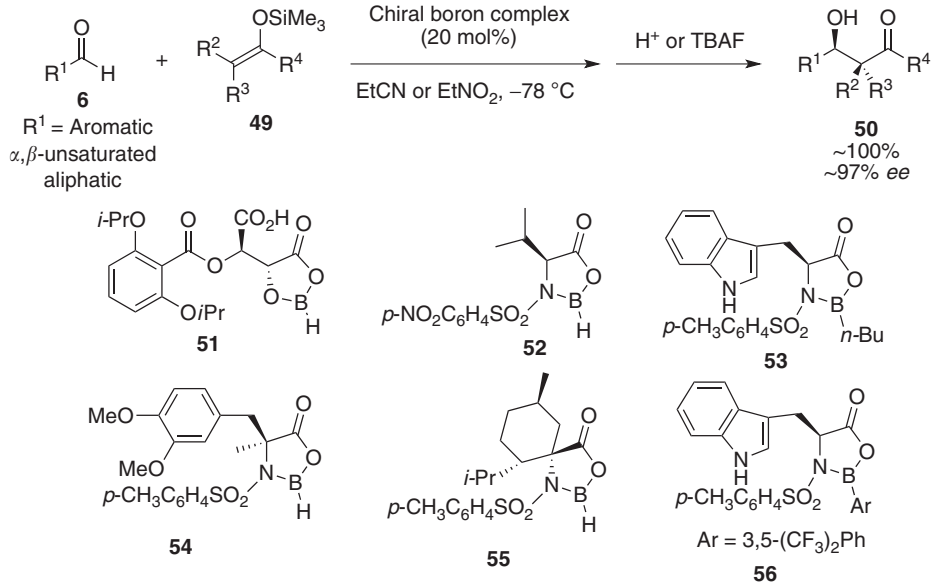
In the twilight of catalytic asymmetric Mukaiyama aldol reaction, the focus was primarily on aldehydes since the differentiation of both enantiofaces of aldehyde carbonyl group was trivial due to the relatively favorable (*E*)-complexation of the metal Lewis acid to the carbonyl oxygen. The pioneering work in chiral Lewis acid-catalyzed Mukaiyama aldol reaction of aldehydes was reported by Mukaiyama in the early 1990s.[20] They utilized chiral tin(II) complexes prepared from $Sn(OTf)_2$ and chiral diamines such as **42** derived from L-proline in the optimized reaction system, and effective catalyst turnover was achieved by the slow addition of the thioester-derived silicon enolate. Using tin oxide as an additive, the desired silylated aldol adducts were obtained in high diastereo- and enantioselectivities (**Scheme 13**). A silicon enolate derived from *α*-benzyloxy acetate was also utilized to obtain *α*,*β*-dihydroxyesters. It should be noted that this work was quite remarkable as it was the first example of a catalytic asymmetric Mukaiyama aldol reaction. Other chiral tin(II) Lewis acids have been also reported as effective chiral catalysts by



Scheme 13 Asymmetric aldol reactions using chiral tin(II) Lewis acids.

Evans. Evans demonstrated that chiral tin(II) triflate complex **47**, bearing a chiral bisoxazoline (BOX) ligand, could be successfully employed for the asymmetric Mukaiyama aldol reaction of glyoxylate with silicon enolates of thioesters.[21] The reactions proceeded smoothly to afford the desired adducts with high *anti*- and enantioselectivities.

Boron compounds are recognized as effective Lewis acids in organic synthesis. Functionalization of boron compounds is relatively easy since boron complexes can be prepared easily from commercially available BH_3 or trialkylboron with chiral ligands. Similar to other asymmetric reactions, chiral boron compounds have been successfully applied in the Mukaiyama aldol reaction (Scheme 14). The chiral ligands were prepared from optically active natural compounds, such as α-amino acid or tartaric acid, etc. Early successful examples were reported by Yamamoto (**51**), Kiyooka (**52**), Corey (**53**), and Masamune (**54**, **55**).[22] Second generation of Corey's boron complex was evaluated by Yamamoto and the catalytic activity of the boron complex **56**, prepared from a modified L-tryptophane derivative, was improved by introducing an aryl group with electron-withdrawing groups, such as 3,5-bis(trifluoromethyl)phenyl group, on the boron atom.[23]

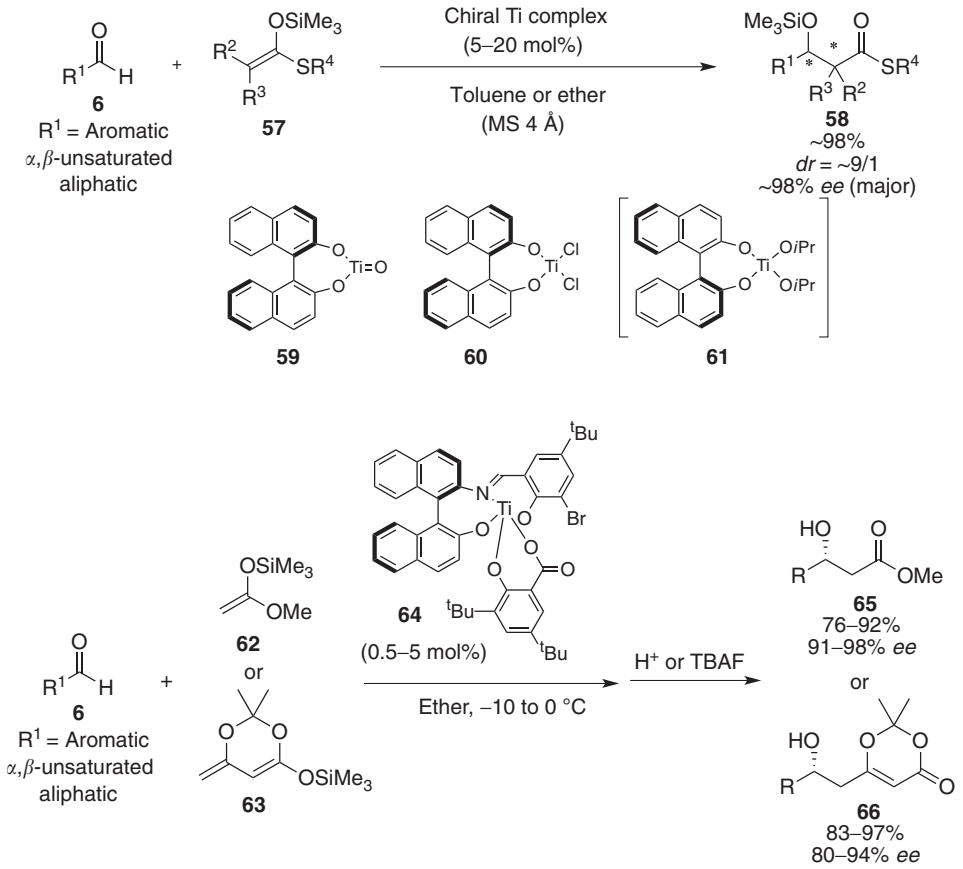


Scheme 14 Asymmetric aldol reactions using chiral boron Lewis acids.

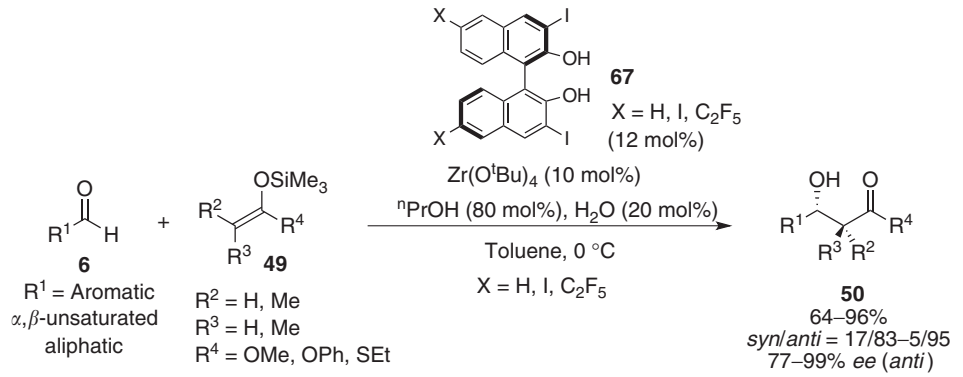
Titanium halides, such as titanium chloride, have been employed as one of the most typical strong Lewis acids in organic synthesis. The other interesting feature of titanium-based Lewis acids is the ability of the counteranion to control their Lewis acidity with anions of weak conjugate acids leading to more mild Lewis acids. To achieve good Lewis acidity and significant stereocontrol, 1,1′-binaphthyl-2,2′-diol (BINOL) derivatives were found to be promising chiral ligands to titanium. Mukaiyama et al. (**59**), Mikami et al. (**60**), and Keck et al. (**61**) have reported effective Ti–BINOL Lewis acids for Mukaiyama aldol reactions, and high stereoselectivities have been realized.[24] Furthermore, Carreira et al. reported a chiral titanium complex **64**, prepared from a chiral ligand composed of BINOL skeleton, a salicylaldehyde Schiff base, and a salicylic acid derivative, as an excellent chiral catalyst for the Mukaiyama aldol reaction (Scheme 15).[25] The titanium catalyst demonstrated high enantioselectivities while operating with lower catalyst loading than previously reported chiral titanium catalysts. In the reaction system, it was assumed that the salicylate counteranion efficiently assisted the silyl cation transfer from the carbonyl to the alkoxy part of the intermediate.

Zirconium is also expected to be an effective group-IV metal Lewis acid similar to titanium species. Chiral zirconium complexes prepared by Kobayashi and coworkers, from zirconium alkoxide and 3,3′-diiodo BINOL derivatives **67**, were found to catalyze highly *anti*-selective Mukaiyama aldol reactions (Scheme 16).[26] Although typical chiral Lewis acid catalysts promoted *syn*-selective asymmetric aldol reaction when silicon enolates of propionate were used, the zirconium catalyst system interestingly showed remarkably general *anti*-selectivity. In this reaction, the role of protic additives was found to be critical in promoting the catalytic process by trapping the silyl cation from the silylated aldol intermediate. Furthermore, a small amount of water was found to be essential for the preparation of the real active catalyst. The unusual *anti*-selectivity was postulated to be caused by the sterically hindered large iodo group at the 3,3′-position of the BINOL system. Introduction of an electron-withdrawing group at the 6,6′-positions of the BINOL ring system was found to be effective to improve the catalytic activity of the zirconium catalyst.

Scandium species are known as very effective Lewis acid catalysts in several kinds of organic transformations. Their remarkable ability to remain stable in water has allowed them to be highly effective catalysts in aqueous media. Chiral scandium Lewis acid **68** has been also extensively investigated, and high enantioselectivity has been achieved for the Mukaiyama aldol reaction with ethyl glyoxylate (Scheme 17).[27] Replacement of one chloro counteranion to less-coordinative hexafluoroantimonate was effective to achieve high enantioselection.

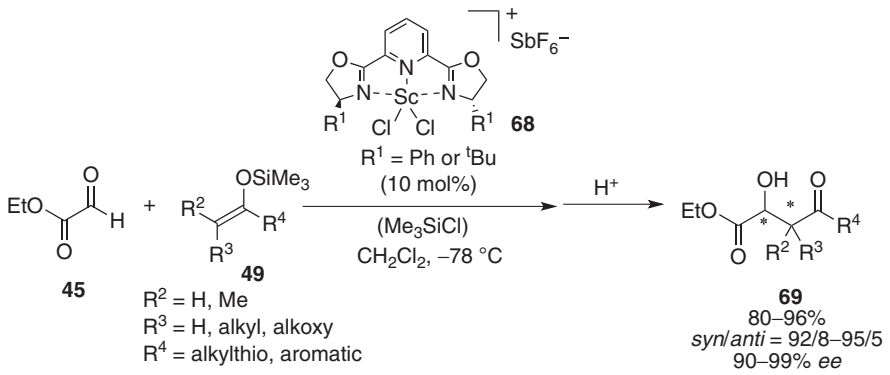


Scheme 15 Asymmetric aldol reactions using titanium Lewis acids.

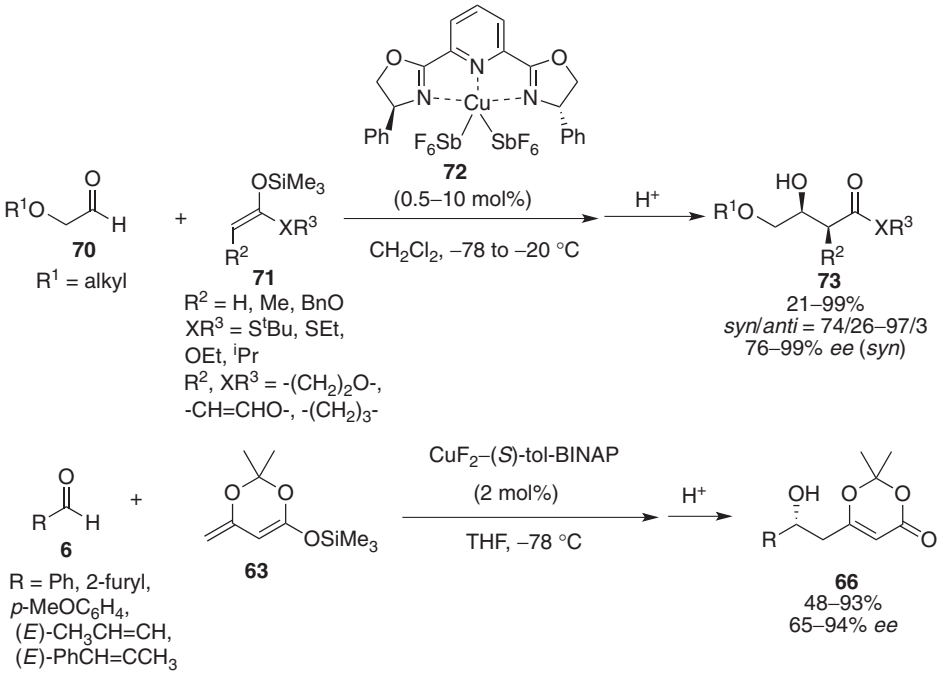


Scheme 16 Asymmetric aldol reactions using zirconium Lewis acids.

Successful chiral copper catalysts prepared from $Cu(SbF_6)_2$ and chiral BOX and pyridinebisoxazoline (PyBox) have been reported by Evans et al. for the asymmetric Mukaiyama aldol reaction of aldehydes (Scheme 18).[28] In the chiral copper catalyst system, acetaldehydes **70** bearing Lewis basic coordination site, an alkoxy moiety, at the α-position is essential to realize high enantioselectivity. It was assumed that the additional coordinative site could interact with copper metal to a form five-membered metallocycle system that generated a rigid and highly enantioselective asymmetric environment. In the aldol reaction using copper–chiral PyBox complex **72**, significant amplification of enantioselectivity was observed when lower *ee* of the ligand was used. This result suggested that the formation of a relatively stable but less-reactive copper complex (copper–(*R*)-ligand–(*S*)-ligand (1:1:1)) exists in the reaction system. Carreira reported a tol-BINAP–copper (II) fluoride-mediated asymmetric aldol reaction using a silicon dienolate **63** prepared from a β-ketoester (Scheme 18).[29] In this system, a reactive copper dienolate could form *in situ* to generate a silicon dienolate via transmetallation with the copper species and subsequently react with aldehydes to afford the desired ε-hydroxy ketoester derivative in high enantioselectivity.



Scheme 17 Asymmetric aldol reactions of silicon enolates using a chiral scandium Lewis acid.



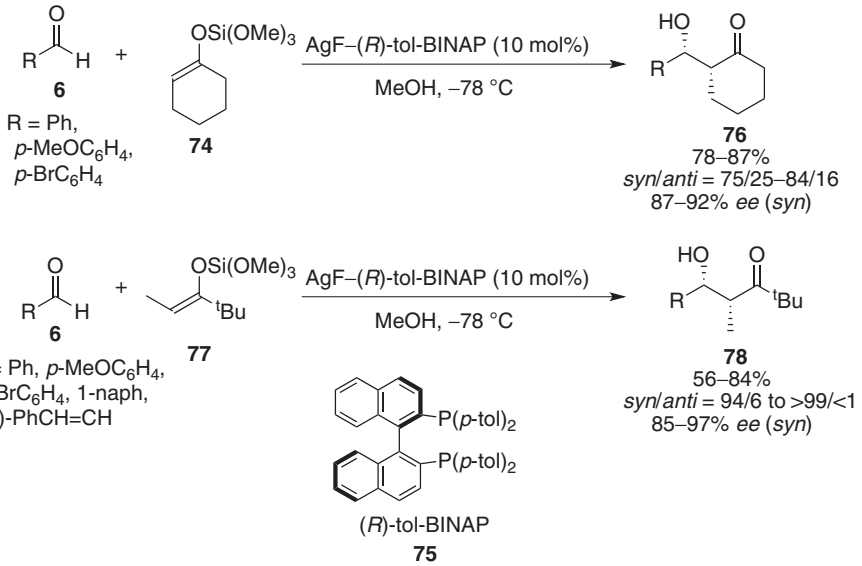
Scheme 18 Asymmetric aldol reactions using chiral copper complexes.

Silver has been known to possess mild Lewis acidity and have been used in Lewis acid-mediated asymmetric carbon–carbon bond formation reactions. Yamamoto and coworkers reported a silver fluoride–tol-BINAP complex-catalyzed asymmetric aldol reaction of enol trimethoxysilyl ethers (Scheme 19).[30] The reaction was shown to proceed smoothly with high *syn*-selectivity that was independent of the *E*/*Z* stereochemistry of the silicon enolate. In their mechanistic studies, the formation of chiral silver enolate could not be confirmed and the reaction was believed to proceed via typical Mukaiyama aldol reaction mechanism.

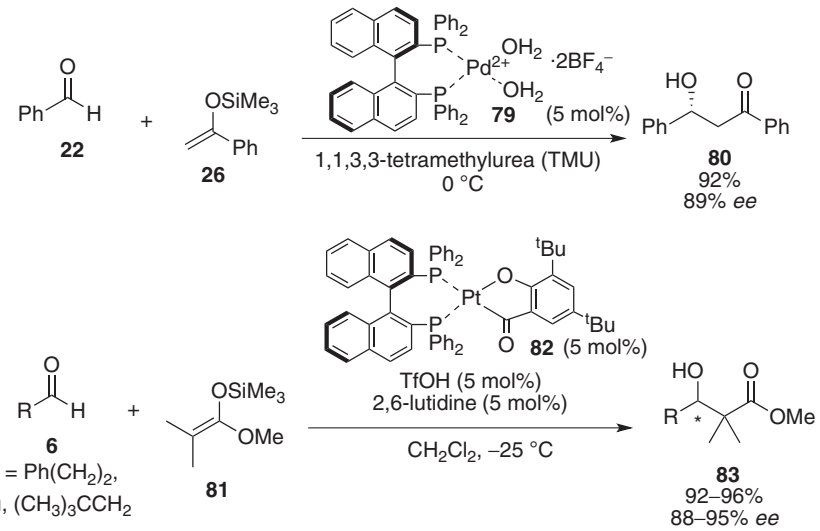
The use of Lewis acidic transition metals (group X) have been reported as effective catalysts for asymmetric Mukaiyama aldol reactions. Shibasaki and Fujiwara revealed that palladium– or platinum–BINAP complexes (**79** or **82**) could be employed for asymmetric aldol reactions with high enantioselectivities (Scheme 20).[31] In both cases, water was found to be essential for the formation of the active catalyst species. In addition, NMR studies suggested that palladium and platinum enolate formed *in situ* from the silicon enolate of the ketone or ester.

Chromium–chiral salen ligand complexes are known as effective chiral Lewis acid complexes in several asymmetric reactions. Katsuki and coworkers have reported an asymmetric addition of trimethylsiloxy furan **84** to aldehydes in the presence of a chiral chromium complex **85** (Scheme 21).[32] In the reaction system, protic additives, such as isopropyl alcohol, were shown to play an important role in suppressing the retro aldol process to improve the diastereoselectivity.

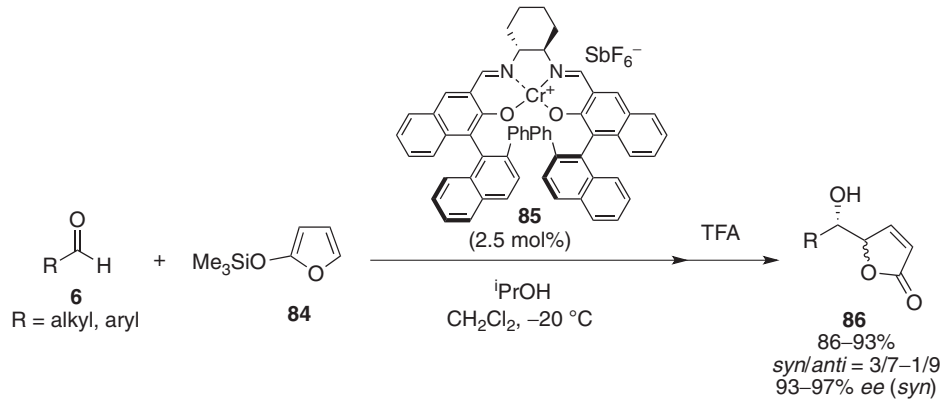
Although chiral metal Lewis acid catalysts have been investigated in asymmetric Mukaiyama aldol reactions, chiral organocatalysts, especially chiral Brønsted acids, have appeared as promising catalysts in the past decade. Hydrogen bonding between the substrates and the organocatalysts was found to be sufficiently effective for controlling asymmetric environment. In 2005,



Scheme 19 Asymmetric aldol reactions using a silver fluoride–chiral bisphosphine.

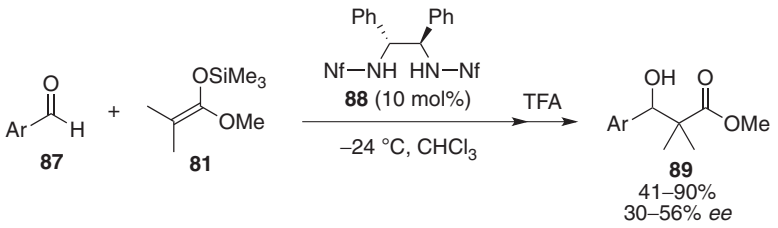


Scheme 20 Asymmetric aldol reactions using a chiral palladium or platinum complex.



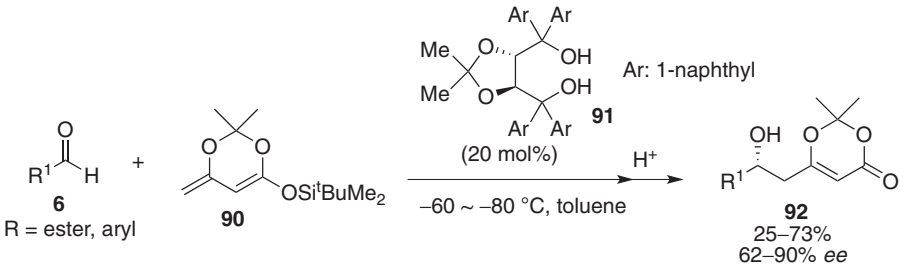
Scheme 21 Asymmetric aldol reactions of siloxy furan using a chiral chromium Lewis acid.

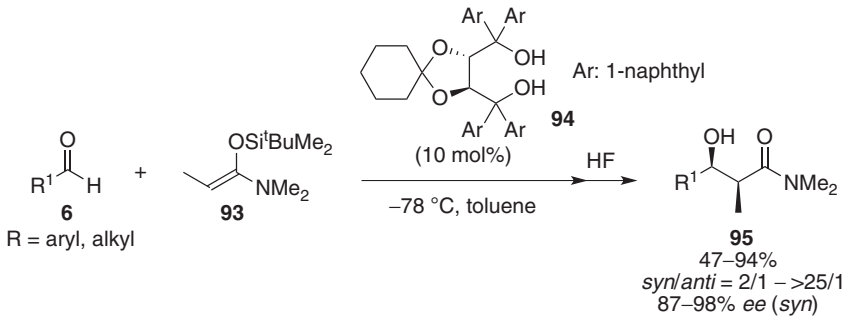
Jørgensen and coworkers successfully reported an asymmetric Mukaiyama aldol reaction catalyzed by a chiral bis-sulfonamide derivative **88**.[33] The asymmetric Mukaiyama aldol reactions of aromatic aldehydes proceeded smoothly to afford the desired aldol adducts in moderate enantioselectivity (Scheme 22).

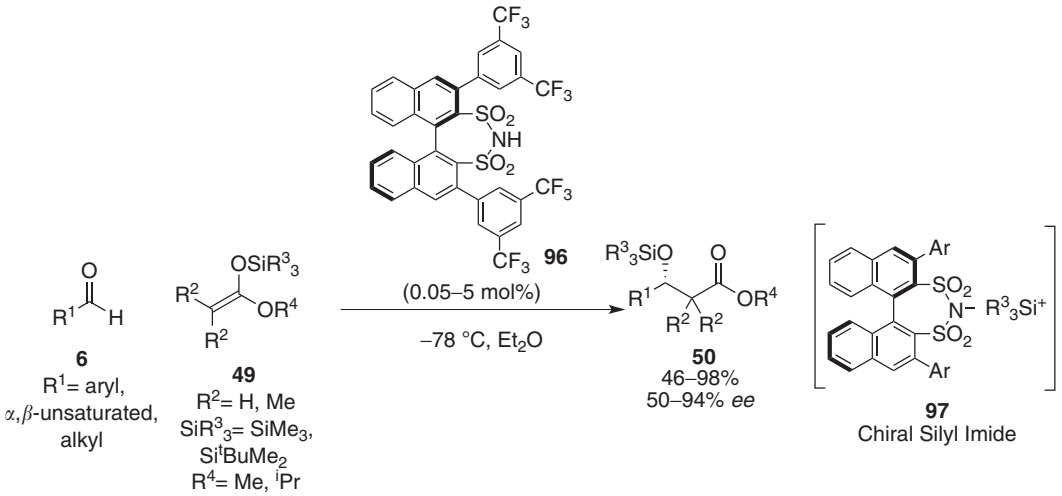


Scheme 22 Asymmetric aldol reactions using a chiral bis-sulfonamide.

Rawal and coworkers also reported an efficient hydrogen-bonding chiral diol catalyst for the asymmetric aldol reactions (Scheme 23).[34] Several chiral diols, including BINOL derivatives, have been investigated, and finally chiral TADDOL derivative **91** was found to be the most effective catalyst to promote Mukaiyama aldol reactions of a silicon dienolate with moderate-to-good yields and good-to-high enantioselectivities. Furthermore, the TADDOL derivative **94** was successfully employed in asymmetric





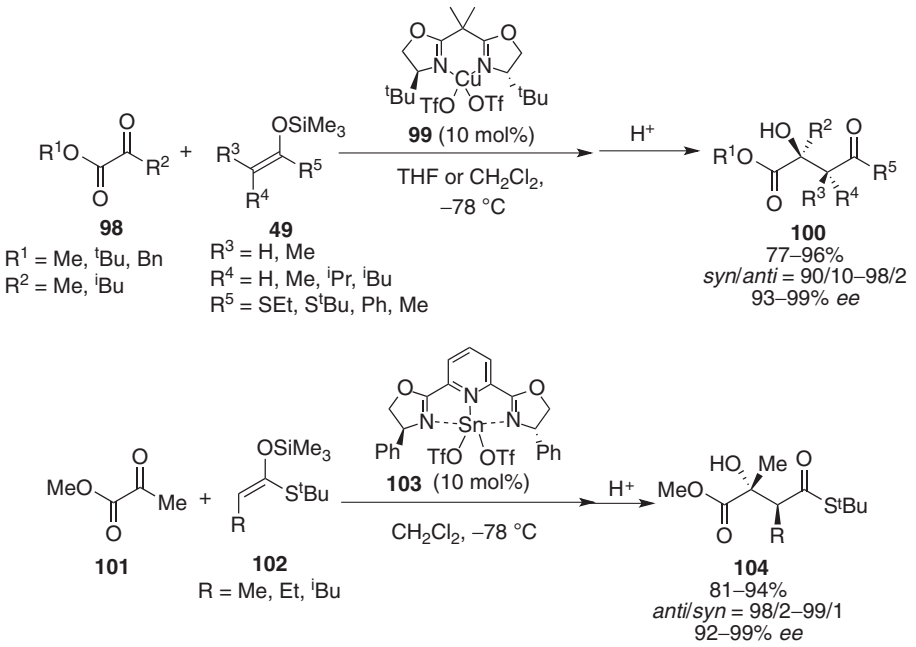


Scheme 23 Asymmetric aldol reactions using chiral TADDOLs and a chiral bis(sulfonamide).

aldol reactions of several aldehydes with a silicon enolate derived from *N*,*N*-dimethylpropionamide. The reactions proceeded at −78 °C to afford the desired *syn*-aldol adducts in good-to-high diastereo- and enantioselectivities. List and coworkers also applied a chiral bis-sulfonamide **96** with a BINOL motif as a chiral Brønsted acid for Mukaiyama aldol reactions.[35] The aldol reactions were shown to proceeded in high yields with high enantioselectivity. In the reaction mechanism, it was proposed that the chiral bis-sulfonamide reacted with silicon enolate to produce *N*-silyl imide, in which the silyl cation could activate the aldehyde, and the chiral imide anion may induce asymmetric induction via a chiral counteranion effect.

Compared to the aldol reactions to aldehydes, the reactions of ketones have not been well explored. This may be due to its reduced reactivity to nucleophiles by steric hindrance and the difficulty to distinguish both substituents on the carbonyl carbon to select one enantioface of the carbonyl group. An exception to this general problem is the use of α-ketoesters, such as pyruvates, which possess high reactivity and the bidentate chelation ability to metal Lewis acids would result in a good, tight asymmetric environment around metal Lewis acids to achieve high enantioselectivities. However, in asymmetric aldol reactions to simple ketones, not trivial and novel catalyst systems that possess highly efficient chiral environment are required to achieve good asymmetric induction.

Some successful examples of asymmetric Mukaiyama aldol reactions of pyruvates were reported using chiral Lewis acids. Evans et al. reported that a copper–Box complex **99** could catalyze asymmetric aldol reaction of α-ketoesters to afford desired aldol adducts in high yields with high *syn*- and enantioselectivity (**Scheme 24**).[36] Evans et al. also reported that chiral tin(II)–PyBox complex **103** could promote the asymmetric aldol reaction of pyruvates, and interestingly, the diastereoselectivity was reversed and the aldol reaction proceeded with high *anti*-selectivity.[37]

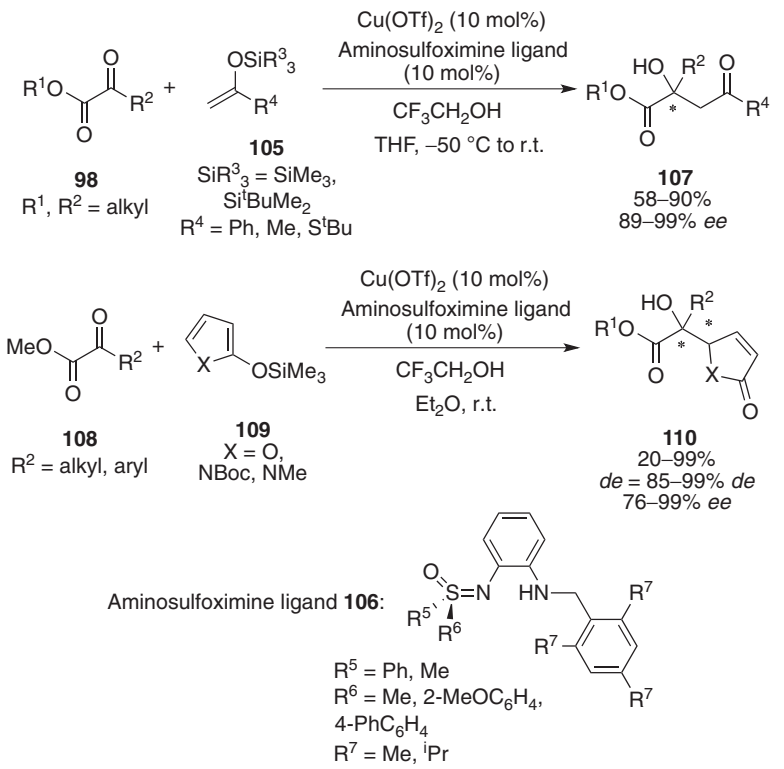


Scheme 24 Asymmetric aldol reactions of pyruvates using chiral copper and tin catalysts.

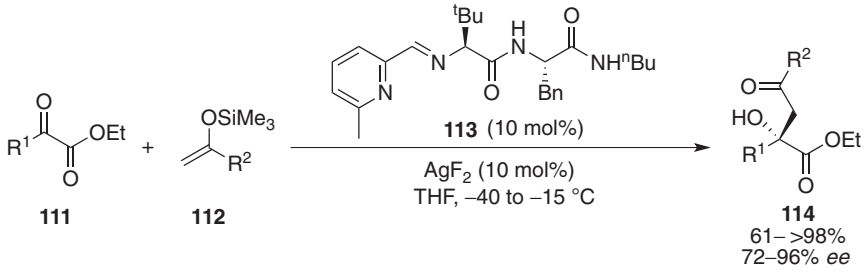
Other silver and copper catalysts have been also successfully employed for the aldol reaction of α-ketoesters. Bolm and coworkers reported that C_1-symmetric aminosulfoximines **106** worked as a chiral ligand to copper Lewis acids, and the Mukaiyama aldol reaction of α-ketoester proceeded in high enantioselectivities (**Scheme 25**).[38] Not only silicon enolate derived from ketones but also siloxy furans or pyrroles were suitable substrates, and the reactions proceeded in high diastereo- and enantioselectivities. Protic additive, 2,2,2-trifluoroethanol (TFE), was found to be effective to enhance the reaction without any loss of stereoselectivities.

Hoveyda and coworkers also developed a silver fluoride–chiral peptide **113** complex for the asymmetric Mukaiyama aldol reaction. The aldol reactions of α-ketoester derivatives proceeded in high enantioselectivities with a wide range of substrates (**Scheme 26**).[39] It was assumed that AgF_2 employed was reduced *in situ* to the catalytically active AgF by the silicon enolate. The catalyst system was shown to be tolerant to both air and moisture as the asymmetric Mukaiyama reaction could be conducted with undistilled solvent in air.

Although challenging, successful examples of asymmetric aldol reactions of simple ketones have been reported. In 2003, Shibasaki and coworkers described an asymmetric Mukaiyama aldol reaction of methyl ketones using a chiral copper fluoride–bisphosphine **117** system. A more general asymmetric catalyst was later developed and Shibasaki and coworkers found that a chiral Cu(I) fluoride–chiral bisphosphine **121** complex promoted the asymmetric aldol reaction of aryl–alkyl or alkyl–alkyl



Scheme 25 Asymmetric aldol reactions of pyruvates using chiral silver and copper Lewis acids.



Scheme 26 Asymmetric aldol reaction using a silver fluoride–chiral peptide ligand.

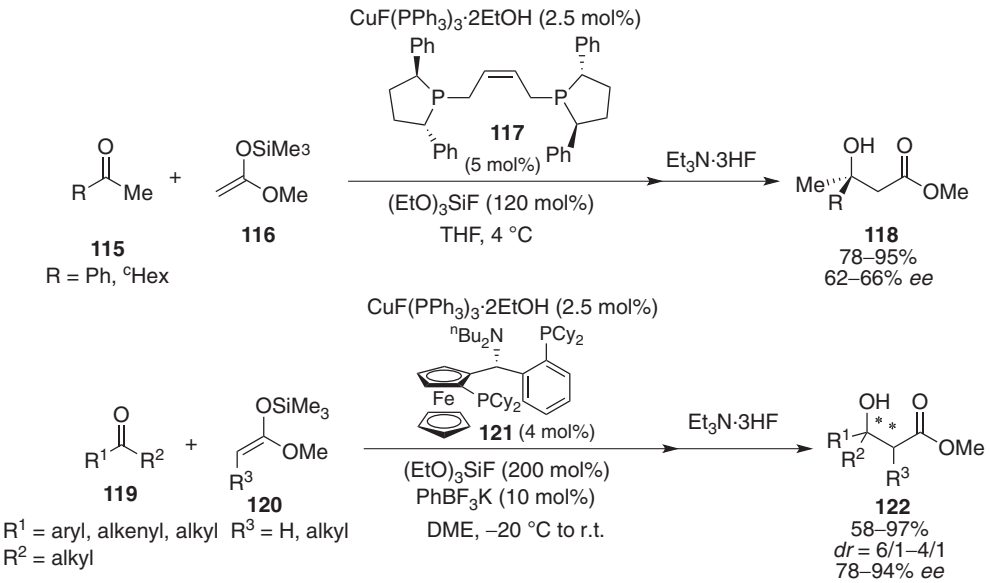
ketones with silicon enolates of esters, and good-to-high stereoselectivities were achieved (Scheme 27).[40] The addition of $(EtO)_3SiF$ and $PhBF_3K$ was found to be important since the formation of highly electrophilic $(EtO)_2SiF_2$ or $(EtO)SiF_3$ species was believed to accelerate catalytic turnover of the copper catalysts by trapping the aldol intermediate.

Campagne and coworkers also reported a chiral copper catalyst for the asymmetric aldol and subsequent cyclization reaction of ketones using a silicon dienolate (Scheme 28).[41] The reaction proceeded in moderate-to-good yields with moderate-to-high enantioselectivities. They successfully applied the developed aldol reaction to the formal synthesis of Taurospongin A.

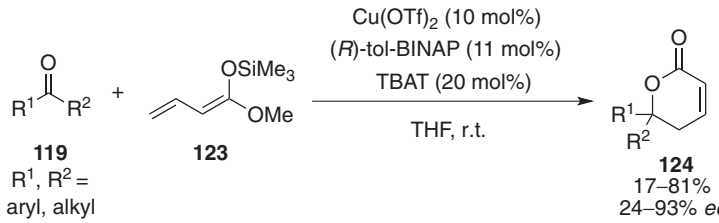
Adachi and Harada reported an asymmetric aldol reaction of ketones using a chiral boron Lewis acid **126** (Scheme 29).[42] In order to overcome the relatively lower reactivity of ketones, a more active silicon enolate bearing dimethylsilyl (DMS) group was employed to obtain the β-hydroxy thioesters in moderate yields and moderate-to-high enantioselectivities.

2.09.3.1.2 Lewis acid-catalyzed Mukaiyama aldol-type reactions of acetals

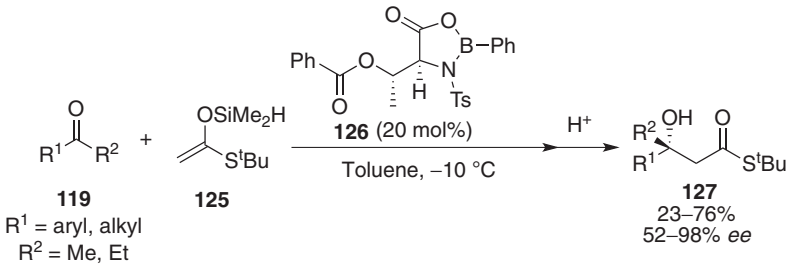
In synthetic organic chemistry, acetals have been often used for the protection of carbonyl groups of aldehydes or ketones. However, acetals can be activated in the presence of Lewis acids, and, in principle, nucleophiles can react with the activated acetal by releasing of one alkoxy moiety. Mukaiyama aldol reactions can be conducted using not only with aldehydes or ketones but also with acetals, in the presence of Lewis acids (Scheme 30).[43] In 1974, Mukaiyama and Hayashi reported that a stoichiometric amount of titanium tetrachloride promotes the reaction of silicon enolates with acetals to afford the aldol products in high yields.[44] It was believed that the titanium Lewis acid activated one alkoxy substituent of the acetal to form reactive oxocarbenium



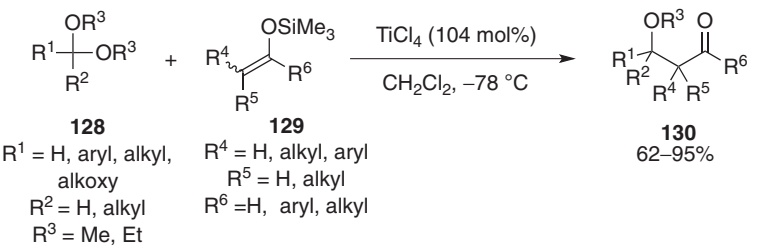
Scheme 27 Asymmetric aldol reactions of simple ketones using chiral copper catalysts.



Scheme 28 Asymmetric aldol reactions and cyclization of simple ketones to form chiral lactones using a chiral copper catalyst.



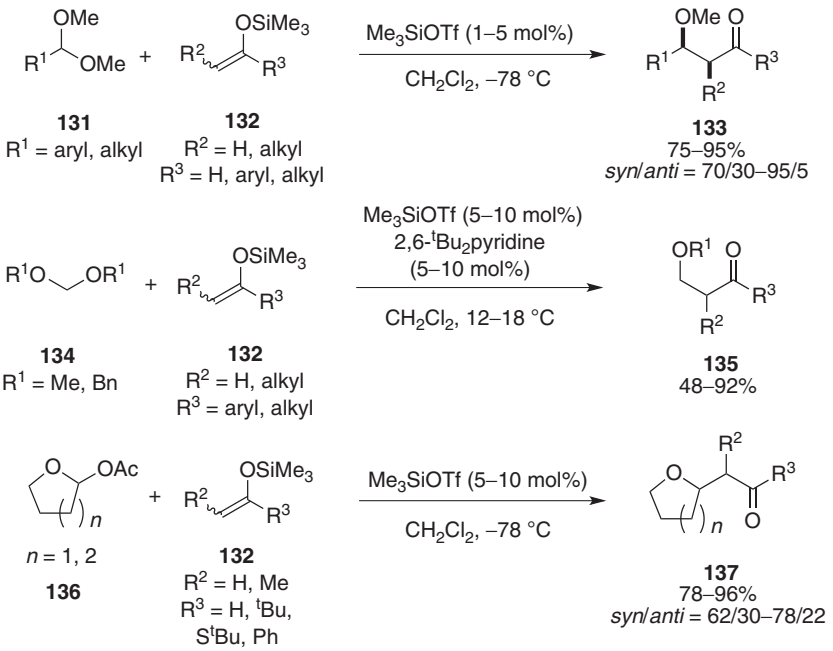
Scheme 29 Asymmetric aldol reactions of simple ketones.



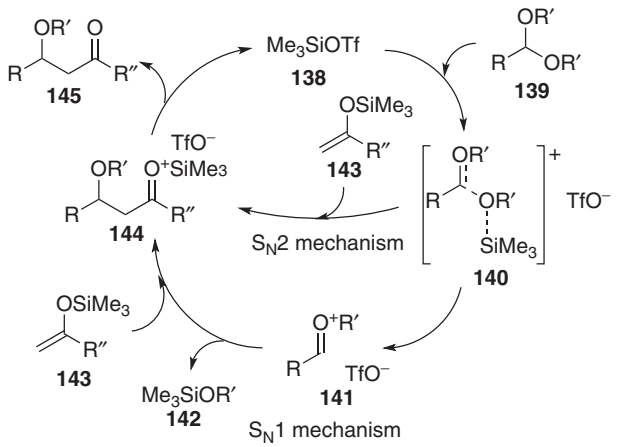
Scheme 30 Mukaiyama aldol-type reactions of dialkyl acetals using titanium chloride.

ion in the reaction system, which reacted with silicon enolate smoothly to afford the desired aldol product. This method has been well applied into macrocyclic system of biologically useful compounds in intramolecular aldol-type reaction of acetal.[45]

Although extensive research has been conducted on Mukaiyama aldol-type reactions of acetals using a stoichiometric amount of Lewis acids such as titanium tetrachloride, the reaction promoted by catalytic amounts of Lewis acids have also been investigated. In 1980, Noyori and coworkers reported trimethylsilyl triflate-catalyzed Mukaiyama aldol-type reaction of acetals (**Scheme 31**).[46] The catalytic use of trimethylsilyl triflate allowed not only aromatic and aliphatic aldehyde-derived acetals, but also formaldehyde-derived acetal, to act as excellent substrates, and the desired *β*-alkoxycarbonyl products could be obtained in high yields. In the catalytic cycle, trimethylsilyl cation activates one of the alkoxy moiety of the acetal to generate active intermediate **140**, which reacts with silicon enolate to afford the desired *β*-alkoxycarbonyl compound and regenerates the trimethylsilyl triflate catalyst. As for the reaction mechanism, there are two distinct possibilities in which an oxocarbenium ion **141** forms and reacts with nucleophilic species in S_N1 fashion or via direct nucleophilic addition to an activated trimethylsilyl triflate–acetal complex (S_N2 mechanism) (**Scheme 32**). Although Noyori proposed a S_N2 mechanism to explain the *anti*-selective condensation of silicon enolates to 2-acetoxytetrahydrofuran and -tetrahydropyran derivatives,[47] a recent study suggested that the Mukaiyama aldol reaction with acetals proceeds mainly through a S_N1 mechanism based on the racemization aldol-type reactions using optically active acetals.[48] In addition, a one-pot silicon enolation formation – aldol-type reaction of acetals using trimethylsilyl triflate as a catalyst – has been also reported.[49]



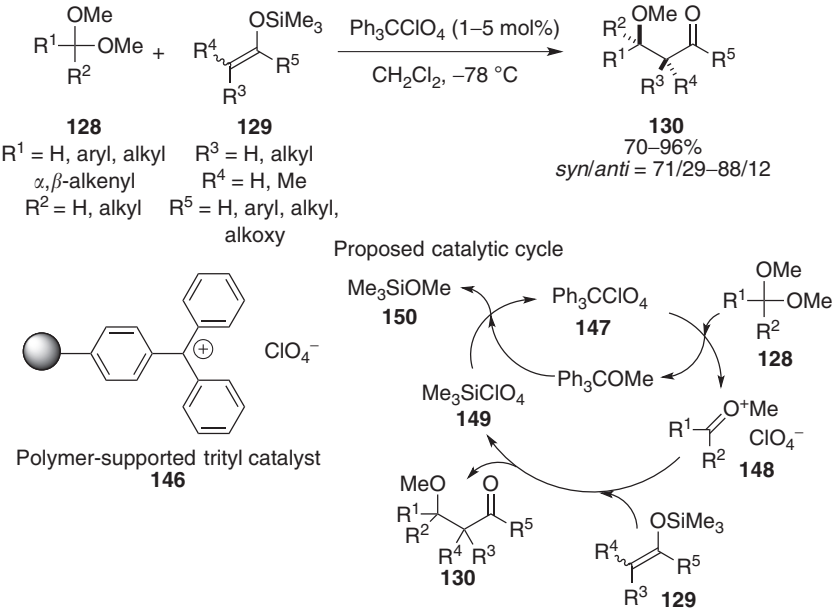
Scheme 31 Catalytic Mukaiyama aldol-type reactions of acetals using trimethylsilyl triflate.



Scheme 32 Assumed catalytic cycle of Mukaiyama aldol-type reactions of acetals using trimethylsilyl triflate as a catalyst.

Sakurai et al. reported the use of trimethylsilyl iodide as an effective catalyst for the *syn*-selective aldol-type reaction of acetals.[50] Interestingly, when the reaction was performed on α,β-unsaturated acetals of aldehydes, the nucleophilic addition of the silicon enolate proceeded chemoselectively on the acetal carbon. Other silicon Lewis acid systems, such as, $^{t}BuMe_2SiCl$-$InCl_3$[51] and $Me_3SiN(SO_2F)_2$[52] have also been reported as excellent catalysts for the Mukaiyama aldol reaction of acetals.

Mukaiyama et al. reported that triphenylmethyl (trityl) perchlorate could effectively promote the aldol-type reaction of acetals (Scheme 33).[53] The catalytic cycle of this reaction was achieved via regeneration of trityl perchlorate from trityl alkoxide and trimethylsilyl perchlorate intermediates. Furthermore, immobilization of the trityl catalyst was realized and successfully employed in not only batch system[54] but also in flow system[43b] to obtain the desired product in good conversion. They also found phosphonium salts could catalyze the aldol-type reaction.[55]



Scheme 33 Catalytic Mukaiyama aldol-type reactions of acetals using triphenylmethyl perchlorate.

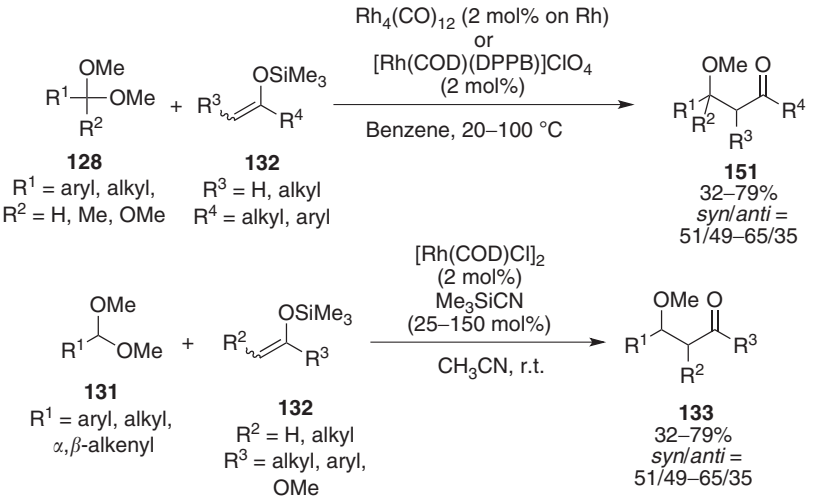
Protic acids were also successfully applied as catalysts for the aldol reactions of acetals. Strong Brønsted acids, such as triflic acid (TfOH), worked well as efficient catalysts. Strong solid acids, such as clay montmorillonite, were found to be a good heterogeneous catalyst for the Mukaiyama aldol reaction of acetals and could be removed easily from the reaction mixture by simple filtration.[56] Mesoporous silica catalysts also promoted the aldol-type reaction in high yields.[57]

Toru et al. investigated the use of electrochemically generated acid as catalysts for aldol-type reactions of acetals. The Mukaiyama reaction proceeded smoothly with the electrochemically generated acid derived from perchlorate salts such as $LiClO_4$, $^{n}Bu_4NClO_4$, and $Mg(ClO_4)_2$ in CH_2Cl_2 using platinum electrodes.[58]

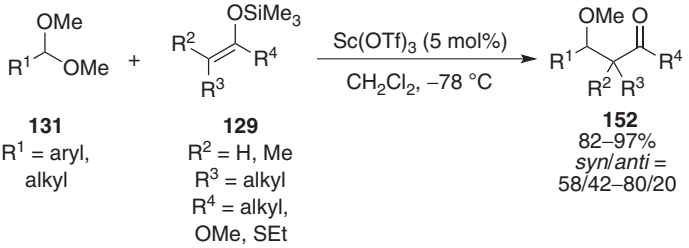
Transition metal compounds have also been well investigated and employed as catalysts in the aldol-type reaction of acetals. Matsuda reported rhodium complexes catalyzed the aldol-type reactions of acetals (Scheme 34). $Rh_4(CO)_{12}$ or [Rh(COD)(DPPB)]ClO_4 promoted the reaction in moderate-to-good yields. However, dealkoxylation of the aldol adducts was observed when the reaction reached high temperatures, [Rh(COD)(DPPB)]ClO_4 was used as a catalyst. Matsuda and coworkers proposed that formation of Rh enolates was plausible.[59] Mukaiyama et al. also reported a [Rh(COD)Cl]$_2$–Me_3SiCN system that could catalyze the nucleophilic addition of silicon enolates to a variety of electrophiles such as aldehydes, imines, and acetals. It was suggested that a positively charged trimethylsilyl group was generated by the coordination of the cyano group of Me_3SiCN to the rhodium metal.[60] Furthermore, bismuth chloride and metallic iodide system was also found to be effective.[61]

Metal triflates are effective and potentially reusable Lewis acid catalysts in organic synthesis. Among them, rare earth metal triflates have been found to be promising Lewis acid catalysts and have been employed in several organic transformations. Kobayashi et al. reported that a water-tolerant Lewis acid, scandium triflate ($Sc(OTf)_3$), was an excellent catalyst for the aldol-type reaction of acetals (Scheme 35).[62] Other lanthanide triflates, such as $Yb(OTf)_3$, $Eu(OTf)_3$, etc., were also found to be good catalysts for the Mukaiyama aldol reactions of acetals.[63] Following those reports, other Lewis acid catalysts, such as Bi compounds,[64] $Bu_2Sn(OTf)_2$,[65] $B(C_6F_5)_3$,[66] MgI_2,[67] and LPDE,[68] have been demonstrated to be viable catalysts for the Mukaiyama aldol reaction of acetals.

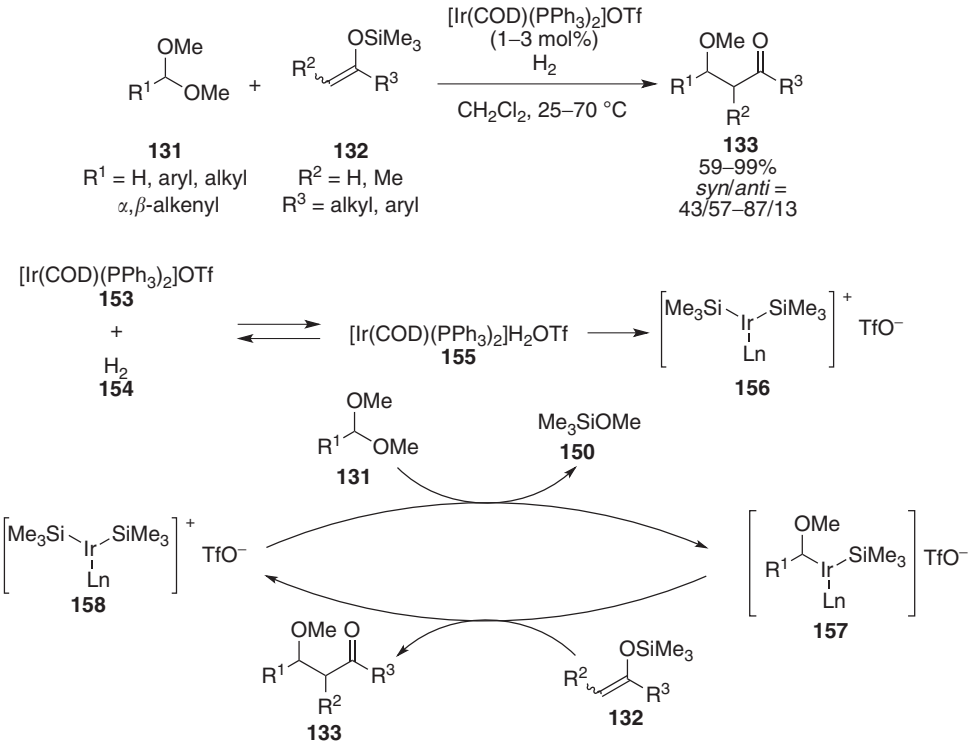
Matsuda et al. reported that Ir–Si species derived from a H_2-activated [Ir(COD)$(PPh_3)_2$]OTf complex catalyzed the aldol-type reaction of acetals (Scheme 36).[69] The proposed mechanism was postulated based on ^1H NMR evidence of a unique Me_3Si signal, assumed to be [Me_3Si–Ir–$SiMe_3$](Ligand)OTf complex **156**, that appeared when equal molar amounts of the silicon enolate and



Scheme 34 Catalytic Mukaiyama aldol-type reactions of acetals using rhodium catalysts.



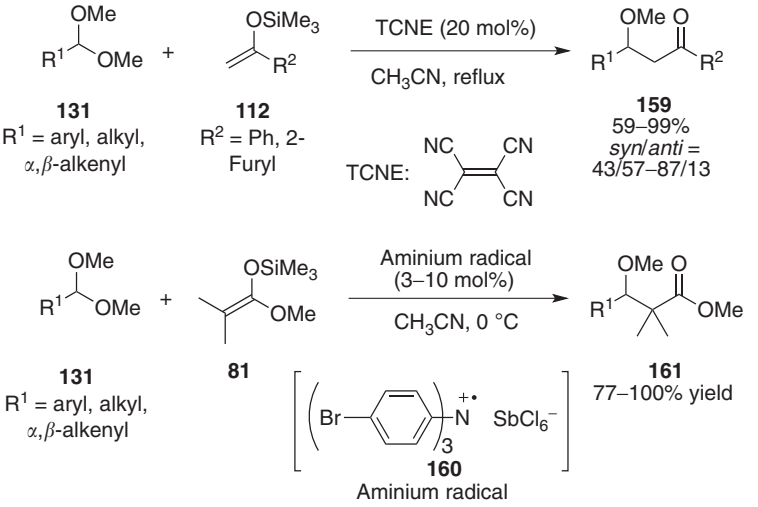
Scheme 35 Catalytic Mukaiyama aldol-type reactions of acetals using scandium triflate.



Scheme 36 Catalytic Mukaiyama aldol-type reactions of acetals using an iridium catalyst.

$[Ir(COD)(PPh_3)_2]OTf$ were exposed to H_2 gas. Matsuda assumed that **156** reacts rapidly with the acetal to form Me_3SiOMe and the active Ir–oxocarbenium ion complex undergoes an aldol-type reaction with the silicon enolate to form the desired addition product and regenerate active catalyst **156**.

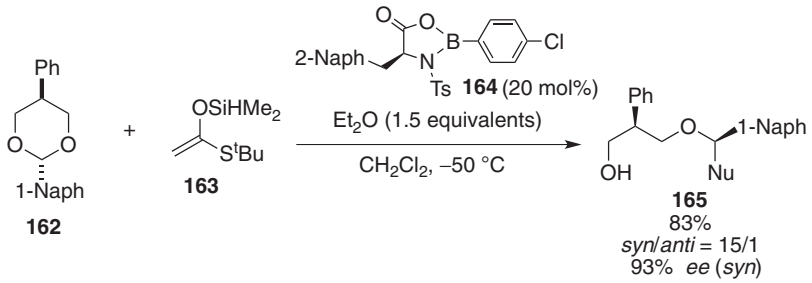
The activation of acetals can occur through a single electron transfer (SET) mechanism and several Mukaiyama aldol-type reactions have been reported (Scheme 37). Masaki and coworkers employed tetracyanoethylene (TCNE) to activate acetals, and obtained the desired adducts in good-to-high yield.[70] Kamata and coworkers reported the aldol-type reactions of acetals by utilizing tris(*p*-bromophenyl)aminium salt **160**[71] or 2,4,6-triarylpyrylium salt[72] as initiators. They proposed that the SET process occurs on the electron-rich silicon enolate to generate a silyl cation, which then activates the acetal substrates to form the reactive oxocarbenium ion intermediate.



Scheme 37 Catalytic Mukaiyama aldol-type reactions of acetals in SET mechanism.

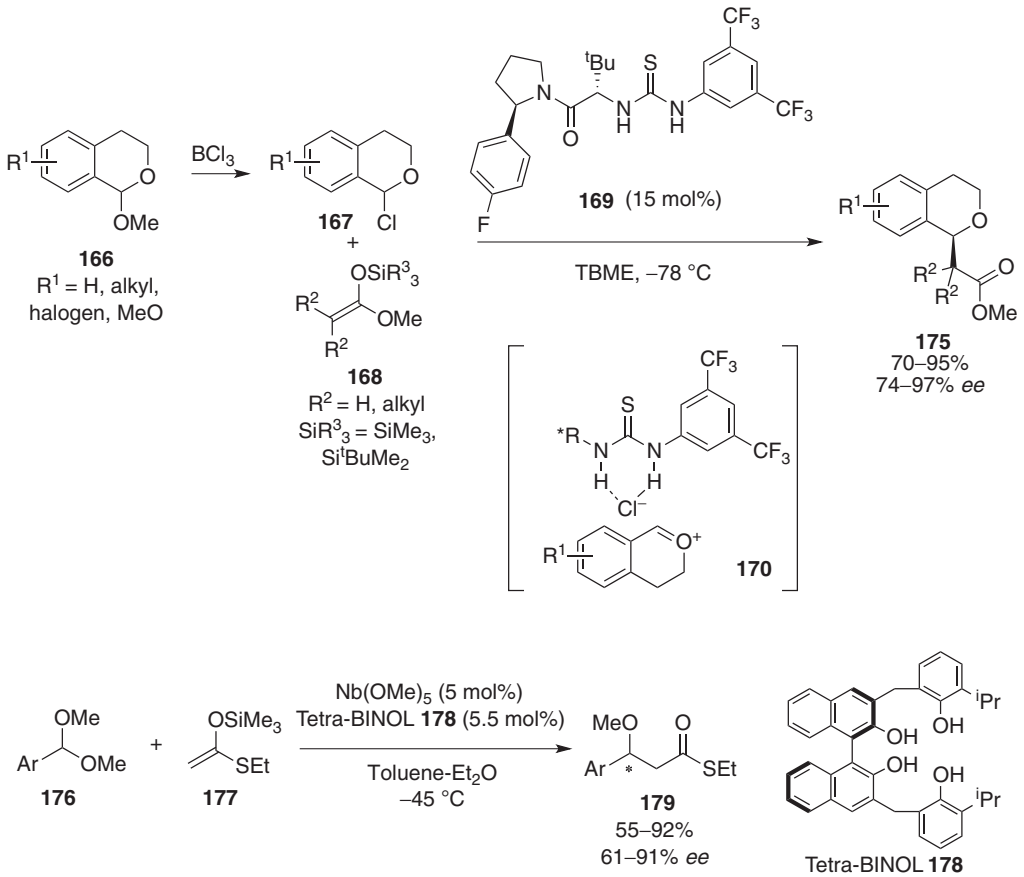
Catalytic asymmetric Mukaiyama aldol-type reactions of acetals using silicon enolates have been recognized to be a challenging endeavor since the distinction of the enantiofaces of the reactive oxocarbenium ion intermediate is normally difficult due to the lack of effective chelation sites on the acetal. Despite extensive research of asymmetric synthesis using chiral acetals,[73] very few successful examples of the Mukaiyama aldol-type reaction of acetals using a chiral catalyst have been reported.

Harada and coworkers reported a successful asymmetric desymmetrization of cyclic meso acetals with silicon enolates in the presence of a chiral boron Lewis acid catalyst **164** (Scheme 38).[74] The initial diastereoselective complexation of the chiral boron Lewis acid with the acetal oxygen, followed by the nucleophilic addition of the silicon enolate to one enantioface of the oxocarbenium ion–boron complex, led to the desired ring-cleavage products in excellent diastero- and enantioselectivity.



Scheme 38 Catalytic asymmetric Mukaiyama aldol-type reactions of acetals using chiral boron Lewis acid.

Jacobsen and coworkers reported an enantioselective Mukaiyama aldol-type reaction of cyclic oxocarbenium ions with silicon enolates by utilizing a chiral thiourea organocatalyst (Scheme 39).[75] By exploiting the chloride-binding ability of thioureas, Jacobsen and coworkers activated 1-methoxychroman using a chiral thiourea catalyst **169** after transformation to 1-chloro-chroman. The aldol-type reaction to the oxocarbenium ion proceeded in good-to-high enantioselectivities at −78 °C under stereocontrol by a chiral thiourea–Cl^- complex **170** as a chiral counteranion. Kobayashi et al. also reported chiral niobium-catalyzed asymmetric Mukaiyama aldol-type reactions of symmetric acyclic acetals.[48] First, they succeeded in the preparation of an optically active acetal, which reacted with a silyl enol ether smoothly to afford the desired adducts in racemic forms.



Scheme 39 Catalytic Mukaiyama aldol-type reactions of acetals using chiral catalysts.

By comparison of the *ee*'s of the products with the *ee*'s of the recovered acetals, they concluded that the aldol-type reactions proceeded not via direct displacement (S_N2) or contact ion pairs (intimate ion pair) (S_N1) but by a free oxocarbenium ion (S_N1) mechanism. Next, a study to achieve asymmetric catalysis of the acetal substitution reactions was conducted. It was found that asymmetric aldol-type reactions of acetals with silyl enol ethers proceeded smoothly to afford the corresponding aldol-type adducts in good yields with high enantioselectivities. The niobium catalyst prepared from Tetra-BINOL **178** activates one of the acetal methoxy group to form oxocarbenium ion, and the niobium–methoxide complex should work as a chiral counteranion for the ion. The aldol-type reactions proceeded in high enantioselectivities in Et_2O.

2.09.3.2 Lewis Base-Mediated Aldol Reactions

As seen in Section 2.09.3.1, the Mukaiyama aldol reaction is principally catalyzed or promoted under acidic conditions. However, due to the ability of silicon atom to adopt higher coordination states, it is possible to catalyze or promote the Mukaiyama aldol reaction under basic conditions (Figure 3).[76] As the silicon center forms an adduct with a Lewis base, redistribution of the electron

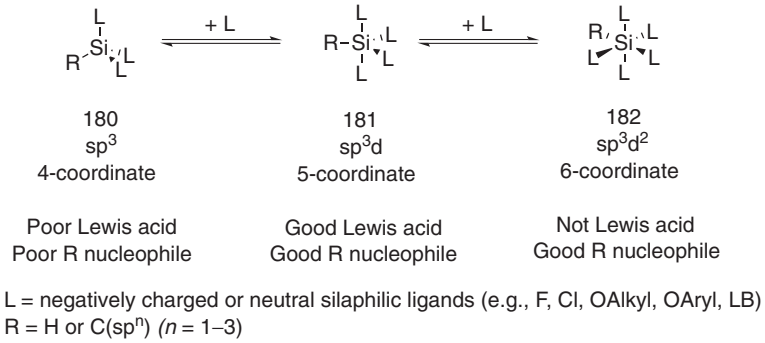


Figure 3 Silicon ability to hypervalency.

density occurs such that polarization of the adjacent bonds occurs and increases the electron density at the peripheral atoms as the electron density at silicon decreases. Thus, the Lewis acidity at the silicon center increases and the migration ability of the R group (R=H, C(sp^n) (n=1–3)) increases. Based on this strategy, Lewis bases were introduced to mediate the Mukaiyama aldol reaction.

2.09.3.2.1 Achiral Lewis base-mediated reaction

2.09.3.2.1.1 Anionic Lewis base

During these past decades, Lewis bases, defined as electron-pair donors, have attracted a great deal of interest in organic chemistry.[77] In 1977, Heathcock and coworkers reported the application of fluoride ions to promote aldol reactions.[78] The use of stoichiometric amounts of a fluoride source allowed for highly *anti*-diastereoselective reactions between ketone-derived silicon enolates and aldehydes. In this case, in which no cation exists to accept the two partially negative oxygen as ligands (chelate model, Figure 4(1)), the authors propose that a transition state such as oxygen must be directed in generally opposite directions to minimize electrostatic repulsion (i.e., the oxygen must be directed in generally opposite directions, Figure 4(2)). Consequently, the enolate attacks the other face of the carbonyl group.

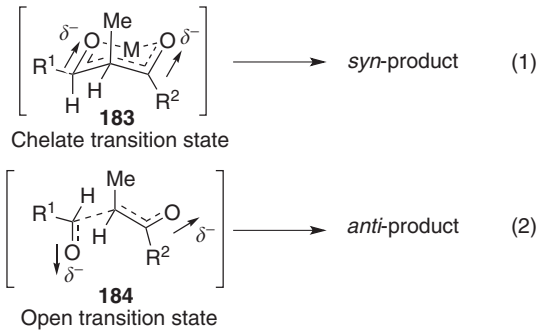
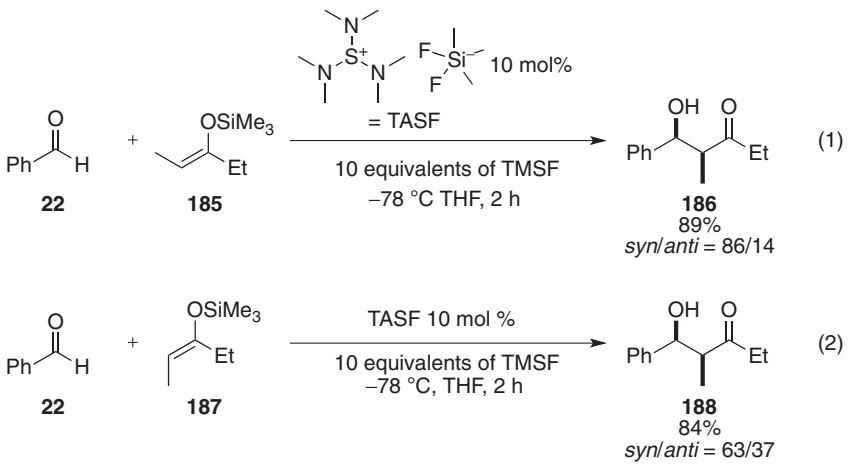


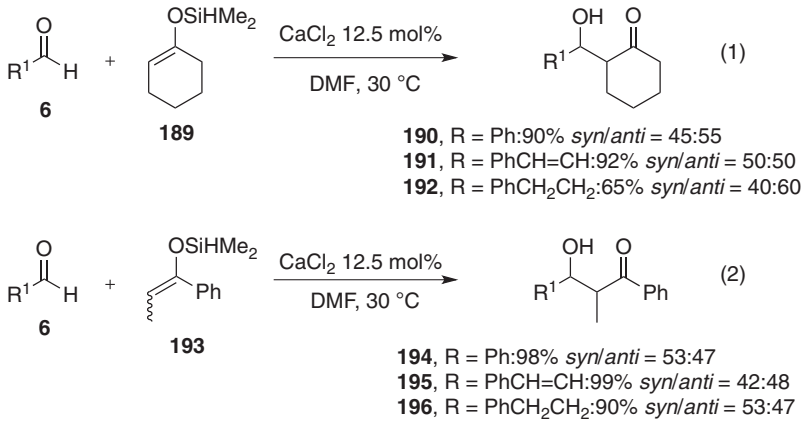
Figure 4 Chelate and open transition state.

In a collaborative effort between the Kuwajima and Noyori research groups, they found that only substoichiometric amounts of soluble fluoride sources were required to provide rapid and high-yielding Mukaiyama aldol reactions.[79] In most cases, the reaction is kinetically controlled and regardless of the enolate configuration, the major products were obtained with *syn*-stereochemistry (Scheme 40). In contrast to normal aldol reactions with Lewis acid-coordinated enolates, the authors suggested that the reaction proceeded via an acyclic, extended transition state.



Scheme 40 Fluoride ion-catalyzed aldol reactions of enoxysilanes.

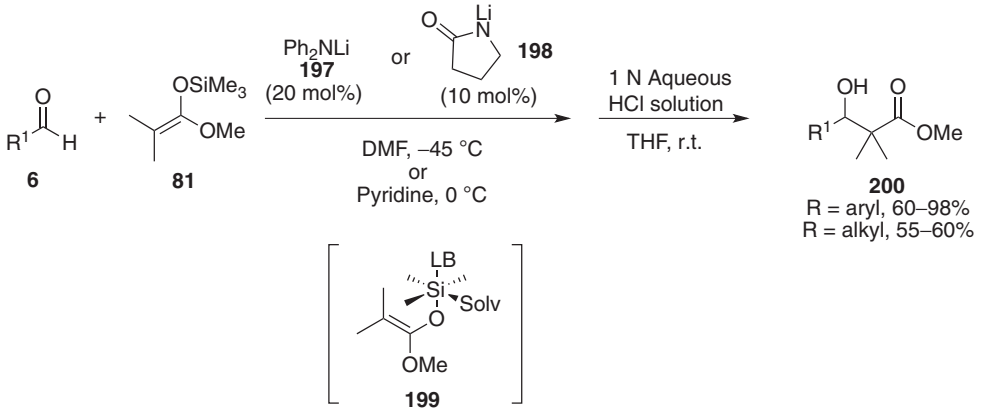
Hosomi and coworkers reported a similar reaction in which $CaCl_2$ works as a Lewis base to promote the aldol reaction of DMS enolates such as **189** or **193** with benzaldehyde, cinnamaldehyde, and hydrocinnamaldehyde even in the presence of water (Scheme 41).[80] Hosomi also examined the Mukaiyama aldol reaction using other alkali earth and alkali-metal salts (e.g., $CaCl_2$ 95%, LiCl 98%, nBu$_4$NCl 67%, $CaBr_2$ 54%, $MgBr_2$ 54%, LiBr 52%, nBu$_4$NBr 67%, CaI_2 32%, LiI 34%, NaI 35%, KI 34%, and nBu$_4$I 40%) and



Scheme 41 Calcium chloride-catalyzed aldol reactions of DMS enol ethers.

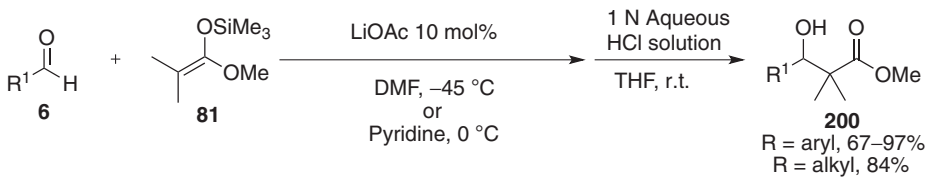
found these halide salts to provide the desired Mukaiyama aldol product in modest-to-good yields. On the basis of the weak Lewis acidity of $CaCl_2$ and the catalytic ability of tetrabutylammonium salts, Hosomi concluded that there was no contribution from the electrophilic activation of the aldehyde and the chloride ion worked as a Lewis base to activate the silicon enolates.

In 2002, Mukaiyama et al. reported both lithium diphenylamide (20 mol%) and lithium 2-pyrrolidinone (5 mol%) acted as efficient Lewis bases to promote the addition of silicon enolate **81** to aldehydes (Scheme 42).[81] The reactions proceeded in high yields either in *N,N*-dimethylformamide (DMF) or pyridine with a wide range of aromatic aldehydes and with lower yields when aliphatic aldehydes were utilized as substrates. In order to explain the strong solvent dependency, Mukaiyama proposed a hexacoordinate adduct **199,** composed of a silyl ketene acetal bound by the anionic Lewis base and a solvent molecule, as the reactive intermediate.



Scheme 42 Lithium amide-catalyzed aldol reactions of silyl ketene acetals.

Mukaiyama and coworkers also demonstrated that lithium acetate, a mild and readily available Lewis base, can be used to catalyze aldol-type reactions with a range of silicon enolates and aromatic aldehydes (Scheme 43).[82] Various metal carboxylates, such as lithium pivalate (^{t}BuCOOLi) and lithium benzoate (PhCOOLi), were found to be effective catalysts for this transformation. Unfortunately, the reactions of propanoate silyl ketene acetals were found to unselective, and Mukaiyama rationalized the diasteroconvergent pathway through an open transition structure involving an enolate as the nucleophile.

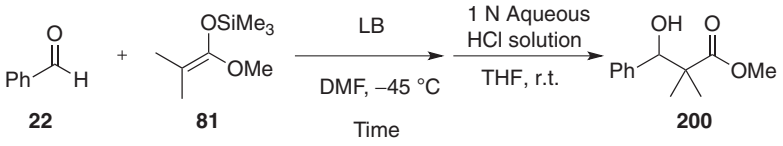


Scheme 43 Lithium acetate-catalyzed aldol reactions of silyl ketene acetals.

Thanks to the advantages of Lewis base catalyst in aldol reactions – (1) silylation of the formed lithium aldolate takes place rapidly to form *O*-silyl ether that is not activated by a lithium cation; (2) when aromatic aldehyde was employed, the reactivities between starting aldehydes and the formed aliphatic aldehydes are differentiated since Lewis base-catalyzed reaction occasionally exhibits the higher reactivity toward aromatic aldehyde than that of aliphatic one; and (3) formation of α,β-unsaturated carbonyl compounds by successive dehydration of the aldol adducts is prevented when weak Lewis base catalysts such as AcOLi are used – the substrate scope of this reaction was expended to trimethylsilyl enolates generated from several aldehydes. The reaction proceeded smoothly with a wide scope of aromatic aldehydes in dry or water-containing DMF in the presence of a catalytic amount of a Lewis base. Successive reduction of the produced aldehydes with sodium borohydride ($NaBH_4$) afforded the corresponding 1,3-diols in good-to-high yields in one pot.

Based on their previous reports, Mukaiyama investigated the possibility of using alkali-metal alkoxides and phenoxides as Lewis bases to mediate the aldol-type reaction (Table 1). The aldol reaction between benzaldehyde **22** and trimethylsilyl enolate **81** was studied by using a wide range of alkoxides (e.g., $PhCH_2OLi$, MeONa, EtONa, ^tBuOK, and PhONa) as catalysts. After extensive screening, lithium benzyloxide was determined to be the best catalyst and demonstrated a wide substrate scope for both aromatic and aliphatic aldehydes.

Table 1 Alkoxide anion-mediated aldol reaction

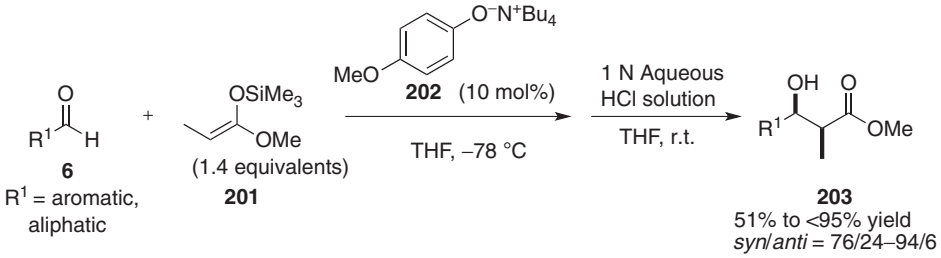


22 **81** **200**

Entry	*LB (x mol%)*	*Time (h)*	*Yield (%)*[a,b]
1	$PhCH_2OH$ (10)	3	98
2	$PhCH_2OH$ (5)	5	97
3	$PhCH_2OH$ (3)	5	97
4	MeONa (9)	5	77 (19)
5	EtONa (9)	4	75 (16)
6	*t*-BuOK (5)	2	96 (4)
7	*t*-BuOK (5)	5	81 (13)
8	PhOLi (5)	2	97
9	$PhONBu_4$ (5)	2	77 (13)

[a]Yield was determined by ^{1}H-NMR using 1,1,2,2-tetrachloroethane as internal standard.
[b]In parentheses, starting material recovered.

Similarly, Mukaiyama and coworkers reported catalytic amounts of tetraalkylammonium phenoxides as activators to promote *syn*-diastereoselective additions of propiophenone silyl enol ether and propanoate-derived thioketene acetals (Scheme 44).[83] Aromatic aldehydes possessing electron-donating or -withdrawing group allowed the aldol-type reaction to proceed smoothly to provide the corresponding aldol products in high yields with good *syn*-selectivities. This reaction was also applicable to an aldehyde containing a basic function. Mukaiyama observed that the yields and the diastereoselectivities (*syn*-selectivity) were irrespective of the geometry of the silicon enolates (*Z* or *E*) and concluded that the reactions proceeded via acyclic transition states.



6
R^1 = aromatic, aliphatic

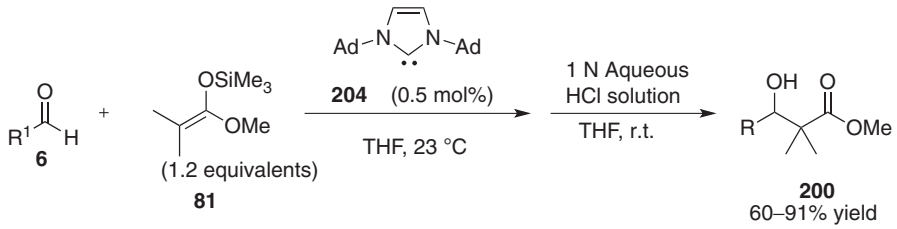
(1.4 equivalents)
201

203
51% to <95% yield
syn/*anti* = 76/24–94/6

Scheme 44 Tetrabutylammonium phenoxides-catalyzed *syn*-selective aldol reaction of various aldehydes.

The use of *N*-heterocyclic carbenes (NHCs) as organocatalysts has attracted considerable attention in recent years. In 2007, Song et al. demonstrated that NHCs could serve as highly efficient organocatalysts for the Mukaiyama aldol reactions.[84] In the presence of only 0.5 mol% of an adamantyl-substituted NHC **204**, a wide range of aldehydes underwent Mukaiyama aldol

reactions in THF with trimethylsilyl ketene acetal **81** at 23 °C to afford the aldol adducts in good yields (Scheme 45). Although the diastereoselectivity was not discussed, Song proposed that the NHC-catalyzed aldol-type additions proceed through a possible pentavalent silicon complex that was formed by the initial attack of NHC on the Si atom of the silicon enolate.



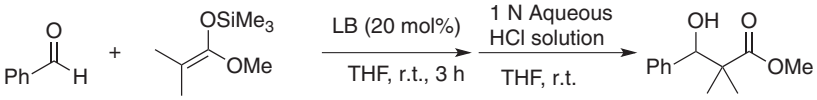
Scheme 45 Mukaiyama aldol reactions with silyl ketene acetal catalyzed by NHC.

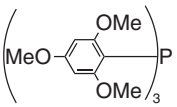
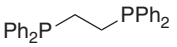
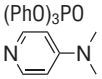
2.09.3.2.1.2 Neutral Lewis base

Based on a previous study reported by Bassindale and Stout,[85] in which the interaction between neutral Lewis bases and electrophilic trialkylsilyl species (triflates, perchlorates, and halides) has been quantified using the changes in the ^{29}Si NMR chemical shifts and dissociation equilibrium constants (order of relative Lewis basicity was established: *N*-methylimidazole > DMAP > HMPA > dimethylimidazlone > *N*-methylpyridone > pyridine-*N*-oxide > triphenylphosphane oxide > DMPU > DMF > pyridine > triethyamine), the use of neutral Lewis bases has emerged as viable catalysts for the Mukaiyama aldol reaction.

In 2000, Yamamoto and coworkers reported that phosphines could catalyze the aldol-type reaction between ketene silyl acetals and aldehydes.[86] Several phosphines were examined, and tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) was found to be the most effective catalyst (Table 2). Yamamoto assumed that the highly nucleophilic and basic properties of TTMPP endowed the phosphine to act as an excellent catalyst for the Mukaiyama aldol reaction, and good results were obtained for both aromatic and aliphatic aldehydes. Other neutral Lewis bases such as phosphine oxides, phosphates, HMPA, and amines were examined, but only low chemical yields were observed in all cases.

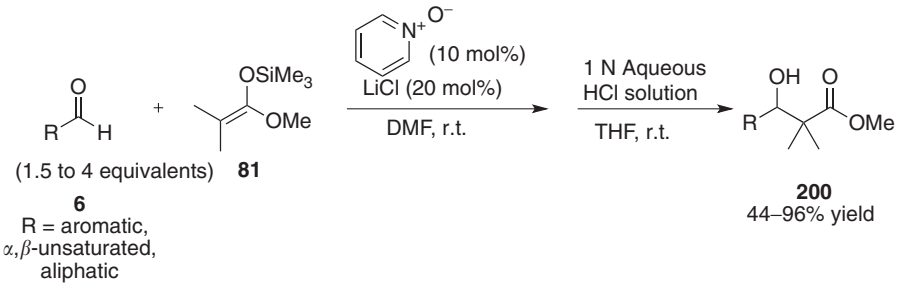
Table 2 Phosphine-catalyzed aldol reaction



Entry	*LB*	*Yield (%)*
1	Ph_3P	70
2	Cy_3P	59
3	*n*-Bu_3P	34
4	*t*-Bu_3P	34
5	 (TTMPP)	89
6		32
7	$(Me_2N)_3PO$	26
8	PPh_3PO	8
9	Cy_3PO	10
10	$(PhO)_3PO$	–
11		27

In 2005, Hagiwara and coworkers described a similar study using catalytic amounts of pyridine-*N*-oxide as Lewis base and LiCl as a cocatalyst for the Mukaiyama aldol reaction of silicon enolates and a variety of aromatic, olefinic, and aliphatic aldehydes

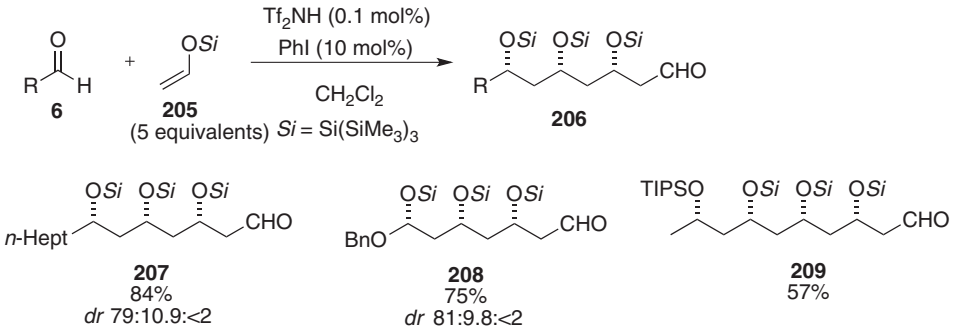
(Scheme 46).[87] Similar to previous reports with Lewis base catalysts, the addition of propanoate-derived silyl ketene acetals was not diastereoselective, and this suggested that the reaction proceeds through an open transition state-structure.



Scheme 46 Pyridine-*N*-oxide-catalyzed aldol reactions.

Hagiwara and coworkers also described the catalytic activity of *N*-methylimidazole with LiCl as a cocatalyst for the aldol-type process with good yield and good substrate generality.[88] It is noteworthy that the reaction was accelerated by microwave irradiation and under these reaction conditions, silicon enolates derived from acetophenone led to aldol products with diverse aldehydes.

In 2010, Albert and Yamamoto reported on the utility of Lewis bases in triple-Mukaiyama aldol cascade reactions for the preparation of 3,5,7-trisilyloxy aldehydes with high diastereoselectivities from a diverse set of simple aldehydes (Scheme 47).[89] This reaction was optimized using iodobenzene as an additive and dichloromethane as the solvent in the presence of catalytic amounts of Tf_2NH. Yamamoto proposed that iodobenzene activates the *in situ*-generated $(Me_3Si)_3SiNTf_2$ through the formation of a Lewis acid–base pair. Yamamoto also examined the effect of modifying the steric and electronic environments of iodobenzene and found that somewhat sterically crowded aryl iodides had little effect on the synthesis of triple-aldol product, whereas very bulky aryl iodides gave diminished yields. Based on these results, better Lewis basic cocatalysts were designed and smaller, yet electronically similar 1-iodoalkynes were found to be superior additives than aromatic iodides.



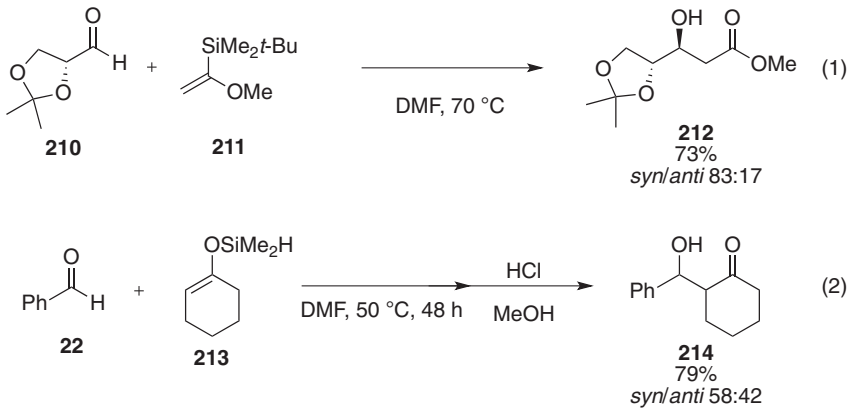
Scheme 47 Triple-aldol reactions catalyzed by triflic imide and iodobenzene.

Kita et al. reported that DMF is able to interact with the silicon atom and act as a solvent and promoter for the addition of both acetate-derived and isobutyrate-derived silicon enolates to isopropylidene glyceraldehyde **210** (Scheme 48, equation 1).[90] Subsequently, Hosomi and coworkers also investigated the 'noncatalyzed' aldol addition of enoxydimethylsilanes in DMF at 50 °C. These reactions gave good yields for aromatic, olefinic, and aliphatic aldehydes (24–79%), but no diastereoselectivity was observed in all cases (Scheme 48, equation 2).[91]

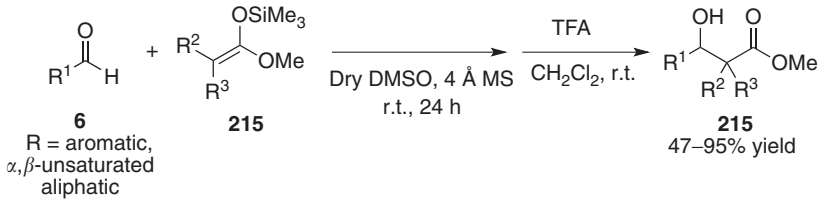
Finally, Génisson and Gorrichon studied the spontaneous 'noncatalyzed' aldol addition of silyl ketene acetals at room temperature in different solvents such as *N*,*N*-dimethylacetamide, DMF, or dimethylsulfoxide (DMSO) was chosen for its superior ability to promote the reaction in the presence of 4 Å molecular sieves (Scheme 49).[92] However, only aromatic and olefinic aldehydes work well and again the base-mediated Mukaiyama aldol reaction proceeds with no diastereoselectivity when propanoate-derived silyl ketene acetals were utilized as a nucleophile.

2.09.3.2.2 Chiral Lewis base-catalyzed reactions

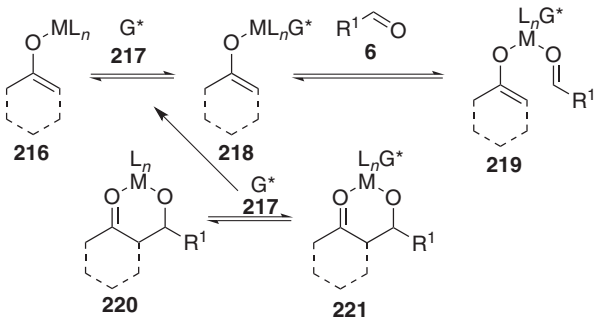
A major breakthrough in the field of Lewis base-catalyzed Mukaiyama aldol reactions was made by Denmark et al. in 1996, where he describes the first enantioselective aldol reaction catalyzed by chiral Lewis bases (Scheme 50).[93] Denmark proposed that a metal enolate moiety capable of expanding its valence by forming a complex with one or two chiral Lewis base G* is essential to



Scheme 48 DMF-mediated aldol reactions.



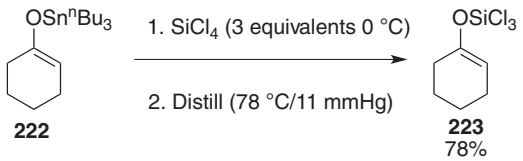
Scheme 49 DMSO-mediated aldol reactions.



Scheme 50 General concept of chiral Lewis base-catalyzed aldol reaction.

have a good catalytic enantioselective process. Denmark found that trichlorosilyl enolates are excellent substrates for the asymmetric Mukaiyama aldol reaction and designed chiral phosphoramides as potential chiral Lewis base catalysts.

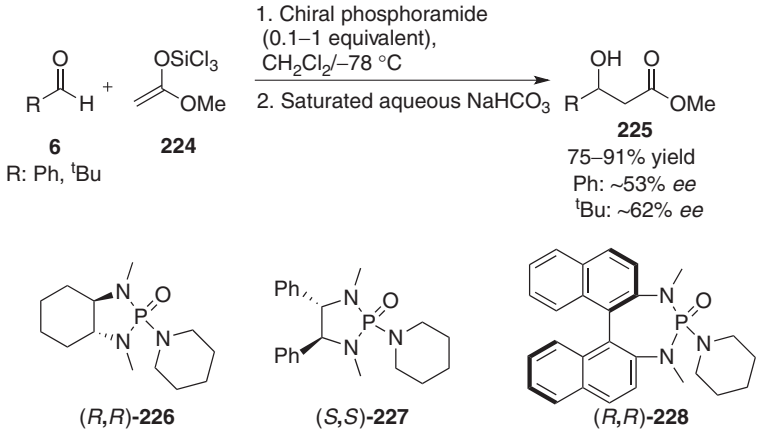
These highly reactive silyl ketene acetals were prepared by $SiCl_4$ metathesis of the stannyl ketones by a procedure reported by Lutsenko et al (Scheme 51).[94]



Scheme 51 Preparation method of trichlorosilyl enolates.

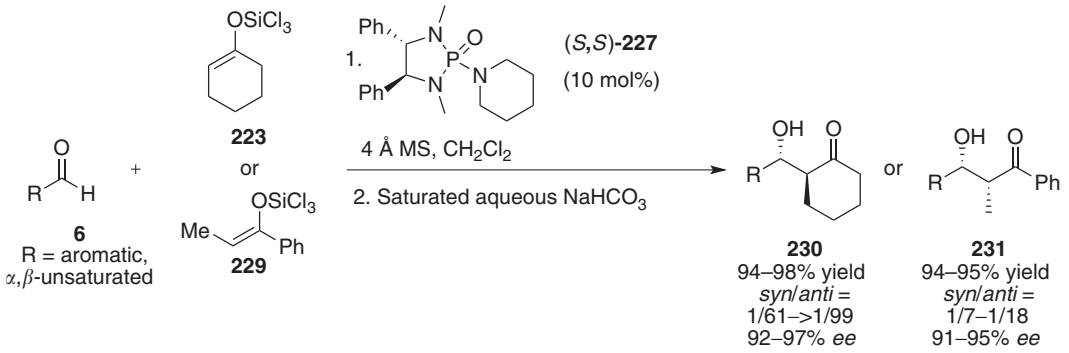
In Denmark's initial study, the methyl acetate-derived trichlorosilyl ketene acetal **224** was shown to react rapidly with aldehydes to lead to the aldol products at −80 °C in the presence of catalytic amounts of hexamethylphosphoric triamide (HMPA).

Based on these observations, new chiral phosphoramides were developed (**226** to **228**) as Lewis base catalysts for the asymmetric Mukaiyama aldol reaction (Scheme 52). The initial results with benzaldehyde were disappointing in terms of enantioselectivities (<40% *ee*) obtained. Control studies using 1.0 equivalent of **227** improved the enantioselectivity only to 53% *ee* and this suggested that the background reaction was operational even at −80 °C. The slightly higher *ee*'s obtained with the more bulky pivalaldehyde also supported this hypothesis. Interestingly, when the reaction conditions were applied to the cyclic enoxychlorosilane **223**, the chiral phosphoramide **227** promoted aldol addition with benzaldehyde and (*E*)-cinnamaldehyde was significantly improved, and the corresponding *anti*-aldol products were obtained in excellent diastereo- (65–99/1) and very good enantioselectivities (88–93% *ee*).



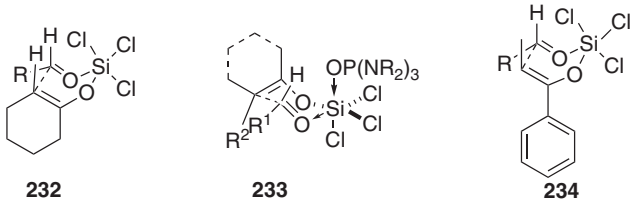
Scheme 52 Catalytic asymmetric aldol reactions.

Encouraged by these results, Denmark et al. continued to investigate further the use of chiral phosphoramides as Lewis bases to promote Mukaiyama aldol reaction.[95] By utilizing less-reactive ketone-derived silicon enolates **223** and **229**, Denmark was able to achieve highly enantioselective Mukaiyama aldol reactions with only catalytic amounts of chiral phosphoramide **227** (Scheme 53).



Scheme 53 Chiral phosphoramide-catalyzed enantioselective aldol reactions.

In order to explain the *syn*- and *anti*-selectivities from (*Z*) or (*E*)-enolate, Denmark proposed some potential transition states (Scheme 54). In the absence of external promoters (i.e., Lewis base), (*E*)-enolate gave the aldol adducts with high yield and *syn*-diastereoselectivity. The production of this *syn*-stereoisomer from an (*E*)-enolate through a closed transition structure implicates a

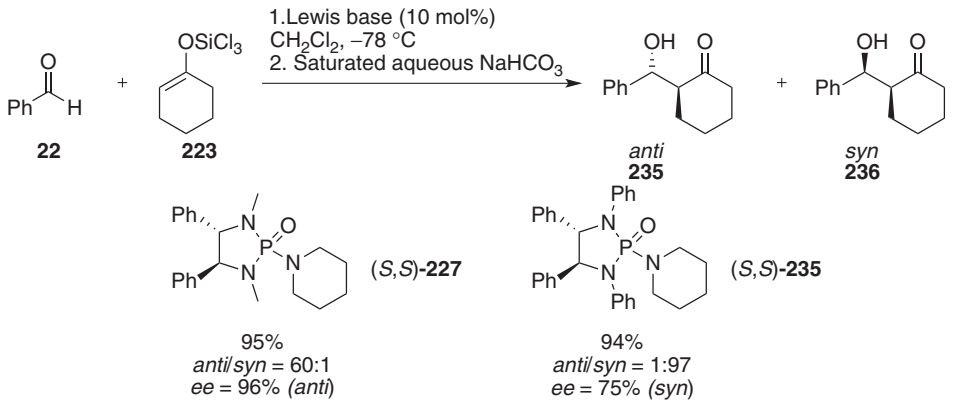


Scheme 54 Transition states.

boat-like arrangement such as **232**. The dramatic reversal in diastereoselectivity (i.e., *anti*-aldol product) observed in the reaction promoted by chiral phosphoramide **227** was rationalized by the change to a chair-like transition structure involving the putative hexacoordinate siliconate species **233**. In case of the (*Z*)-enolate, the poor *anti*-diastereoselectivity for the unpromoted reaction can be explained by an expected boat-like (closed transition) structure in pentacoordinate siliconates **234**, whereas the *syn*-selectivity of the Lewis base promoted was explained by the switch from boat- to chair-like transition structures.

Denmark et al. developed a convenient preparation method for trichlorosilyl enolates from trimethylsilyl enol ethers using mercury and expanded the scope of the chiral Lewis base-catalyzed Mukaiyama aldol reaction to five-, six-, and seven- membered cyclic silyl enols ethers.[95b] These enolates reacted spontaneously with aldehydes to provide the aldol adducts in excellent yields with high *syn*-diastereoselectivity via a boat-like transition structure organized around a trigonal bipyramidal, pentacoordinate siliconate. Additionally, Denmark found that more electron-rich aldehydes provided higher diastereoselectivity for the uncatalyzed aldol additions. Aldol-type additions of trichlorosilyl enolates catalyzed by the chiral phosphoramide **(*S*,*S*)-227** provided aldol adducts in excellent yield with high *anti*-diastereoselectivities and moderate-to-high enantioselectivities in the *anti*-manifold.

Additional investigations by Denmark et al. revealed a dramatic relationship between the observed *syn*-/*anti*-diastereoselectivities and the bulkiness (e.g., R=*N*-alky or *N*-aryl groups) and loadings of the Lewis base catalyst (**Scheme 55**).[95c,96] For example, with the phosphoramide **227** (R=Me), the *anti*-adduct was obtained in high *dr* and *ee* (60:1, 96%) and in the presence of phosphoramide **235** (R=Ph), the opposite, *syn*-adduct was obtained in high *dr* and *ee* (1:97, 75%).



Scheme 55 Diastereoselectivity dichotomy of phosphoramide.

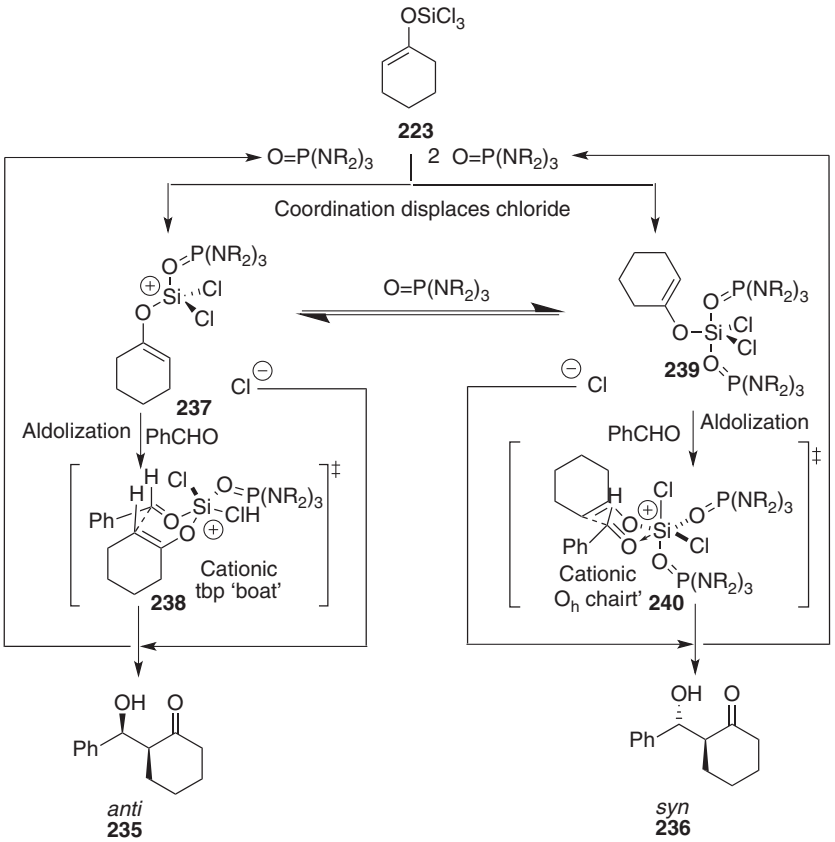
To rationalize the stereodivergence, Denmark proposed that the reaction proceeded through independent pathways to the two diastereoisomers, which responds differently to the catalyst size and concentration. Thus, Denmark postulated that a competition between one and two phosphoramide pathways occurs and the former operates at lower catalyst concentration (to the *syn*-isomer), whereas the latter is operational at higher catalyst concentrations (to the *anti*-isomer) (**Scheme 56**).

In support of this hypothesis, Denmark demonstrated that catalyst **227** exhibits a positive nonlinear effect, fitting well with Kagan's two-ligand model. In addition, the more-hindered catalyst **235** shows linear asymmetric induction, providing an indirect evidence that a single phosphoramide is present in the configuration-determining step. Moreover, Denmark believed that both reaction pathways most likely involved the ionization of chloride to afford cationic silicon intermediates that greatly enhanced the relative rates of both reactions when compared to the uncatalyzed pathway.

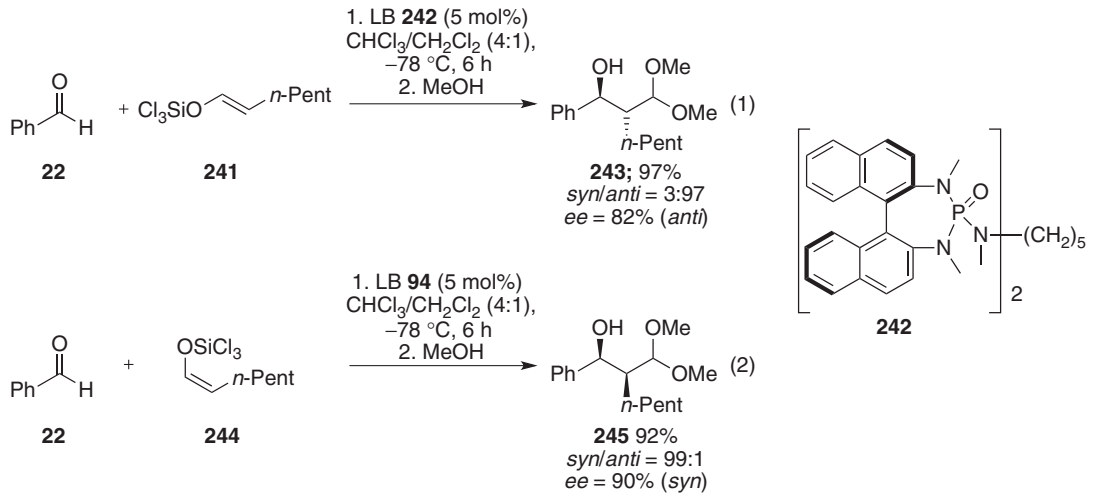
In 2001, Denmark et al. reported the first catalytic, diastereoselective, and enantioselective cross-aldol reactions of aldehydes (**Scheme 57**).[97] Geometrically defined trichlorosilyl enolates of aldehydes were shown to undergo high yielding, diastereoselective additions to a wide range of aldehydes albeit with variable levels of enantioselectivities (5–90% *ee*). For example, the reaction of **241** with **22** lead to the formation of *syn*-product **243**, with very good enantioselectivity, whereas **244** afforded *anti-product* **245** with somewhat attenuated enantioselectivity. It was noteworthy that the use of a dimeric chiral Lewis base such as **242** as the catalyst was critical for achieving useful enantioselectivities.

Inspired by the intensive work of Denmark, other groups have developed new chiral Lewis bases to promote the Mukaiyama aldol reaction. Nakajima et al. described chiral *N*,*N*′-dioxides and monodentate *N*-oxides as active Lewis bases for enantioselective aldol-type reactions of trichlorosilyl enol ethers (**Scheme 58**).[98] With cyclic (*E*)-silyl enol ethers, *N*,*N*′-dioxides such as **246** or **247** provided *anti*-adducts with moderate diastereoselectivities and enantioselectivities. Interestingly, monodentate *N*-oxides such as **248** or **249** predominantly provided the *syn*-adducts with moderate diastereoselectivities and enantioselectivities.

Along the same line, Nakajima and coworkers demonstrated that chiral phosphine oxides such as BINAP oxide can be used as Lewis base catalyst to promote the Mukaiyama aldol reaction with a similar reactivity to previous reports.[99] In 2004, Nakajima et al. reported an enantioselective aldol reaction of trimethoxysilyl enol ether catalyzed by lithium binaphtholate.[100] The use of trimethoxysilyl enol ether instead of trichlorosilyl enol ether represents a significant advancement since these silicon enolates are easy to prepare and are stable enough to survive aqueous workup and silica gel column chromatography.[101] Screening several



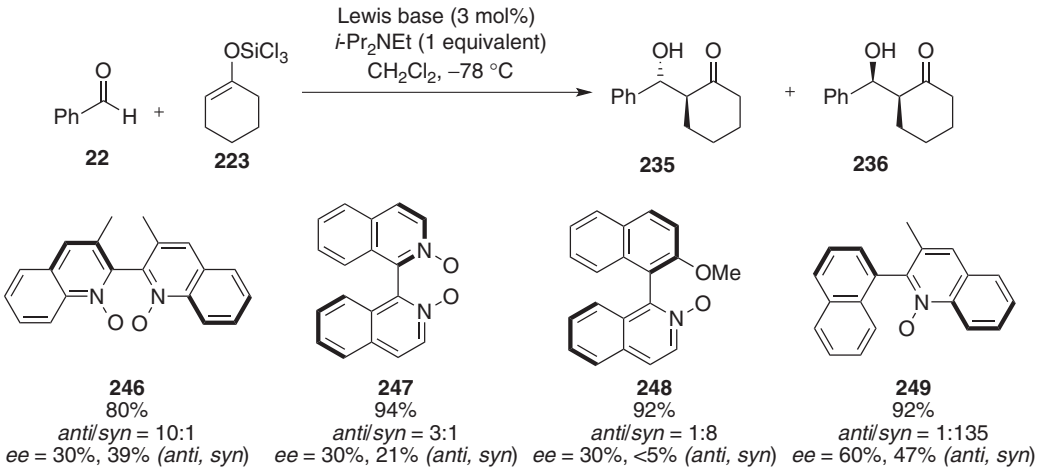
Scheme 56 Divergent mechanistic and stereochemical pathways.



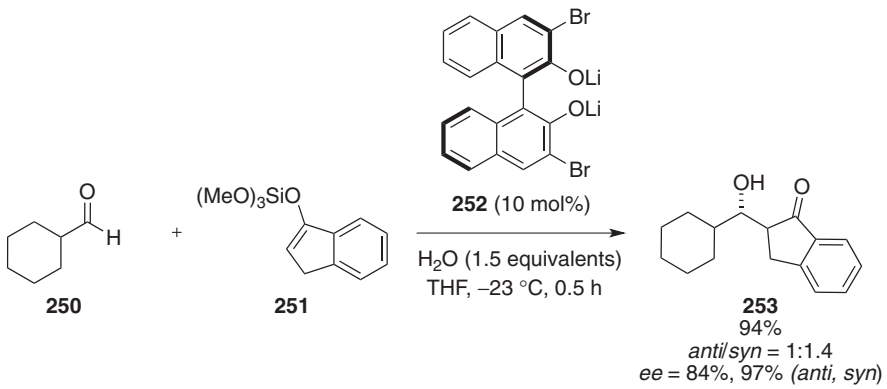
Scheme 57 Lewis base-catalyzed enantioselective cross-aldol reactions of aldehydes.

binaphthol derivatives revealed that the dilithium salt of 3,3′-dibromobinaphthol **252** was the best result and provided the aldol adducts with low diastereoselectivity (*anti*/*syn* = 1:1.4) but with good enantioselectivity (84%, 97%) (Scheme 59).

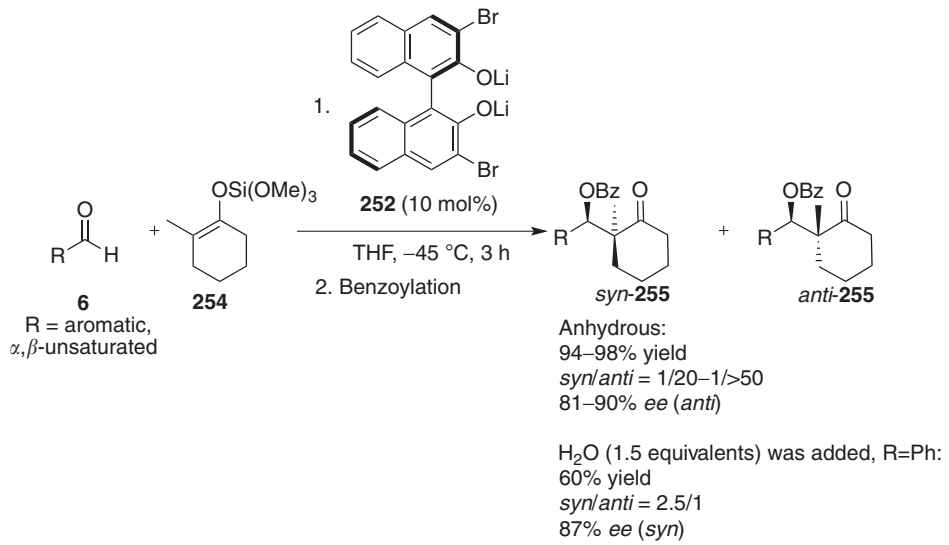
In 2012, Nakajima and coworkers applied the dilithiated catalyst **252** for the construction of quaternary chiral centers (Scheme 60).[102] The aldol-type reactions of trimethoxysilyl enol ethers **254** catalyzed by lithium binaphtholate **252** provided the quaternary carbon containing aldol adducts with high *anti*-selectivity and relatively good enantiomeric excess. The stereoselectivities were found to be greatly affected by the presence of water in the reaction mixture. For example, when cyclic trimethoxysilyl enol ether was used as a substrate, the Lewis base-catalyzed Mukaiyama aldol reaction proceeded to form the *anti*-adduct under



Scheme 58 *N,N'*-Dioxides- and monodentate *N*-oxides-promoted asymmetric aldol reaction.



Scheme 59 Lithium binaphtholate-catalyzed aldol reaction of trimethoxysilyl enol ether.



Scheme 60 Asymmetric quaternary center formation by Lewis base-catalyzed aldol reactions.

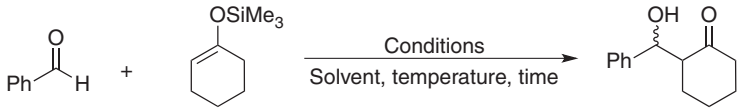
anhydrous conditions. However, the *syn*-adduct was preferentially obtained when water was used as an additive, though there were some exceptions to this phenomenon.

2.09.3.3 Mukaiyama Aldol Reactions in Water/Aqueous Media

2.09.3.3.1 Rate enhancement by water in Mukaiyama aldol reactions

Due to the compatibility and immiscibility between water molecules and many reagents or reactive species, organic solvents have been deemed to be essential reaction mediums for conducting organic reactions.[103] Whereas, some pioneer contributions have disclosed that utilizing water as a solvent may lead to unexpected and unpredicted results, such as reaction rate acceleration and enhancement of selectivity.[104] The potentialities of performing organic reactions in water have thus stimulated chemists' ingenuous curiosity. Among them, Lubineau demonstrated that the Mukaiyama aldol reaction in water was feasible and was accompanied by significant rate acceleration compared with that in organic solvents (Table 3).[105] The stereoselective preference of the product was reverse in comparison with conventional $TiCl_4$-catalyzed reaction.[106]

Table 3 Water-accelerated Mukaiyama aldol reaction

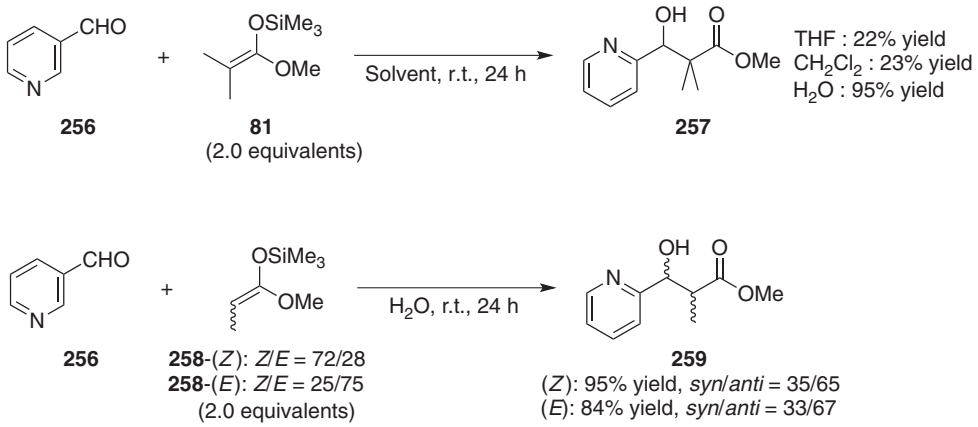


22 **254** (*X* equivalent) **255**

Entry	*X*	*Solvent*	*Temperature (°C)*	*Condtions*[a]	*Time*	*Yield*[b] (%)	*syn/anti*[b]
1[e]	1	CH_2Cl_2	20	$TiCl_4$	2 h	82	25/75
2[f]	1	CH_2Cl_2	60	10 kbar	9 days	90	75/25
3	2	H_2O	20	ST[c]	5 days	45 (43)[d]	74/26

[a]All reactions were carried out under atmospheric pressure at a concentration of 0.4 M of the limiting component.
[b]Determined by NMR analysis.
[c]Vigorous magnetic stirring or violent shaking.
[d]Isolated yield.
[e]Reference 2.
[f]Reference 109.

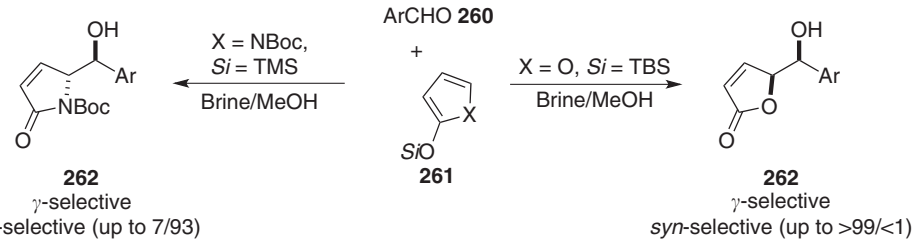
More conspicuous rate acceleration was observed in the Mukaiyama aldol reactions using ketene silyl acetals and the reaction of 2-pyridinecarboxyaldehyde in water was found to be approximately 4 times faster than that in organic solvents (Scheme 61).[107]



Scheme 61 Water-accelerated Mukaiyama aldol reactions of ketene silyl acetals.

It is noteworthy that the rate acceleration and the stereochemical outcome in pure water bears a striking resemblance to the reaction performed under high pressure. As shown in Table 3, curious coincidence between reactions in water and under high pressure has been observed ever since.[108] The pressure studies shown by Yamamoto et al.[109] indicated that the transition state for the *syn*-selective pathway is more compact. As is often the case for reactions that possess a negative molar volume of the transition

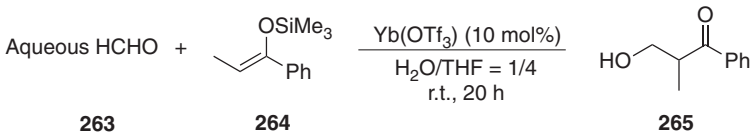
state, a key factor of the rate acceleration in water is the entropy-driven aggregation as a result of hydrophobic interactions. It has been considered that these attractive outcomes were ascribed to the unique properties of water, such as its high dielectric constant and high cohesive energy density (estimated 22 kbar) relative to conventional organic solvents.[110,111] Not only is water nontoxic, inexpensive, and environmentally benign, but it also offers many advantages such as simplicity of the reaction conditions and high efficiency in reactions that involve water-soluble substrates or reagents. The dual role of water as a reaction medium and promoter was also highlighted in vinylogous Mukaiyama aldol reactions of pyrrole and furan 2-silyloxy dienes in aqueous media.[112] *N*-Boc-2-(trimethylsilyloxy)pyrrole reacted with benzaldehyde to afford the desired product in water with almost complete γ-site selectivity and good diastereomeric ratio in favor of the *anti*-configured isomer, whereas the reaction failed in producing the product in organic solvents or under neat conditions. A remarkable switch of diastereoselectivity was observed when passing from pyrrole to furan (Scheme 62).



Scheme 62 Diastereoselective vinylogous Mukaiyama aldol reactions in aqueous media: pyrrole versus furan 2-silyloxy dienes.

2.09.3.3.2 Lewis acid/base catalysts that can function in aqueous media/water

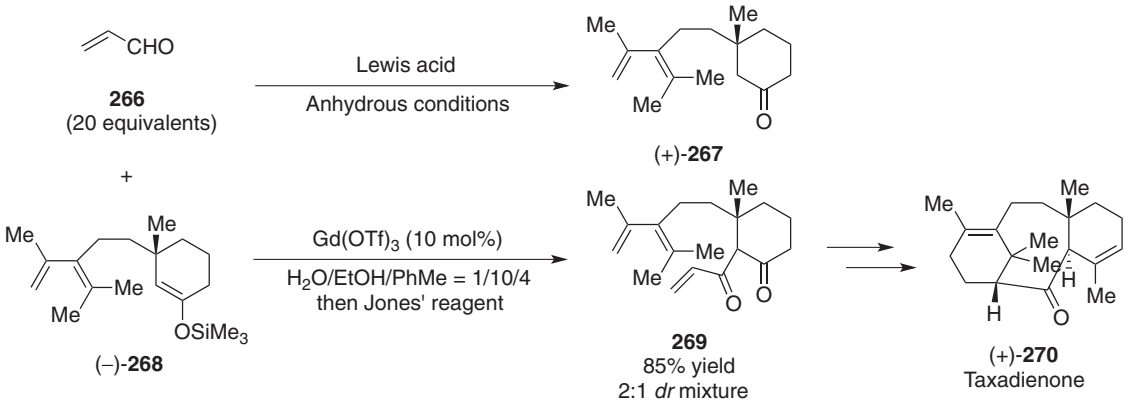
Without activation by Lewis acid catalyst, the Mukaiyama aldol reaction in water suffers from low yields and low reaction rates. Although traditional Lewis acid catalysis such as Al^{III}, Ti^{IV}, Sn^{IV}, etc., work well in organic solvents, these catalysts often decompose rapidly in the presence of water. In 1991, rare earth metal trifluoromethanesulfonates[113] such as $Sc(OTf)_3$, $Y(OTf)_3$, and $Ln(OTf)_3$ have been found to be water-compatible Lewis acid catalysts.[114] For example, $Yb(OTf)_3$ was revealed to exhibit superior performance in Mukaiyama aldol reactions of aqueous formaldehyde with various silicon enolates in water–THF (Scheme 63)[115] or water–ethanol–toluene[116] cosolvent systems.



Scheme 63 $Yb(OTf)_3$-catalyzed Mukaiyama aldol reaction in aqueous media.

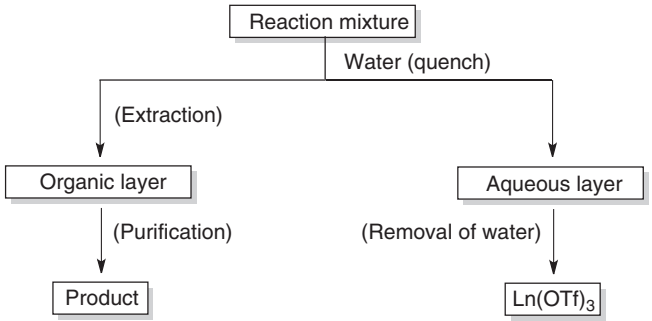
Likewise, a wide variety of aldehydes other than formaldehyde could be activated successfully by lanthanide triflates to give cross-aldol adducts; even water-soluble aldehydes such as acetaldehyde, acrolein, and chloroacetaldehyde or aldehydes possessing coordinating heteroatoms such as salicylaldehyde and 2-pyridinecarboxyaldehyde were reacted successfully.[117] The reactions carried out without water failed to give the corresponding aldols products, thus verifying the intriguing nature of water for these catalysts. (The aldols were obtained only in *c.* 10% yields.) Thus, water-compatible Lewis acid catalysis may offer many advantages over traditional $TiCl_4$-promoted reactions performed under strictly anhydrous conditions. For example, performing the Mukaiyama aldol reaction in aqueous media enabled the use of aqueous formaldehyde as C1 source. In general, hydroxymethylation reactions using formaldehyde as one of the most-valuable C1 electrophiles have received immense attention in organic synthesis.[118] Although user-unfriendly toxic formaldehyde gas and paraformaldehyde in organic solvents can be employed as a C1 electrophile, tedious and harmful procedures to generate the formaldehyde monomer from oligomers (e.g., paraformaldehyde and trioxane) are the main disadvantages. $Yb(OTf)_3$-catalyzed hydroxymethylation has been employed to construct complex molecules in the total synthesis of various natural compounds such as A-seco taxane[119] and (−)-sclerophytin A[120]. More practical attachment of hydroxymethyl function on the α-carbon adjacent to the carbonyl group has been enlisted in the total synthesis of biologically active compounds such as diazonamide A[121], (−)-strychnine[122], and acutifolone A[123], in which the initial formation of a silyl enol ether (TMSCl and Et_3N) served to create a latent nucleophile that was subsequently unleashed on $Yb(OTf)_3$ or $Sc(OTf)_3$-catalyzed Mukaiyama aldol reaction with aqueous formaldehyde. Such a two-step, one-pot procedure was developed by Toyota and coworkers for a δ-lactone synthesis protocol.[124] Baran and coworkers, when faced with a seriously facile desilylation in Mukaiyama aldolization for a total synthesis of taxanes, utilized the two-step procedure with surprising success.[125] The formation of undesired desilylated ketone was often the sole pathway when attempting Mukaiyama aldol reactions with conventional methodology. Gratifyingly, the desired reaction of the TMS enolate **268** with acrolein **266** proceeded smoothly with

$Gd(OTf)_3$ in water–ethanol–toluene system (1:10:4) to afford the corresponding keto-enone **269** as a 2:1 mixture of diastereomers after subsequent oxidization with Jones' reagent (Scheme 64). Their endeavor bears eloquent testimony to the overwhelming ascendancy of aqueous $Ln(OTf)_3$ system as a powerful catalyst for the Mukaiyama aldol reaction.



Scheme 64 Mukaiyama aldol reaction of **268** with acrolein.

Another striking feature of lanthanide triflates is the ease of recovery from the reaction mixture. Since these metal triflates are soluble in water, they can be recovered quantitatively from the aqueous layer and the product can be obtained through simple extraction from the organic layer (Scheme 65).

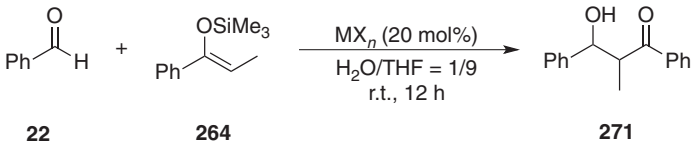


Scheme 65 Recovery of the catalyst.

The emergence of water-compatible Lewis acid catalysts has definitely broken down the wall of traditional prejudice that water is a detrimental contaminant in organic synthesis, and also offered industrially beneficial methodologies which facilitate recovery and reuse of these catalysts. Extensive research has led to expanding the availability of water-compatible Lewis acid catalysts. As a model reaction in Mukaiyama aldol addition of benzaldehyde **22** with propiophenone-derived silicon enolate **264**, group 1–15 metal chlorides, perchlorates, and triflates were screened in a water–THF cosolvent system (Table 4).[126]

With the exception of rare earth metal cations, Fe^{II}, Cu^{II}, Zn^{II}, Cd^{II}, and Pb^{II} were disclosed to function as efficient and promising Lewis acids in an aqueous medium, and this implied an establishment of the criteria on the catalytic activity of the metal cations. Superior catalytic activity was observed in the presence of metal cations surrounded by bold squares in Table 4. Given the correlation between metal cations and the catalytic activity, hydrolysis constants (K_h) and exchange rate constants for substitution of inner-sphere water ligands (water exchange rate constants (WERC)) were suitable factors for estimating the catalytic activity of Lewis acids.[127] These active metal compounds were found to have pK_h values in the range from approximately 4 (4.3 for Sc^{III}) to 10 (10.08 for Cd^{II}) and WERC values greater than $3.2 \times 10^6\ M^{-1}\ s^{-1}$. Cations with large pK_h values do not generally undergo efficient hydrolysis. In the case of pK_h values being less than 4, cations are readily hydrolyzed to produce protons in sufficient number to cause rapid decomposition of the silicon enolate. However, when the pK_h values were higher than 10, the Lewis acidities of the cations are too low to catalyze the aldol reaction. In order to act as an efficient catalyst in water, large WERC values may be necessary to have sufficiently fast exchange between the water molecules coordinated to the metal and the aldehyde substrate. 'Borderline' species such as Mn^{II}, Ag^{I}, and In^{III}, whose pK_h and WERC values are close to the criteria limits, provides the aldol adducts in moderate yields. Whereas the precise activity of Lewis acids in aqueous media cannot be quantitatively predicted by pK_h and WERC values, these values have been instrumental in the identification of promising metal compounds as water-compatible Lewis acid catalysts,[128] and have also provided mechanistic insight into Lewis acid catalysis in aqueous media. By taking account of the high coordination number of these effective metals, the phenomenal rate acceleration by water seems to be attributed to the predominant ionic properties in the interaction between the Lewis acidic metals and the counter anions. Indeed,

Table 4 Hydrolysis constants and exchange rate constants for substitution of inner-sphere water ligands



22 **264** **271**

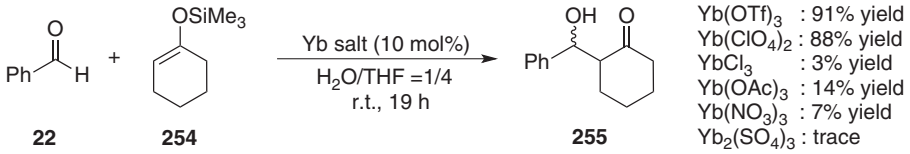
Li $^{+1}$ 13.64 **4.7x10^{7}**	Be — —					M $^{+n}$ pK_h [a] WERC[b]						**B** $^{+3}$ — —	C — —	N — —
Na $^{+1}$ 14.18 **1.9x10^{8}**	**Mg** $^{+2}$ 11.44 5.3x10^{5}											**Al** $^{+3}$ 4.97 1.6x10^{0}	**Si** $^{+4}$ — —	**P** $^{+5}$ — —
K $^{+1}$ 14.46 **1.5x10^{8}**	**Ca** $^{+2}$ 12.85 **5x10^{7}**	**Sc** $^{+3}$ **4.3** **4.8x10^{7}**	**Ti** $^{+4}$ ≤ 2.3 —	**V** $^{+3}$ 2.26 1x10^{3}	**Cr** $^{+3}$ 4.0 5.8x10^{-7}	**Mn** $^{+2}$ **10.59** **3.1x10^{7}**	**Fe** $^{+2}$ **9.5** **3.2x10^{6}**	**Co** $^{+2}$ **9.65** 2x10^{5}	**Ni** $^{+2}$ **9.86** 2.7x10^{4}	**Cu** $^{+2}$ **7.53** **2x10^{8}**	**Zn** $^{+2}$ **8.96** **5x10^{8}**	**Ga** $^{+3}$ 2.6 7.6x10^{2}	**Ge** $^{+4}$ — —	As — —
Rb — —	Sr — —	**Y** $^{+3}$ **7.7** **1.3x10^{7}**	**Zr** $^{+4}$ 0.22 —	**Nb** $^{+5}$ (0.6) —	**Mo** $^{+5}$ — —	Tc — —	**Ru** $^{+3}$ — —	**Rh** $^{+3}$ 3.4 3x10^{-8}	**Pd** $^{+2}$ 2.3 —	**Ag** $^{+1}$ 12 **>5x10^{6}**	**Cd** $^{+2}$ **10.08** **>1x10^{8}**	**In** $^{+3}$ 4.00 4.0x10^{4}	**Sn** $^{+4}$ — —	**Sb** $^{+5}$ — —
Cs — —	**Ba** $^{+2}$ 13.47 **>6x10^{7}**	**Ln** $^{+3}$ **7.6–8.5** **10^{6}–10^{8}**	**Hf** $^{+4}$ 0.25 —	**Ta** $^{+5}$ (–1) —	**W** $^{+6}$ — —	**Re** $^{+5}$ — —	**Os** $^{+3}$ — —	**Ir** $^{+3}$ — —	**Pt** $^{+2}$ 4.8 —	**Au** $^{+1}$ — —	**Hg** $^{+2}$ 3.40 **2x10^{9}**	**Tl** $^{+3}$ 0.62 7x10^{5}	**Pb** $^{+2}$ **7.71** **7.5x10^{9}**	**Bi** $^{+3}$ 1.09 —

La $^{+3}$ **8.5** **2.1x10^{8}**	**Ce** $^{+3}$ **8.3** **2.7x10^{8}**	**Pr** $^{+3}$ **8.1** **3.1x10^{8}**	**Nd** $^{+3}$ **8.0** **3.9x10^{8}**	Pm — —	**Sm** $^{+3}$ **7.9** **5.9x10^{8}**	**Eu** $^{+3}$ **7.8** **6.5x10^{8}**	**Gd** $^{+3}$ **8.0** **6.3x10^{7}**	**Tb** $^{+3}$ **7.9** **7.8x10^{7}**	**Dy** $^{+3}$ **8.0** **6.3x10^{7}**	**Ho** $^{+3}$ **8.0** **6.1x10^{7}**	**Er** $^{+3}$ **7.9** **1.4x10^{8}**	**Tm** $^{+3}$ **7.7** **6.4x10^{6}**	**Yb** $^{+3}$ **7.7** **8x10^{7}**	**Lu** $^{+3}$ **7.6** **6x10^{7}**

[a] pK_h = log K_h. Reference 130a,b.

[b] Exchange rate constants for substitution of inner-sphere water ligands. Reference 130c.

the catalysis of ytterbium salts with more nucleophilic counter anions such as Cl^-, OAc^-, NO_3^-, and SO_4^- were far lower when compared to the effective catalysis of ytterbium salts with less-coordinating counter anions such as OTf^- (91% yield, *syn*/*anti*=73/27) or ClO_4^- (88% yield, *syn*/*anti*=76/24) (Scheme 66).[117b]



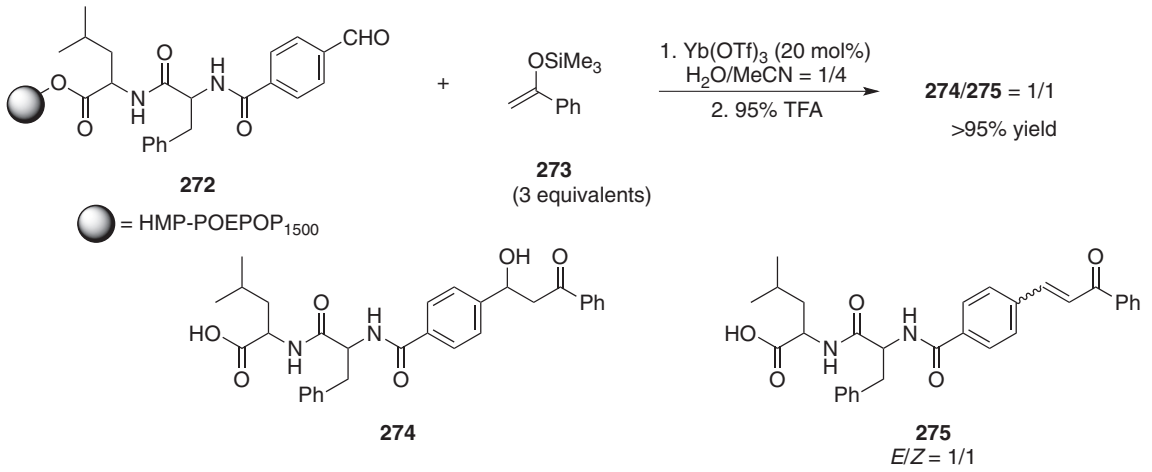
22 **254** **255**

Scheme 66 Effect of Yb salts.

The best yields were obtained when the percentage of water was approximately 10–20%. Water seems to be prone to unstabilize silicon enolates through hydrolysis of ytterbium salts. (The pHs of $Yb(OTf)_3$ solutions were measured as follows: 5.90 (1.6×10^{-2} mol l^{-1}, H_2O/THF=1/4), 6.40 (8.0×10^{-2} M, H_2O).) The amount of water governed the stereochemical outcome as well as the consequent catalytic turnover in water/THF solution. Although the reaction of benzaldehyde with cyclohexanone-derived silicon enolates proceeded with *anti*-preference in the absence of water, the stereochemistry of the product underwent a change in accordance with the increasing amount of water with the selectivity became unchanged when more than 15 equivalents of water was added. An unequivocal interrelationship between the coordination environment of lanthanide triflates and steady-state reaction rate on the Mukaiyama aldol reaction was also proven through luminescence-decay measurements in combination with high-performance liquid chromatography analyses.[129] These phenomena can be explained as follows. The predominant coordination of a THF molecule to $Yb(OTf)_3$ stabilizes the cyclic six-membered transition state that led to the lower activity and *anti*-selectivity in the reaction when no or small amount of water was added.[130] However, when the equivalent of water is gradually increased, the coordination of water produces the naked active ytterbium cation with high WERC (8×10^3 according to ref. 130) to activate aldehydes effectively and catalyze the reaction via acyclic transition state.[46] Thus, the elaborate exploitation of unique properties of water in irreversible Mukaiyama aldol reactions is expected to facilitate the catalytic turnover with simultaneous

desilylation as a direct access to aldol adducts, whereas in conventional acid- or base-catalyzed aldol reactions, the reaction yields of the aldol adducts are destined to depend on their thermodynamic stabilities due to their reversibility.

Polar polyoxyethylene–polyoxypropylene (POE–POP) resin, derivatized with a 4-hydroxymethyl phenoxy linker, was employed as a solid support for $Ln(OTf)_3$-catalyzed Mukaiyama-type solid-phase aldol reactions.[131] The utilization of an aqueous media was crucial for the acquisition of sufficient reactivities and high yields were attained for an N-terminal peptide aldehyde substrate (Scheme 67).



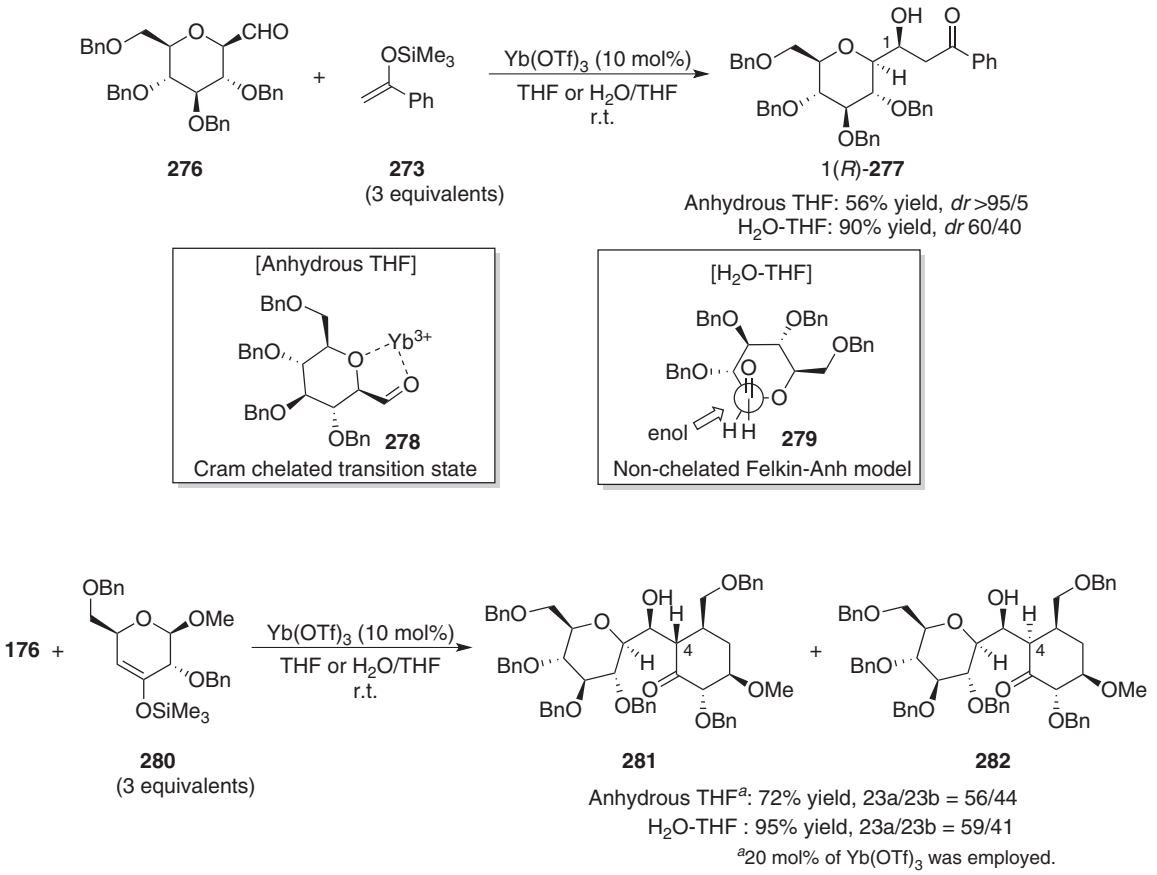
Scheme 67 Solid-phase Mukaiyama aldol reactions of a model peptide substrate.

A series of fluoroalkyl end-capped 2-acrylamido-2-methylpropanesulfonic acid polymers (R_F-$(AMPS)_n$-R_F; R_F = fluorinated group such as $CF(CF_3)OC_3F_7$) hydrogel containing $Sc(OTf)_3$ were employed in Mukaiyama aldol reaction in aqueous methanol.[132] A gelation was derived from the synergistic interaction between the aggregation of end-capped fluoroalkyl segments and the ionic interactions of the betaine segments in water under noncross-linked conditions.[133] Not only did the reaction proceed smoothly, but the catalyst was also recovered quantitatively and the catalytic activity of recovered catalyst did not decrease. Lewis acid-catalyzed Mukaiyama aldol reaction in aqueous media could also be efficiently applied for the preparation of *C*-glycosides and *C*-disaccharides starting from formyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside **276** (Scheme 68).[134] $Yb(OTf)_3$ in aqueous media led to the aldol adducts in high yields with moderate diastereoselectivities for the synthesis of *C*-glycosides. Interestingly, a significant drop in reactivity as a single isomer was observed when the reaction was performed in anhydrous THF. The better diastereoselectivity observed in anhydrous THF could be rationalized from the Cram cyclic chelated model, where the ytterbium atom may coordinate the carbonyl group and the endocyclic α-oxygen atom of the sugar moiety. In aqueous media, the attack of the electrophile may not be preferentially directed to one of the π-faces of the enolate as depicted in the nonchelating Felkin–Anh model. In the Mukaiyama aldol reaction of the sterically hindered silicon enolate **280**, a low degree of diastereoselection was observed for the C-4 alkylation, which might be attributed to a poor steric control induced by the substituents adjacent to the reactive center (at C-6 and C-2 positions).

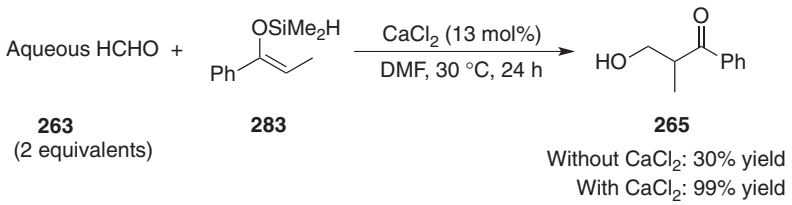
Thermal treatment of montmorillonite K10 was also applicable to the Mukaiyama aldol reactions in water.[135] The catalytic activity was attributed to the structural features of the clay and its inherent Brønsted acidity.

Lewis base catalysis can be also applicable to the Mukaiyama aldol reactions in the presence of water, albeit with a limited number of examples. Hosomi disclosed that the uncatalyzed reaction of benzaldehyde with DMS enolates proceeded comparatively smoothly under thermal conditions in DMF, whereas trimethylsilyl enolates hardly reacted.[91] Extensive examination of additives to promote the Mukaiyama aldol reactions led to the discovery of calcium chloride as a catalyst. The rate-accelerating ability of calcium salt depends on intrinsic nucleophilicity of the counteranion: $TfO^- < I^- < Br^- < Cl^-$. Tetrabutylammonium chloride also exhibited good catalytic activity for the Mukaiyama aldol reaction of DMS enolates. Given the diametrical observation on rate acceleration between TMS and DMS enolate, higher nucleophilicity of chloride ion than bromide or iodide ion in aprotic solvent such as DMF and the low Lewis acidity of $CaCl_2$ ($CaCl_2$ has been reported to be ineffective in the reaction with TMS enolate), chloride ion was determined to function as a Lewis base to activate the DMS enolate. In spite of a much lower tolerance to water, DMS enolate turned out to be a competent nucleophile in the presence of $CaCl_2$ in water or aqueous DMF. Consequently, the $CaCl_2$-promoted system could be utilized for the reaction of aqueous aldehydes such as aqueous formaldehyde, phenylglyoxal, and chloral, and this was the first example of Lewis base-catalyzed Mukaiyama aldol reactions in aqueous media (Scheme 69).

Following their previous studies for the aldol-type reactions carried out under anhydrous conditions,[81,136] Mukaiyama reported that 10 mol% of lithium acetate could function as a Lewis base catalyst to catalyze the reaction between benzaldehyde and ketene silyl acetal at −45 °C in $DMF/H_2O = 50/1$ (Scheme 70).[82a] Not only lithium acetate, but several metal carboxylates, such as sodium acetate, lithium benzoate, and so on, were found to act as catalysts. They assumed that the role of the carboxylate in the



Scheme 68 Synthesis of *C*-glycosides and *C*-disaccharides using Mukaiyama aldol reaction in aqueous media.

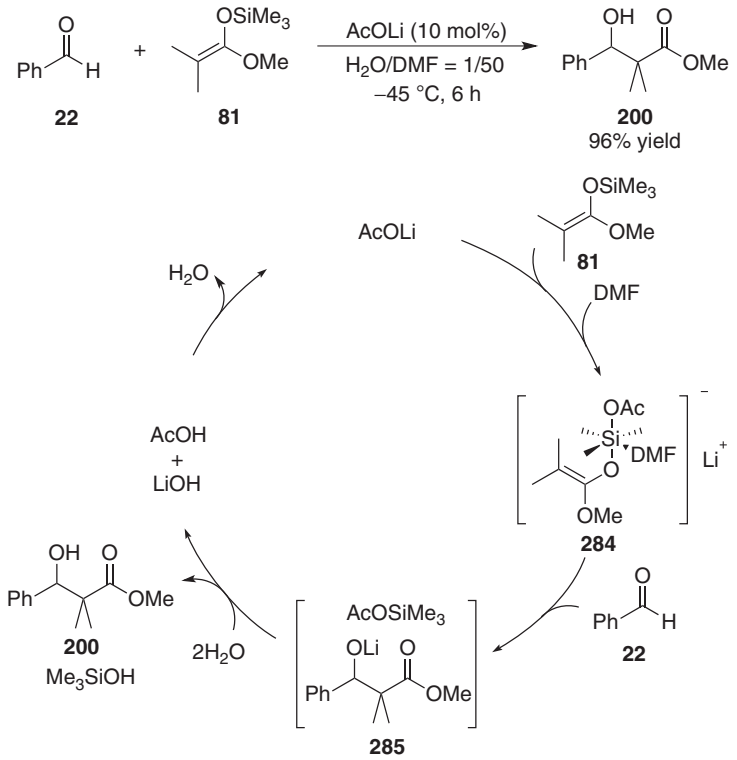


Scheme 69 $CaCl_2$-catalyzed Mukaiyama aldol reaction using aqueous formaldehyde.

catalytic cycle was the formation of a lithium aldolate, via a hexa-coordinated hypervalent silicate, that undergoes rapid hydrolysis and subsequent neutralization to regenerate lithium acetate catalyst. The significant dependence of reactivity on the electrophilicity of the starting aldehydes supported their hypothesis.

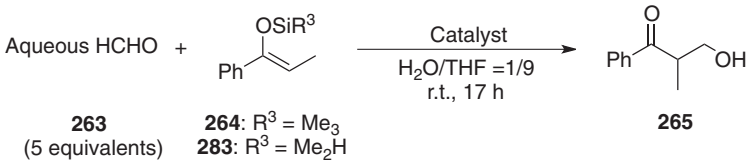
Scandium fluoride was disclosed to be a novel catalyst for the hydroxymethylation reaction of DMS enolate with aqueous formaldehyde in aqueous tetrahydrofuran solution.[137] Comparison of the reactivity between TMS and DMS enolates derived from propiophenone for hydroxymethylation reactions were examined by using general Lewis acids or bases (Table 5). The hydroxymethylation was sluggish without a catalyst, whereas both enolates reacted to afford the product in moderate yields in the presence of a Lewis acid catalyst (scandium chloride) with TMS enolate providing a higher yield. The product was also obtained from both enolates in the presence of KF and 18-crown-6 with the TMS enolate demonstrating better reactivity. The addition of HF resulted in lower yields with both enolates. Interestingly, scandium fluoride produced the product only from DMS enolate. This unique character of scandium fluoride denoted that its reactivity toward TMS and DMS enolates was different from that of conventional Lewis acid or fluoride ion[138] (Lewis base)-catalyzed reactions. Some reports have shown that fluoride ions can activate silicon enolates effectively, even in protic solvent.[139] Therefore, the detailed mechanism of the preferential activation of DMS enolate by scandium fluoride still remains unknown.

Even with brilliant catalysts that can function in aqueous media, the Mukaiyama aldol reaction in water has always suffered from low yields and low reaction rates due to the insolubility of the substrates. Micellar systems containing anionic (e.g., sodium



Scheme 70 AcOLi-catalyzed Mukaiyama aldol reaction in aqueous DMF.

Table 5 Comparison of the reactivity of TMS or DMS enolates with various catalysts



Entry	*Catalyst (mol%)*	*Yield*[a](%)	
		264	*283*
1	None	2	24
2	ScF_3 (20)	Trace	81
3	$ScCl_3$ $6H_2O$ (20)	69	41
4	KF (20) + 18-crown-6 (20)	63	51
5	HF (20)	14	13

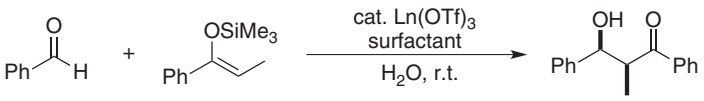
[a]Isolated yield.

dodecylsulfate (SDS), etc.) or nonionic surfactant (e.g., Triton X, etc.) has led to remarkable enhancement of the reactivity even in the case of ketene silyl acetals (Table 6).[140] Only cetyltrimethylammonium bromide (CTAB) was found to be an effective surfactant due to the possibility of hydrolysis of the silicon enolate.

$FeCl_3$ was also reported as a catalyst for the Mukaiyama aldol reactions and the diastereoselectivities were found to be controlled kinetically in water with the coexistence of a surfactant.[141] The significant rate acceleration and higher diastereoselectivity was attained in water than in water–THF solution.

Unfortunately, one fundamental challenge of performing the Mukaiyama aldol reactions in water is the competition of rapid hydrolysis of silicon enolates, which can lower reactivity and narrow the substrate generality. In order to make the desired catalytic pathway dominant over the competitive hydrolysis of silicon enolates, the calix[6]arene derivatives bearing sulfonate groups on the upper rim and the alkyl groups on the lower rim were developed.[142] These macrocycles stabilized the labile silyl enolates to promote the aqueous Mukaiyama aldol reactions with slight *anti*-selectivities (*syn*/*anti* = 31/69 to 40/60). These structures could be

Table 6 Effect of surfactants on Mukaiyama aldol reaction in water



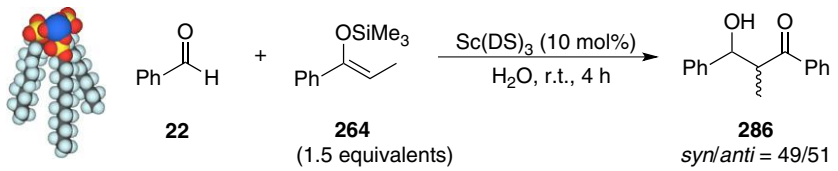
22 **264** **286**

Entry	*Catalyst (mol%)*	*Surfactant (mol%)*	*Time (h)*	*Yield*[a] (%)
1	$Yb(OTf)_3$ (20)	–	48	17
2	$Yb(OTf)_3$ (20)	SDS (10)	48	19
3	$Yb(OTf)_3$ (20)	SDS (20)	48	50
4	$Yb(OTf)_3$ (20)	SDS (100)	48	22
5	$Sc(OTf)_3$ (10)	SDS (20)	4	88
6	$Sc(OTf)_3$ (10)	Triton X-100 (20)	60	89
7	$Sc(OTf)_3$ (10)	CTAB (20)	4	Trace

[a]Isolated yield

regarded as a bundle of aromatic anionic surfactants. Indeed, the combination of aromatic surfactants and aryl aldehydes was favorable for the activation in the hydrophobic cavities.[143] The recyclable inclusion complex formed from cyclodextrin (CD) and ytterbium tris(perfluoroalkanesulfonyl)amide was also applied to the Mukaiyama aldol reaction with ketene silyl acetal in water, albeit with slightly lower reactivity than that in CH_2Cl_2.[144] It was reported that due to hydrophobic interactions, CD forms inclusion complexes with the fluorocarbon surfactants.[145] Since the chain length of the perfluorobutane group is nearly equal to the length of the CD ring, it was assumed that the metal locates just outside the hydrophobic pockets of CD.

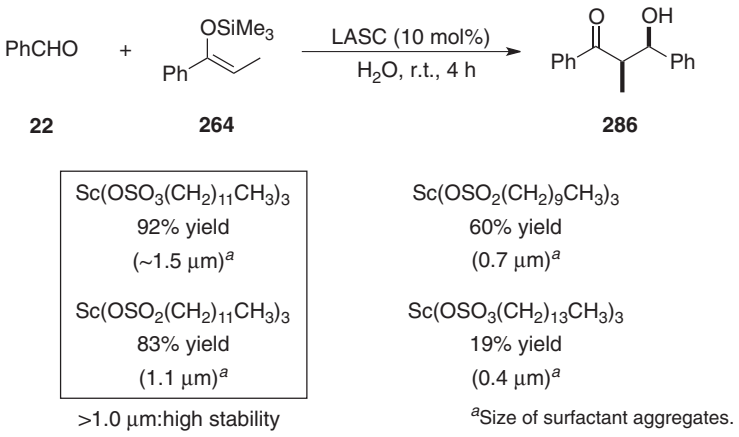
The major disadvantage of Lewis acid catalysis aided by surfactants was the large excess of the surfactant required to achieve good results. Due to the high affinity of water-compatible Lewis acids in water, the relative concentration of the catalyst in the hydrophobic micelle is low and necessitates a large excess of the surfactant. In 1998, Kobayashi and Wakabayashi introduced a novel concept, Lewis acid-surfactant combined catalyst (LASC), in which a Lewis acid possessed ligands with properties of a surfactant to construct an efficient hydrophobic environment surrounding a Lewis acidic cation.[146,147] Scandium tris(dodecylsulfate) (STDS, $Sc(DS)_3$ ($DS = OSO_3C_{12}H_{25}$)) was shown to dissolve in water and after the addition of organic substrates, a white dispersion was formed (**Scheme 17**). These oily particles, made of organic substrates and STDS, were stabilized and dispersed in water to promote the Mukaiyama aldol reactions (**Scheme 71**). Since $Sc(OTf)_3$ does not react with SDS to form STDS, the catalytic efficiency of STDS was superior to that of $Sc(OTf)_3$–SDS system.[146a] Indeed, the $Sc(OTf)_3$–SDS system makes a kind of micelle (not dispersion).



22 **264** (1.5 equivalents) **286** *syn*/*anti* = 49/51

Scheme 71 (left) Schematic representation of STDS and (right) LASC-catalyzed Mukaiyama aldol reaction.

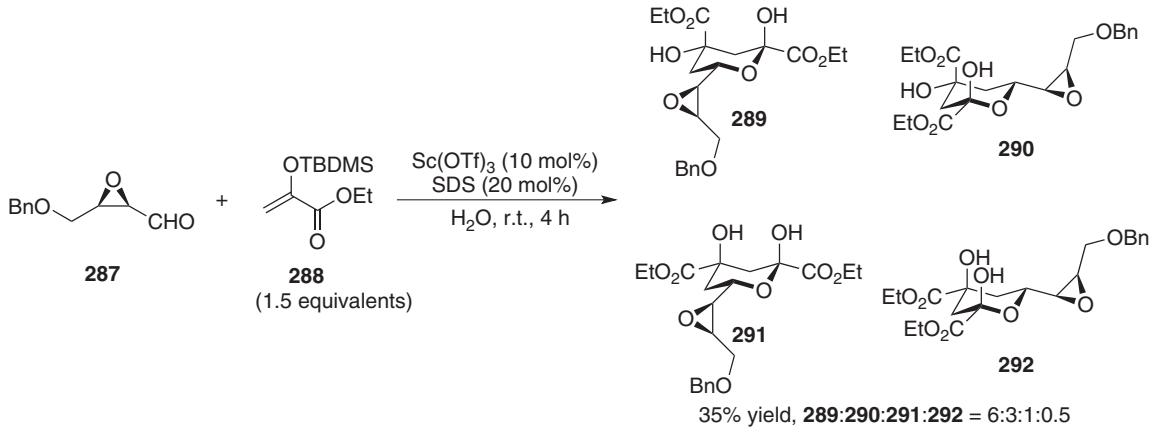
The use of STDS to construct highly reactive microenvironments in water enabled the broadening of the substrate scope to include very labile silicon enolates. The Mukaiyama aldol reaction was found to proceed 5×10^3 times faster in water than in dichloromethane.[146a] It was also shown that multifarious LASCs were applicable to various reactions in water.[148,149] In aqueous solution, surfactants aggregate into structures called micelles, where the hydrophobic portions of the molecules are protected from contact with water.[150] Normally, micelles in aqueous solution form with the surfactant molecules orienting themselves into spherical or elliptical structures with their hydrophobic tails oriented toward the center and their hydrophilic heads oriented toward the surrounding water. Cabane demonstrated in an NMR study that the micelles formed by SDS have approximately 1/3 of their surface covered by the hydrophilic head groups, and the remaining 2/3 covered by hydrocarbon tails.[151] The formation of micelles can be explained by thermodynamics; they can form spontaneously as a result of a balance between entropy and enthalpy. Despite reducing their entropy caused by surfactant aggregation, in water, the hydrophobic effect is the driving force for micelle formation. Micelles do not form unless the concentration of surfactant is greater than the critical micelle concentration (CMC) and there exists a critical temperature (Krafft temperature) above which solubility rapidly increases (be equal to CMC).[152] Theoretically, CMC decreases as the polar head becomes smaller and with increasing alkyl chain length. The correlation between size of colloidal dispersion measured by dynamic light scattering and reactivity was evaluated for LASCs (**Scheme 72**).[153] In the case of an ineffective catalyst for the Mukaiyama aldol reaction, $Sc(OSO_2C_{14}H_{29})_3$, the dispersion system was stable only within a



Scheme 72 Correlation between size of colloidal dispersion and reactivity.

few minutes and quick measurement was required. Since typical emulsion sizes created in water is 1 μm, this low stability of the dispersion might be the reason for the low yields observed. All the particles formed from the mixture of $Sc(OSO_2C_{12}H_{25})_3$ and benzaldehyde in water have a diameter of 1 μm and the molecular area of $Sc(OSO_2C_{12}H_{25})_3$ was determined to be 132 Å. Based on these facts, only approximately 0.08 mol% $Sc(OSO_2C_{12}H_{25})_3$ with respect to benzaldehyde is sufficient to form monolayers around the aldehyde. In other words, excess LASCs should be stacked at the interface between water and benzaldehyde phase in the presence of more than 0.08 mol% $Sc(OSO_2C_{12}H_{25})_3$. The remarkable enhancement of reactivity by Brønsted acids was observed in LASC-mediated Mukaiyama aldol reactions in water (*vide infra*).[154] An NMR study of SDS micelles labeled with paramagnetic ions such as $Co(DS)_2$ revealed that the paramagnetic ions were weakly adsorbed and remained fully hydrated.[155]

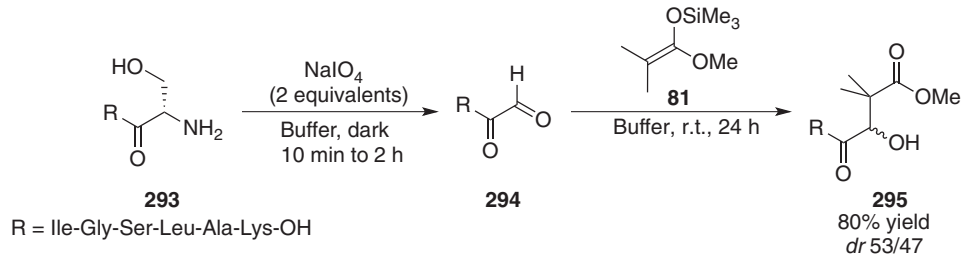
The Mukaiyama aldol reactions of *cis* and *trans* α,β-epoxyaldehydes with ketene silyl acetals were also reported for the Sc $(OTf)_3$–SDS system.[156] The use of cosolvents failed to generate the aldol adducts, whereas the best results were obtained when operating under a micellar system with high *anti*-diastereofacial preference. The reaction between benzylated epoxyaldehyde **287** and ketene silyl acetal **288** derived from ethyl pyruvate led to ulosonic ester derivatives (Scheme 73).



Scheme 73 Aqueous Mukaiyama aldol reaction of α,β-epoxyaldehydes.

The vigorous stirring of the dipeptide aldehyde generated by periodate oxidation from polypeptide and ketene silyl acetal in 10 mM sodium phosphate buffer (pH 7.0) was also discovered to lead to the aldol product with high efficiency (Scheme 74).[157] The Mukaiyama aldol reaction could be applied to various N-terminal aldehydes of peptides and proteins bearing a wide range of functional groups under very mild conditions. As shown in the case of myoglobin, the reaction could be carried out without disturbing either the tertiary structure or the enzymatic activity of the protein.

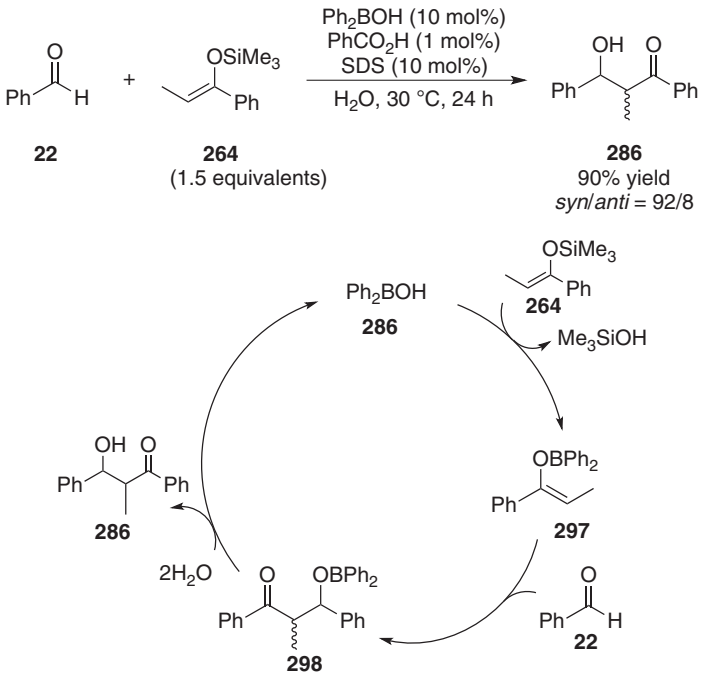
Aimed at easy recovery and reuse, polymer-supported (PS) catalysts were also established for the Mukaiyama aldol reactions in aqueous environments. Kobayashi modified their previously reported LASC system by introducing polymer chain spacers as the hydrophobic component to the metallosurfactant catalyst.[158] The Mukaiyama aldol reaction of benzaldehyde with 1-ethylthio-1-trimethylsiloxy-2-methyl-1-propene reacted almost quantitatively in the presence of 3.2 mol% of this heterogeneous catalyst and wider substrate generality was achieved by further modification.[159] The catalytic activity of PS-Sc was dependent on the hydrophobicity in water and thus superior to that of STDS. A heterogeneous scandium catalyst coated with an ionic liquid, [DBIm]SbF_6, Silica–Sc–IL, also worked efficiently in the Mukaiyama aldol reaction.[160] The reaction rate was much faster in water than in organic



Scheme 74 Mukaiyama aldol reactions of a peptide aldehyde.

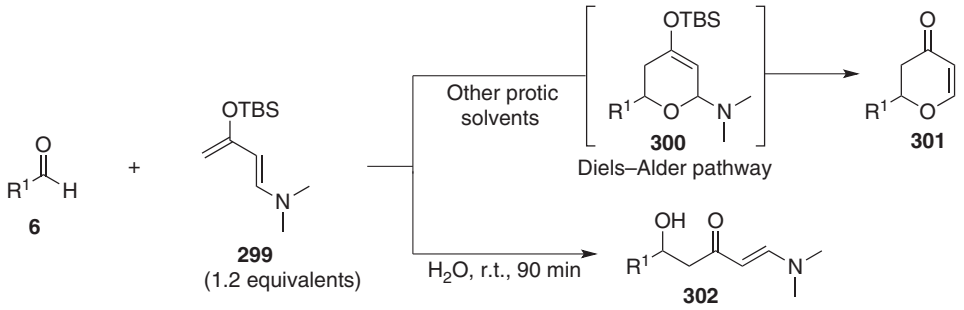
solvents or under neat conditions. It was determined that the ionic liquid played a crucial role in the construction of efficient hydrophobic environments in water. Asymmetric catalysis could be also realized with this heterogeneous catalyst (*vide infra*). Cross-linked dendrimers heterogeneous catalyst with Lewis acidic properties have been reported for the Mukaiyama aldol reactions in water.[161] Despite the heterogeneous material being nonporous, catalysis was achieved and the catalytically active scandium centers were accessible for the reaction to occur. Nanostructured, PS-Sc catalyst utilizing a cross-linked inverted hexagonal lyotropic liquid–crystal phase was prepared and utilized as an efficient catalyst for the aldol-type reaction.[162] $Sc(OTf)_3$ or STDS exhibited no diastereoselectivity, whereas nanostructured scandium catalyst exhibited diastereoselectivity favoring *syn*-isomer (*syn*/*anti* = 76/24).

However, diastereoselective aldol reactions have been successfully performed in water in the presence of a catalytic amount of a boron source (diphenylboronic acid).[163] Only trace amount of product was obtained in organic solvents and much lower yield than that in water was obtained under neat conditions (24% yield, *syn*/*anti* = 90/10). It was found that the catalytic use of benzoic acid was greatly beneficial for the reaction. When stronger acids such as hydrochloric acid or *p*-toluenesulfonic acid were employed, the reaction yield decreased due to the promotion of competitive hydrolysis of the silyl enol ether and diastereoselectivities were also lowered presumably due to the Brønsted acid-catalyzed reaction pathway. The careful tuning of diarylboronic acid structure led to a discovery that trifluoromethyl group at the *para*-position brought about significant rate acceleration compared with unsubstituted one. Introduction of an electron-donating group at the *para*-position made both the yield and selectivity decrease, whereas high selectivity was maintained in the case of electron-withdrawing substituents. The first-order kinetics with respect to the amount of silicon enolate supported the boron enolate mechanism rather than the Lewis acid mechanism (Scheme 75). The exchange from silicon to boron was assumed to be the rate-determining step. A significant dependence of diastereoselectivity on the enolate geometry implied the formation of a chair-like six-membered transition state in the aldol condensation step. Although traditional boron-mediated aldol reactions entailed lower temperature and strictly anhydrous conditions, this methodology enabled the Mukaiyama aldol reaction to be performed in water at ambient temperature.



Scheme 75 Mukaiyama aldol reaction using diphenylboronic acid in water.

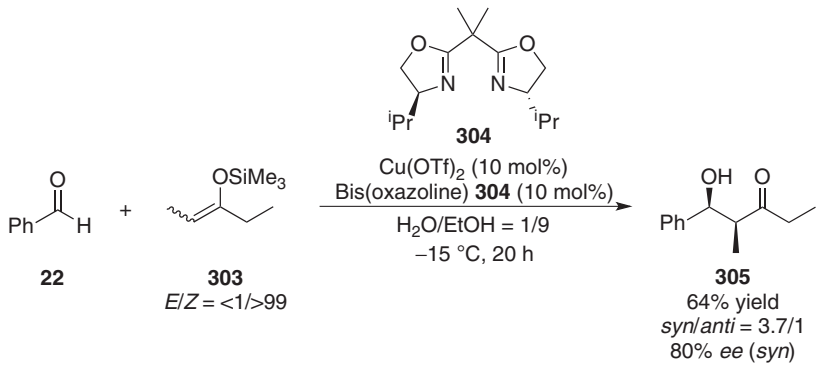
Mukaiyama aldol reaction of electron-rich Rawal's diene **299** with carbonyl compounds proceeded without any activator in pure water (Scheme 76).[164] The ^{1}H NMR analyses indicated that the reaction solvent influenced the reaction pathway and the aldol adducts were obtained in water, whereas in other protic solvents, as Rawal and coworkers previously reported,[165] the cycloadduct was obtained through the Diels–Alder pathway.



Scheme 76 Reaction of Rawal's diene **299** in water.

2.09.3.3.3 Asymmetric catalysts in aqueous media/water

The various water-compatible Lewis acid catalysts that have been reported thus far has resulted in a remarkable breakthrough in the development of environmentally benign synthetic methodologies. The recent advances in Mukaiyama aldol reaction in aqueous media led chemists to examine the possibility of asymmetric catalysis in an aqueous environment. Indeed, almost all successful examples reported in organic solvents since 1990[166] entailed absolutely aprotic anhydrous conditions, as well as quite low reaction temperatures (e.g., − 78 °C). Therefore, the emergence of facile, convenient, and environmentally benign methodology without tedious operation is desirable. However, a major difficulty in achieving asymmetric catalysis in aqueous media is the weakness of noncovalent interactions between substrates, chiral ligands, and metal ions under competitive polar conditions. Conversely, if capable of being highly controlled, the construction of asymmetric environments in the presence of water is anticipated to inhibit undesired achiral side reactions and imposing stricter stereochemical regulation than other organic solvents through hydrogen bond network, specific solvation, and hydrophobic interactions. Despite the formidable task of controlling stereochemistry efficiently in an aqueous environment, recent attempts at this challenging endeavor have been successfully achieved. Previously, reports of copper(II) aqua structures formed with chiral bis(oxazoline) templates were depicted although prepared even under normally anhydrous conditions.[167,168] These results seemed to allude to the latent stability of copper(II)–bis(oxazoline) **304** complex in an aqueous environment. Due to the well-known Lewis acid activity of copper(II) and its apparent stability in water, Kobayashi examined copper(II)–bis(oxazolines) complexes as catalysts for asymmetric synthesis in aqueous media.[169] The Mukaiyama aldol reactions of (*Z*)-enolate were catalyzed by chiral copper(II) complex efficiently in aqueous ethanol (H_2O/EtOH = 1/9) to afford the desired adduct in moderate-to-good yields and enantioselectivities (Scheme 77). It was noteworthy that much lower yields and selectivities were observed without water.



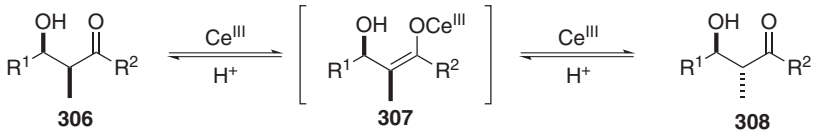
Scheme 77 First example of asymmetric Mukaiyama aldol reaction in aqueous media.

Exploitation of multicoordination system was another possible solution for the instability of chiral metal complexes in an aqueous environment. The simple examination of the combination of chiral crown ethers **312** and metal triflates on the basis of ionic radii[170] and the hole sizes[171] led to the discovery of an efficient chiral lead(II) catalyst for the asymmetric Mukaiyama aldol reactions in aqueous media.[172,173] (Ionic diameter of Pb^{2+} (CN = 8) is 258 pm (see ref. 170) and the hole size of 18-crown-6 was

reported to be 260–320 pm.) Quantitative recovery of $Pb(OTf)_2$ and chiral crown ether **312** was ascertained to be possible by simple extraction. Furthermore, the multicoordination system enabled the application of thioester-derived silyl acetals as nucleophiles for the Mukaiyama aldol reaction. A kinetic study performed for chiral reaction and $Pb(OTf)_2$-catalyzed achiral reaction resulted in the observation of almost comparable reaction rates and the same levels of diastereoselectivity.

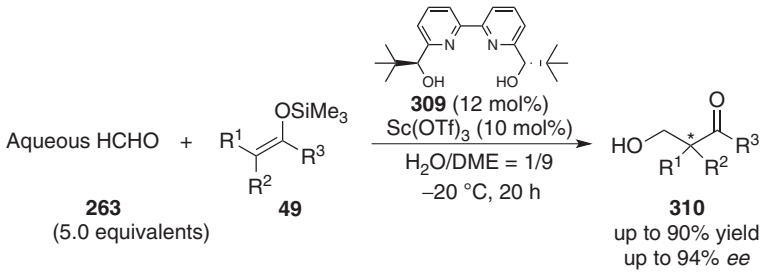
Inspired by these marvelous successes, intensive effort has been dedicated to stereoselective synthesis in an aqueous environment and has led to the emergence of highly efficient catalytic asymmetric Mukaiyama aldol reactions using water-compatible Lewis acids with chiral ligands. For example, the chemical evolution of the catalysts for the reaction of benzaldehyde **22** with propiophenone-derived silyl enol ether is described in Scheme 84 (*vide infra*). The catalysts composed of lanthanide triflates with chiral bis-pyridino-18-crown-6 **313** exhibited higher diastereo- and enantioselectivity.[130,174,175] The size-fitting between the crown ether and the metal cations is a prominent factor to attain high selectivities; with the larger cations such as La, Ce, Pr, and Nd providing the aldol adduct with high diastereo- and enantioselectivities, whereas the smaller cations such as Dy, Ho, Yb, Y, and Sc resulted in lower selectivities. Introduction of an electron-donating (MeO) group at the 4-position of the pyridine rings led to high selectivities for the larger cations and lower for the smaller cations. In the case of electron-withdrawing (Br) group, a similar tendency was observed but the effect of ionic radii was more significant. Asymmetric reaction with lanthanide complexes slightly decelerated the reaction rate despite the strong coordination of Lewis base, compared with achiral pathway without the chiral crown ether. In order to explore lanthanide catalysis,[176] macrocyclic gadolinium-containing polyaminopolycarboxylate-based contrast agents for magnetic resonance imaging[177] was modified and Eu(III) or Nd(III) complexes were applied to the asymmetric Mukaiyama aldol reactions in aqueous media. Unfortunately these complexes possessed quite low catalytic activities and the activities were highly dependent on the substrate.[178]

Despite the progress made with chiral lanthaindes, the precise stereochemical control of lanthanides still remains a very formidable task. Lanthanides, such as Ce(III), are known to promote the epimerization between *syn*- and *anti*-adduct via keto-enolization presumably due to their greater Lewis acidity in aqueous media (Scheme 78).[179]



Scheme 78 Plausible epimerization induced by lanthanides.

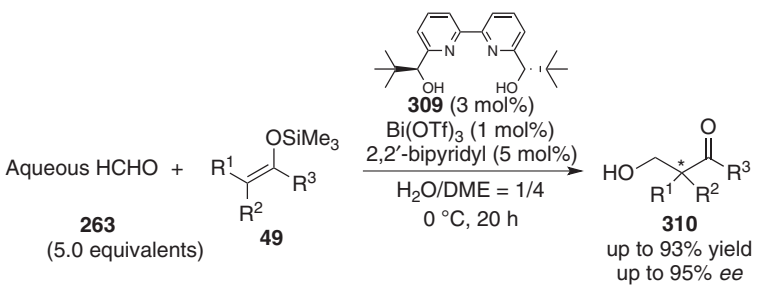
The highly coordinative nature of these chiral crown ethers appears to be key to understanding the catalyst behavior of lanthanides in an aqueous environment. In organic solvents, the coordination of heteroatoms generally leads to the loss of Lewis acidity on metals, due to the behavior of the heteroatoms as Lewis bases. In contrast, it is known that subsequent coordination of water molecules generates a naked metal cation, which functions as a Lewis acid in an aqueous environment. Aiming to develop catalysts with higher levels of stereoselective control, Kobayashi embarked on the establishment of a new methodology for asymmetric hydroxymethylation reaction using aqueous formaldehyde, a convenient C1 source. Previously, Cinchona alkaloids catalyst[180] and rhodium(I) complex coordinated with *trans*-chelating chiral diphosphine TRAP[181] had been reported as effective catalysts for asymmetric hydroxymethylation. However, both catalysts required active methine groups in the substrate structure and construction of the asymmetric tertiary center was impossible. Therefore, the emergence of catalytic system where aqueous formaldehyde can be used has been desired. A catalytic system comprising of $Ln(OTf)_3$ and chiral bis-pyridino-18-crown-6 **313** in aqueous tetrahydrofuran was found to be effective for the asymmetric hydroxymethylation reaction (six examples, 52–92% yield, 41–55% *ee*).[182] At the same time, a bifunctional system of (*R*)-BINAP–AgOTf complex with a fluoride source was applied as a Lewis base catalyst for the asymmetric hydroxymethylation of trimethoxysilyl enol ethers derived from cyclohexanone (31% yield, 57% *ee*) or α-tetralone (18% yield, 57% *ee*) in aqueous tetrahydrofuran, albeit in quite low yield.[183] In 2004, a new excellent catalytic system, based on a chiral scandium complex, was reported with the higher level with respect to yields and enantioselectivities when compared with previous systems (Scheme 79).[184]



Scheme 79 Scandium-catalyzed asymmetric hydroxymethylation in aqueous media.

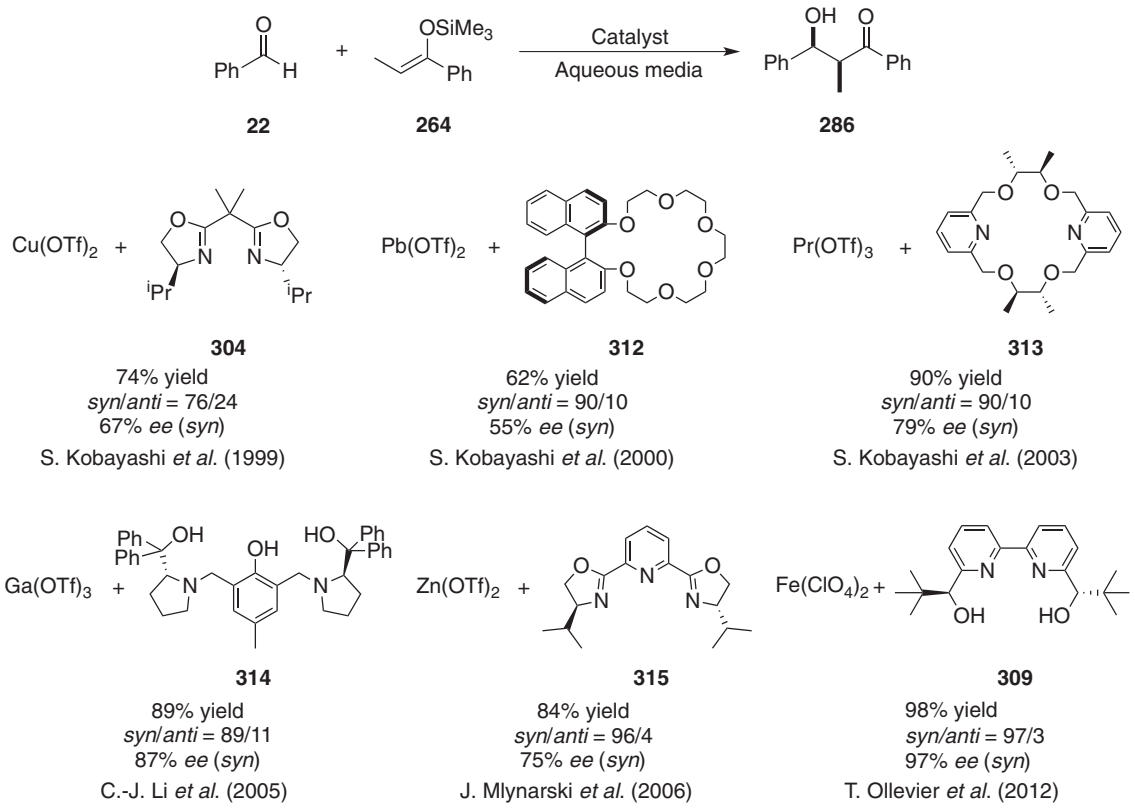
It has been demonstrated for the first time that chiral 2,2′-bipyridine **309**[185] can act as an exceedingly effective ligand for a catalytic asymmetric reaction in an aqueous environment. Given its potential to chelate with many transition metal ions, the 2,2′-bipyridine backbone may represent a 'privileged' ligand structure that could catalyze many unique chemical reactions in an aqueous environment in a selective manner. Chiral scandium complex formed with **309** functioned most effectively in H_2O/DME solution. Under the optimal conditions, asymmetric quaternary carbons could be constructed with high selectivities and this methodology could be extended to various substrates such as thioester-derived silyl enol ethers. In some cases, competitive hydrolysis of silicon enolates occurred, but could be resolved by the addition of 2,6-di-*tert*-butylpyridine as a proton scavenger.[186] Judging from X-ray analysis, the chiral scandium complex adopts a pentagonal bipyramidal structure where the chiral ligand is bound to the central scandium in a tetradentate manner. In the kinetic study,[187] a first-order dependence of the silicon enolate and the catalyst with $K_{sub} = 0.31\ h^{-1}$ and $K_{cat} = 5.10\ h^{-1}$ represents an overall rate law of: Rate = k[silicon enolate][Catalyst]. The observation of first-order dependence on both the silyl enol ether and the catalyst negates the possible formation of scandium enolate as an intermediate and the involvement of discrete molecules of catalyst. Moreover, since saturation kinetics were not observed, this also denies the direct bond formation between the chiral scandium catalyst and the silicon enolate.

An extensive effort dedicated to the asymmetric hydroxymethylation in aqueous media led to the discovery of a new catalytic system composed of $Bi(OTf)_3$ and chiral 2,2′-bipyridine **309** (Scheme 80).[188] Given the ease of hydrolyzation in the presence of water,[189] as well as the great discrepancy in the ionic diameters between bismuth (2.34 Å for 8-coordination) and scandium (1.74 Å for 8-coordination), this unexpected result offered interesting insight into asymmetric catalysis in an aqueous environment. Indeed, only a trace amount of hydroxymethylated adduct was obtained using $Bi(OTf)_3$ in the absence of **309**, probably due to the rapid decomposition of the silicon enolate promoted by TfOH generated readily from $Bi(OTf)_3$ in water. The ligand acceleration effect of **309** suggests that the stabilization of $Bi(OTf)_3$ occurs due to the coordination of **309** in water. Chiral bismuth catalyst comprising of 1 mol% of $Bi(OTf)_3$, 3 mol% of **309**, and 5 mol% of 2,2′-bipyridine was shown to afford the desired product in high yields with high enantioselectivities. Fundamental elucidation of the catalyst structure through NMR spectroscopy has been already conducted.[190] In contrast to significant development in asymmetric hydroxymethylation reactions, the asymmetric Mukaiyama aldol reactions between hydrophobic substrates are relatively scarce. The representative catalyst systems for the reaction of benzaldehyde **22** with propiophenone-derived silyl enol ether **264** are summarized in Scheme 81.



Scheme 80 Bismuth-catalyzed asymmetric hydroxymethylation in aqueous media.

In 2002, $Ga(OTf)_3$ with chiral Trost-type semicrown ligand **314**[191] was discovered as an efficient catalyst for asymmetric Mukaiyama aldol reactions in aqueous media.[190] The UV-vis titration and ESI-MS analysis confirmed this gallium complex to be a 1:1 complex.[192] Control experiment performed without ligand suggested that the ligand played a key role in accelerating the reaction and suppressing the hydrolysis of the silicon enolates. Comparably, wide substrate scope was attained with satisfactory levels of diastereo- and enantioselectivities containing thioketene silyl acetals. However, the C_2-symmetric bis(oxazolines) disubstituted with two Fréchet-type polyether dendrimers exhibited the similar reactivities and enantioselectivities (up to 78% yield, *syn*/*anti* = 2.2/1, 64% *ee* (*syn*)) for the asymmetric Cu(II)-catalyzed aldol reaction in aqueous media in comparison to Kobayashi's previous work (98% yield, *syn*/*anti* = 2.6/1, 61% *ee* (*syn*)).[193] Another promising Lewis acid shown by Mlynarski and coworkers focused on the Lewis acidity of Zn(II) and Fe(II) to develop chiral catalysts formed with $Zn(OTf)_2$ and ^{i}Pr-*pybox* ligand **315**[194] or $FeCl_2$ and hydroxymethyl-*pybox* ligand[195] for the asymmetric Mukaiyama aldol reactions in aqueous media. In order to overcome the instability, capriciousness, and sensitivity of chiral iron(II) complex to many reaction factors, tuned and lipophilic *pybox* ligands were designed.[196] In spite of these vigorous explorations pursuing efficient catalytic system, there have still been insurmountable limitations in catalytic activity and substrate scope; not only did almost all catalytic systems require 10–20 mol% of Lewis acids and 12–48 mol% of chiral ligands, but these methodologies possessed limited substrate scope to some substrates, such as aliphatic aldehydes, for which a remarkable drop in enantioselectivity was commonly observed. In 2012, wider substrate scope with outstanding stereoselectivity was achieved in the presence of chiral iron(II) complex comprising $Fe(ClO_4)_2$ and chiral 2,2′-bipyridine ligand **309**.[197] Nevertheless, in this catalytic system, excess amount of chiral ligand was required. Crystallographic investigations revealed that the central iron(II) ion to be in an almost square-planer fashion and the axial position of the



Scheme 81 Catalytic asymmetric Mukaiyama aldol reaction in aqueous media.

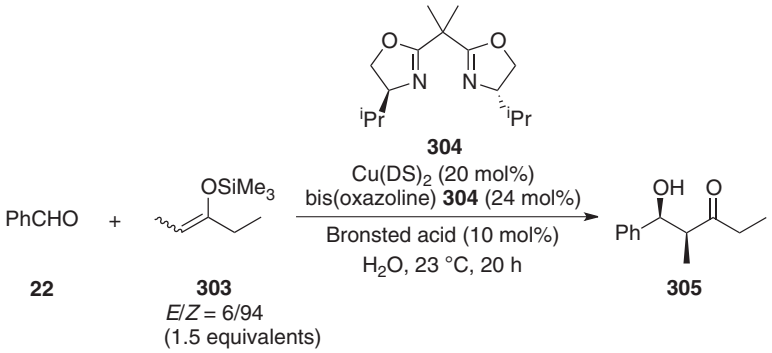
pentagonal bipyramidal iron(II) complex is occupied by an additional water molecule. ESI-MS measurements corroborated the formation of a 1:1 complex in the reaction solution.[198]

Given the dominance of 'Lewis acid–Lewis base interactions' over other interactions and the resulting loss of their acidity on coordination to chiral ligands, Lewis acid-catalyzed asymmetric reactions in water using hydrophilic substrates are recognized as highly challenging even though chiral induction can be achieved in aqueous media.[199] The first example of Lewis acid-catalyzed asymmetric aldol reactions in pure water was an application of LASC. As an extension of the chiral copper(II) catalyst in the water–ethanol system, the combination of $Cu(DS)_2$ and chiral bis(oxazoline) **304** was employed.[200] LASC/Brønsted acid system mentioned in Section 2.09.3.3.2 was further extended to this asymmetric reaction (Table 7).[201,202] Benzoic acid and lauric acid as additives were effective for not only reactivity but also enantioselectivity (up to *syn*/*anti* = 2.8/1, 69% *ee* (*syn*)). Neither strong Brønsted acid (CSA) nor a weaker one (phenol) could improve the reaction. Even by using a stoichiometric amount of a scandium salt, the Brønsted acid was also found to accelerate the reaction. This implied that the rate-determining step accelerated by the Brønsted acid was not the catalyst turnover step, but nucleophilic addition step.[203,204]

Catalytic asymmetric hydroxymethylation reactions were successfully carried out with 10 mol% of $Sc(DS)_3$ and 12 mol% of chiral 2,2′-bipyridine **309** in the presence of Triton X-705 or with 10 mol% of $Sc(OSO_2C_{12}H_{25})_3$ and 12 mol% of chiral *N*-oxide ligand **316**[205] in the presence of $C_{12}H_{25}SO_3Na$ to afford the desired aldol adducts in high yields with high enantioselectivities (Scheme 82).[206] A wide range of silicon enolates including thioketene silyl acetals reacted smoothly and high levels of enantioselectivities were attained. The centrifugation of the reaction mixture (3000 rpm, 20 min) led to the successful separation of the colloidal dispersion into three phases; the upper, middle, and bottom phases corresponded to the water, surfactant, and organic layers, respectively.

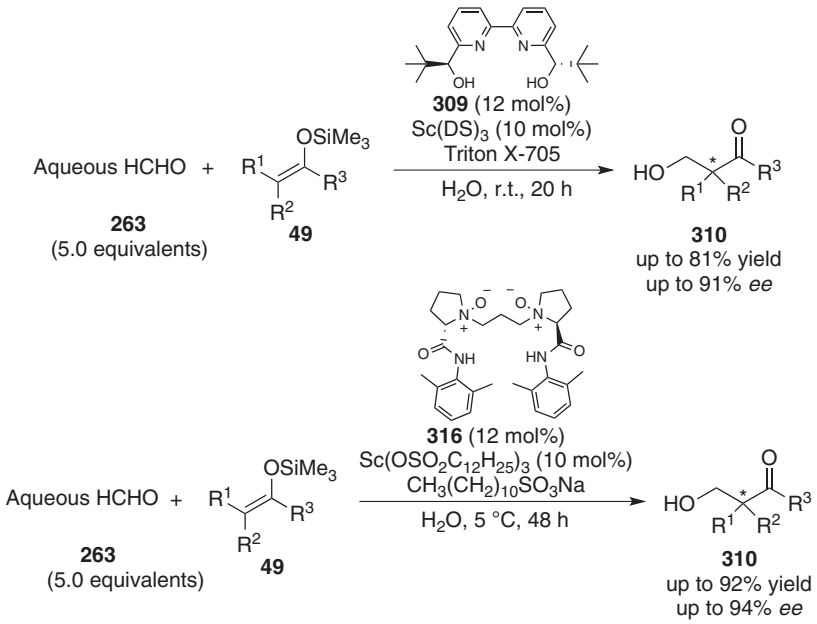
Chiral disulfonated binaphthyl dialkyl ethers with $Ga(OTf)_3$ and $Cu(OTf)_2$ catalyzed the asymmetric Mukaiyama aldol reactions more efficiently than that of $Sc(OTf)_3$ in water with moderate *ee* values (up to 52% *de*, 48% *ee*). The chiral amphiphile was employed in an equimolar amount relative to the substrate.[207] PEG-supported chiral bis(oxazoline) has been employed in combination with copper(II) salts as a catalyst for the Mukaiyama aldol reaction between ketene silyl acetal of methyl isobutyrate in water (up to 41% yield, 63% *ee*).[208] Silica–Sc–IL system was also rendered asymmetric by the addition of **309** (up to 28% yield, 66% *ee*). The high solubility of these ligands in water allowed a very convenient catalyst-recycling procedure. Chiral surfactants, which have been mainly applied in enantiomer separation by capillary electrochromatography[209], was prepared (sulfonate derivatives of chiral 1,1′-BINOL) and utilized for the Mukaiyama aldol reaction in water in the presence of $Cu(OTf)_2$ as Lewis acid (up to *syn*/*anti* = 76/24, 48% *ee* (*syn*)).[210]

Table 7 Effect of Brønsted acids on asymmetric Mukaiyama aldol reactions in water



Entry	*Brønsted acid*	*Yield*	*syn/anti*[a]	*ee (syn)*[b]
1	None	23	3.2/1	58
2	$PhCO_2H$	76	2.7/1	63
3	(+)-CSA	34	3.0/1	63
4	PhOH	15	2.7/1	60
5	4-$O_2NC_6H_4CO_2H$	63	2.4/1	64
6	4-$MeOC_6H_4CO_2H$	73	3.0/1	61
7	Lauric acid	76	2.8/1	69

[a]Determined by NMR analysis.
[b]Determined by chiral HPLC analysis.



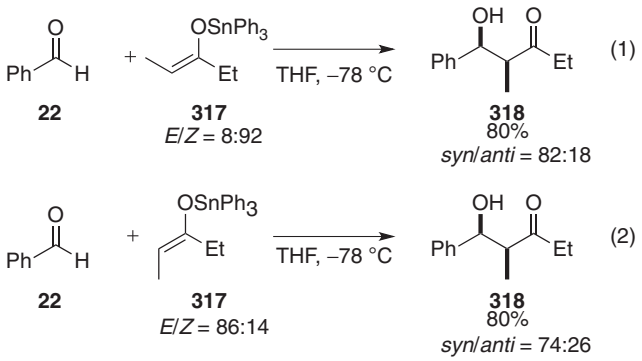
Scheme 82 Asymmetric Mukaiyama aldol reaction using formaldehyde in water.

2.09.4 Tin Enolate

2.09.4.1 Tin Enolates in Aldol Reactions

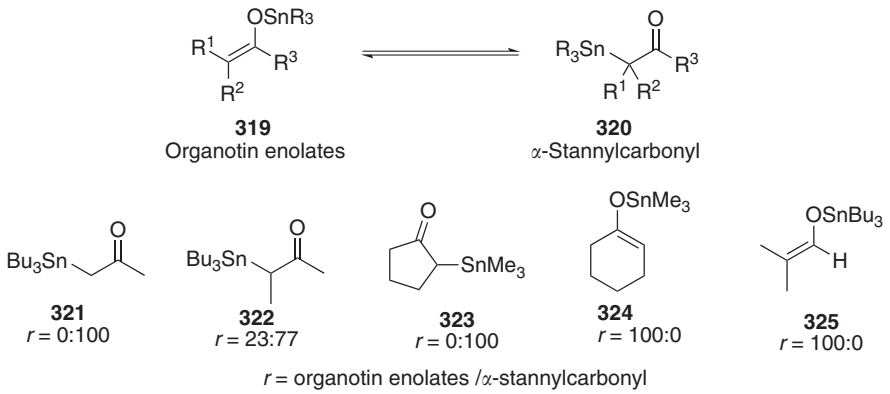
Organostannanes are very useful reagents for the construction of C–C bonds (e.g., Stille coupling, allylation, crotylation, etc.). In 1981, Yamamoto et al. introduced tin(IV) enolates for aldol reactions and found that the reaction between triphenyltin enolates such as **317** and aldehydes led to the *syn*-aldol product with a relative good diastereoselectivity that was independent of the

tin-enolate geometry (Scheme 83).[211] In order to explain this selectivity, Yamamoto proposed an acyclic transition state. Tin(IV) enolate was synthesized from lithium enolate homolog by a treatment with triphenyltin chloride and directly used without purification in aldol reaction. The authors supposed that this *in situ* reaction and the excess of triphenyltin chloride can affect the geometrical integrity of tin(IV) enolate (i.e., isomerization to (*Z*)-triphenyltin enolates during the reaction) and explain the no diastereoselectivity change in function of tin(IV) enolate configurations.



Scheme 83 *Syn*-selective aldol reaction via triphenyltin(IV) enolates.

Before further discussion of tin(IV) enolates in aldol reactions, it is noteworthy to mention that organotin(IV) enolates (vinyloxystannanes), containing an Sn–O bond, are in metallotropic equilibrium with the corresponding Sn–C-bonded α-stannylcarbonyl compounds (stannylotropy) (Scheme 84).[212]

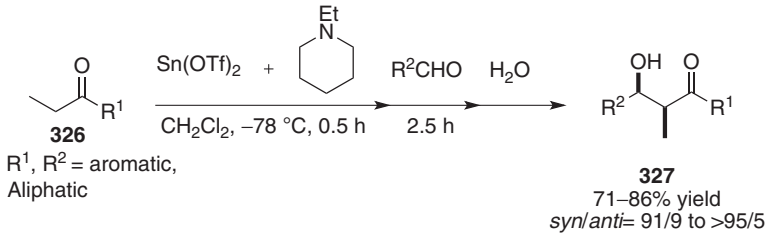


Scheme 84 Enol/keto proportions of stannyl enolates in $CDCl_3$ solution at room temperature.

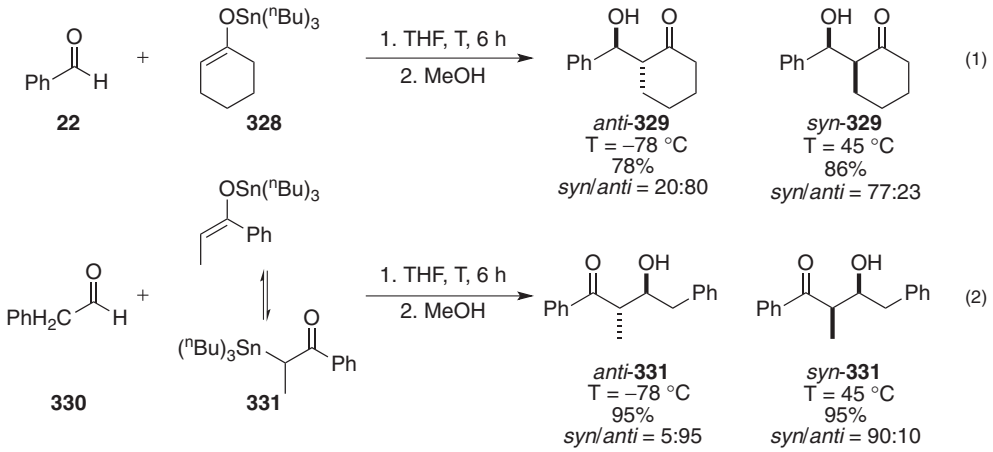
The position of the equilibrium has been studied by IR, and ^{1}H-, ^{115}Sn-, ^{117}Sn-, and ^{119}Sn-NMR spectroscopies[213] and was determined that the equilibrium is dependent on the nature of the substituents, particularly their size, with bulky groups favoring the less-sterically congested enol form. In addition to the structure, solvent, temperature, and ligands of the tin can also affect the keto/enol equilibrium. In the presence of an appropriate ligand (HMPT, Bu_3PO, or Bu_4NBr), the 5-coordinate enolate complex is formed and the *de facto* the equilibrium is shifted in favor of the enolate and the enolate nucleophilicity is enhanced.[214]

In 1982, Mukaiyama et al. reported the *in situ* preparation of tin(II) enolates, from ketones using tin triflate and amine, and utilized them as nucleophiles for aldol-type reactions with aldehydes to provide *syn*-aldol adducts with good diastereoselectivity (Scheme 85).[215] Stannous triflate was treated with ketones in the presence of *N*-ethyl piperidine in dichloromethane at −78 °C to generate *in situ* the tin(II) enolates that can react with aldehydes to afford *syn*-adducts. Ketone–ketone cross-couplings are also successfully carried out in this tin(II) aldol reactions. When a chital diamine derived from L-priline was used as a chiral ligand of Sn, asymmetric aldol reactions were successfully carried out and the desired aldol adducts were obtained in high yields with high diastereo- and enantioselectivities.[216]

Stille and coworkers also reported a similar work by utilizing isolated tin(IV) enolates and observed opposite diastereoselectivity (Scheme 86).[217] The reaction of the enol stannanes of cyclohexanone **328** or propiophenone **331** – present in both form, O-enolate and C-enolate – with various aldehydes under kinetic control (−78 °C) gave predominantly the *anti*-aldols (95:5). This selectivity was ascribed to the presence of a cyclic transition state. At a higher temperature (+45 °C) predominant *syn*-selectivity was observed.



Scheme 85 Aldol reactions using *in situ*-prepared tin(II) enolates.



Scheme 86 Stereoselective aldol condensations of organotin reagents with aldehydes.

2.09.4.2 Achiral Lewis Acid-Catalyzed Reactions

By analogy with the developed chemistry with silyl enol ethers or ketene silyl acetals and due to limited studies on tin(IV) enolates, Yamamoto and coworkers decided to investigate the effect of different Lewis acid (metal triflate) on the diastereoselectivity of the aldol-type reaction.[218] The reaction between tributyl(cyclohex-1-en-1-yloxy)stannane **328** and benzaldehyde in the presence of 5 mol% of different metals triflates were conducted (Table 8).

Among them, TMSOTf and $Pd(OTf)_2$ provided the *anti*-aldol adduct with high selectivity in THF (Table 8, entries 8 and 11). In contrast, moderate *syn*-selectivity was observed for $Cu(OTf)_2$ and $Zn(OTf)_2$ (Table 8, entries 5 and 6). The authors observed that the *anti*/*syn* ratio of the aldol reaction is dependent on the solvent, and higher *anti*-selectivity was generally obtained in less-polar solvent.

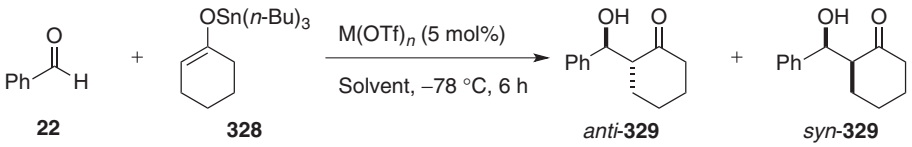
2.09.4.3 Chiral Lewis Acid-Catalyzed Reactions

In 1997, Yamamoto and coworkers reported an enantioselective aldol reaction of tin enolates with aldehydes in the presence of a chiral binaphthol silver triflate complex.[219] This was the first example in which tin enolates were utilized for the enantioselective Mukaiyama aldol reaction. *O*- or *C*-Tin enol ethers were prepared from the enol acetate on reaction with tributyltin methoxide in the absence of solvent. In the presence of *R*-BINAP–AgOTf complex (Scheme 87), the reaction proceeded at low temperature (−20 °C).

Although acyclic and unsubstituted (R^3, R^4 = H) tributyltin enolates provided only modest yields and enantioselectivities, the chiral silver-catalyzed aldol-type reaction with cyclic or substituted enol stannanes with benzaldehyde furnished the desired products with excellent diastereo- and enantioselectivities. In contrast to the Mukaiyama aldol reaction with silicon enolates, the dependency on the enolate geometry to the diastereoselection implied that cyclic transition states A and B are predominant (Figure 5). Similar six-membered cyclic models containing a BINAP-coordinated silver atom instead of tributylstannyl group were also considered as possible alternatives when the transmetalation to silver enolate is sufficiently rapid.

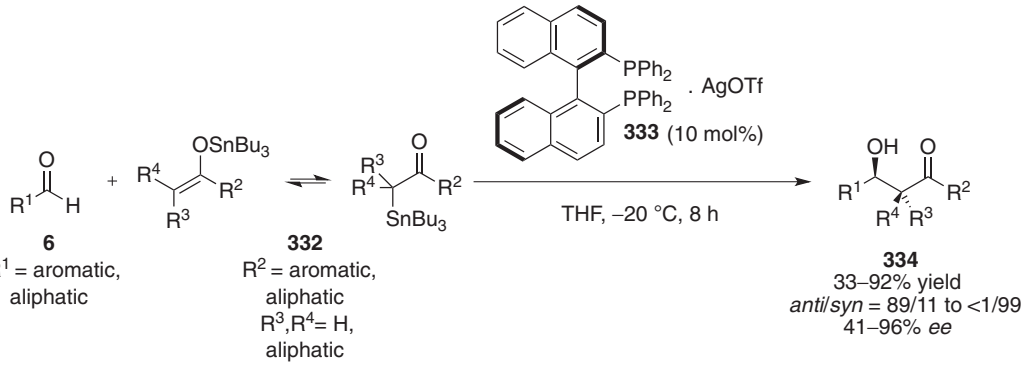
Continuing their investigations in the field of tin enolates, Yamamoto and coworkers reported the first example of the aldol-type reaction using a catalytic amount of tin enolate in an asymmetric version with BINAP–silver (I) complex previously employed.[220] Yamamoto discovered a rapid formation of tin enolate in high yield (>99% after 30 min) from enol trichloroacetate, when the latter was treated with tributyltin methoxide at −20 °C in THF. Based on this observation, Yamamoto proposed the possibility of the catalytic use of tin methoxide to activate enol trichloroactates.

Table 8 Diastereoselective aldol reaction of tin enolate in the presence of various metal triflates



Entry	*M(OTf)*$_n$	*Solvent*	*Yield (%)*[a]	*anti/syn*[b]
1	–	THF	16	57:43
2	AgOTf	Toluene	67	82:18
3	CuOTf	Toluene	75	89:11
4	$Cu(OTf)_2$	Toluene	77	47:57
5	$Zn(OTf)_2$	THF	59	35:65
6	$Zn(OTf)_2$	Toluene	78	57:43
7	$Sn(OTf)_2$	THF	69	74:26
8	TMSOTf	THF	72	87:13
9	$Y(OTf)_3$	THF	64	66:34
10	$Sc(OTf)_3$	THF	53	45:52
11	$Pd(OTf)_2$	Toluene	76	94:4

[a]Isolated yield.
[b]Determined by ^{1}H-NMR.



Scheme 87 Diastereoselective and enantioselective aldol reactions of tin enolates with aldehydes catalyzed by BINAP–AgOTf complex.

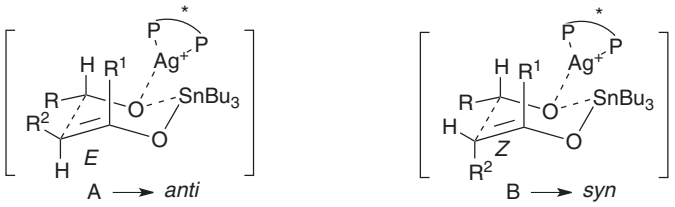
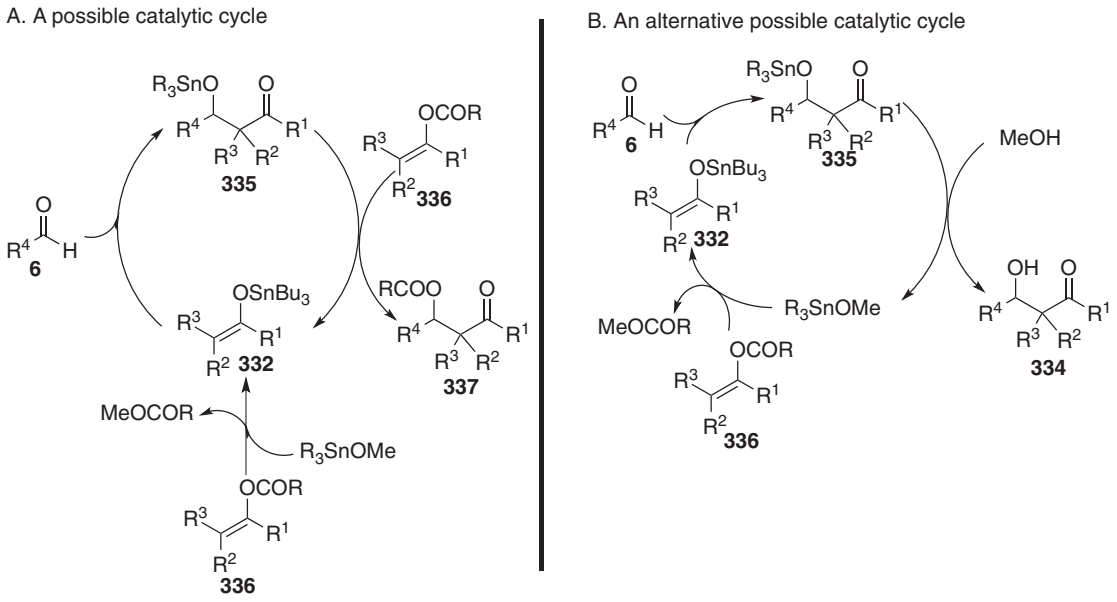
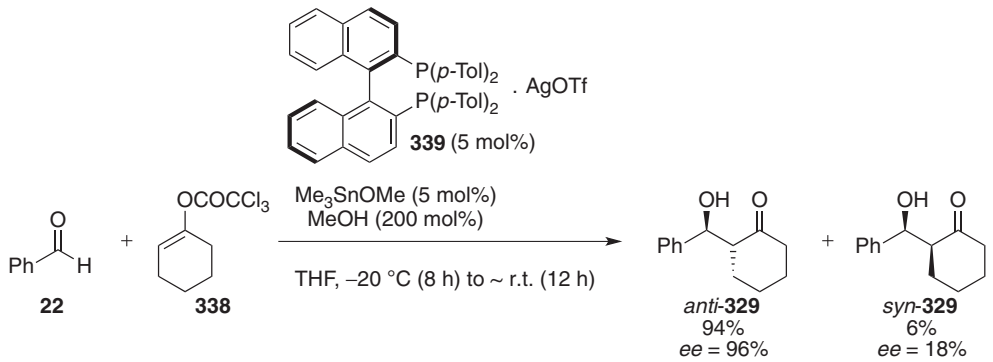


Figure 5 Probable cyclic transition-state structures.

Yamamoto proposed two plausible catalytic pathways to achieve this goal. First, R_3SnOMe reacts with an enol trichloroacetate to generate the trialkyltin enolate species and methyl trichloroacetate. Subsequent addition of the tin enolate to an aldehyde provides the aldol adduct. Two divergent pathways may occur during the hydrolysis step when either the aldol adduct – containing the tin group – reacts with another enol trichloroacetate to continue the catalytic cycle (Scheme 88) or protonolysis of the alkoxide by MeOH regenerates the tin methoxide (Scheme 88). Based on this hypothesis and their previous work (i.e., *R*-BINAP–silver catalyst) high enantioselective aldol catalysis in tin was conducted (Scheme 89). For example, the trichloroacetate **338** derived from cyclohexanone reacted with aldehydes in the presence of catalytic amount of methoxytrimethylstannane, the BINAP–silver complex, and 2 equivalents of methanol to give *anti*-aldol product **329** with high yield, and high diastereoselectivity and enantioselectivity.



Scheme 88 Possible catalytic cycles.



Scheme 89 Enantioselective aldol reactions catalyzed by tin methoxide and BINAP–silver(I) complex.

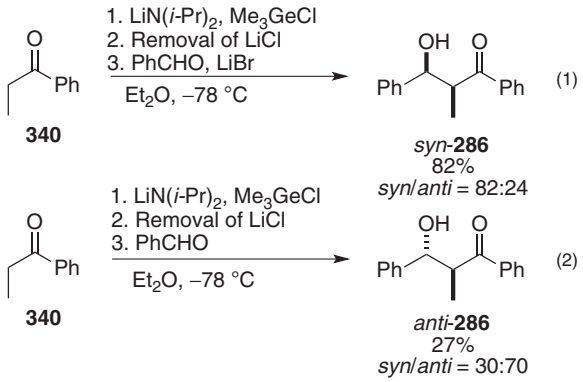
2.09.5 Germanium and Lead Enolates

The use of other metals belonging to the group IV elements (i.e., germanium and lead) for aldol reaction is more anecdotal and there is practically no example in the literature. However, in 1988, Yamamoto and Yamada, intrigued by opposite diastereoselectivity observed using tin enolates when compared to the silicon enolates, decided to investigate germanium enolates as nucleophiles.[221] The trimethylgermanium enolates were generated *in situ* from lithium enolates with trimethylgermanium chloride, and reacted directly with aldehydes. Yamamoto noted the important effect of lithium chloride on the selectivity; with predominantly the *syn*-aldol product in the presence of lithium chloride, whereas the absence of lithium chloride affords the *anti*-aldol preferentially (Scheme 90).

2.09.6 Summary

The aldol reactions of group IV enolates have been surveyed. Among group IV enolates, silicon enolates are the most useful enolates in modern organic chemistry. As surveyed, a variety of silicon enolates have been developed, and they serve as convenient carbonyl equivalent donors through nucleophilic additions to aldehydes and ketones in the presence of even a substoichiometric amount of Lewis acid catalyst. Asymmetric variants of these reactions have also been intensively studied over the past two decades, and silicon enolates have played a vital role in the development of many useful chiral Lewis acids.

Despite their versatile utility, there are some drawbacks in silicon enolate chemistry, mainly from the viewpoint of atom economy. Although most silicon enolates are isolable and storable, they are prepared from the corresponding carbonyl compounds using stoichiometric amounts of bases such as lithium diisopropylamide (LDA) or tertiary amines. Moreover, adducts of



Scheme 90 Aldol condensation via germanium enolates.

silicon enolates have Si–heteroatom bonds, which are cleaved in many cases by treatment with an acid or a fluoride anion to provide the desired products. If catalytic generation of silicon enolates could be attained, these drawbacks would be overcome. An ideal catalytic cycle includes *in situ* generation of silicon enolates using a substoichiometric amount of a silicon Lewis acid and a base. However, this catalytic cycle has long been thought to be unlikely because silicon species might be incorporated into products through the formation of a covalent bond between silicon and a heteroatom of the products.

Catalytic use of silicon enolates in asymmetric reactions may be one of future goals in this field.

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2.10 The Aldol Reaction: Transition Metal Enolate

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This chapter is a revision of the previous edition chapter by Ian Paterson, Vol. 2, pp 301–319, © 1991, Elsevier Ltd.

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Glossary

Aldol donor and acceptor The aldol reaction unites two carbonyl compounds to form a β-hydroxy-carbonyl product, where one carbonyl compound acts as a nucleophilic donor via its enolate or enol form and the other, a ketone or an aldehyde, acts as an electrophilic acceptor.

Carbon-bound, oxygen-bound, and oxa-π-allyl enolate Transition metal enolates can exist in three forms: η^1-*C*-bound metal enolates, η^1-*O*-bound metal enolates, and η^3-π-allyl metal enolates. Interconversion among these three forms is often observed.

Carroll rearrangement This reaction is a thermal rearrangement for preparing γ,δ-unsaturated ketones from β-keto allyl esters. The reaction is a variant of the Claisen rearrangement, accompanied by decarboxylation.

Double stereo-differentiation; matched and mismatched pair of reactants When a chiral reagent (e.g., chiral enolate) and a chiral substrate (e.g., chiral aldehyde) react to produce a pair of diastereomers with a new stereogenic center(s), the diastereoselectivity of the reaction is governed by the multiplicativity of the diastereofacial selectivity of both components. When the sense of the selectivity of the two components is in the same direction (matched pair), the enhanced selectivity is achieved. In contrast, for the pair of components with the opposite sense of the selectivity (mismatched pair), the lower selectivity is observed.

 doi:10.1016/B978-0-08-097742-3.00211-1

Pincer complex A pincer complex consists of a metal center and a pincer skeleton. The pincer skeleton is a tridentate ligand connected to the metal via at least one metal–carbon σ bond. The most common type of pincer skeleton is an aryl anion, which is connected to the metal via only one metal–carbon σ bond; substituents *ortho* to this σ bond are held in a fixed position and can coordinate to the metal site via O, S, N, or P donor atoms. The inflexibility of the pincer–metal interaction confers high thermal stability to the pincer complexes.

Tishchenko reaction In the Tishchenko reaction, 2 equivalents of a nonenolizable aldehyde (RCHO) undergo coupling with disproportionation to produce an ester (RCO_2CH_2R). The reaction is catalyzed by aluminum alkoxides [$Al(OR')_3$] and proceeds through a mechanism involving intramolecular 1,3-hydride shift of a hemiacetal intermediate [$(R'O)_3Al^-–O–CH(R)–O–C^+(H)R$].

Vinylogous aldol reaction In the vinylogous aldol reaction, an 'extended dienolate' generated from a γ-enolizable α,β-unsaturated carbonyl compound undergoes addition to an acceptor carbonyl substrate at the γ-position to give an α,β-unsaturated δ-hydroxy-carbonyl compound.

Zimmerman–Traxler-type transition state In 1957, Howard E. Zimmerman and Marjorie D. Traxler proposed that some aldol reactions have 'six-membered transition states having a chair conformation.' The transition-state model predicts that *E*- and *Z*-enolates give rise to *anti* and *syn* products, respectively. The factors that control selectivity are the preference for placing substituents equatorially and the avoidance of *syn*–pentane interactions in the six-membered transition state.

2.10.1 Introduction

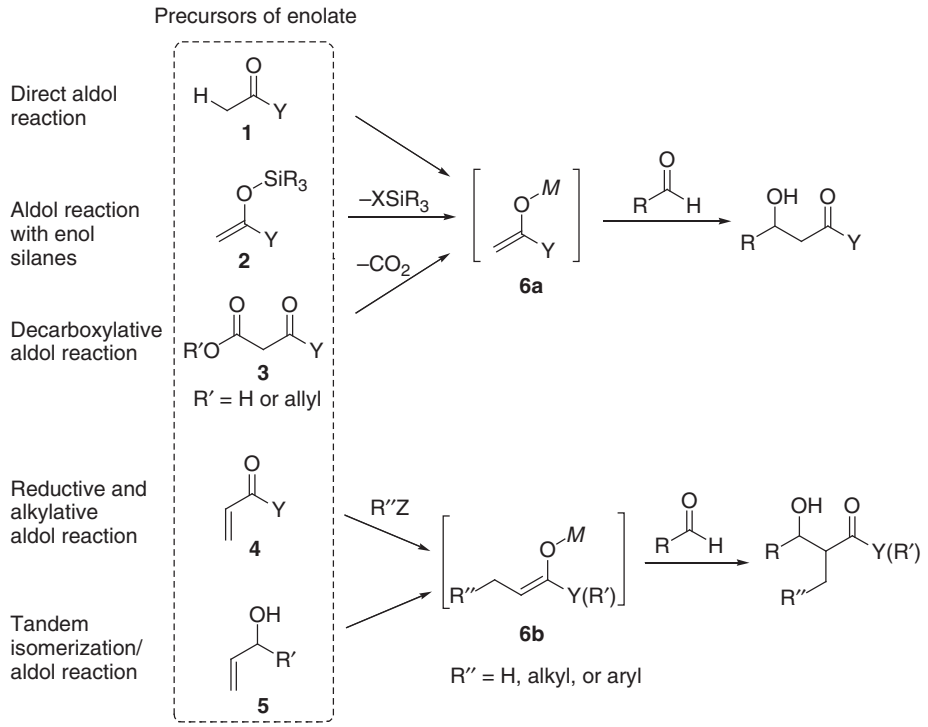
The aldol reaction is one of the most powerful methods for the construction of carbon–carbon bonds in organic chemistry. A donor and an acceptor carbonyl component are coupled in this process to generate one or two stereogenic center(s) in the resulting β-hydroxy-carbonyl (aldol) product. Over the years, the control of the chemo-, regio-, diastereo-, and enantioselectivity of the aldol reaction has been a leading subject in synthetic organic chemistry. Various powerful stoichiometric methods have been developed to enable the selective formation of desired aldol products in a highly controlled manner. The stoichiometric aldol reactions have been employed as reliable, standard tools in organic synthesis. However, the high levels of control in the aldol process are achieved by sacrificing the atom economy with stoichiometric by-product formation. In recent years, considerable interest has been devoted to the development of atom-economical, catalytic methods that retain the high level of chemo-, regio-, diastereo-, and enantio-control. To date, a variety of catalysts for the aldol reaction have been reported, including enzymes, catalytic antibodies, organocatalysts, and metal complexes.[1,2] In such a diverse and rapidly growing area of the aldol reaction, this chapter will focus on the catalytic reaction involving transition metal enolate intermediates.[3]

One of the most intriguing features of the transition-metal-catalyzed aldol reaction is its excellence in versatility with respect to the aldol donor components. Although other catalytic systems have been mostly applied to ketone and aldehyde donors leading to β-hydroxyketones and -aldehydes, a wide range of aldol products including β-hydroxyesters, -amides, and -nitriles are obtained in a highly controlled manner by the transition metal catalysis. To describe the basis and degree of developments in the transition-metal-catalyzed aldol reactions, this chapter is organized into the categories of donor components (Scheme 1). In the direct aldol reaction, active transition metal enolate species **6a** are generated from carbonyl compounds **1** by deprotonation. Catalytic systems in which enolates **6a** are formed *in situ* from enol silanes **2** and malonic acid derivatives **3** with the loss of the silyl and the carboxyl group, respectively, have been reported. α,β-Unsaturated carbonyl compounds **4** serve as precursors of metal enolates **6b** through conjugate reduction and conjugate addition in the reductive and alkylative aldol reaction, respectively. Finally, in the tandem isomerization/aldol reaction, the enolate intermediates are generated by isomerization of allylic alcohols **5**.

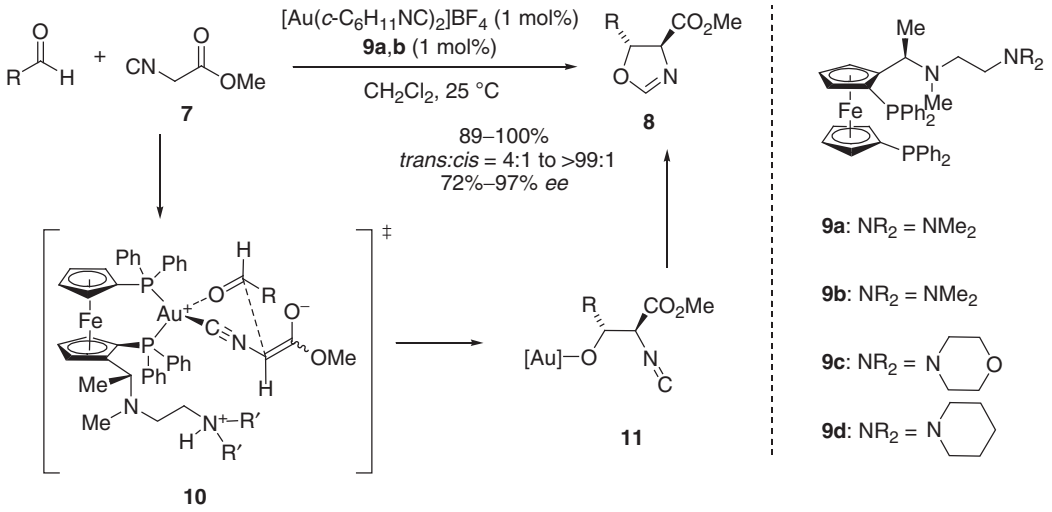
2.10.2 Transition-Metal-Catalyzed Direct Aldol Reaction

In 1986, the first metal-catalyzed enantioselective direct aldol reaction was reported by Ito et al. (Scheme 2).[4,5] The Au(I)-catalyzed reaction of aldehydes with α-isocyanoacetate **7** produces *trans*-oxazolines **8** in high yield, diastereo- and enantioselectivity. The observed stereoselectivity was rationalized by a transition-state model **10**, in which the chiral cationic Au(I) catalyst binds both the enolate and the aldehyde, with the morpholine amino group of ligand **9** acting as a base to generate the enolate. The seminal report clearly demonstrated that transition metal catalysis is one of the most powerful approaches to the direct aldol reaction endowing chemo-, regio-, diastereo-, and enantioselectivity that had been hitherto achieved by stoichiometric processes. Since this pioneering work, significant advances have been made in the field of the transition-metal-catalyze direct aldol reaction.[2,6]

The metal-catalyzed direct aldol reaction contains three reaction steps (Scheme 3): deprotonation of donor carbonyl compound **ii** by metal complex [M]Z to generate enolate **iv** (step 1), addition of enolate **iv** to acceptor carbonyl compound **i** to give metal aldolate **v** (step 2), and protonation of aldolate **v** to form aldol product **iii** (step 3). The diastereo- and enantioselectivity of the reaction are determined in step 2, where the multiple coordination ability of transition metals plays a distinctive role in stereocontrol as exemplified in transition-state structure **10**. When enolate formation (step 1) and protonation of aldolate (step 3) take place concurrently (equation 5), the most straightforward catalytic cycle for the direct aldol reaction is established, in which



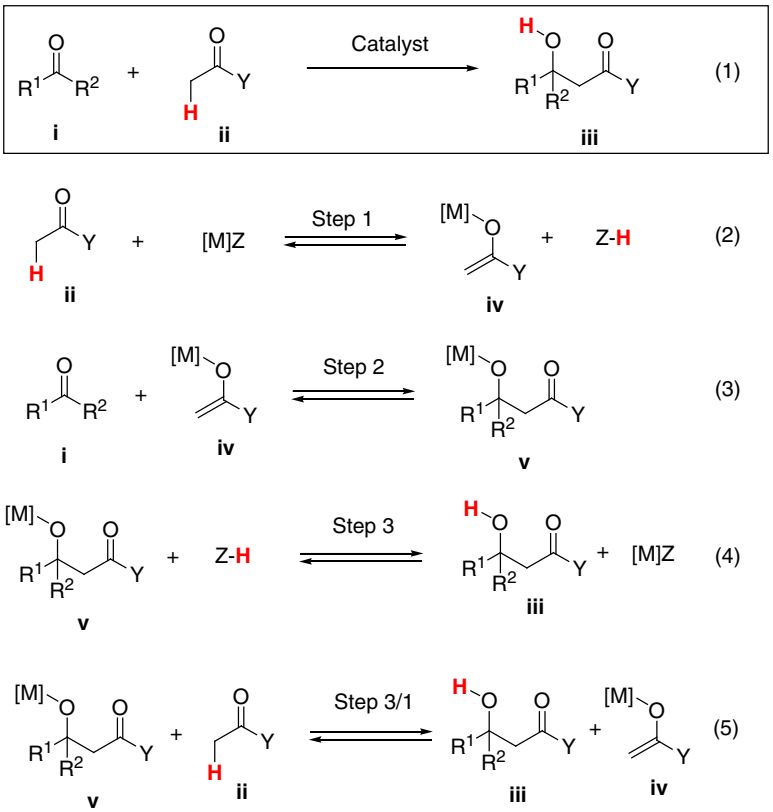
Scheme 1



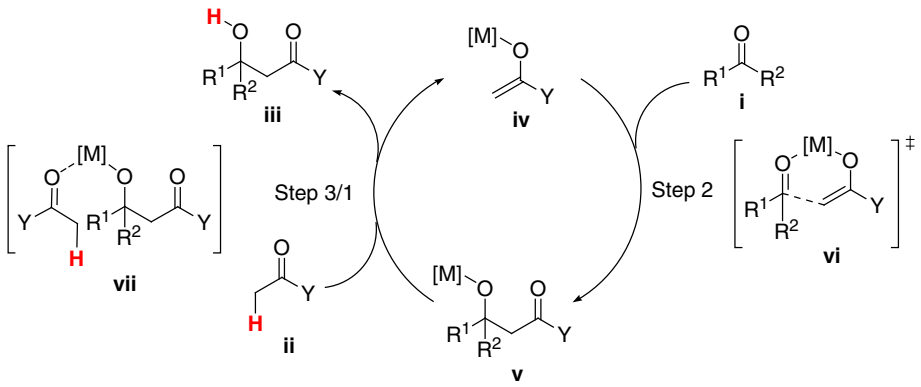
Scheme 2

metal aldolate **v** serves as a base (i.e., [M]*Z*) to generate enolate **iv** with simultaneous formation of product **iii** (Scheme 4). However, direct aldol reactions involving such simple catalytic cycle are relatively uncommon.

Addition of metal enolate **iv** (step 2) is inherently a reversible process. To achieve high diastereo- and/or enantioselectivity, it is indispensable that aldolate **v** picks up a proton before undergoing retro-aldol process. Otherwise, kinetically controlled stereoselectivities in step 2 would be severely eroded. For this reason, several methods involving modified catalytic cycles have been developed to facilitate protonation of the aldolate intermediates and to suppress the retro-aldol process. Another crucial issue in the direct aldol reaction is the chemoselective enolization of donor carbonyl compounds in the presence of enolizable aldehydes or ketones in step 1. In particular, the less acidic carboxylic acid derivatives require the harsh conditions for their deprotonation as aldol doors, limiting the scope-compatible acceptor carbonyl compounds. A transition metal catalyst such as soft Lewis acid has been extensively exploited to solve this problem through a specific activation and enolization of soft aldol donors, such as thioamides and nitriles.[7]



Scheme 3



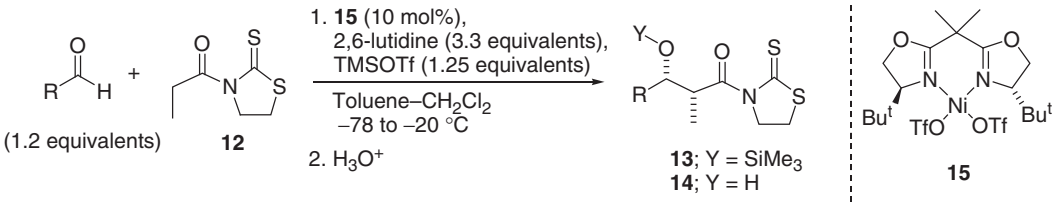
Scheme 4

2.10.2.1 Carboxylic Acid Derivatives as Donor

2.10.2.1.1 Thiazolidinethione

In 2003, the first example of catalytic enantioselective direct aldol reaction with carbonyl donors in the carboxylic oxidation state was reported by Evans et al. (Scheme 5).[8] In the presence of [Ni((*S*,*S*)-Bu^t-box)](OTf)$_2$ **15** (10 mol%), 2,6-lutidine (3.3 equivalents), and TMSOTf (1.25 equivalents), thiazolidinethione **12** underwent addition to a variety of aldehydes (1.2 equivalents) to produce silyl aldolates **13**, which was hydrolyzed to give the corresponding *syn*-aldol products **14** with high diastereo- and enantioselectivity (Table 1). Notably, addition to aliphatic enolizable aldehydes proceeded efficiently without competing self-aldol process (entries 4–6).[9]

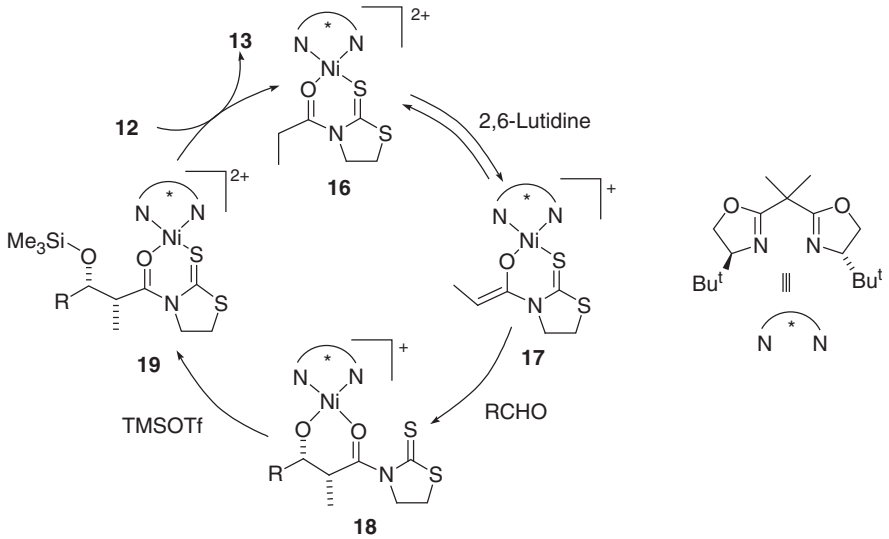
It was proposed that thiazolidinethione **12** is activated selectively in the presence of aldehydes by complexation to the soft dicationic Ni(II) with the soft thiocarbonyl group (Scheme 6). The resulting catalyst–substrate complex **16** is deprotonated by 2,6-lutidine to yield enolate **17**. Subsequent carbonyl addition affords aldolate **18**, which is trapped by TMSOTf, facilitating catalyst turnover through decomplexation of the product as a silyl aldolate **13**. An alternative mechanism involving initial silylation of



Scheme 5

Table 1 Ni(II)-catalyzed enantioselective direct aldol reaction of thiazolidinethione **12** (Scheme 5)

Entry	*R*	*Yield (%)*	ds	ee *(%)*
1	Ph	81	16:1	97
2	4-ClC_6H_4	81	9.0:1	91
3	MeCH=CH	46	13:1	97
4	Me	86	32:1	93
5	Et	84	32:1	90
6	Pr^i	70	49:1	90



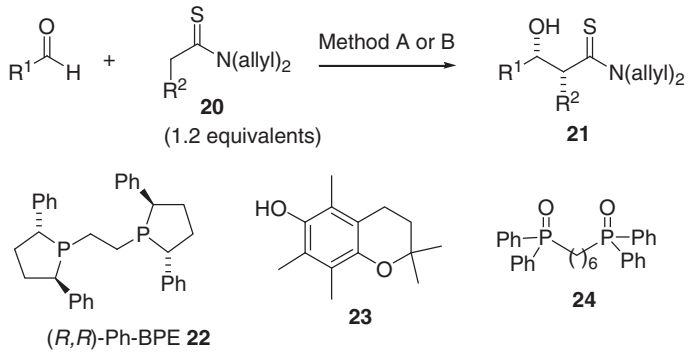
Scheme 6

enolate **17** followed by the Mukaiyama aldol process was considered to be unlikely based on the fact that no silyl ketene acetal derived from **12** was observed under the reaction conditions in the absence of aldehydes.

2.10.2.1.2 Thioamides

Shibasaki and coworkers have developed a Cu(I)-catalyzed enantioselective direct aldol reaction of thioamides taking advantage of the high affinity of a Cu(I) atom (soft acid) to a sulfur atom (soft base) (Scheme 7).[10] The reaction does not require more than stoichiometric amounts of base and silylating reagent. Thus, treatment of aliphatic aldehydes and thioacetamide **20** (R^2=H) (1.2 equivalents) in the presence of $[Cu(CH_3CN)_4]PF_6$, (*R*,*R*)-Ph-BPE **22**, and the Li alkoxide of chromanol derivative **23** (3 mol% each) in *N*,*N*-dimethylformamide (DMF) at −60 °C afforded the corresponding aldol products **21** in excellent yield and enantioselectivity (Table 2, Method A). Although nonbranched aliphatic aldehydes are susceptible to self-condensation under basic conditions, the cross-aldol products were obtained without the formation of self-aldol products (entries 1–4). For the reaction of aromatic aldehydes, modified conditions, using 4-$MeOC_6H_4OLi$ as a base and tetrahydrofuran (THF)-DMF as solvents, were employed to suppress retro-aldol reaction and *β*-elimination of the corresponding aldol product (entry 5).[11]

Application of the conditions optimized for thioacetamides to the reaction of thiopropionamide **20** (R^2=Me) resulted in poor stereoselectivities, likely due to a rapid retro-aldol process via a sterically more congested Cu(I) aldolate intermediate. For such



Method A: $[Cu(CH_3CN)_4]PF_6$, (*R,R*)-**22**, Li alkoxide of **23** (3 mol% each), DMF, –60 °C

Method B: $[Cu(CH_3CN)_4]PF_6$, (*R,R*)-**22**, Li alkoxide of **23** (3 mol% each), **23** (2 mol%), **24** (1.5 mol%), THF, –70 °C

Scheme 7

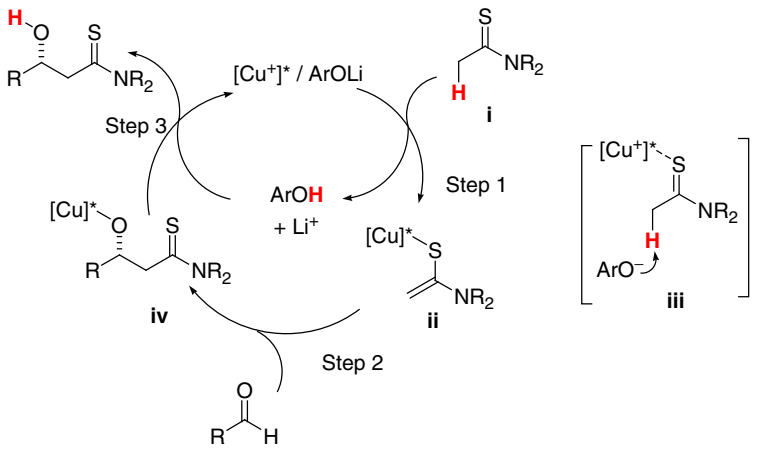
Table 2 Cu-catalyzed enantioselective direct aldol reaction of thioamides and aldehydes (Scheme 7)

Entry	R^1	R^2	*Method*	*Yield (%)*	ds	ee *(%)*	*References*
1	Pr^i	H	A	87	–	91	10a
2	*c*-C_6H_{11}	H	A	98	–	92	10a
3	*n*-C_7H_{15}	H	A	80	–	89	10a
4	$PhCO_2(CH_2)_7$	H	A	82	–	90	10a
5[a]	Ph	H	A	94	–	79	11a
6	Pr^i	Me	B	93	>20:1	95	10b
7	*n*-C_7H_{15}	Me	B	95	>20:1	97	10b
8	$BzO(CH_2)_7$	Me	B	96	>20:1	97	10b
9	$TBSOCH_2CH_2$	Me	B	74	20:1	95	10b
10	2-$PyCH_2CH_2$	Me	B	76	20:1	92	10b

[a]The reaction was carried out with $[Cu(CH_3CN)_4]PF_6$, **22**, and 4-$MeOC_6H_4OLi$ (5 mol% each) in THF–DMF (1:7) at –70 °C.

reaction, the use of less basic THF as a solvent together with a hard Lewis basic additive, 1,6-bis(diphenylphosphino)hexane dioxide (**24**) (1.5 mol%), was effective (Method B).[10b] Under modified conditions, the reaction of aliphatic aldehydes proceeded efficiently to give the corresponding *syn*-aldol products **21** with high diastereo- and enantioselectivity (entries 6–10).

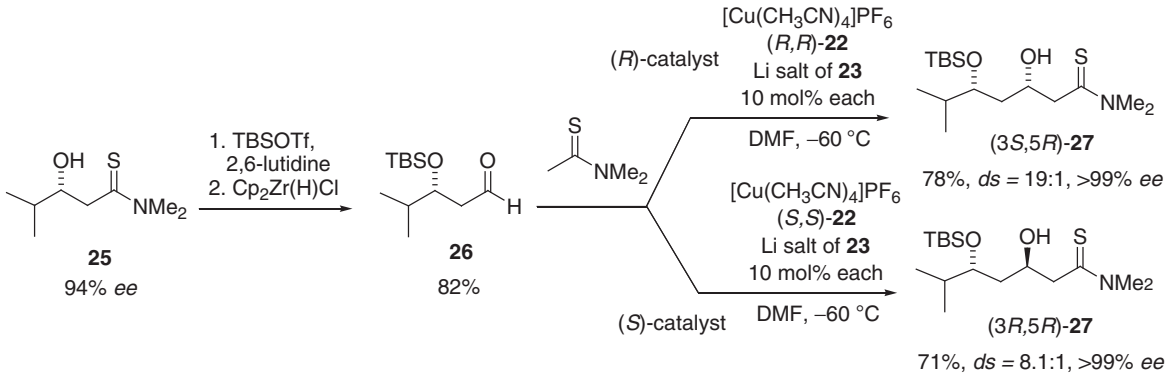
A catalytic cycle involving the selective activation of thioamides by complexation with a soft cationic Cu(I) atom has been proposed (Scheme 8).[12] Deprotonation of the thioamide–Cu complex **iii** by the phenoxide (a hard base) (step 1) and subsequent



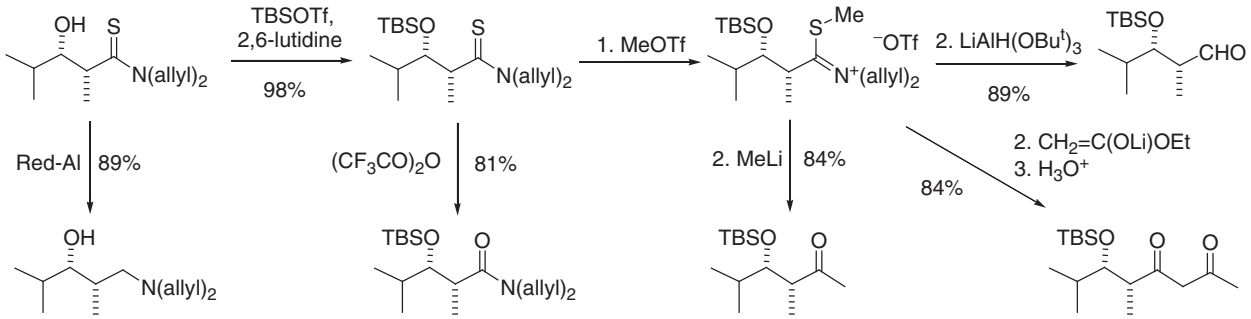
Scheme 8

addition of the resulting Cu(I) thio-enolate **ii** to an aldehyde (step 2) produces Cu(I) aldolate **iv**. The crucial proton transfer between aldolate **iv** and the phenol (step 3) completes the catalytic cycle. Lewis basic solvent DMF and additive **24** are likely to facilitate the catalyst turnover step.

The enantioselective direct aldol reaction was successfully applied to 1,3-diol synthesis (Scheme 9).[10b] Aldol product **25** (94% *ee*) was converted to aldehyde **26** by *tert*-butyldimethylsilyl protection followed by reduction with Schwartz reagent. Subjection of **26** to the second direct aldol reaction with the catalyst derived from (*R,R*)-**22** and (*S,S*)-**22** stereoselectively afforded (3*S*,5*R*)-**27** and (3*R*,5*R*)-**27**, respectively, indicating that the newly constructed stereogenic center was largely controlled by chirality of the catalyst. The thioamide functionality in the aldol products was transformed to a variety of functional groups other than aldehyde, demonstrating the synthetic utility of the reaction (Scheme 10).[10b]

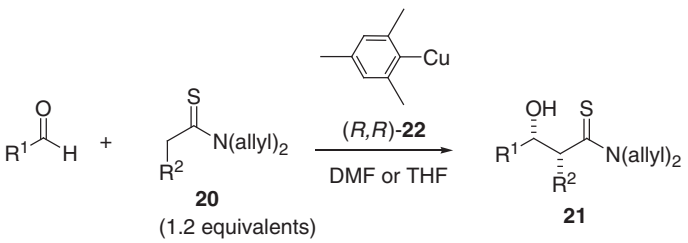


Scheme 9



Scheme 10

Recently, Shibasaki and coworkers reported a simplified catalyst system comprising mesitylcopper and (*R,R*)-Ph-BPE **22**, which exhibited a comparable or improved catalytic efficiency without using Li aryloxides as an additive (Scheme 11).[12,13] The reaction of aliphatic aldehydes with thioacetamide **20** (R^2=H) (1.2 equivalents) was carried out at 3 mol% catalyst loading in DMF at −60 °C (Method A), affording the corresponding aldol products **21** (R^2=H) in high yield and enantioselectivity (Table 3, entries 1–3).



Method A: Mesitylcopper, (*R,R*)-**22** (3 mol% each), DMF, –60 °C

Method B: Mesitylcopper, (*R,R*)-**22** (0.5 mol% each), THF, –70 °C

Scheme 11

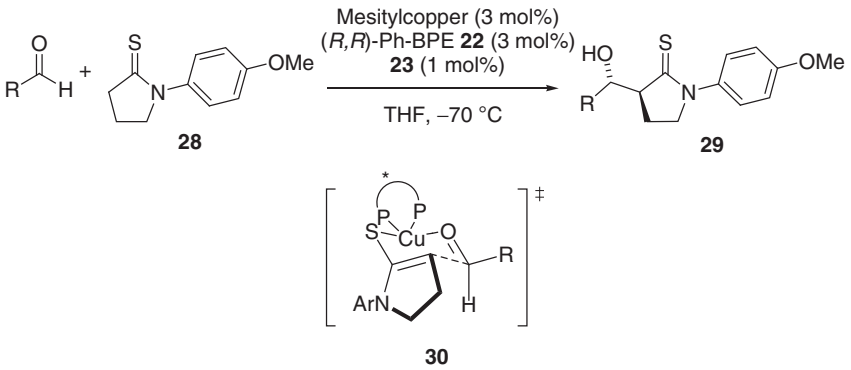
For thiopropionamide **20** (R^2 = Me), highly *syn*-selective and enantioselective reaction was achieved when the reaction was performed with 0.5 mol% of the catalyst in THF at −70 °C (Method B) (entry 4). Interestingly, the reaction at 3 mol% catalyst loading resulted in a significantly decreased stereoselectivity (entry 5).

Table 3 Cu-catalyzed enantioselective direct aldol reaction of thioamides and aldehydes (Scheme 11)

Entry	*R^1*	*R^2*	*Method*	*Yield (%)*	ds	ee *(%)*	*References*
1	Pr^i	H	A	81	–	94	12
2	*n*-C_7H_{15}	H	A	79	–	89	12
3	$PhCO_2(CH_2)_6$	H	A	66	–	89	12
4	Pr^i	Me	B	91	>20:1	95	13
5[a]	Pr^i	Me	B	99	2.5:1	4[b]	13

[a]The reaction was carried out at 3 mol% catalyst loading.
[b](2*S*,3*R*)-Product was obtained as a major enantiomer.

The catalyst system comprising mesitylcopper and (*R*,*R*)-Ph-BPE **22** also exhibited high performance in the enantioselective direct aldol reaction of thiolactam **28** (Scheme 12).[13] The reaction was carried out at 3 mol% catalyst loading in the presence of phenolic additive **23** (1 mol%) in THF (Table 4). Without the additive, decrease in the catalytic efficiency was observed. The reaction exhibited high *anti*-selectivity, in contrast to the *syn*-selectivity observed for thiopropionamide. The *anti*-selectivity was rationalized by a Zimmerman–Traxler-type transition state **30**[14] involving a fixed Cu(I) (*E*)-enolate. In contrast, selective generation of (*Z*)-enolate from thiopropionamide was suggested to explain the opposite *syn*-selectivity.



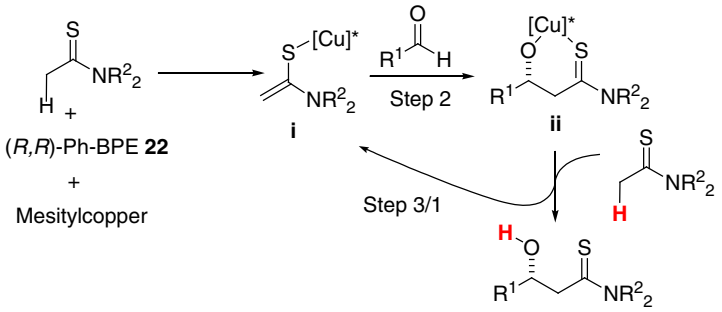
Scheme 12

Table 4 Cu(I)-catalyzed enantioselective direct aldol reaction of thiolactam **28** and aldehydes (Scheme 12)

Entry	*R*	*Yield (%)*	ds	ee *(%)*
1	Pr^i	94	17:1	94
2	Me_2CHCH_2	92	13:1	96
3	Et	95	10:1	92
5	$EtOOC(CH_2)_2$	89	7.1:1	95
6	2-$Py(CH_2)_2$	74	10:1	95
7	$Pht(CH_2)_2$[a]	74	>20:1	82
8	Ph	88	1.3:1	95

[a]Pht = *N*-Phthaloyl.

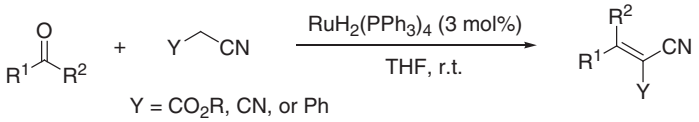
The straightforward catalytic cycle depicted in Scheme 4 is established in the catalytic system with mesitylcopper. Thus, chiral Cu(I) thio-enolate **i** is first generated by deprotonation of a thioamide with mesitylcopper in the presence of chiral ligand **22** (Scheme 13). The enolate then undergoes addition to an aldehyde to give aldolate **ii**, which, as a base, picks up a proton from the starting thioamide to give the aldol product with simultaneous regeneration of enolate **i**. The beneficial effect of phenolic additive **23** in the reaction of thiolactams was suggested to be due to the acceleration of the proton-transfer process, similar to the catalytic cycle depicted in Scheme 8.



Scheme 13

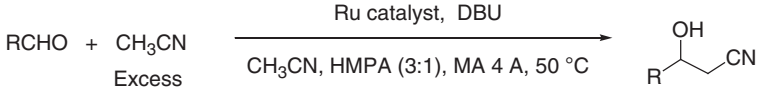
2.10.2.1.3 Nitrile

The aldol-type reaction of nitriles leading to β-hydroxynitriles is of synthetic importance since the cyano group is recognized as a masked carboxylic group and an amino group. In 1989, Murahashi and coworkers reported a Ru-catalyzed condensation of aldehydes and ketones with nitriles to give α,β-unsaturated nitriles (equation 6).[15,16] Activated nitriles, such as cyanoacetates and malononitrile, underwent condensation in the presence of $RuH_2(PPh_3)_4$ (3 mol%) in THF at room temperature. In the presence of 1,3-bis(diphenylphosphino)propane (dppp) (6 mol%), phenylacetonitrile also underwent the condensation reaction. Mechanistic study based on the isolation of key intermediates and reaction kinetics revealed that a Ru(0) species undergoes oxidative addition to the α C–H bond of the nitriles (YCH_2CN) to generate a Ru(II) complex [HRu(YCHCN)], which reacts with carbonyl compounds. Although dehydration of the aldol-type intermediate proceeded under these conditions, their study demonstrated the possibility of transition metal catalysis for developing a direct aldol-type reaction with nitriles.



(6)

To achieve chemoselective generation of α-metalated species from simple alkylnitriles of relatively low acidity (pK_a~31) in the presence of enolizable carbonyl acceptors, soft Lewis basic character of the cyano group has been exploited through a specific activation with soft Lewis acidic transition metal catalysts. After screening various soft Lewis acid metal complexes and additives, Shibasaki and coworkers found that the direct aldol-type reaction of acetonitrile could be realized by a combined use of cationic Ru(II) catalysts and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 14).[17] Treatment of aldehydes with a catalyst system comprising $[CpRu(PPh_3)(CH_3CN)_2]PF_6$ (**31a**) (5 mol%), DBU (5 mol%), and $NaPF_6$ (10 mol%) in an acetonitrile/hexamethylphosphoramide (HMPA) mixed solvent system (3:1) at 50 °C afforded the corresponding aldol-type products in excellent yields (Table 5, Method A). The reaction was applicable to a variety of aldehydes including aromatic, α,β-unsaturated, and α-branched aliphatic aldehydes. For more enolizable, nonbranched aldehydes, self-condensation proceeded extensively in the presence of $NaPF_6$. The limitation was overcome by the use of cationic Ru(II) diphosphine complex $[CpRu(PPh_3)_2(CH_3CN)]PF_6$ (**31b**).[18] Thus, complex **31b** (10 mol%) in combination with DBU (25 mol%) chemoselectively catalyzes addition of acetonitrile to such enolizable aldehydes to afford the corresponding β-hydroxynitriles in good yields (Method B).



Method A: $[CpRu(PPh_3)(CH_3CN)_2]PF_6$ (**31a**) (5 mol%), DBU (5 mol%), $NaPF_6$ (10 mol%)
Method B: $[CpRu(PPh_3)_2(CH_3CN)]PF_6$ (**31b**) (10 mol%), DBU (25 mol%)

Scheme 14

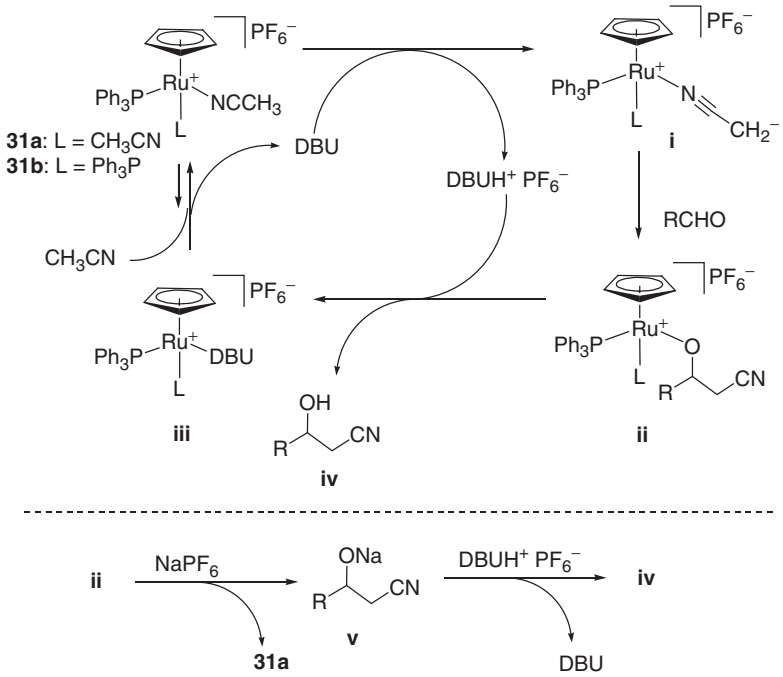
A catalytic cycle shown in Scheme 15 has been proposed based on a mechanistic study.[17,18] NMR and ESI-MS analysis of **31a,b** indicated that Ru(II) coordinated predominantly to acetonitrile, rather than to an aldehyde or HMPA, to activate for deprotonation. Rate-determining deprotonation by DBU produces Ru-bound metalated nitrile **i** (step 1), which undergoes addition to an aldehyde to form Ru(II) alkoxide **ii** (step 2). In Method B, it was postulated that alkoxide **ii** is protonated by $DBUH^+$ PF_6^- to give product **iv** and DBU complex **iii** (L=Ph_3P), which undergoes reversible ligand exchange with acetonitrile to regenerate catalyst **31b** (step 3). This equilibrium is suggested to favor acetonitrile complex **31b** owing to the large steric constraint around the

Table 5 Ru(II)-catalyzed direct aldol-type reaction of acetonitrile and aldehydes (Scheme 14)

Entry	*R*	*Method*	*Yield (%)*	*References*
1	Ph	A	93	17
2	4-ClC_6H_4	A	93	17
3	4-$(MeO_2C)C_6H_4$	A	82	17
4	$PhCH{=}CH_2$	A	84	17
5	$BnOCH_2C(CH_3)_2$	A	77	17
6[a]	*c*-C_6H_{11}	A	82	17
7	C_6H_{13}	B	76	18
8	$CH_2{=}CH(CH_2)_8$	B	63	18
9	$CbzNH(CH_2)_2$	B	74	18
10	$PhCO_2(CH_2)_7$	B	82	18
11	$HO(CH_2)_7$	B	87	18
12	4-$CH_3COC_6H_4(CH_2)_3$	B	75	18

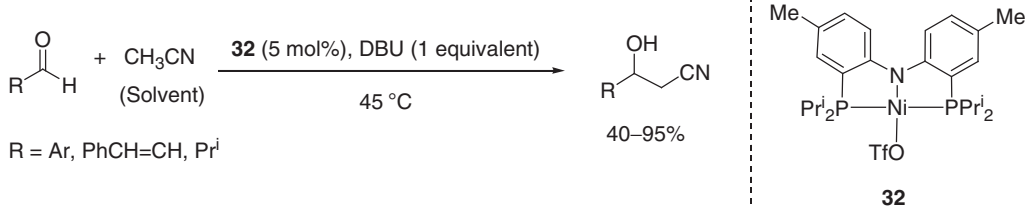
[a]DBU (10 mol%) was used.

Ru center. However, for the sterically less congested monophoshine complex **31a**, a catalytic cycle would be halted at DBU complex **iii** (L=CH_3CN) due to unfavorable equilibrium. In Method A, $NaPF_6$ was added to prevent the formation of **iii** (L=CH_3CN) through cation exchange from alkoxide **ii** (L=CH_3CN) into Na-alkoxide **v** and **31a**.



Scheme 15

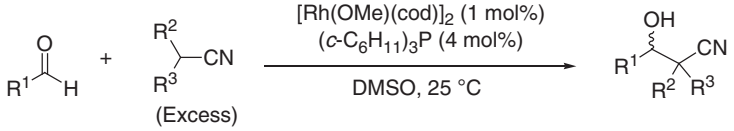
A relevant Ni catalyst system has been reported by Fan and Ozerov (Scheme 16).[19] In the presence of diarylamido-based PNP pincer-type Ni(II) complex **32** (5 mol%) and DBU (1 equivalent), aromatic aldehydes reacted with solvent acetonitrile at 45 °C to



Scheme 16

afford aldol-type products in good-to-high yield. The reaction was applicable to isobutyraldehyde but not to an α-nonbranched aliphatic aldehyde. A catalytic cycle similar to that for Ru(II) catalyst **31b** has been proposed.

A Rh(I)-catalyzed aldol-type reaction of alkylnitriles without using a basic additive has been reported by Saito and coworkers (equation 7).[20] The Rh catalyst was prepared by treatment of $[Rh(OMe)(cod)]_2$ (1 mol%) with $(c\text{-}C_6H_{11})_3P$ (4 mol%) in toluene and used after the removal of the solvent and COD *in vacuo*. The catalyst was highly active to drive the reaction of a variety of aldehydes, including enolizable aliphatic derivatives, with acetonitrile (19 equivalents) in DMSO at 25 °C (Table 6, entries 1–6). Notably, the reaction was applicable also to higher alkylnitriles (entries 7–10). By using 3 equivalents of the nitriles, the corresponding aldol-type products were obtained in high yield, albeit without diastereoselectivity. It was shown that the Rh catalyst is also effective in hydration of the nitrile functionality under essentially neutral pH and ambient conditions.[21] The formal aldol products of acetamide were obtained from aldehydes and CH_3CN in one-pot operation by the catalytic aldol-type reaction followed by hydration using the same Rh catalyst (equation 8).

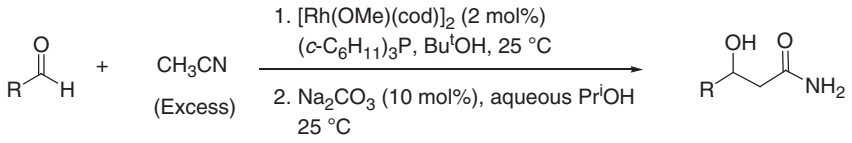


(7)

Table 6 Rh(I)-catalyzed aldol-type reaction of alkylnitriles (equation 7)

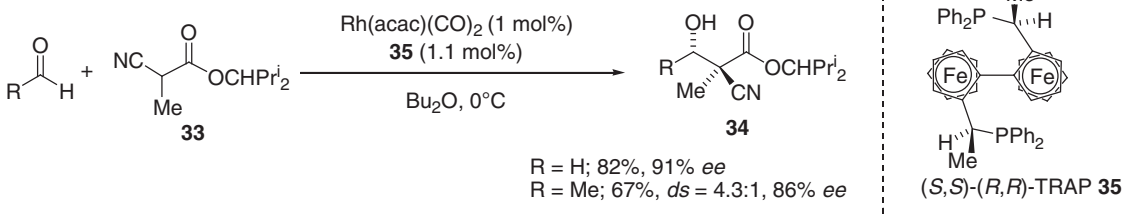
Entry	*R^1*	*R^2*	*R^3*	*Yield (%)*
1	Ph	H	H	99
2	2-$MeOC_6H_4$	H	H	93
3	3-Pyridyl	H	H	99
4	PhCH=CH	H	H	89
5	*c*-C_6H_{11}	H	H	99
6	*n*-Bu	H	H	76
7	Ph	Me	H	98
8[a]	Ph	*n*-Bu	H	81
9	Ph	Ph	H	99
10	Ph	Me	Me	95

[a] $[Rh(OMe)(cod)]_2$ (2 mol%) and $(c\text{-}C_6H_{11})_3P$ (8 mol%) were employed.



(8)

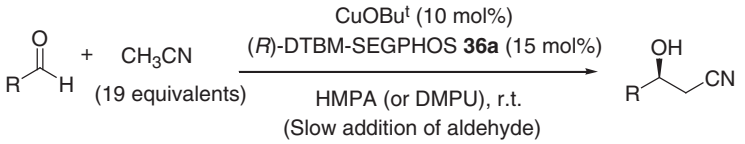
The first example of enantioselective direct aldol-type reaction of nitrile derivatives was reported by Ito and coworkers in 1998 (Scheme 17).[22] In the presence of a catalyst prepared from $Rh(acac)(CO)_2$ (1 mol%) and chiral *trans*-chelating ligand (*S,S*)-(*R,R*)-TRAP **35** (1.1 mol%), the reaction of aqueous solution of paraformaldehyde with 2-cyanopropionate **33** afforded the corresponding product **34** (R=H) in 91% *ee*. The enantioselective reaction was also observed for aliphatic aldehydes, albeit with moderate diastereoselectivity.

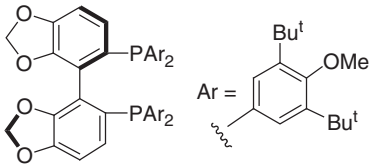


Scheme 17

A Cu(I)-catalyzed enantioselective direct aldol-type reaction of nonactivated acetonitrile of itself was reported by Shibasaki and coworkers in 2005 (Scheme 18).[23,24] In the presence of a catalyst prepared from $Cu(OBu^t)$ (10 mol%) and (*R*)-DTBM-SEGPHOS

36a (15 mol%) in HMPA or *N,N′*-dimethylpropyleneurea (DMPU) at room temperature, the reaction of aldehydes with acetonitrile (19 equivalents) proceeded efficiently to give the aldol-type products in good enantioselectivity. Slow addition of aldehydes and the use of the coordinating solvents were necessary to avoid the self-aldol reaction.



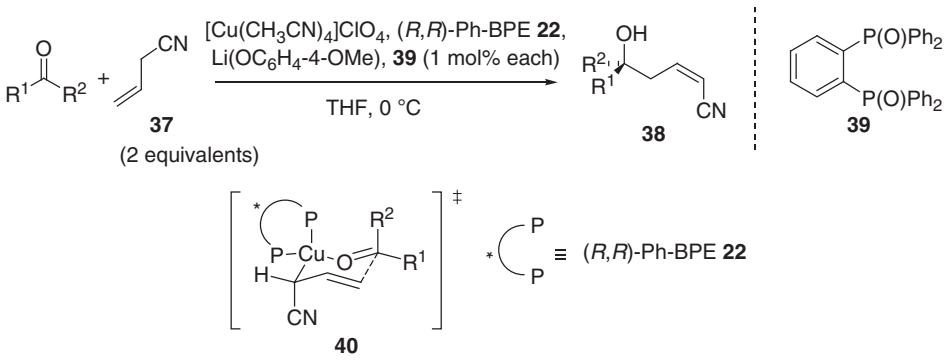


(*R*)-DTBM-SEGPHOS **36a**

R	Yield (%)	*ee* (%)
n-C$_6$H$_{13}$	72	74
c-C$_6$H$_{11}$	91	75
Ph	85	51

Scheme 18

The chiral Cu(I) catalyst system for the enantioselective aldol reaction of thioamide (Scheme 7) was also effective in the aldol-type reaction of ketones[2f] with allylcyanide **37** (Scheme 19).[25] When the reaction was carried out at 0 °C in THF with a catalyst system comprising [Cu(CH$_3$CN)$_4$]ClO$_4$, (*R,R*)-Ph-BPE **22**, Li(OC$_6$H$_4$–4-OMe), and bisphosphine dioxide **39** (1 mol% each), *γ*-addition products (*Z*)-**38** were obtained with excellent enantioselectivity. As shown in Table 7, the reaction is applicable to aromatic and *α,β*-unsaturated ketones. The *Z*-selectivity was rationalized by a six-membered cyclic transition state **40**, in which addition proceeded through a carbon-bound *α*-copper species with the CN group occupying the pseudoaxial position to avoid steric repulsion with the phenyl group of Ph-BPE **22**.



Scheme 19

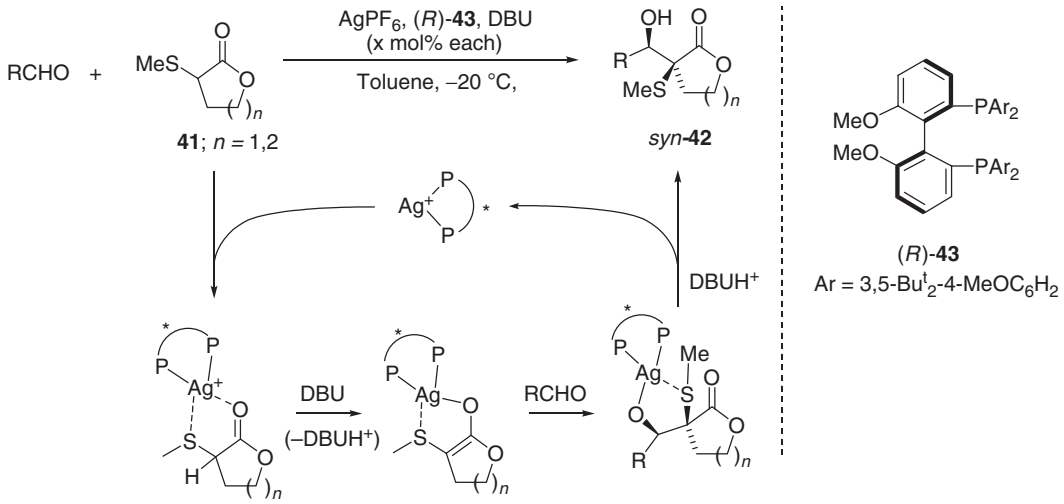
Table 7 Cu(I)-catalyzed enantioselective direct aldol-type reaction of ketones and allylcyanide (**Scheme 19**)

Entry	*R^1*	*R^2*	*Yield (%)*	ee *(%)*
1	Ph	Me	86	99
2	3-MeOC$_6$H$_4$	Me	85	98
3	2-Naphthyl	Me	81	98
4	PhCH=CH	Me	62	88
5	1-Cyclohexenyl	Me	48	>99
6	Ph	Et	68	96
7	1-Tetralone		53	98

2.10.2.1.4 Other donors

A Ag-catalyzed enantioselective direct aldol reaction between aldehydes and *α*-sulfanyl lactones **41** was developed (Scheme 20).[26] Treatment of aldehydes (1.2 equivalents) and lactones **41** in the presence of AgPF$_6$, chiral BIPHEP-type ligand (*R*)-**43**, and DBU

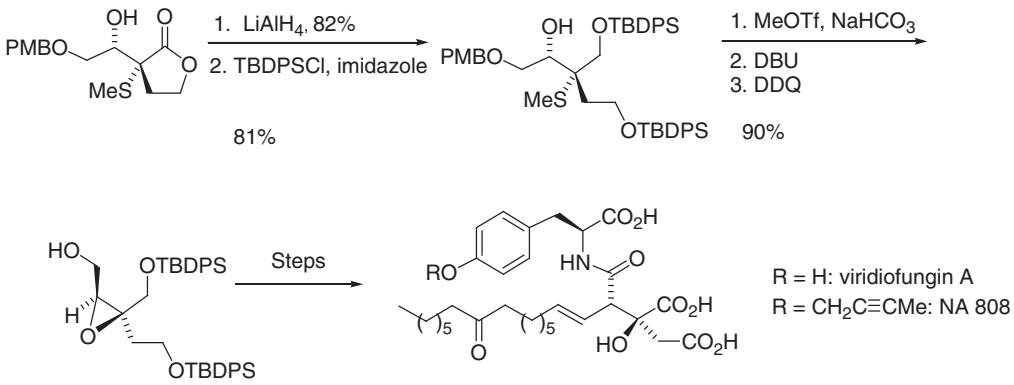
(3 or 5 mol% each) in toluene at −20 °C afforded the corresponding aldol product *syn*-**42** with high diastereoselectivity and with excellent enantioselectivity (Table 8). The reaction is applicable to various combinations of aldehyde acceptors, including enolizable and functionalized ones, and γ- and δ-lactone donors. The sulfide functionality of the products could be utilized through stereospecific displacement as exemplified in the asymmetric syntheses of serine palmitoyl transferase inhibitors, viridiofungin A and NA808 (Scheme 21). It was proposed that the chemoselective activation of lactones **41** was made possible through the specific coordination of the sulfur atom to the soft Ag^+, resulting in the preferential formation of the corresponding enolate intermediated in the presence of enolizable aldehydes.



Scheme 20

Table 8 Ag-catalyzed enantioselective direct aldol reaction of α-sufanyl lactones (Scheme 20)

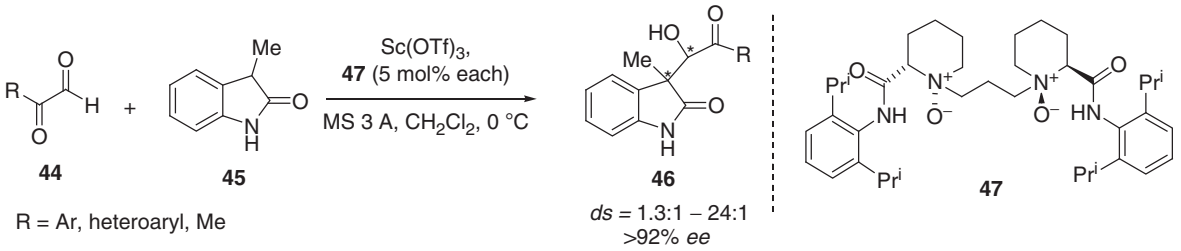
Entry	*R*	*n*	*x (mol%)*	*Yield (%)*	ds	ee *(%)*
1	$PhCH_2CH_2$	1	3	93	18:1	99
2	Bu^i	1	5	81	10:1	99
3	$BnOCH_2$	1	3	85	9:1	99
4	$CbzNHCH_2CH_2$	1	5	89	10:1	98
5	$PhCH_2CH_2$	2	3	79	>20:1	99
6	$BnOCH_2$	2	3	92	>20:1	99



Scheme 21

A Sc(III)-catalyzed enantioselective direct aldol reaction of glyoxal derivatives **44** with oxindole **45** was reported by Feng and coworkers (Scheme 22).[27] In the presence of a complex prepared *in situ* from $Sc(OTf)_3$ and chiral *N*,*N*′-dioxide ligand **47**

(5 mol% each) at 0 °C in CH_2Cl_2, the aldol reaction proceeded efficiently to give the corresponding products **46** diastereo- and enantioselectively. Sc(III)-Enolate intermediates complexed with the dioxide ligand were detected by ESI-MS analysis.



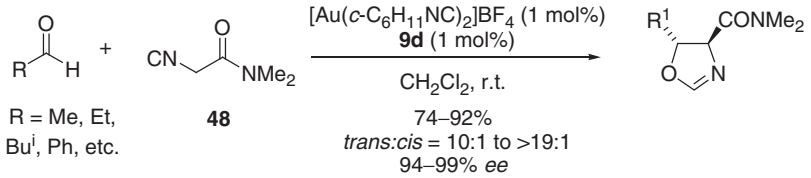
Scheme 22

2.10.2.2 Active Methylene Compounds as Donor

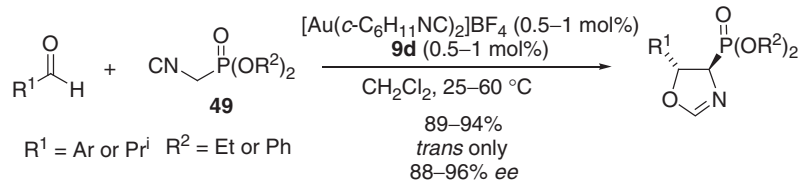
When 1,3-dicarbonyl and other active methylene compounds are employed in the direct aldol reaction, the donor carbonyl compounds with the lower pK_a undergo chemoselective enolization in the presence of enolizable acceptors in step 1 (Scheme 3). However, the retro-aldol process is facilitated due to the stability of the corresponding enolates, resulting in erosion of the kinetic stereoselectivity induced in step 2. For this reason, the aldolization step is often coupled with a subsequent irreversible process in the successful enantioselective direct aldol reactions with relatively acidic carbonyl donors to suppress the retro-aldol process.

2.10.2.2.1 α-Isocyano esters

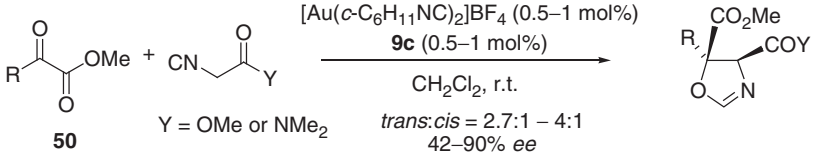
The Au(I)-catalyzed coupling reaction of α-isocyanoacetates and aldehydes (Scheme 2) is a typical example.[4,5] The high diastereo- and enantioselectivity, induced by a chiral cationic Au(I) catalyst, are retained in the oxazoline product **8** through a rapid intramolecular reaction of aldolate intermediate **11**. The scope of the chiral ferrocenylphosphine-Au(I)-catalyzed aldol reaction leading to the oxazoline derivatives has been extensively investigated to establish optimal conditions not only for the reaction of α-isocyanoacetates **7**,[28] α-isocyanoacetamide **48** (equation 9),[29] and isocyanomethylphosphonates **49** (equation 10)[30] as aldol donors but also for the reaction of α-keto esters **50** as acceptors (equation 11).[31]



(9)



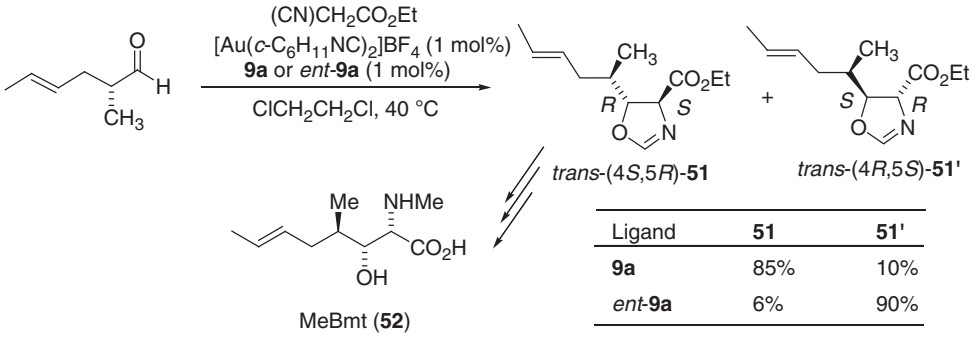
(10)



(11)

The utility of the Au(I)-catalyzed aldol reaction is illustrated in the application to the asymmetric synthesis of unusual amino acid MeBmt (**52**) (Scheme 23).[32] By employing ligand **9a**, the reaction of chiral (*R*)-2-methyl-4-hexenal with ethyl isocyanoacetate afforded the desired *trans*-(4*S*,5*R*)-**51** as a major product, which was transformed to **52** in several steps. When opposite enantiomer *ent*-**9a** was employed as a ligand, *trans*-(4*R*,5*S*)-**51′** was produced with higher diastereoselectivity. This result implies that the

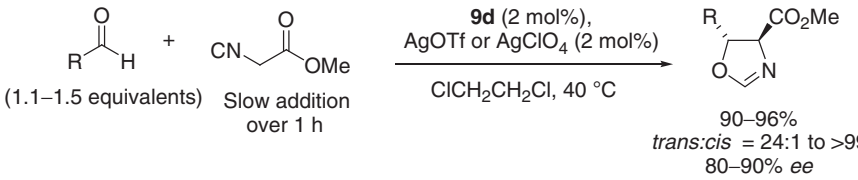
stereochemistry of the reaction is controlled mainly by the chirality of the catalyst with minor influence of the stereogenic center in the aldehyde (matched with *ent*-**9a** and mismatched with **9a**).



Ligand	**51**	**51'**
9a	85%	10%
ent-**9a**	6%	90%

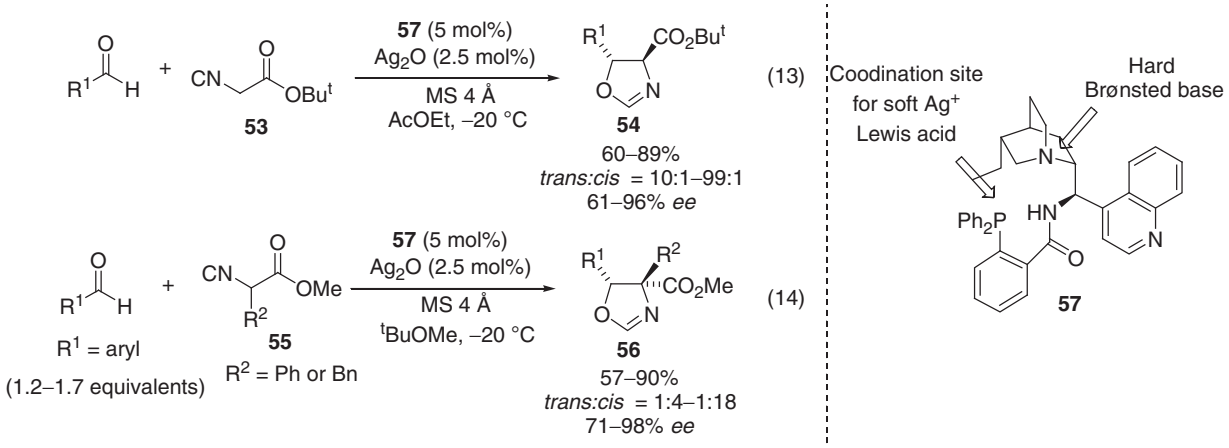
Scheme 23

The chiral ferrocenyl ligand **9d** has been also used in a Ag(I)-catalyzed direct aldol reaction of an isocyanoacetate (equation 12).[33,34] Although the Au(I) complex adopts a tricoordinate structure [**9**·Au$^+$(CN-CH$_2$CO$_2$Me)] even in the presence of excess isocyanoacetate, the corresponding Ag(I) complex readily takes the second molecule of the isocyanide to form a tetracoordinated complex [**9**·Ag$^+$(CN-CH$_2$CO$_2$Me)$_2$], which exhibits decreased selectivity. For this reason, the Ag(I)-catalyzed reaction was carried out with slow addition of the isocyanoacetate to obtain high enantioselectivity.



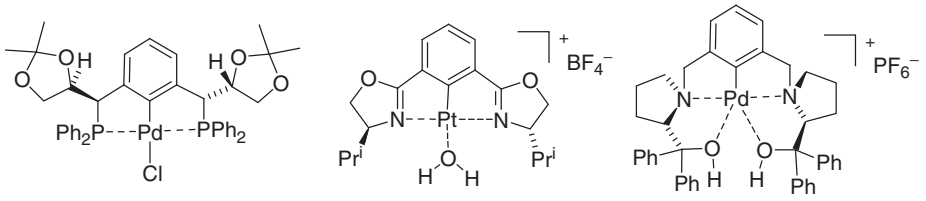
(12)

Recently, a cinchona-derived amino-phosphine ligand **57** was developed by Dixon and coworkers (Scheme 24) with the idea that a selective binding of the phosphine to the soft metal ion would provide a catalyst bearing a hard Brønsted base site, promoting the aldol process through a transition structure analogous to **10** (Scheme 2).[35] With Ag$_2$O (2.5 mol%) and ligand **57** (5 mol%), isocyanocarboxylates **53** and **55** underwent aldol addition to aromatic and hindered aliphatic aldehydes (1.2–1.7 equivalents) to give the corresponding oxazoline derivatives **54** and **56**, respectively, in high diastereo- and enantioselectivity (equations 13 and 14). Interestingly, in the reaction of α-substituted **55**, the reversal in a facial selectivity was observed for the isocyanocarboxylate whereas that for the aldehyde remained the same.



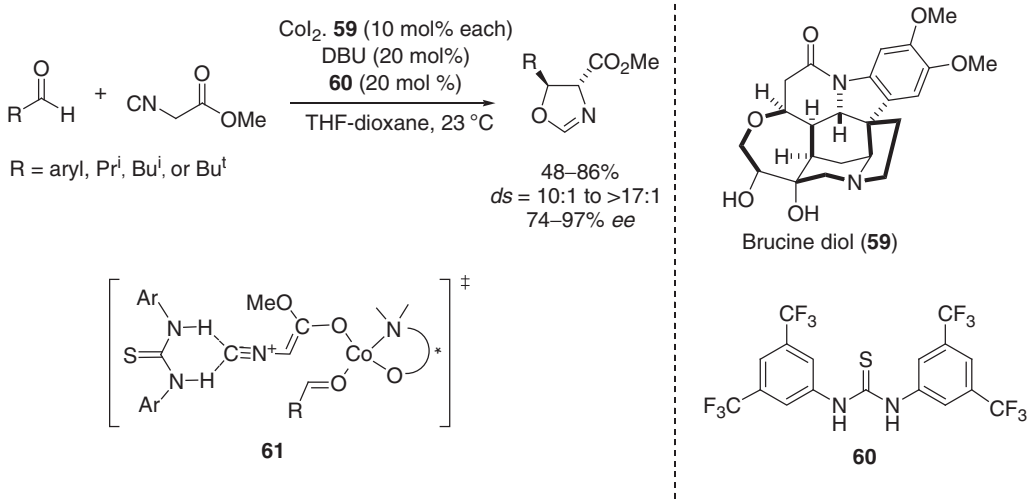
Scheme 24

A variety of chiral Pd(II) and Pt(II) pincer complexes, such as **58a–c**, have been designed and examined as a catalyst for the enantioselective direct aldol reaction of isocyanoacetates.[36,37] So far, only marginal enantioselectivities have been reported.



58a[37b] **58b**[37h] **58c**[37l]

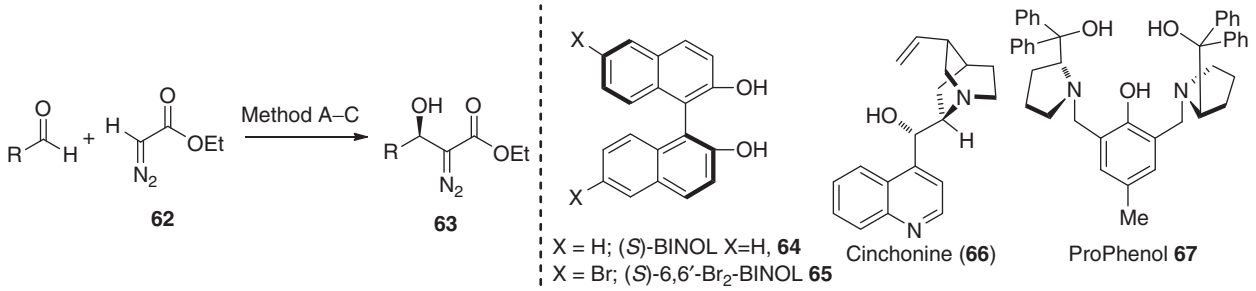
A new type of catalyst system comprising a Co(II) complex derived from CoI_2 and brucine diol **59** (10 mol% each), *N,N′*-diaryl thiourea **60** (20 mol%), and DBU (20 mol%) has been reported by Kim and Oh (Scheme 25).[38] The reaction of aldehydes with methyl isocyanoacetate (1 equivalent) proceeded at room temperature in a mixed solvent of THF–dioxane to give *trans*-oxazoline products with high diastereo- and enantioselectivity. In control experiments, the enantioselectivity was considerably reduced in the absence of either one of the four catalyst components. A mechanism involving a cooperative catalyst activity between the chiral Co (II) catalyst and the achiral thiourea through a transition-state structure **61** has been proposed.[39]



Scheme 25

2.10.2.2.2 α-Diazo esters

α-Diazo esters have a relatively acidic α-proton and can be employed as donor carbonyl components in a catalytic direct aldol reaction leading to β-hydroxy ester derivatives.[40,41] In 2003, Yao and Wang reported the first enantioselective direct aldol reaction of aldehydes with ethyl diazoacetate **62** (Scheme 26, Method A).[42] With a chiral catalyst (20 mol%) derived from BINOL **64**



Method A: $Zr(OBu^t)_4$ (20 mol%), **64** (44 mol%), H_2O (20 mol%), **62** (3 equivalents), DME, –35 °C, 3 days.

Method B: $Ti(OPr^i)_4$ (5 mol%), **64** (5 mol%), **66** (5 mol%), H_2O (15 mol%), **62** (3 equivalents), THF, 0 °C, 6 days.

Method C: Bu_2Mg (10 mol%), **67** (5 mol%), *cis*-1,2-cyclopentanediol (5 mol%), **62** (1 equivalent), THF, –20 °C, 18 h.

Scheme 26

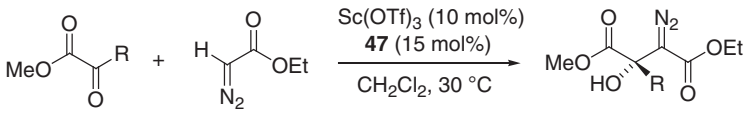
(or 6,6′-dibromo derivative **65**), $Zr(OBu^t)_4$, and H_2O at −35 °C in dimethoxyethane (DME), the aldol reaction of various aldehydes, including enolizable derivatives, proceeded slowly to give β-hydroxy α-diazo esters **63** with moderate-to-good enantioselectivity (Table 9). Recently, Wang et al. reported an improved method with a relevant BINOL-derived chiral Ti(IV) catalyst employing cinchonine (**66**) as an additional component (Method B).[43] Although it is out of the scope of this chapter dealing with transition metal enolates, it should be noted that dinuclear Mg catalyst derived from ProPhenol **67** exhibited high performance and wide scope for aldehydes in this reaction (Method C).[44]

Table 9 Catalytic enantioselective direct aldol reaction of ethyl diazoacetate (Scheme 26)

Entry	*R*	*Method*	*Yield (%)*	ee *(%)*	*References*
1	Ph	A[a]	65	87	42
2	3-$CF_3C_6H_4$	A[b]	61	65	42
3	4-ClC_6H_4	A[b,c]	59	72	42
4	PhCH=CH	A[b]	72	79	42
5	Pr^n	A[b,c]	82	57	42
6	Ph	B	62	91	43
7	4-ClC_6H_4	B	78	87	43
8	*n*-C_5H_{11}	B	74	64	43
9	Ph	C	92	95	44
10	4-ClC_6H_4	C	85	96	44
11	Pr^i	C	56	97	44
12	PhCH=CH	C	50	94	44

[a](*S*)-**65** was used.
[b](*R*)-**64** was used. The product is *ent*-**63**.
[c]$MgBr_2$ (1.5 equivalents) was added.

A Sc(III)-catalyzed enantioselective direct aldol reaction of α-keto esters with ethyl diazoacetate was reported by Feng and coworkers (equation 15).[45] In the presence of a Sc(III) complex prepared from chiral *N*,*N*′-dioxide **47** (15 mol%) and $Sc(OTf)_3$ (10 mol%), the reaction of aromatic α-keto esters in CH_2Cl_2 at 30 °C for 72 h gave the corresponding tertiary alcohols **68** in high enantioselectivity.



68

R = Ph; 76%, 93% *ee*
R = *c*-C_6H_{11}; 35%, 52% *ee*

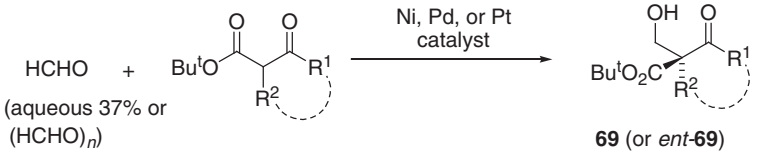
(15)

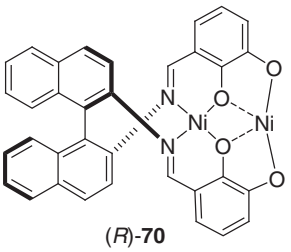
2.10.2.2.3 β-Keto ester

The use of formaldehyde as an acceptor carbonyl component in the transition-metal-catalyzed enantioselective direct aldol reaction of active methylene compounds has been exploited (Scheme 27). Shibasaki and coworkers have reported chiral dinuclear Ni(II)$_2$-salen complex **70** catalyzed reaction (Method A).[46] The catalyst is air-stable and moisture-tolerant, exhibiting excellent enantioselectivity at low catalyst loadings (0.1–1 mol%) in the reaction of β-keto esters using formalin as a formaldehyde source (Table 10, entries 1, 3, and 6–8). To suppress undesirable retro-aldol and background racemic aldol process, the reactions were performed under diluted conditions (0.02 M) with a limited amount of the catalyst. The direct aldol reaction of formaldehyde catalyzed by chiral dicationic Pd(II) complex (*R*)-**71** (Method B) and Pt(II) complex (*R*)-**72** (Method C) was reported by Sodeoka and coworkers.[47] Aldol products *ent*-**69** were obtained in good enantioselectivity by using paraformaldehyde as a source of the aldehyde.

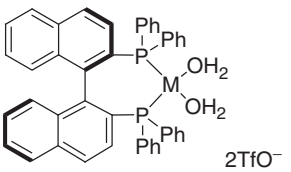
2.10.2.3 Ketones as Donor

The direct aldol reaction of ketones as donors has been extensively developed by the use of chiral organocatalysts via *in situ*-generated enamine intermediates (*see* Chapter 2.07). Efficient chiral metal catalyst systems have been also developed for the reaction of ketones. The pK_a of the α-proton of ketones is in between that of carboxylic acid derivatives and active methylene compounds. Accordingly, selective enolization of the aldol donors in the presence of enolizable aldehydes and suppression of the undesirable retro-aldol process are major concerns in the metal-catalyzed reaction. The issues have been successfully overcome by the development of bimetallic catalysts,[48] such as LLB **73**,[49] Zn_2-ProPhenol **74**,[50] and Et_2Zn-linked-BINOL **75** complexes,[51] which are equipped with both a Lewis acidic site and a Brønsted basic site. The bimetallic catalysts exhibit excellent performance in the reaction of arylketones,[50a] acetone,[50b] α-hydroxyl ketones,[49c,50c,51] methyl vinyl ketone,[50e] and methyl ynones.[49d]



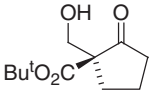
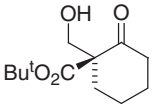
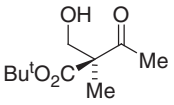
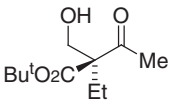

(*R*)-**70**

Method A: (*R*)-**70** (0.1 or 1 mol%), aqueous HCHO (1–10 equivalents), Pr^i_2O, 40 °C.
Method B: (*R*)-**71** (5 mol%), $(HCHO)_n$ (5 equivalents), THF, 0 °C to r.t.
Method C: (*R*)-**72** (5 mol%), $(HCHO)_n$ (5 equivalents), THF, 10 °C.

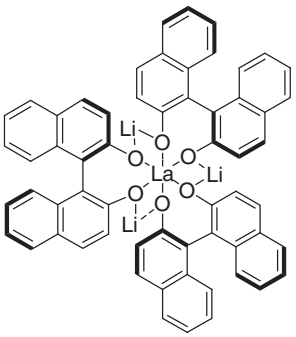

(*R*)-**71**; M = Pd^{2+}
(*R*)-**72**; M = Pt^{2+}

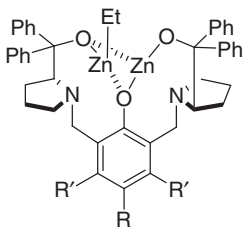
Scheme 27

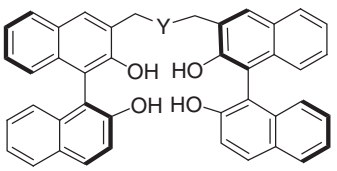
Table 10 Transition-metal-catalyzed enantioselective direct aldol reactions of β-keto esters and formaldehyde (**Scheme 27**)

Entry	R^1	R^2	*Method*	*Mol%*	*Product*	*Yield (%)*	ee *(%)*	*References*
1	$-(CH_2)_3-$		A	0.1	 **69a**	94	93	46
2	$-(CH_2)_3-$		B	5	*ent*-**69a**	82	86	47
3	$-(CH_2)_4-$		A	1	 **69b**	91	85	46
4	$-(CH_2)_4-$		B	5	*ent*-**69b**	84	60	47
5	$-(CH_2)_4-$		C	5	*ent*-**69b**	92	71	47
6	Me	Me	A	0.1	 **69c**	79	81	46
7	Me	Et	A	1	 **69d**	32	79	46
8	Me	Et	A[a]	0.1		79	89	46

[a]Paraformaldehyde was used.

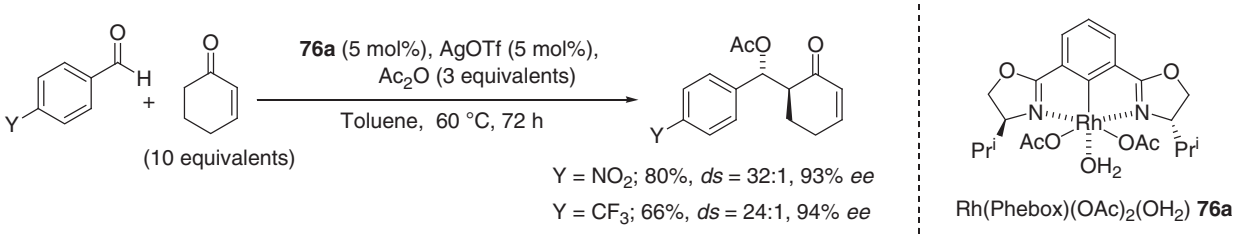

LLB **73**


Zn_2-ProPhenol **74**

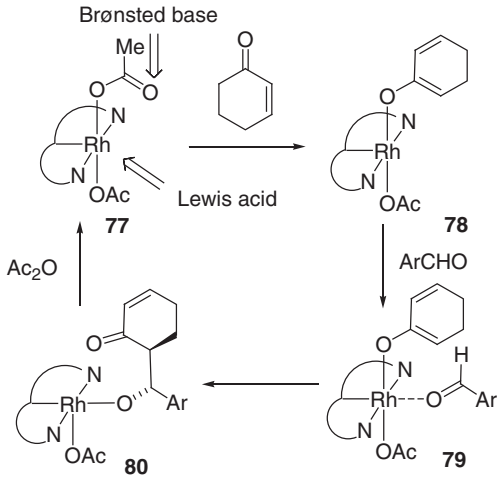

Linked-BINOL **75**

2.10.2.3.1 Cyclic ketone

For transition metal catalysis, Nishiyama and coworkers reported the enantioselective direct aldol reaction of aromatic aldehydes with cyclic enones catalyzed by Rh(III)-Phebox complex **76a** (Scheme 28).[52,53] Reactions were carried out with AgOTf as a cocatalyst and Ac_2O (3 equivalents) at 60 °C in toluene for 72 h. Under these optimized conditions, cyclohex-2-enenone underwent addition to the electron-deficient aromatic aldehydes at the α'-position to give the corresponding *anti*-aldol products as acetates with high diastereo- and enantioselectivity. In this reaction, active Rh-Phebox catalyst **77**, generated by dissociation of the aqua ligand on **76a**, acts as both Lewis acid and Brønsted base at the metal center and at the acetate ligand, respectively (Scheme 29). It was proposed that Rh-enolate **78**, generated by the synergic action of **77**, undergoes diastereo- and enantioselective addition to the aldehydes through a cyclic transition state **79**. The resulting aldolate **80** is trapped by Ac_2O to afford the aldol products with regeneration of **77**. *In situ* acetylation of the aldol products is considered to be effective to suppress retro-aldol process of **80** that would erode diastereo- and enantioselectivity.



Scheme 28



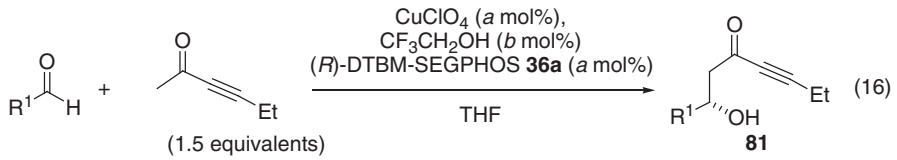
Scheme 29

2.10.2.3.2 Ynone

The approach based on the chemoselective deprotonation through soft metalation by a Cu(I) alkoxide was also applied successfully to the direct catalytic enantioselective aldol reactions between aldehydes and conjugated ynones, which are likely to interact with the soft Cu(I) center at the C≡C bond moiety to form **82** (Scheme 30).[54] With a catalyst system derived from $CuClO_4$, DTBM-SEGPHOS ligand **36a**, and CF_3CH_2OH, the aldol reaction of aldehydes with hex-3-yn-2-one (1.5 equivalents) proceeded efficiently to afford the corresponding aldol products **81** in high yield and enantioselectivity. CF_3CH_2OH was used in excess not only to generate a $Cu(OCH_2CF_3)$ species but also to suppress the retro-aldol reaction of the products that occurs through their reversible conversion to Cu(I) aldolates. A catalytic method for the asymmetric synthesis of dihydropyranones **83** was developed by combining the Cu-catalyzed aldol reaction with subsequent AgOTf-catalyzed oxy-Michael reaction (equation 17). By choosing proper conditions for aliphatic and aromatic aldehydes, a variety of dihydropyranones could be synthesized with high enantioselectivity (Table 11).

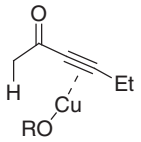
2.10.2.3.3 Ti-catalyzed reaction

Ti(IV) enolates, generated from ketones and carboxylic acid derivatives by the action of $TiCl_4$ and tertiary amines, participate in highly stereoselective aldol reactions.[48e,55] The reaction has been well established[56,1b] and recognized as a reliable method in the

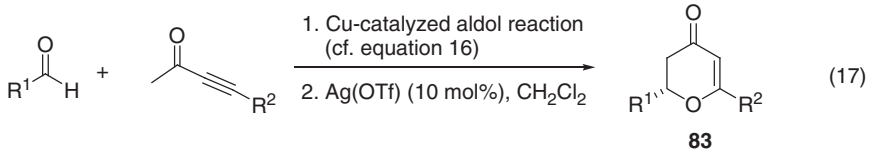


R^1 = Pr^i (Method A: *a* = 3, *b* = 40, –40 °C); 96%, 88% *ee*

R^1 = Ph (Method B: *a* = 5, *b* = 200, –60 °C); 100%, 93% *ee*



82; RO = CF_3CH_2O and/or aldolate



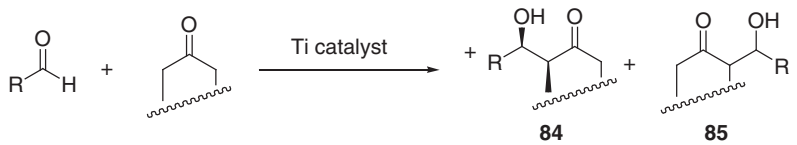
Scheme 30

Table 11 Asymmetric synthesis of dihydropyranones from ynones and aldehydes (equation 17)

Entry	R^1	R^2	*Method*[a]	*Yield (%)*	ee *(%)*
1	Pr^i	Et	A	81	88
2	$PhCH_2CH_2$	Et	A	55	75
3	Bu^t	Ph	A	65	95
4	Bu^t	$HOCH_2CH_2$–	A	73	93
5	Ph	Et	B	99	91
6	*N*-Boc-3-indolyl	Et	B	75	83
7	PhCH=CH	Et	B	63	76

[a]See equation 16.

total synthesis of natural products such as polyketides.[57] In contrast to the stoichiometric reaction of Ti enolates, Mahrwald and Gündogan reported a direct aldol reaction of aldehydes with ketones catalyzed by $TiCl_4$ in the absence of amines (Scheme 31, Method A).[58] The reaction was carried out with 10 mol% of $TiCl_4$ in toluene at room temperature. Under these conditions, the reaction occurred regioselectively at the more hindered α-side of unsymmetrical ketones to give aldol products **84** (Table 12). *Syn*-selectivity was observed, in general, except for the reaction of phenylacetone (entry 8). Notably, enolizable aldehydes, such as butanal and 2-methylpropanal, could be used as acceptors in this reaction (entries 3, 4, and 7). It was also shown that the tetranuclear Ti complex *rac*-$Ti_4(\mu$-BINOLato$)_6(\mu_3$-OH$)_4$ (**86**)[59] is a more active catalyst (Method B).[60] The catalyst loading could be reduced to as little as 0.2 mol%. The reaction of unenolizable aldehydes with unsymmetrical ketones afforded the sterically more encumbered product **84** regioselectively (entries 2, 6, and 9). Notably, when applied to the intramolecular aldol reaction of trione **87**, bicyclo[3.2.1] product **88** was obtained with high diastereoselectivity without by-product formation of enedione **89** (equation 18).

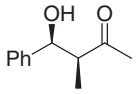
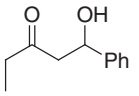
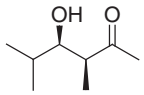
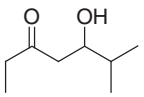
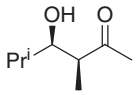
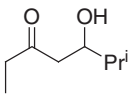
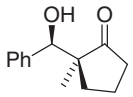
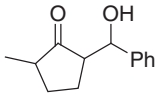
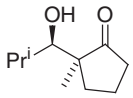
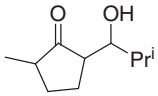
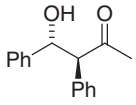
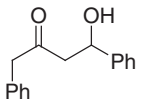


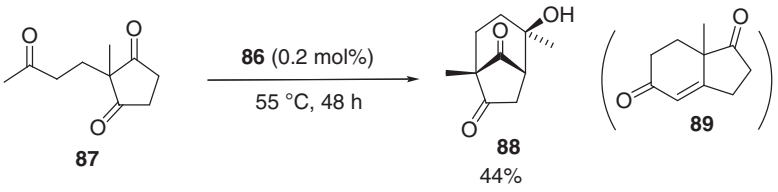
Method A: $TiCl_4$ (10 mol%), toluene, r.t.

Method B: *rac*-$Ti_4(\mu$–BINOLato$)_6(\mu_3$-OH$)_4$ (**86**) (0.2 mol%), CH_2Cl_2, r.t., 7 days

Scheme 31

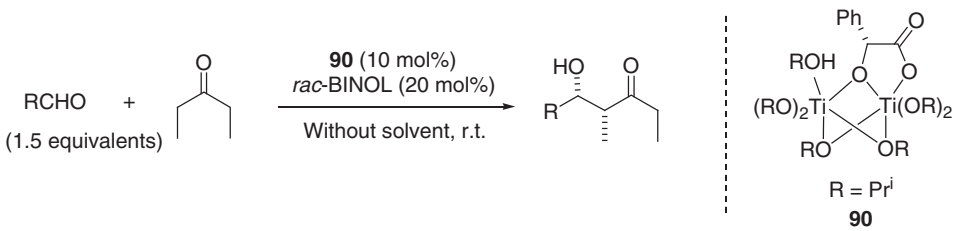
Table 12 Ti(IV)-catalyzed direct aldol reaction of aldehydes with ketones (Scheme 31)

Entry	*R*	*Ketone*	*Method*	*Major* ***84***	*Minor* ***85***	*Combined yield (%)*	*Regioselectivity*	ds	*References*
1	Ph	MeCOEt	A	 **84a**	 **85a**	83	32:1	19:1	58
2			B			74	19:1	1.1:1	60
3	Pr^i		A	 **84b**	 **85b**	72	10:1	3.2:1	58
4	Pr^n		A	 **84c**	 **85c**	68	8.1:1	4.9:1	58
5	Ph		A	 **84d**	 **85d**	88	99:1	>49:1	58
6			B			85	>19:1	1.1:1	60
7	Pr^i		A	 **84d**	 **85d**	81	19:1	5.3:1	58
8	Ph	$MeCOCH_2Ph$	A	 **84e**	 **85e**	91	>99:1	3.8:1	58
9			B			78	>19:1	>19:1	60



(18)

Mahrwald and Ziemer have reported the enantioselective version of the Ti(IV)-catalyzed cross-aldol reaction of aldehydes with ketones (Scheme 32).[61] Chiral Ti catalysts were prepared by the reaction of $Ti(OPr^i)_4$ (2 equivalents) and (*R*)-mandelic acid followed by treatment of the resulting dinuclear complexes **90** with *rac*-BINOL (2 equivalents). In the presence of 10 mol% of the Ti complex without using solvents at room temperature, the reaction of aldehydes (1.5 equivalents) with 3-pentanone afforded the corresponding cross-aldol products with high enantioselectivity as well as with high *syn*-selectivity (Table 13).



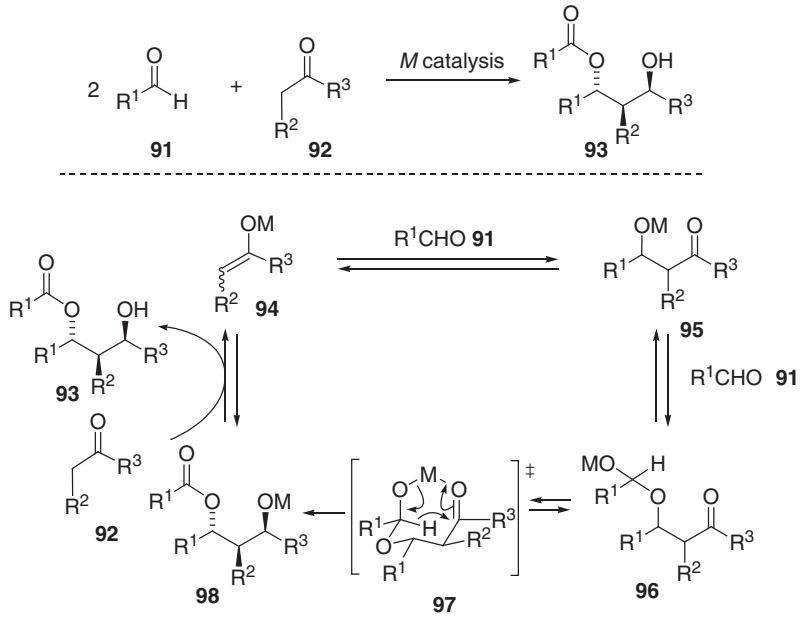
Scheme 32

Table 13 Chiral Ti-catalyzed enantioselective direct aldol reaction of aldehydes with 3-pentanone (Scheme 32)

Entry	*R*	*Yield (%)*	ds	ee *(%)*
1	Ph	85	10:1	91
2	Bu^t	71	7.3:1	93
3	Pr^i	43	3.8:1	71
4	Et	78	2.6:1	74

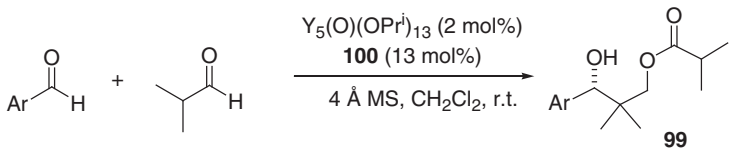
2.10.2.3.4 Aldol–Tishchenko reaction

The catalytic aldol–Tishchenko reaction, by which an enolizable aldehyde or ketone **92** undergoes coupling with 2 equivalents of aldehydes **91** with a full atom economy to afford 1,3-diol monoesters **93**, is an attractive alternative to the direct aldol reaction (Scheme 33).[62] The reaction occurs by a mechanism involving reversible aldolization and formation of hemiacetal alkoxide **96**, followed by a rate-determining intramolecular hydride transfer of **96** and subsequent protonation of the resulting alkoxide **98** to produce monoester **93** with regeneration of enolate **94**. The major diastereomer **93** is proposed to be derived from transition state **97** in which all substituents at the six-membered ring occupy equatorial positions.[63] Although the direct aldol reaction of methylene ketones **92** is often hampered by a strong tendency toward retro-aldolization, the issue has been overcome by coupling a reversible aldolization step with an irreversible, enantioselective reduction step.

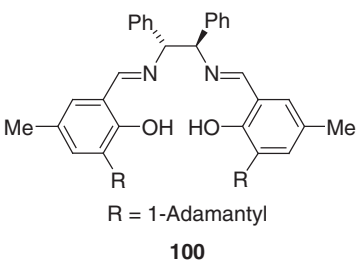


Scheme 33

In 2001, Morken and coworkers reported the enantioselective aldol–Tishchenko reaction between aromatic aldehydes and isobutyraldehyde catalyzed by a chiral yttrium(III)-salen complex derived from $Y_5(O)(OPr^i)_{13}$ (2 mol%) and **100** (13 mol%) (Scheme 34).[64] The reaction afforded 1,3-diol monoesters **99** in good enantioselectivity. The absolute configuration of **99** was rationalized by a six-membered ring transition state with Y(III) complexed by the chiral salen ligand.

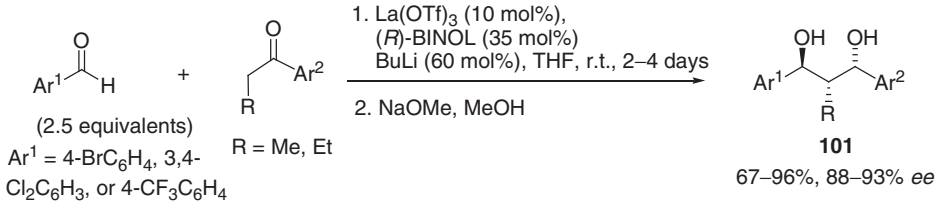


Ar	Yield (%)	*ee (%)*
Ph	70	74
4-BrC_6H_4	55	70
2-Naphthyl	50	64

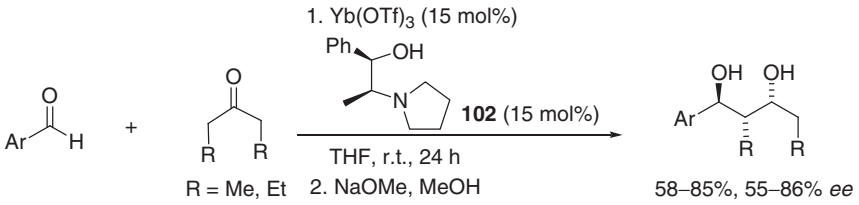


Scheme 34

The enantioselective aldol–Tishchenko reaction between aromatic aldehydes and alkyl aromatic ketones was reported by Shibasaki and coworkers (equation 19).[65] The reaction was carried out with a bimetallic catalyst, prepared from $La(OTf)_3$ (10 mol %), (*R*)-BINOL (30 mol%), and BuLi (56 mol%), in THF at room temperature for 2–4 days. After methanolysis, 1,2-*anti*-, 1,3-*anti*-diols **101** were obtained in high yield and enantioselectivity. Mlynarski et al. reported a chiral catalyst derived from $Yb(OTf)_3$ and amino alcohol **102** (15 mol% each), which exhibited good enantioselectivity for the reaction of 3-pentanone and 4-heptanone (equation 20).[66,67] The activity of both catalyst systems is relatively low, requiring rather high loadings. A catalyst system with improved performance is awaited for this synthetically valuable transformation.[68]

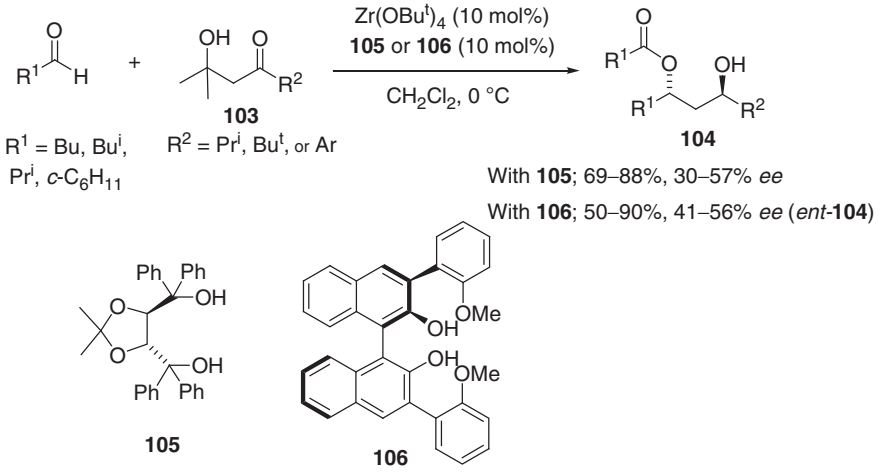


(19)



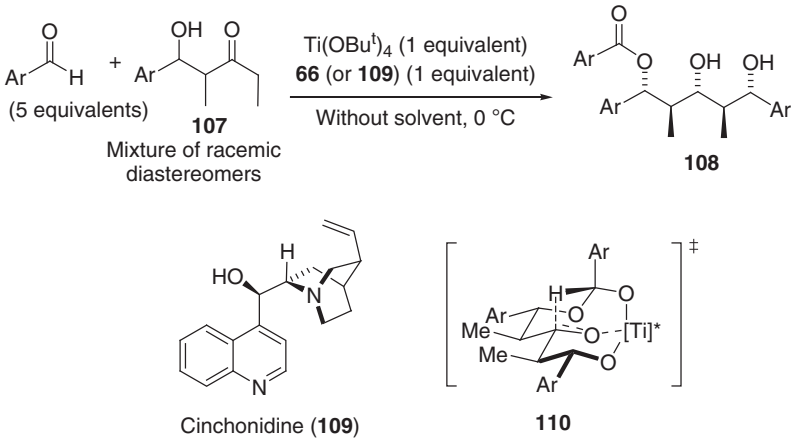
(20)

The retro-aldol reaction of tertiary aldols **103** has been utilized in the generation of the enolate intermediate in the aldol–Tishchenko reaction (Scheme 35). It was reported that, by the catalysis of achiral Al-[69] and Zr-alkoxides,[70] the reaction of **103** with aldehydes provided *anti*-1,3-diol monoesters **104** diastereoselectively with minor acyl migration by-product. It should be noted that enolizable aliphatic aldehydes could be employed as acceptor carbonyl compounds. Schneider and Hansch reported the asymmetric version of the reaction by employing either TADDOL **105**[71] or BINOL derivative **106**[72] in combination with $Zr(OBu^t)_4$.



Scheme 35

Mahrwald et al. reported the enantioselective aldol–Tishchenko reaction between aromatic aldehydes and racemic aldol **107** (Scheme 36).[73] By employing stoichiometric amount of cinchonine (**66**) and $Ti(OBu^t)_4$, the reaction afforded 1,3,5-triol monoesters **108** as a single diastereomer in high enantioselectivity (Table 14, entries 1, 3, and 5). The opposite enantiomer *ent*-**108** was also obtained in high diastereo- and enantioselectivity by the use of cinchonidine (**109**), a pseudoenantiomeric amino alcohol (entries 2, 4, and 6). Interestingly, the diastereoselectivity of this reaction is unusual in light of 1,2-*anti*-, 1,3-*anti*-configuration predicted by the transition-state model **97** (Scheme 33). An explanation for the exceptional high stereoselectivity was given by the assumption of a tricyclic transition-state model **110**.



Scheme 36

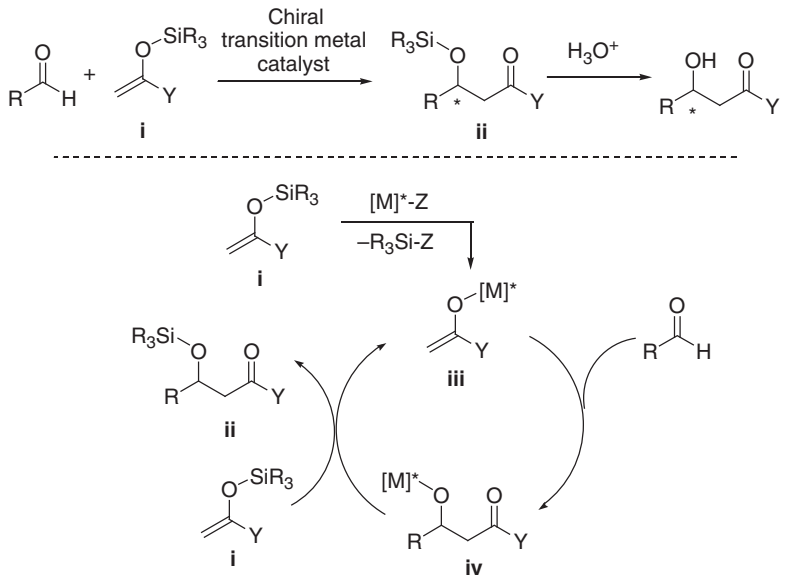
Table 14 Enantioselective aldol–Tishchenko reaction between aldehydes and aldols (Scheme 36)

Entry	*Ar*	*Amino alcohol*	*Product*	*Yield (%)*	ee *(%)*
1	Ph	**66**	**108a**	52	>98
2		**109**	*ent*-**108a**	59	97
3	4-$MeOC_6H_4$	**66**	**108b**	61	96
4		**109**	*ent*-**108b**	65	>98
5	4-$NO_2C_6H_4$	**66**	**108c**	36	97
6		**109**	*ent*-**108c**	32	>98

2.10.3 Transition-Metal-Catalyzed Aldol Reaction Employing Latent Enolates

2.10.3.1 Enol Silanes as Precursor

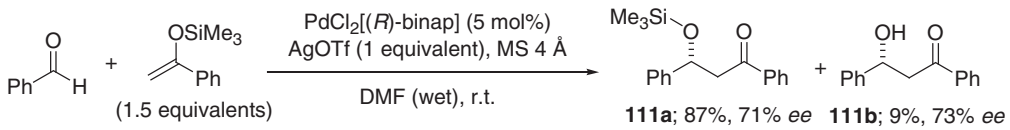
Enol silanes have not only been utilized in the chiral Lewis acid-catalyzed enantioselective Mukaiyama aldol reaction as nucleophiles[74] but also employed in the transition-metal-catalyzed aldol reactions as precursors of chiral metal enolates (Scheme 37) (*see* Chapter 2.09). The transition-metal-catalyzed reaction proceeds through a general mechanism involving a catalytic cycle in which aldolate **iv**, formed by the addition of transition metal enolate **iii** to an aldehyde, undergoes silylation by



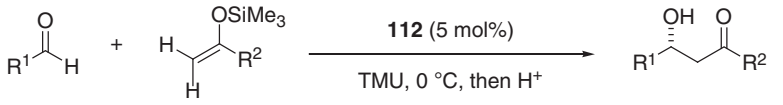
Scheme 37

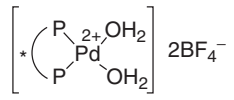
enol silane **i** to give silyl aldolate **ii** with generation of **iii**. In the transition-metal-catalyzed aldol reaction, Pd(II), Pt(II), and Cu(I) complexes coordinated by chiral diphosphines have been used as catalysts, which first react with **i** to form enolates **iii** to start the reaction.

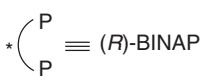
In 1995, Sodeoka and coworkers reported an enantioselective aldol reaction catalyzed by a chiral cationic Pd(II) complex (equation 21).[75] The Pd catalyst was prepared by treatment of $PdCl_2$[(*R*)-binap] (5 mol%) with AgOTf (5 mol%) in wet DMF in the presence of molecular sieves. The reaction of benzaldehyde with acetophenone enol silyl ether proceeded at room temperature to give silyl aldolate **111a** (87% yield, 71% *ee*) and aldol product **111b** (9% yield, 73% *ee*). Based on NMR experiments, it was shown that the aldolization took place via a chiral Pd(II) enolate. Later, well-characterized dicationic diaqua complex **112** was found to be a more active catalyst (**Scheme 38**).[76,77] In the presence of **112** (5 mol%) at 0 °C in tetramethylurea (TMU), aldol products were obtained in high yield with improved enantioselectivity after hydrolysis of the reaction mixture.[78,79] The reaction was proposed to proceed through the mechanism shown in **Scheme 37** in which [M]* = [(*R*)-binap]Pd(II).



(21)



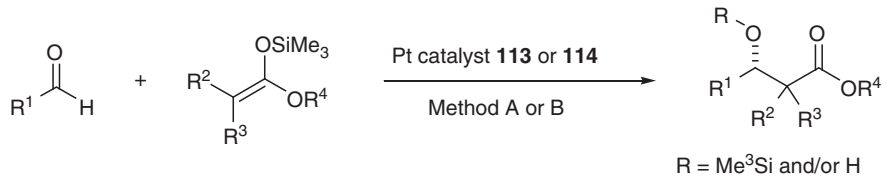


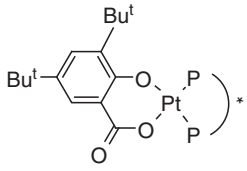


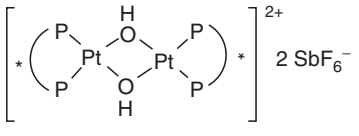
R^1	R^2	Yield (%)	*ee* (%)
Ph	Ph	92	89
Ph	2-Naphthyl	89	87
$PhCH_2CH_2$	Ph	88	81

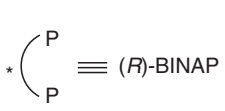
Scheme 38

Although the Pd catalyst system was not suitable to the aldol reaction with ketene silyl acetals,[75] Fujimura reported that a relevant Pt(II) catalyst system was effective in the reaction (**Scheme 39**).[80] In the presence of a catalyst derived from chiral Pt(II) complex **113**, TfOH, and 2,6-lutidine (5 mol% each) in CH_2Cl_2 at −25 °C, the reaction of benzaldehyde with $Me_2C{=}C(OMe)OSiMe_3$ (1.4 equivalents) afforded the corresponding aldol product as a mixture of silyl aldolate and aldol product in 99% yield in 59% *ee* (Method A) (**Table 15**, entries 1 and 3). Based on a NMR study, cationic Pt(II) complex, [Pt{(*R*)-binap}(OH)(OH_2)]$^+$ OTf^-, was









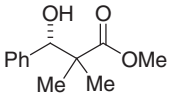
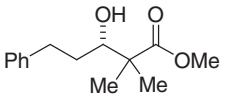
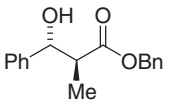
Method A: **113** (5 mol%), TfOH (5 mol%), 2,6-lutidine (5 mol%), CH_2Cl_2, −25 °C

Method B: [{(*R*)-binap}Pt(μ-OH)]$_2$ $(SbF_6)_2$ **114** (2.5 mol%), DMF, r.t., then H_3O^+

Scheme 39

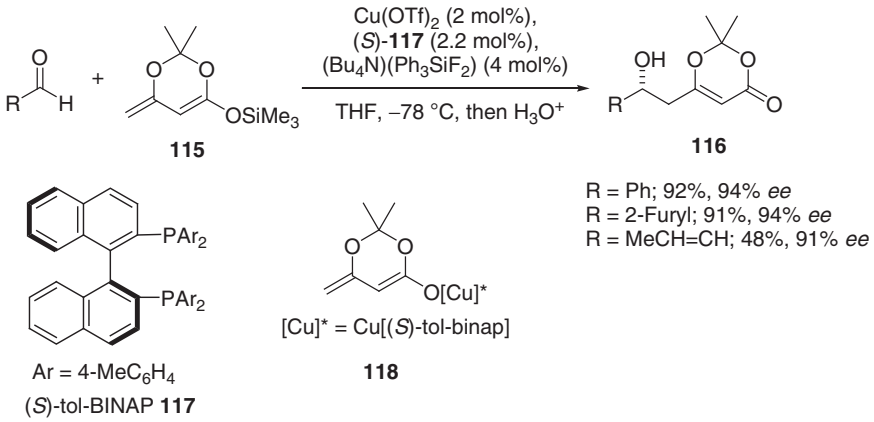
proposed as an active catalyst. Kiyooka et al. reported improved results by using characterized isolable Pt(II) complex **114** (2.5 mol%) (Method B).[81] The reaction with $Me_2C{=}C(OMe)OSiMe_3$ (1.5 equivalents) afforded the aldol adducts in good enantioselectivity (entries 2 and 4). In the reaction with propanoate-derived ketene silyl acetals, *anti*-selectivity was observed irrespective of the *E*, *Z* geometry (entries 5 and 6).

Table 15 Pt(II)-catalyzed enantioselective aldol reaction of ketene silyl acetals (**Scheme 39**)

Entry	R^1	R^2	R^3	R^4	*Method*	*Product*	*Yield (%)*	ds	ee *(%)*	*References*
1	Ph	Me	Me	Me	A		99[a]	–	59	80
2					B		87	–	84	81
3	$PhCH_2CH_2$	Me	Me	Me	A		94[a]	–	95	80
4					B		76	–	90	81
5[b]	Ph	H	Me	Bn	B		88	6:1	84	81
6[b]	Ph	Me	H	Bn	B		92	6:1	89	81

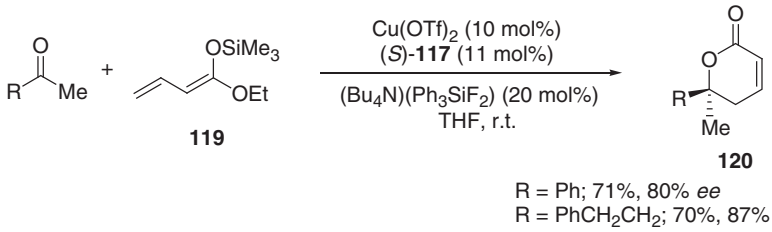
[a]The combined yield of the silyl aldolate and aldol product.
[b]DMF–HMPA was used as solvents.

In 1998, Krüger and Carreira reported an enantioselective aldol reaction of aldehydes with silyl dienolate **115** catalyzed by a chiral Cu(I) complex (**Scheme 40**).[82] In the presence of (*S*)-tol-BINAP (**117**) (2.2 mol%), $Cu(OTf)_2$ (2 mol%), and $(Bu_4N)(Ph_3SiF_2)$ (4 mol%), **115** underwent smooth addition to aldehydes at −78 °C to provide the vinylogous aldol product **116** in high enantioselectivity.[83,84] Based on spectroscopic and chemical evidence, it was shown that CuF[(*S*)-tol-binap] was formed from the catalyst precursors. The reaction was proposed to proceed according to the general mechanism (**Scheme 37**) involving Cu(I) dienolate **118**.[85] In accord with the mechanism, the reaction was catalyzed also by $Cu(OBu^t)$[(*S*)-tol-binap].



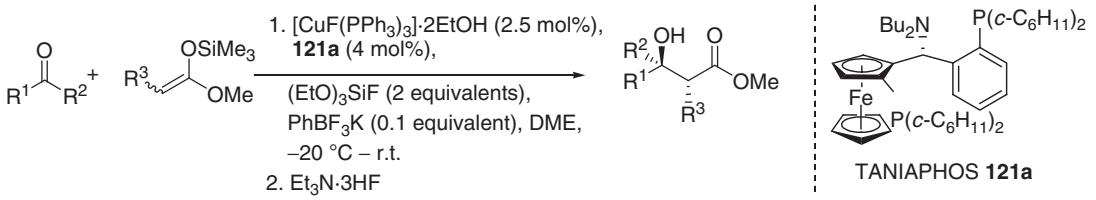
Scheme 40

Taking advantage of the high reactivity of Cu(I) enolates, Campagne and coworkers applied Carreira's chiral Cu catalyst successfully to the reaction of less-reactive ketones (equation 22).[86] The reaction of methyl ketones with silyl ketene acetal **119** gave enantiomerically enriched lactones **120** with a tertiary carbinyl moiety via a Cu(I) aldolate intermediate. High enantioselectivities were reported for the reaction of aliphatic methyl ketones.



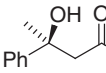
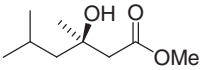
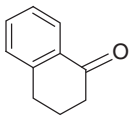
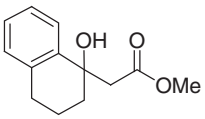
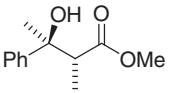
(22)

An efficient catalytic aldol addition of simple trimethylsilyl ketene acetals to ketones, involving a chiral Cu(I) enolate intermediate, has been developed by Shibasaki and coworkers (Scheme 41).[87] The reaction was carried out with $[CuF(PPh_3)_3]\cdot 2EtOH$ (2.5 mol%), TANIAPHOS ligand **121a** (4 mol%), $(EtO)_3SiF$ (2 equivalents), and $[PhBF_3]K$ (10 mol%) in DME. High levels of enantioselection were reported not only for methyl ketones but also for cyclic aromatic ketones (Table 16, entries 1–3). The reaction of silyl ketene acetals derived from propanoate was also enantioselective (entries 4 and 5). The *erythro* product was obtained diastereoselectively, independent of the *E*/*Z* ratio of the silyl ketene acetal.



Scheme 41

Table 16 Cu(I)-catalyzed enantioselective aldol reaction of ketones with silyl ketene acetals (Scheme 41)

Entry	*R^1*	*R^2*	*R^3*	*Product*	*Yield (%)*	ds	ee *(%)*
1	Ph	Me	H		93	–	92
2	Me_2CHCH_2	Me	H		73	–	84
3			H		92	–	90
4	Ph	Me	(*E*)-Me		96	4:1	91
5	Ph	Me	(*Z*)-Me		58	6.1:1	94

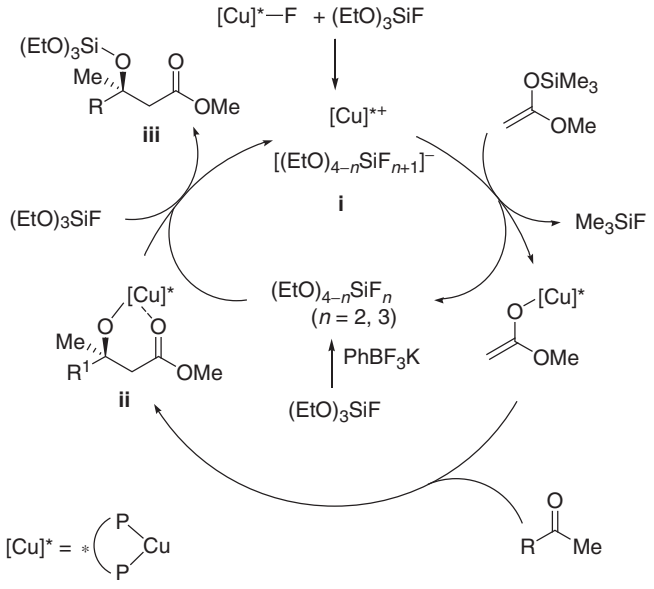
According to a proposed catalytic cycle (Scheme 42),[87] $(EtO)_3SiF$ plays roles both in the generation of an active cationic Cu(I) catalyst **i** and in the fluoride exchange of Cu-aldolate **ii**, leading to the formation of triethoxysilyl aldolate **iii** and regeneration of the catalyst. For the ketone aldol reaction, intermediate **ii** is a Cu(I) *tert*-alkoxide, which is basic enough to induce the undesirable enolization of a substrate ketone. It was suggested that $PhBF_3K$ as an additive is effective in promoting the rate-determining catalyst-turnover step by generating more electrophilic $(EtO)_2SiF_2$ and/or $(EtO)SiF_3$ *in situ*.

2.10.3.2 β-Keto-Acid and Malonic Acid Derivative as Precursor: Decarboxylative Aldol Reaction

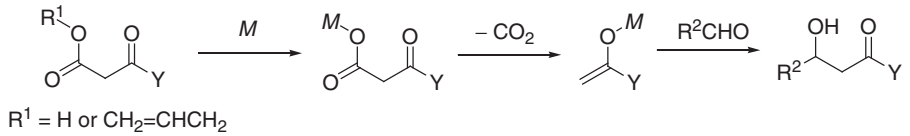
One of the potentially useful approaches to the regioselective generation of transition metal enolates involves decarboxylation of metal β-keto-carboxylates prepared from β-keto-acid or allyl ester precursors (Scheme 43). In the presence of aldehydes or ketones, the resulting enolates may undergo aldol reaction to give adducts. Indeed, a few reports have appeared on the use of thus generated transition metal enolates in aldol chemistry.[88]

2.10.3.2.1 Allyl β-keto ester

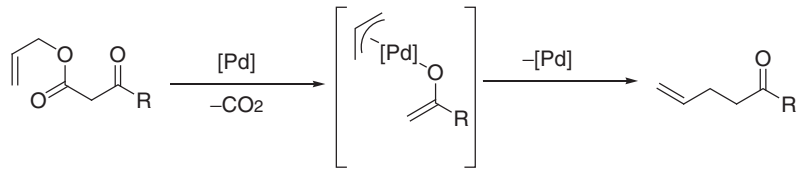
Allyl β-keto-carboxylates are known to undergo decarboxylative rearrangement (the Carroll rearrangement) by Pd(0) catalysis to give γ,δ-unsaturated ketones (Scheme 44). The reaction proceeds through a mechanism involving oxidative coupling of π-allyl enolates.[89] In an attempt to trap the transient enolate, Tsuji and coworkers examined the reaction of allyl β-keto esters **122** tethered to an aldehyde in the presence of $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) in acetonitrile (Scheme 45).[90] The reaction afforded intramolecular aldol products **123** in high yield without diastereoselectivity. The formation of aldol products, rather than diketones **124**, was somewhat unexpected since Pd(0) species should be regenerated from the Pd(II) aldolate to close the assumed catalytic cycle.



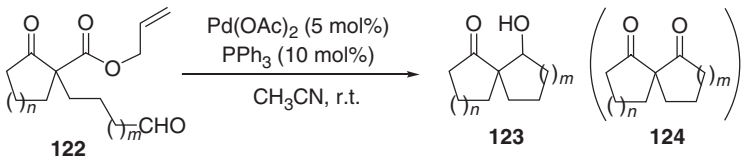
Scheme 42



Scheme 43



Scheme 44

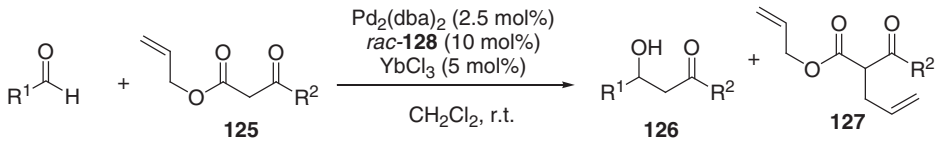


n	*m*	Yield (%)	*ds*
1	1	90	1:1
2	1	69	1:1
8	1	85	1:1
1	2	93	1:1

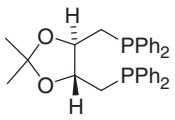
Scheme 45

An intermolecular version of the Pd-catalyzed decarboxylative aldol reaction was developed by using $YbCl_3$ as a Lewis acid cocatalyst (Scheme 46).[91,92] Treatment of allyl β-keto esters **125** (2.5 equivalents) and aldehydes in the presence of $Pd_2(dba)_2$ (2.5 mol%), *rac*-DIOP **128** (10 mol%), and $YbCl_3$ (5 mol%) in CH_2Cl_2 at room temperature afforded the aldol products **126** in good-to-high yields. In the absence of the cocatalyst, the Carroll rearrangement of **125** overwhelmed the aldol reaction. In this

reaction, more than 2 equivalents of **125** were necessary because it was also consumed in the formation of α-allylation by-product **127**. The formation of **127** was explained by a mechanism in which addition of Pd(II)-enolates to aldehyde was mediated by Yb (III) salt and the resulting alkoxide **129** underwent protonation by **125** to form **126** with simultaneous formation of enolate **131**, which underwent an alkylation reaction with a Pd(II) allyl species **130** to regenerate a Pd(0) species and yield by-product **127** (Scheme 47).

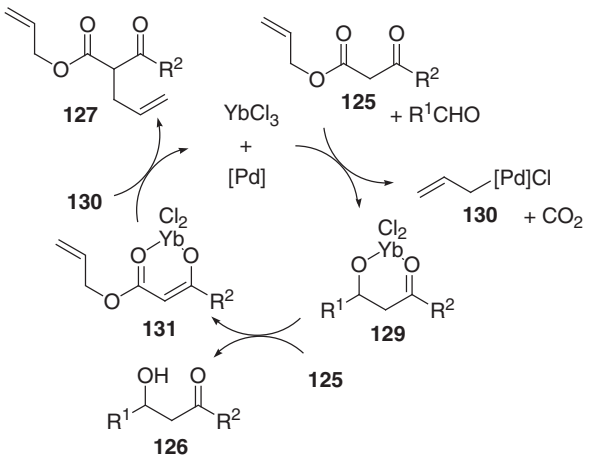


R^1	R^2	Yield (%)
$PhCH_2CH_2$	Me	81
Ph	Bu^t	70
$TBSOCH_2$	Me	72
$Pr^iCH(NHBoc)$	Me	77 (*syn*:*anti* = 6:1)



rac-DIOP **128**

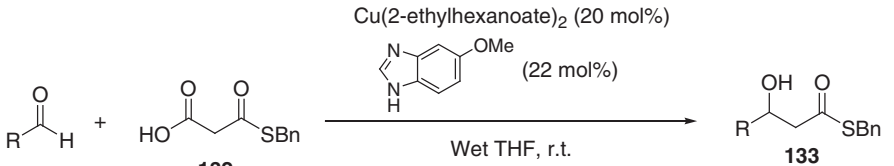
Scheme 46



Scheme 47

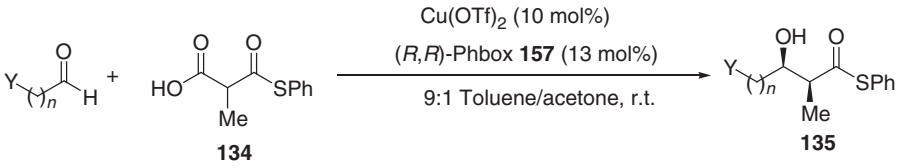
2.10.3.2.2 Malonic acid half thioester

The decarboxylative aldol reaction of malonic acid half thioesters to aldehydes has been developed by Shair and coworkers (equation 23).[93] Treatment of a 1:1 mixture of half thioester **132** and aldehydes with Cu(2-ethylhexanoate)$_2$ (20 mol%) and 5-methoxybenzimidazole (22 mol%) in wet THF afforded the aldol products **133** in high yield. The asymmetric version of the reaction was realized by using a chiral Cu catalyst system derived from Cu(OTf)$_2$ (10 mol%) and (*R*,*R*)-Phbox **136** (13 mol%) (Scheme 48).[94] The reaction was carried out with 2-methylmalonic acid derivative **134** at room temperature to give *syn*-aldol products **135** diastereo- and enantioselectively. It should be noted that the reaction is compatible with protic functional groups and enolizable aldehydes. In the absence of an aldehyde, decarboxylation of the half thioester was not observed. A mechanistic study revealed that decarboxylation occurs after aldol addition of an enolate derived from the half thioester.[95]

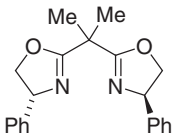


R = *c*-C_6H_{11}; 81%
R = $PhCH_2CH_2$; 82%
R = 3-$NO_2C_6H_4$; 82%

(23)



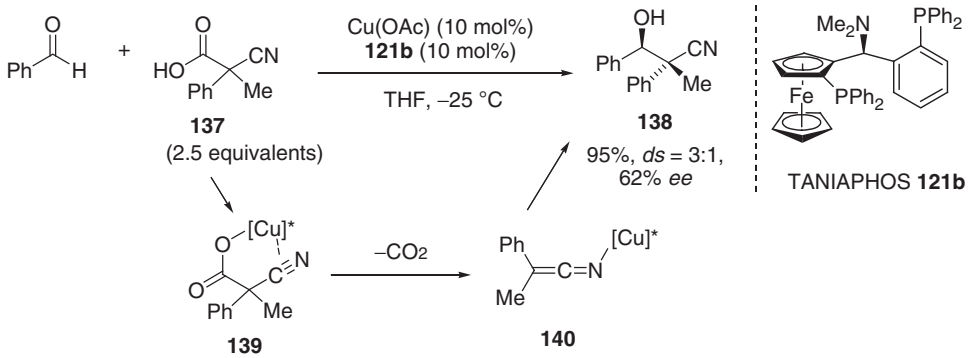
n	*Y*	Yield (%)	*ds*	*ee (%)*
6	Me	80	9:1	92
8	MeCO	71	6.5:1	93
8	(*R*)-MeCH(OH)	79	8:1	91



(*R*,*R*)-Phbox **136**

Scheme 48

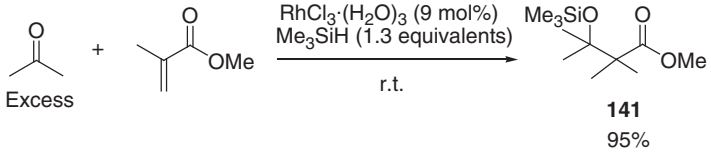
Very recently, Shibasaki and coworkers reported a Cu(I)-catalyzed enantioselective decarboxylative aldol-type reaction of *β*-cyano carboxylic acids (Scheme 49).[96] In the presence of a chiral Cu(I) catalyst derived from Cu(OAc) (10 mol%) and TANIAPHOS **121b** (10 mol%), 2-cycano-2-phenylpropionic acid (**137**) reacted with benzaldehyde with liberation of CO_2 to give the aldol-type product **138** in high yield with moderate diastereo- and enantioselectivity. In contrast to the reaction of malonic acid half thioesters, the aldolization step was preceded by the decarboxylation step. It was proposed that the extrusion of CO_2 is facilitated by a soft–soft interaction between Cu(I) and nitrile (**139**), leading to the generation of Cu(I)-ketenimide **140**. The analogous catalytic system was successfully applied to the enantioselective decarboxylative Mannich-type reaction of *β*-cyano carboxylic acids.[96,97]



Scheme 49

2.10.3.3 Reductive Aldol Reaction

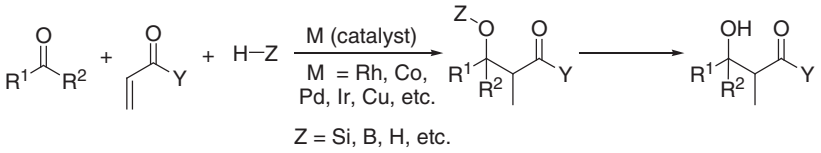
One of the most powerful methods for generating transition metal enolates under catalytic conditions involves the conjugate reduction of *α*,*β*-unsaturated carbonyl compounds. In 1987, Revis and Hilty reported a unique method for the coupling of *α*,*β*-unsaturated esters and carbonyl compounds to give aldol products, mediated by a hydrosilane and catalyzed by a Rh complex (equation 24).[98] The reaction of methyl methacrylate, acetone, and Me_3SiH in the presence of $RhCl_3{\cdot}(H_2O)_3$ (9 mol%) afforded trimethylsilyl aldolate **141**. Ketene silyl acetal $Me_2C{=}C(OMe)OSiMe_3$ would be formed by hydrosilylation of the methacrylate. However, the control reaction of acetone and the silyl acetal in the presence of the catalyst only gave a trace amount of **141**, excluding its involvement in the aldolization step and suggesting the participation of a Rh-enolate intermediate.



(24)

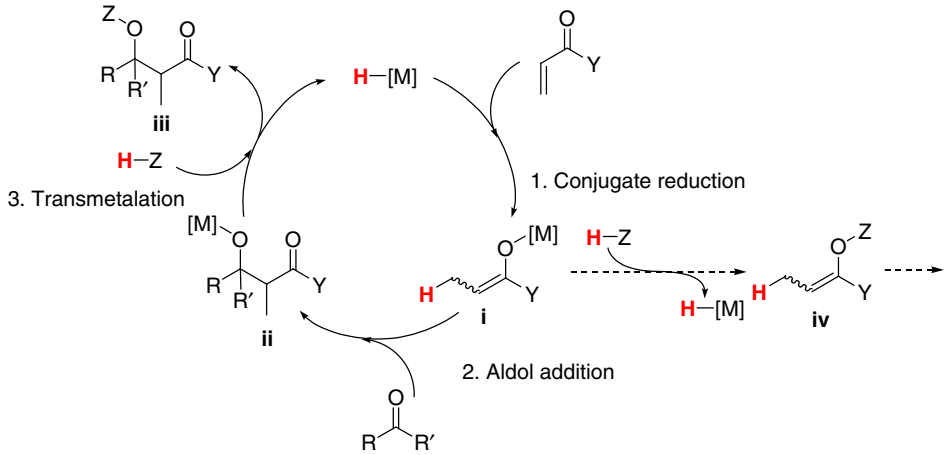
Following this seminal report, great advances have been made in the transition-metal-catalyzed reductive aldol reactions in which transition metal enolates are generated *in situ* by the conjugate reduction of *α*,*β*-unsaturated carbonyl compounds

(Scheme 50). These advancements include (1) the expansion of the scope of unsaturated carbonyl enolate precursors (esters, ketones, amides, etc.) and carbonyl acceptors (aldehydes and ketones), (2) improvement in atom economy by the use of molecular hydrogen as a hydrogen source, (3) application to intramolecular reactions, (4) progress in diastereo- and enantioselective aldol reactions, and (5) the development of a variety of transition metal catalyst systems.



Scheme 50

A common reaction pathway involved in the transition-metal-catalyzed reductive aldol reaction is shown in Scheme 51. The reaction proceeds through (1) initial conjugate reduction by a transition metal hydride species (H–[M]), (2) subsequent aldolization of the resulting transition metal enolate **i** to form aldolate **ii**, and (3) the final transformation of **ii** to product **iii** by the action of a hydrogen source (H–Z, Z=H, Si, B, etc.) with concurrent regeneration of H–[M]. Transition metal enolate **i** may undergo transmetalation with H–[Z] to form enolate **iv**, which may also participate in the aldol reaction. In certain cases, this pathway competes with the former main pathway, thus affecting the overall stereoselectivity of the reaction. Hitherto reported methods are categorized into two groups with respect to the transition metal catalysts used. One major group of the reductive aldol reactions is catalyzed by late-transition metals, mainly Rh(I). Another group is the one catalyzed by Cu(I) complexes. In the following Sections 2.10.3.3.1 and 2.10.3.3.2, representative methods for the reductive aldol reactions are described with emphasis on the viability in organic syntheses, such as substrate scope, efficiency, and stereoselectivity.[99]

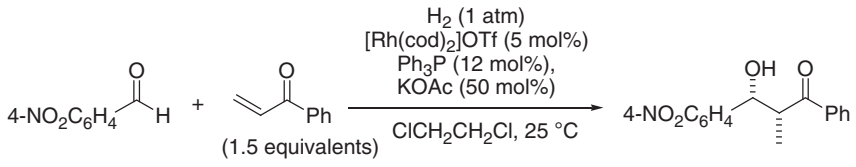


Scheme 51

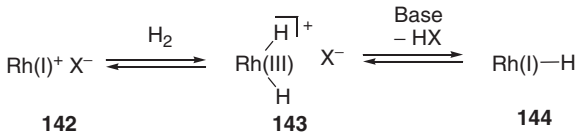
2.10.3.3.1 Intermolecular reaction

2.10.3.3.1.1 Reaction of aldehydes with enones

In 2002, Krische and coworkers disclosed an atom-economical method for the reductive aldol reaction in which enolates are generated from conjugated enones using molecular hydrogen as a hydrogen source.[100a] For example, in the presence of $[Rh(cod)_2]OTf$ (5 mol%), PPh_3 (12 mol%), and KOAc (50 mol%) under H_2 (1 atm), the reaction of phenyl vinyl ketone and 4-nitrobenzaldehyde gave the corresponding aldol product in 92% yield with moderate *syn*-selectivity (equation 25). In this reaction, cationic Rh(I) complexes **142** were employed in the presence of basic additives to generate Rh(I)–H **144** by the reductive deprotonation of $Rh^+(III)(H)_2$ species **143** (equation 26).

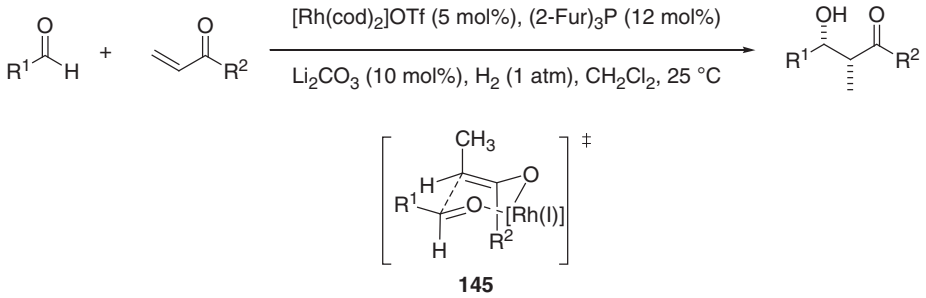


(25)



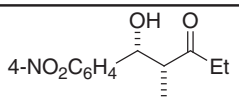
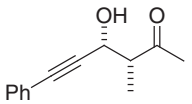
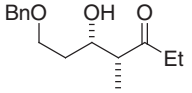
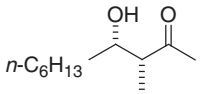
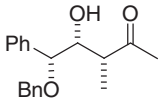
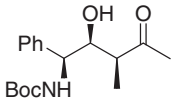
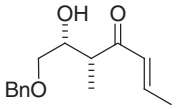
(26)

In subsequent years, the reaction was extensively optimized with respect to ligands and bases. It was established that a catalytic system employing $(2\text{-Fur})_3P$ as a ligand in combination with Li_2CO_3 as a base exhibits a wide scope for α,β-unsaturated ketones (Scheme 52, Table 17).[101] The coupling of alkyl vinyl ketones and aldehydes afforded the corresponding *syn*-aldol products in high yield and high diastereoselectivity (entries 1–4). The *syn*-selectivity was rationalized by a Zimmerman–Traxler-type transition-state model **145**[14] involving a Rh(I) (*Z*)-enolate. Functional groups, such as nitro, alkynyl, and benzyloxy groups, that are sensitive to hydrogenation or hydrogenolysis were intact. The reaction of a simple aliphatic aldehyde required higher catalyst loadings (entry 4). The reaction of chiral α-alkoxy and α-amino aldehydes exhibited high *syn*-aldol and *anti*-Felkin–Anh selectivity to give a



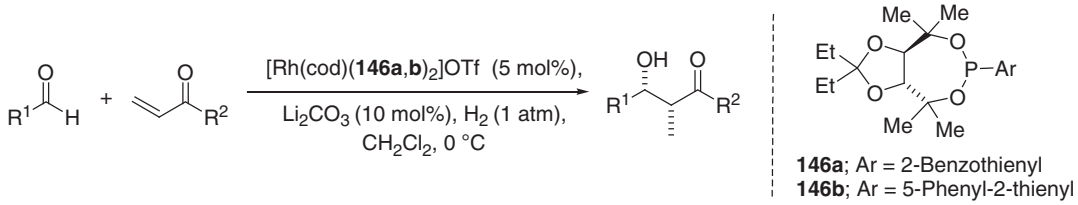
Scheme 52

Table 17 Rh-catalyzed reductive aldol reaction of α,β-unsaturated ketones and aldehydes (Scheme 52)

Entry	*R^1*	*R^2*	*Mol%*	*Product*	*Yield (%)*	ds	*References*
1	$4\text{-}NO_2C_6H_4$	Et	5		90	28:1	101
2	PhC≡C	Me	2		65	8:1	101
3	$BnOCH_2CH_2$	Et	5		73	20:1	101
4	$n\text{-}C_6H_{13}$	Me	10		62	10:1	101
5	(*R*)-PhCH(OBn)	Me	5	 2,3-*syn*, 3,4-*syn*	76	8:1	102
6	(*S*)-PhCH(NHBoc)	Me	5	 2,3-*syn*, 3,4-*syn*	81	>20:1	102
7	$BnOCH_2$	CH=CHMe	5		80	9:1	103

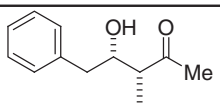
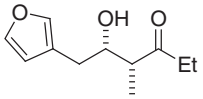
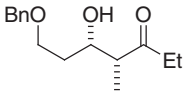
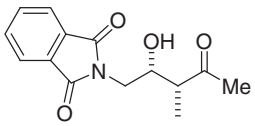
2,3-*syn*, 3,4-*syn* product diastereoselectively (entries 5 and 6).[102] As illustrated in entry 7, unsymmetric divinyl ketones reacted at the less-substituted olefin giving rise to β'-hydroxy-enones that would be a valuable precursor in polypropionate synthesis.[103]

Recently, Krische and coworkers reported the asymmetric version of the reaction by utilizing TADDOL-like phosphonite ligands **146a**,**b** (Scheme 53).[104] The reductive aldol reaction of vinyl ketones with various aldehydes in the presence of the phosphonite-derived Rh(I) complexes (5 mol%) furnished the corresponding *syn*-aldol products with high diastereo- and enantioselectivity (Table 18).

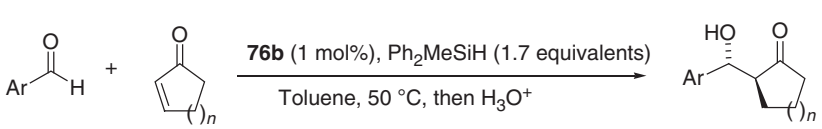


Scheme 53

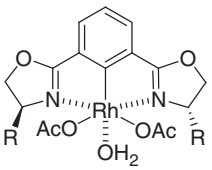
Table 18 Rh(I)-catalyzed enantioselective reductive aldol reaction of α,β-unsaturated ketones and aldehydes (Scheme 53)

Entry	*R^1*	*R^2*	*Ligand*	*Product*	*Yield (%)*	ds	ee *(%)*
1	$PhCH_2$	Me	**146a**		70	25:1	90
2	3-FurylCH_2	Et	**146a**		83	25:1	88
3	$BnOCH_2CH_2$	Et	**146b**		70	30:1	91
4	$PhtCH_2$	Me	**146a**		88	50:1	96

For the enantioselective reductive aldol reaction of cyclic enones, Nishiyama and coworkers reported an efficient method, which is catalyzed by Rh(Phebox) **76b** (1 mol%) (Scheme 54).[105] Ph_2MeSiH (1.7 equivalents) was employed as a hydride source and aldol products were obtained after hydrolysis of the initially produced silyl aldolates. Characteristically, the reaction exhibited high *anti*-diastereoselectivity. The catalyst system was first developed for the reductive aldol reaction of α,β-unsaturated esters[106] as will be described in the following Section 2.10.3.3.1.2.



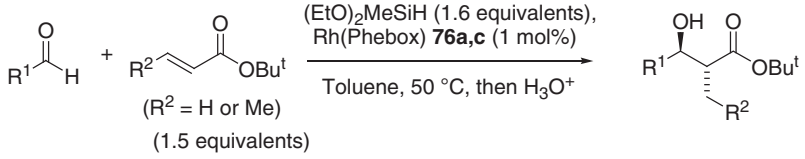
Ar	*n*	Yield (%)	*ds*	*ee* (%)
Ph	1	80	19:1	85
1-Naphthyl	1	90	16:1	90
1-Naphthyl	2	31	13:1	80



Scheme 54

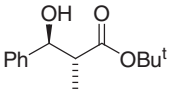
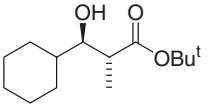
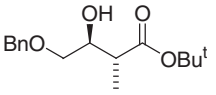
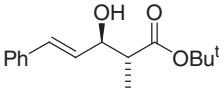
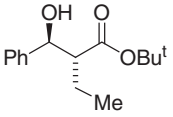
2.10.3.3.1.2 Reaction of aldehydes with α,β-unsaturated esters

One of the most successful catalytic systems for the reductive coupling reaction of aldehydes and α,β-unsaturated esters is the one employing Rh(Phebox) **76a,c** developed by Nishiyama et al. (equation 27).[107] In the presence of **76a,c** (1 mol%) and $(EtO)_2$-MeSiH (1.5 equivalents), aldehydes underwent the reductive coupling reaction with *t*-butyl acrylate (1.5 equivalents) at 50 °C in toluene to give aldol products in high yields and in high enantioselectivities (**Table 19**).[106a] The reaction exhibited high *anti*-selectivity, contrary to that generally observed for acyclic enones and enoates (*vide infra*). The reaction is applicable to a variety of aldehydes including aromatic, α,β-unsaturated, alicyclic, and α-alkoxy-aldehydes (entries 1–4). The reaction with crotonate afforded α-ethyl-β-hydroxy esters in high efficiency (entry 5).



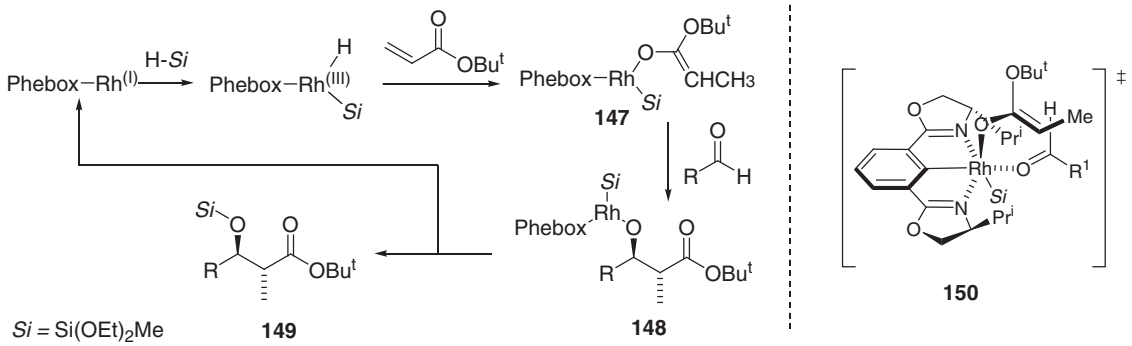
(27)

Table 19 Rh(Phebox)-catalyzed *anti*- and enantioselective reductive aldol reaction of α,β-unsaturated esters with aldehydes (equation 27)

Entry	R^1	R^2	Catalyst	Product	Yield (%)	ds	ee (%)
1	Ph	H	**76c**		98	49:1	94
2	*c*-C_6H_{11}	H	**76c**		72	6.1:1	93
3	$BnOCH_2$	H	**76a**		75	2.6:1	93
4	PhCH=CH	H	**76a**		56	4.3:1	93
5[a]	Ph	Me	**76a**		93	13:1	97

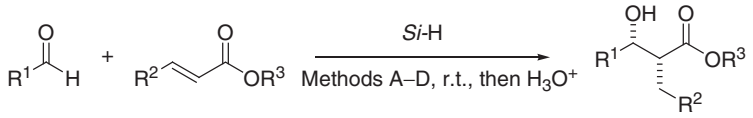
[a]The reaction was carried out with Me_2PhSiH.

The reaction was thought to proceed through a catalytic cycle involving Rh(I)(Phebox) as an active catalyst (**Scheme 55**). Oxidative addition of the hydrosilane followed by the reaction of the resulting [Rh(III)]–H species produces Rh(III) enolate **147**. The observed *anti*-(2*R*,3*S*) selectivity was rationalized by a chair-like transition state **150**[14] leading to Rh(III) aldolate **148**. Reductive elimination completed the catalytic cycle to produce silyl aldolate **149** and the chiral Rh catalyst.



Scheme 55

Morken and coworkers reported the *syn*-selective and enantioselective reductive aldol reaction of α,β-unsaturated esters with aldehydes catalyzed by a Rh(binap) complex (**Scheme 56**, Method A).[108] Treatment of aldehydes and phenyl acrylate (1.2 equivalents) with Et_2MeSiH (1.2 equivalents) in the presence of $[Rh(cod)Cl]_2$ (2.5 mol%) and (*R*)-BINAP (6.5 mol%) provided the *syn*-aldol products with moderate diastereoselectivity and in good enantioselectivity (**Table 20**, entries 1 and 2). For the reaction of α,β-unsaturated aldehydes, a cationic complex, $[(cod)Rh\{(R)\text{-binap}\}]BF_4$ (5 mol%), of enhanced activity was employed (Method B) (entry 3).[109] The reaction of β-substituted esters also proceeded satisfactorily by using $EtMe_2SiH$ (5 equivalents) in excess (e.g., entry 2).[108]

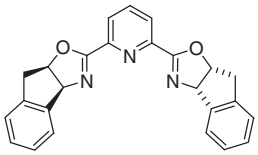


Method A: $[Rh(cod)Cl]_2$ (2.5 mol%), (*R*)-BINAP (6.5 mol%), unsaturated ester (1.2 equivalents), Et_2MeSiH (1.2 equivalents), CH_2Cl_2

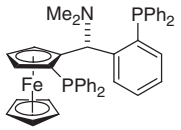
Method B: $[(cod)Rh((R)\text{-binap})]\ BF_4$ (5 mol%), aldehyde (5 equivalents), Et_2MeSiH (1.75 equivalents), CH_2Cl_2

Method C: $[(cod)IrCl]_2$ (2.5 mol%), **151** (7.5 mol%), unsaturated ester (1.2 equivalents), Et_2MeSiH (1.2 equivalents), $ClCH_2CH_2Cl$, r.t.

Method D: $[CuF(PPh_3)_3]_2{\cdot}MeOH$ (1 mol%), **121c** (1.2 mol%), unsaturated ester (1.2 equivalents), Ph_2SiH_2 (1.4 equivalents), toluene, –50 °C



Indane-Pybox **151**



TANIAPHOS **121c**

Scheme 56

Morken et al. also developed a chiral Ir catalyst system for the *syn*- and enantioselective reaction.[110] The reactions were carried out using $[Ir(cod)Cl]_2$ (2.5 mol%) and indane-Pybox **151** (7.5 mol%) with Et_2MeSiH (1.2 equivalents) (Method C). Relatively high diastereoselectivity and enantioselectivity were obtained for benzaldehyde, α-, and β-oxygenated aliphatic aldehydes (entries 4–6), whereas nonsubstituted propanal exhibited very low reactivity under these conditions. A significant level of double stereodifferentiation was observed in reductive aldol reactions with α-chiral aldehydes. Thus, the coupling reaction of (*R*)-2-(benzyloxy) propanal, a matched substrate enantiomer, provided 2,3-*syn*, 3,4-*anti* product almost exclusively (>19:1) (entry 7), whereas the reaction with a mismatched (*S*)-aldehyde resulted in exclusive carbonyl reduction.

A highly efficient chiral Cu(I) catalyst system for the reductive coupling of ketone and α,β-unsaturated ester has been developed by Riant and coworkers (*vide infra*).[111] Application of the same catalyst system to the reaction of α-branched aliphatic aldehydes provided the corresponding *syn*-aldol products diastereo- and enantioselectively (Method D, entry 8).[112]

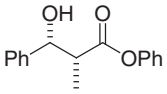
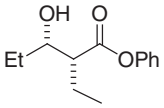
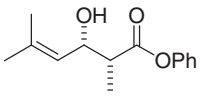
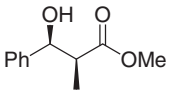
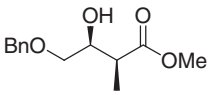
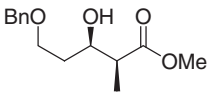
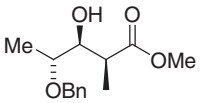
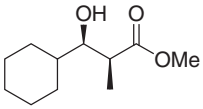
Riant and coworkers have reported that the *N*-heterocyclic carbene (NHC) Cu(I) complex, (IMes)Cu(dbm) **152**, is a highly active achiral catalyst of the reductive coupling of acrylates and aldehydes (**Scheme 57**).[113] The reaction proceeded efficiently at 1 mol% of the catalyst loading furnishing racemic silyl aldolates in high yields with moderate *anti*-selectivity. Under similar conditions, the reaction of a crotonate gave the corresponding α-ethyl adducts in high yield as well. The catalyst system was applied successfully in the reductive coupling reaction of α,β-unsaturated ketones and nitriles.

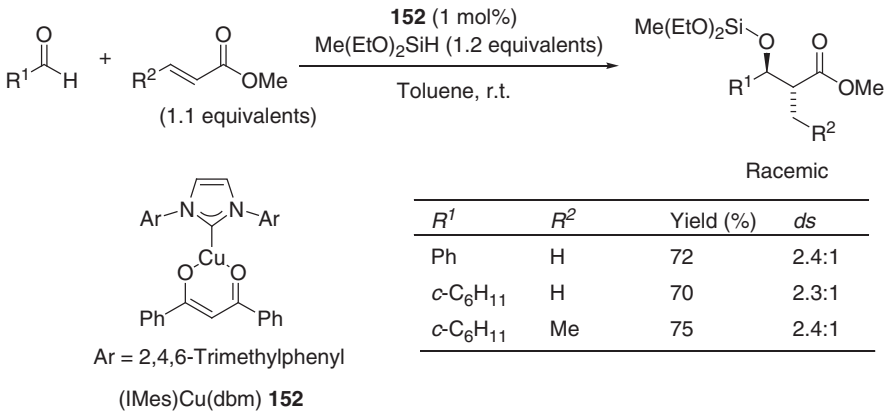
Nonasymmetric reductive aldol reaction of methyl acrylate exhibiting high *syn*-selectivity has been reported by Morken and coworkers.[114] The reaction was carried out by a one-pot, two-step procedure (**Scheme 58**). Initial treatment of methyl acrylate with $MeCl_2SiH$ (2 equivalents) in the presence of a catalyst derived from $[Rh(cod)Cl]_2$ (1.25 mol%) and Me-Duphos **154** (2.7 mol%) generated (*E*)-silyl ketene acetal **153** stereoselectively. Subsequent treatment with aldehydes afforded the corresponding racemic *syn*-aldol products in high yields. The aldol addition was proposed to proceed through a boat-like transition state involving a penta-coordinate silicate as observed for the enoxytrichlorosilanes.[115] Ynals and enals reacted with high *syn*-selectivity, as do aliphatic and aromatic aldehydes.

2.10.3.3.1.3 Reaction of ketones with α,β-unsaturated esters and amides

Catalytic enantio- and/or diastereoselective aldol reaction to ketones affords functionalized products with two-contiguous stereogenic centers, one of which is a chiral tertiary alcohol. The reaction is a challenging task considering the lower reactivity and

Table 20 *Syn*- and enantioselective reductive aldol reaction of α,β-unsaturated esters with aldehydes (**Scheme 56**)

Entry	R^1	R^2	R^3	*Method*	*Product*	*Yield (%)*	ds	ee *(%)*	*References*
1	Ph	H	Ph	A		72	3.4:1	87	108
2	Et	Me	Ph	A		76	4.3:1	88	109
3	$Me_2C=CH$	H	Ph	B		86	6:1	83	109
4	Ph	H	Me	C		68	6.6:1	94	110
5	$BnOCH_2$	H	Me	C		49	9.9:1	96	110
6	$BnOCH_2CH_2$	H	Me	C		65	2.7:1	82	110
7	(*R*)-MeCH(OBn)	H	Me	C	 2,3-*syn*, 3,4-*anti*	50	>19:1	–	110
8	*c*-C_6H_{11}	H	Me	D		99	7.3:1	97	112

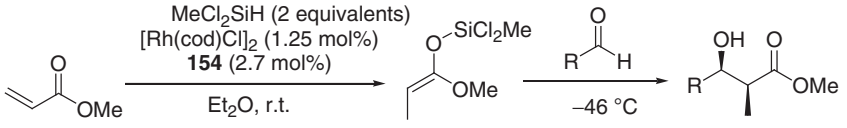


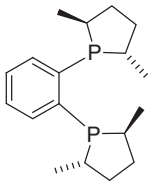
R^1	R^2	Yield (%)	*ds*
Ph	H	72	2.4:1
c-C_6H_{11}	H	70	2.3:1
c-C_6H_{11}	Me	75	2.4:1

Scheme 57

difficult stereo-regulation in comparison with aldehydes.[2f] Despite such difficulties, several successful reactions have been developed by transition-metal-catalyzed reductive aldol reaction.

Riant and coworkers developed a chiral Cu(I) complex-catalyzed enantioselective reductive coupling reaction of aryl methyl ketones and methyl acrylate mediated by $PhSiH_3$ (**Scheme 59**).[111] A Cu(I) complex generated *in situ* from $[CuF(PPh_3)_3]\cdot 2MeOH$ (1–3 mol%) and TANIAPHOS **121d** (1–3 mol%) catalyzed the reaction in toluene at 50 °C to give the corresponding *erythro*-aldol products in high yields with high diastereo- and enantioselectivity. The CuF salt was supposed to generate the corresponding [Cu]–H species by the action of the hydrosilane in light of the previous finding by Mori et al.[116] The [Cu]–H species then undergoes conjugate addition to the acrylate to generate a Cu(I) enolate, which is trapped by ketone with C–C bond formation.

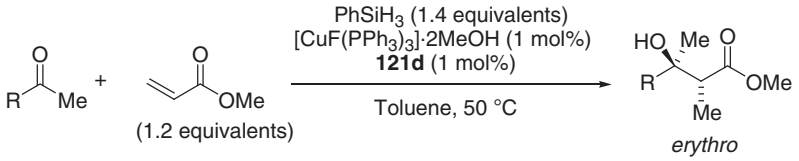


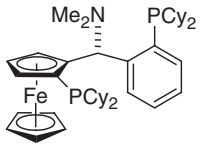


Me-DuPhos **154**

R	Yield (%)	*ds*
Et	71	10:1
Ph	96	>60:1
PhCH=CH	95	13:1
$C_5H_{11}C{\equiv}C$	91	>20:1

Scheme 58





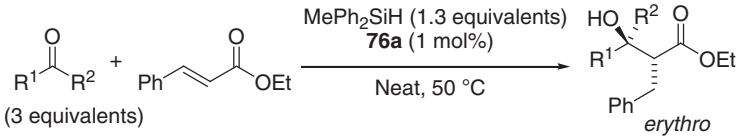
(Cy = *c*-C_6H_{11})
TANIAPHOS **121d**

R	Yield (%)	*ds*	*ee* (%)
Ph	98	12:1	95
4-ClC_6H_4	95	6.1:1	90
3-Thienyl	95	19:1	95

Scheme 59

The resulting Cu-aldolate reacts with $PhSiH_3$ to produce a silyl aldolate with simultaneous regeneration of the Cu–H species (Scheme 51; [M]=[Cu(I)], Z=SiR_3).

Rh(Phebox) catalyst **76a** has been successfully applied in the reaction of ketones and *β*-substituted unsaturated esters (Scheme 60).[117] Reactions were carried out without solvent at 50 °C using $MePh_2SiH$ (1.3 equivalents). Reaction with the symmetric ketones, such as acetone and cyclohexanone, provided the corresponding (*R*)-aldol products in high enantioselectivity. Reaction with acetophenone gave *erythro* adduct (R^1=Ph, R^2=Me) diastereo- and enantioselectively. Significant lowering in the product yield and enantioselectivity were observed in the reaction of benzyl acrylate without a *β*-substituent.

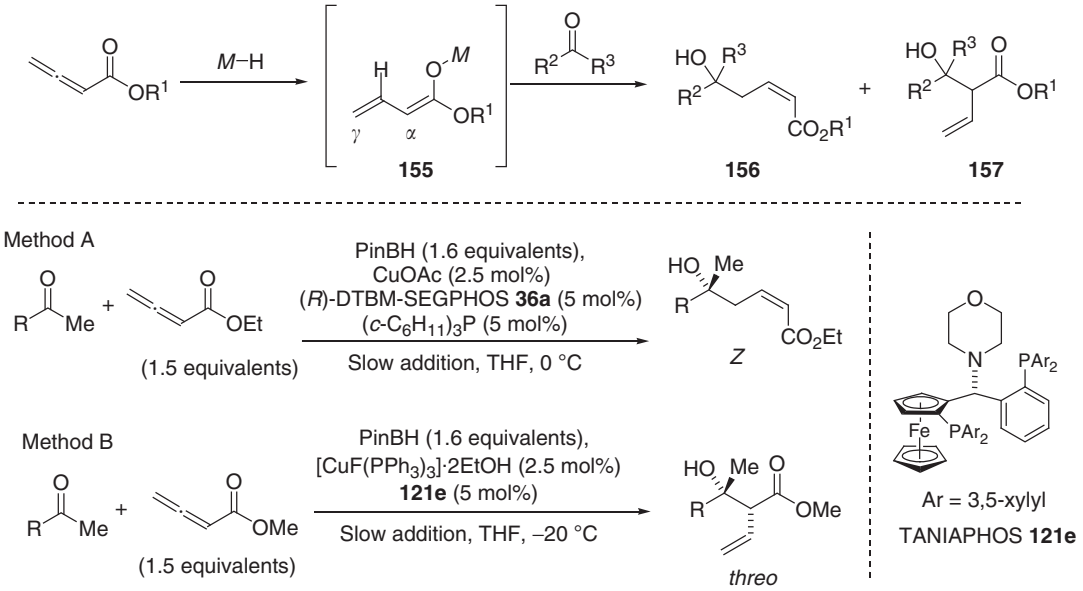


R^1	R^2	Yield (%)	*ds*	*ee* (%)
Me	Me	83	–	97
–$(CH_2)_5$–		82	–	96
Ph	Me	90	24:1	97

Scheme 60

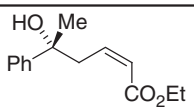
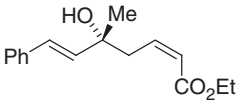
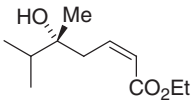
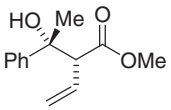
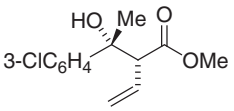
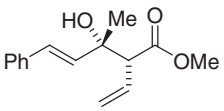
When reductive aldol reaction is applied to allenic esters, the putative dienolate **155** may attack the ketone carbonyl group either at the *γ* or *α* position to give adduct **156** and **157**, respectively (Scheme 61). Therefore, the control of the regioselectivity becomes the additional issue. Shibasaki and coworkers reported a remarkable ligand effect in the regioselectivity of such reaction.[118] While (*R*)-DTBM-SEGPHOS **36a** alone with Cu(OAc) gave a mixture of regioisomers (*γ*:*α*=1.8:1), exclusive formation of

the γ-adduct, with high enantio- and *Z*-selectivity, was observed in the presence of the achiral phosphine additive [$(c\text{-}C_6H_{11})_3P$] (Method A). The reaction was demonstrated to be applicable to various methyl ketones including aromatic, aliphatic, and α,β-unsaturated ketones (Table 21, entries 1–3). In contrast to the reaction with SEGPHOS ligand **36**, exclusive formation of the α-adduct, with high enantio- and *threo*-selectivity, was observed with TANIAPHOS **121e** in combination with [$CuF(PPh_3)_3$]·2EtOH (Method B) (entries 4–6). In both reactions, pinacolborane (PinBH) was employed as a hydride source.



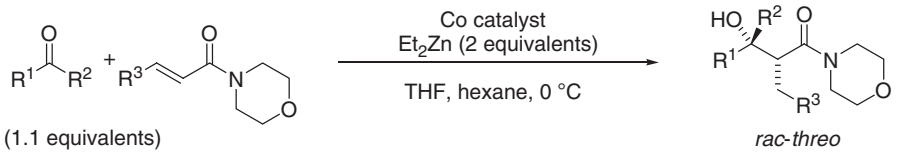
Scheme 61

Table 21 Cu(I)-catalyzed enantioselective reductive aldol reaction of allenic esters with ketones (Scheme 61)

Entry	*R*	*Method*	*Product*	*Yield (%)*	*Selectivity*	ee *(%)*
1	Ph	A		96	25:1[a]	99
2	PhCH=CH	A		97	30:1[a]	84
3	Pr^i	A		80	>8:1[a]	98
4	Ph	B		90	10:1[b]	84
5	3-ClC_6H_4	B		89	8:1[b]	83
6	PhCH=CH	B		87	9:1[b]	67

[a] γ:α.
[b] *Threo*:*erythro*.

Nonasymmetric reductive coupling of α,β-unsaturated amides and ketones catalyzed by $Co(acac)_2{\cdot}2H_2O$ (5 mol%) (Method A) or a complex derived from $CoCl_2$ (5 mol%) and $(c\text{-}C_6H_{11})_2PPh$ (5.5 mol%) (Method B) was reported by Lam and coworkers (Scheme 62, Table 22).[119] Et_2Zn (2 equivalents) was employed as a hydride source. The reaction of acetophenone and propiophenone derivatives gave the aldol products with high *threo*-selectivity. The reaction is proposed to proceed with the intermediacy of (*Z*)-Zn enolates.



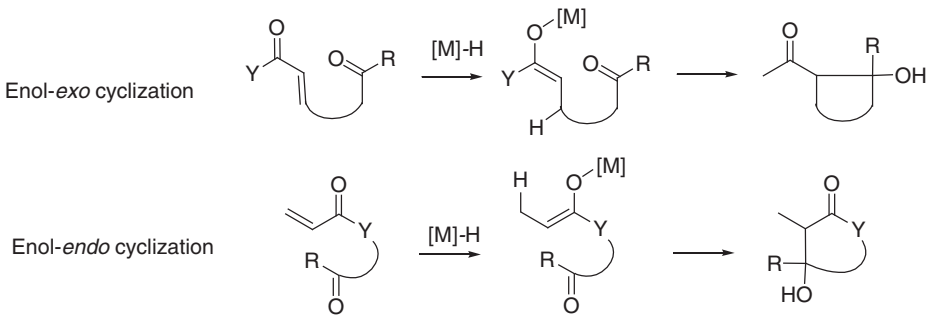
Scheme 62

Table 22 Co(II)-catalyzed reductive aldol reaction of α,β-unsaturated amides with ketones (Scheme 62)

Entry	R^1	R^2	R^3	*Method*	*Yield (%)*	ds
1	Ph	Me	H	A	80	5.5:1
2	Ph	Et	H	A	75	6:1
3	2-Furyl	Me	H	A	72	3:1
4	Ph	Me	Ph	A	71	>19:1
5	Ph	Me	Bu^i	B	85	>19:1

2.10.3.3.2 Intramolecular reaction

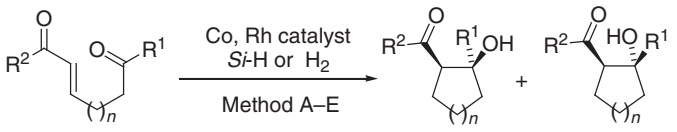
Thanks to the mild reaction conditions for generating transition metal enolates, the reductive aldol reaction of α,β-unsaturated carbonyl compounds and aldehydes (or ketones) can be ideally performed in an intramolecular fashion, given that requisite bifunctional precursors are readily available. The reaction provides an opportunity in rapidly building up functionalized cyclic skeletons, especially those with congested quaternary carbon centers. Intramolecular reductive aldol reactions involving both *exo*- and *endo*-cyclization of enolate moieties have been reported (Scheme 63).



Scheme 63

2.10.3.3.2.1 *Enol*-exo *cyclization*

The first example of the intramolecular reductive aldol reaction was reported by Krische and coworkers in 2001 (Scheme 64, Method A).[120] Treatment of aldehyde-enones **158a,b** (R^1=H) with $PhSiH_3$ (1.2 equivalents) in the presence of $Co(dpm)_2$ (dpm=dipivaloylmethane) (5 mol%) yielded the corresponding five- and six-membered ring cyclization products **159a,b** in high yield with high *cis*-selectivity (Table 23, entries 1 and 3). In the intramolecular process, the geometrical requirements are supposed to be stringent for bond formation (cf. **160**), enhancing *cis*- (or *syn*-) selectivity in comparison with the intermolecular reactions.



Method A: $Co(dpm)_2$ (5 mol%), $PhSiH_3$ (1.2 equivalents), $ClCH_2CH_2Cl$, 25 °C.

Method B: $Rh(cod)_2OTf$ (10 mol%), $(4\text{-}CF_3C_6H_4)_3P$ (24 mol%), H_2, KOAc (30 mol%), $ClCH_2CH_2Cl$, 25 °C.

Method C: $Rh(cod)_2OTf$ (10 mol%), Ph_3P (24 mol%), H_2, KOAc (80 mol%), $ClCH_2CH_2Cl$, 25 °C.

Method D: $RhCl(PPh_3)_3$ (1 mol%), Et_3SiH (2.1 equivalents), toluene, 50 °C.

Method E: $RhH(PPh_3)_4$ (1 mol%), Et_3SiH (2.1 equivalents), toluene, 50 °C.

Scheme 64

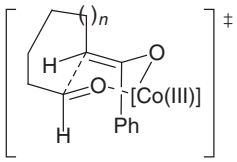
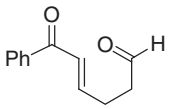
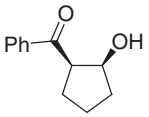
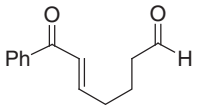
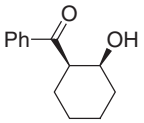
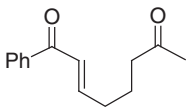
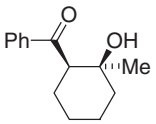
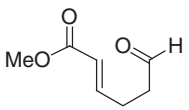
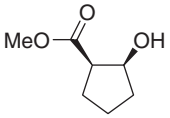
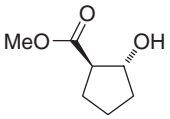
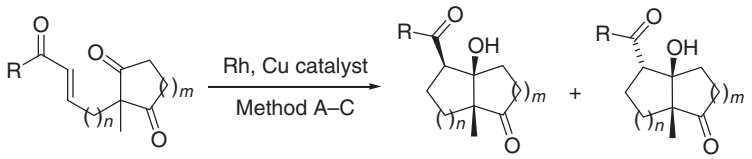


Table 23 Enol-*exo* reductive cyclization (**Scheme 64**)

Entry	*Starting material*	*Method*	*Product*	*Yield (%)*	ds	*References*
1		A		70	>99:1	120a
2	**158a**	B	*cis*-**159a**	71	24:1	100a
3		A		87	>99:1	120a
4	**158b**	B	*cis*-**159b**	89	10:1	100a
5	 **158c**	C	 *cis*-**159c**	72	19:1	100b
6	 **158d**	D	 *cis*-**159d**	81	3:1	121
7		E	 *trans*-**159d**	81	11:1	121

Alternatively, the reductive cyclization of aldehyde-enones **158a,b** and keto-enone **158c** was achieved with high *cis*-selectivity using H_2 as a hydrogen source by the catalysis of Rh(I) complexes derived from $[Rh(cod)_2]OTf$ (10 mol%) and triarylphosphines (Methods B and C, entries 2, 4, and 5).[100] The reductive aldol reaction of aldehyde-enoate **158d** was reported by Motherwell and coworkers.[121] When the reaction was performed with Et_3SiH (2.1 equivalents) and $RhCl(PPh_3)_3$ (1 mol%), the corresponding cyclization product *cis*-**159d** was obtained with moderate diastereoselectivity (Method D, entry 6). In contrast, highly *trans*-selective cyclization was observed when $RhH(PPh_3)_4$ (1 mol%) was employed as a catalyst (Method E, entry 7).

In comparison with mono-ketone derivatives, dione-enones **161** are more reactive by virtue of inductive effects and relief of dipole–dipole interactions (Scheme 65, Table 24). Dione-enones **161a,b** underwent facile reductive cyclization by the catalyst system derived from $[Rh(cod)_2]OTf$ (10 mol%) and Ph_3P (24 mol%) under H_2 atmosphere to give diastereoselectively *cis,syn*-**162a,b** of three-contiguous stereogenic centers, including two-contiguous quaternary centers (Method A, entries 1 and 2).[100b] For the intermolecular reductive aldol reactions of α,β-unsaturated aldehydes, reported examples are limited to those with highly reactive glyoxal.[122] However, the intramolecular reaction of dione-enal **161c,d** (R=H) was reported to proceed well using a catalyst system derived from $[Rh(cod)_2]OTf$ and $(2\text{-Furyl})_3P$ (Method B, entries 3 and 4).[123]

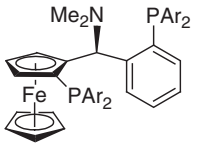


161 *cis,syn*-**162** *cis,anti*-**162**

Method A: $Rh(cod)_2OTf$ (10 mol%), Ph_3P (24 mol%), H_2, KOAc (80 mol%), $ClCH_2CH_2Cl$, 25 °C.

Method B: $Rh(cod)_2OTf$ (10 mol%), $(2\text{-Furyl})_3P$ (24 mol%), H_2, K_2CO_3 (100 mol%), THF, 40 °C.

Method C: $[CuF(PPh_3)_3]\cdot 2MeOH$ (1 mol%), TANIAPHOS **121f** (1 mol%), $PhSiH_3$ (1.4 equivalents), toluene, –50 °C.



Ar = $(3,5\text{-}Me_2\text{-}4\text{-}OMe)C_6H_2$

TANIAPHOS **121f**

Scheme 65

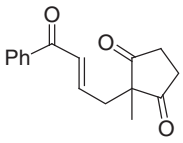
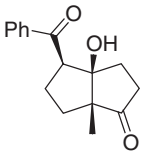
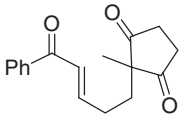
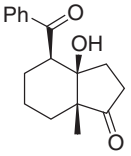
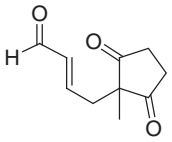
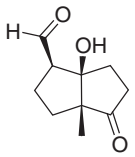
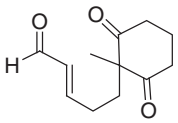
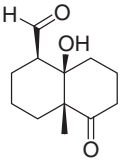
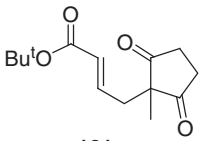
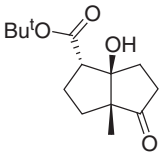
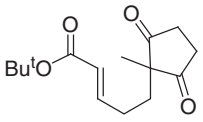
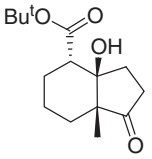
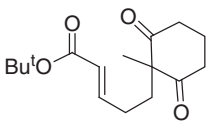
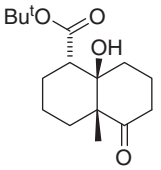
Enantioselective reductive cyclization of dione-enoate **161e–g** ($R=OBu^t$) was successfully achieved by a chiral Cu(I) catalyst derived from $[CuF(PPh_3)_3]\cdot 2MeOH$ and TANIAPHOS **121f** (Method C, entries 5–7).[124] As observed in the intermolecular reactions, the reaction of enoates exhibited a diastereoselectivity opposite to that observed generally for enones, yielding bicyclic products *cis,anti*-**162e–g** as major isomers. Good-to-high enantioselectivity was observed depending on the ring sizes of newly formed and previously existing carbocycles.

Lipshutz et al. demonstrated that the Cu-catalyzed intramolecular reductive aldol reaction is successfully employed in generating three new contiguous asymmetric stereocenters (Scheme 66).[125] In the presence of $Cu(OAc)_2\cdot H_2O$ (3–5 mol%) and JOSIPHOS **165a** (1 mol%), reductive cyclization of (*E*)-keto-enone (*E*)-**163a,b** with $Me(EtO)_2SiH$ (1.5 equivalents) afforded the single diastereomer of 1,2,3-trisubstituted cyclohexanols **164a,b** in high yield and high enantioselectivity (Table 25, entries 1 and 3). Under similar conditions, the reaction of (*Z*)-keto-enone (*Z*)-**163a** gave the same diastereomer of opposite configuration (*ent*-**164a**) enantioselectively. When applied to the formation of cyclopentanol derivative **164c**, two diastereomers were obtained both with high enantioselectivity (entry 4). The Cu-catalyzed reaction of keto-enone (*E*)-**163a** was also successful under similar conditions using a heterogeneous copper-in-charcoal (Cu/C) in lieu of $Cu(OAc)_2\cdot H_2O$.[126] Best results were obtained in the presence of NaOPh (10–20 mol%) and $Me(EtO)_2SiH$ (4 equivalents) to afford **164a** (84% yield, 98% *ee*).[127]

2.10.3.3.2.2 *Enol*-endo *cyclization*

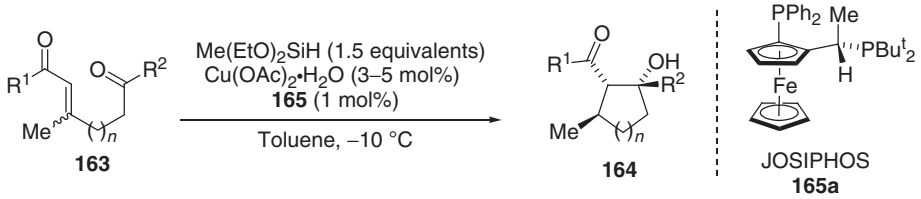
The diastereo- and/or enantioselective *endo*-cyclization of keto esters **166** (Y=O) and keto amides **166** (Y=NR) has been reported (Scheme 67, Table 26). Lam and Joensuu reported that Cu(I) diphosphine complexes catalyzed reductive cyclization of keto-enoates in the presence of 1,1,3,3-tetramethylhydrosiloxane (TMDS; $Me_2(H)SiOSi(H)Me_2$) as a hydride source, affording five- and six-membered ring lactones in high yields.[128] When a complex derived from $Cu(OAc)_2\cdot H_2O$ (5 mol%) and 1,1′-bis(diphenylphosphino)ferrocene (DPPF) (5 mol%) was employed, a variety of lactones **167** (Y=O, $n=1$, 2, R^1=H, aryl, or alkyl, R^2=aryl or alkyl) were obtained with high *cis*-selectivity (Method A, e.g., entries 1 and 2). Under similar conditions, the reaction of keto-enamides provided *cis*-valerolactams **167** [Y=*N*-PMP (PMP=4-methoxylphenyl), *N*-OMP (OMP=2-methoxyphenyl), $n=1$, R^1=H or Me, R^2=alkyl or aryl] diastereoselectively (>19:1) in good yields (entries 8, 9, and 11).[129] Chiral keto-enamide **169**,

Table 24 Enol-*exo* reductive cyclization of diketo-enals, -enones, and -enoates (**Scheme 65**)

Entry	*Starting material*	*Method*	*Product*	*Yield (%)*	ds	ee *(%)*	*References*
1	 **161a**	A	 *rac-cis,syn*-**162a**	84	>19:1	[a]	100b
2	 **161b**	A	 *rac-cis,syn*-**162b**	86	>19:1	[a]	100b
3	 **161c**	B	 *rac-cis,syn*-**162c**	72	2:1	[a]	123
4	 **161d**	B	 *rac-cis,syn*-**162d**	73	10:1	[a]	123
5	 **161e**	C	 *cis,anti*-**162e**	85	1:0	66	124
6	 **161f**	C	 *cis,anti*-**162f**	80	8.1:1	97	124
7	 **161g**	C	 *cis,anti*-**162g**	85	16:1	80	124

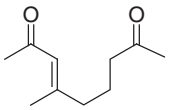
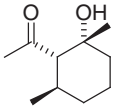
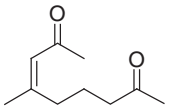
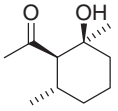
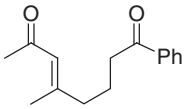
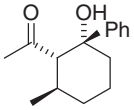
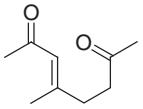
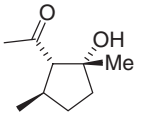
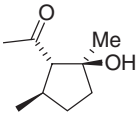
[a]The product is racemic.

which was prepared in enantioenriched form by L-proline-catalyzed direct enantioselective Mannich reaction,[130] underwent stereoselective cyclization to give *cis*-lactone **170** as a major diastereomer (equation 28). For the enantioselective catalytic reactions, good levels of enantioselectivity were obtained when chiral diphosphines, such as (*R*)-3,5-di-Pr^{i}-MeO-BIPHEP **168** and (*S*)-SEGPHOS **36b** (5 mol%), were employed in the reaction of keto-enoates **166c** (Method B, entries 3 and 4).[128]

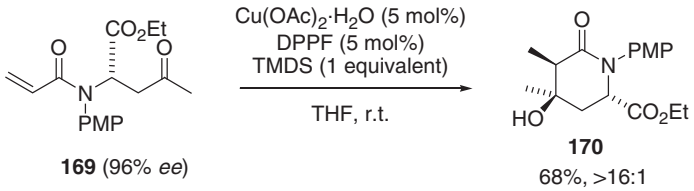


Scheme 66

Table 25 Cu-catalyzed enantioselective intramolecular reductive aldol reaction of β-substituted keto-enones (Scheme 66)

Entry	*Starting material*	*Product*	*Yield (%)*	ds	ee *(%)*
1	 (*E*)-**163a**	 **164a**	91	1:0	96
2	 (*Z*)-**163a**	 ***ent*-164a**	88	1:0	96
3	 **163b**	 **164b**	77	1:0	97
4	 **163c**	 **164c** major  **164c** minor	75	1.4:1	97 (92)[a]

[a] *ee* value for the minor diastereomer.

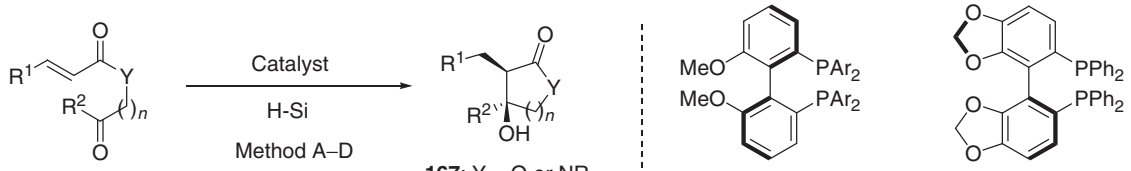


(28)

$Co(acac)_2$-catalyzed, Et_2Zn-mediated reductive aldol reactions developed by Lam et al. (*vide supra*) could be applied to the intramolecular reaction of keto-enamides, giving rise to *cis*-lactams **167e**,**i**,**l** diastereoselectively (Method C, entries 6, 10, and 13).[132] When mediated by Et_2Zn, $Ni(acac)_2$ (5 mol%) also catalyzes the reductive cyclization to give *cis*-lactones **167d** and *cis*-lactams **167f**,**k**,**m** with high diastereoselectivity (Method D, entries 5, 7, 12, and 14).[131] The Ni-catalyzed reaction is limited to the β-substituted derivatives (**166** ($R^1 \neq H$)). Otherwise, conjugate addition of the ethyl group and hydride concurrently occurs, resulting in the major formation of alkylative aldol products (*vide infra*).

2.10.3.4 Alkylative Aldol Reaction

The conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds and the subsequent use of the resulting metal enolates in the aldol reaction to the second carbonyl compounds provide a highly convergent method for constructing complex carbon skeletons in a stereodefined fashion. Such tandem three-component coupling reaction or alkylative aldol reaction



Method A: $Cu(OAc)_2 \cdot H_2O$ (5 mol%), DPPF (5 mol%), TMDS (1 equivalent), THF, r.t.

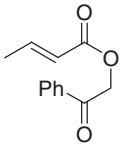
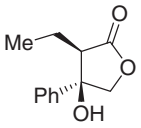
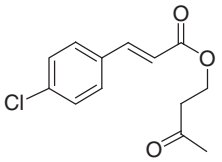
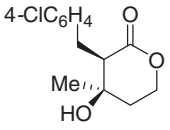
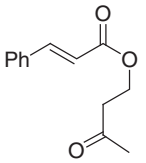
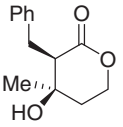
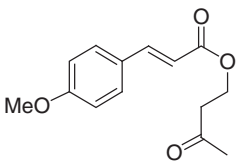
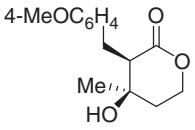
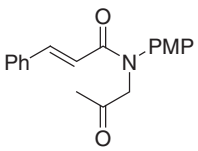
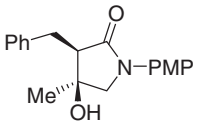
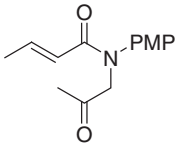
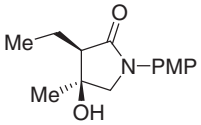
Method B: $Cu(OAc)_2 \cdot H_2O$ (5 mol%), (*R*)-**168** (entry 3) or (*S*)-**36b** (entry 4) (5 mol%).

Method C: $Co(acac)_2 \cdot 2H_2O$ (5 mol%), Et_2Zn (2 equivalents), THF, hexane, 0 °C to r.t.

Method D: $Ni(acac)_2$ (5 mol%), Et_2Zn (2 equivalents), THF, hexane, 0 °C to r.t.

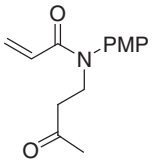
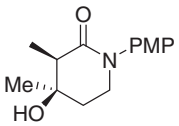
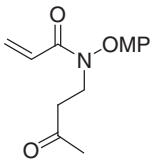
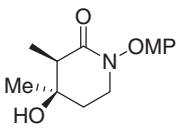
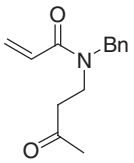
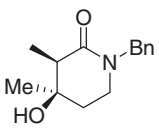
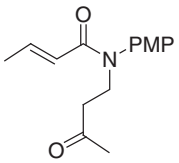
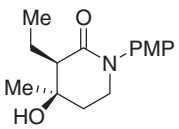
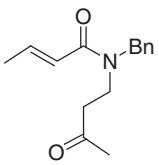
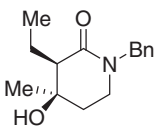
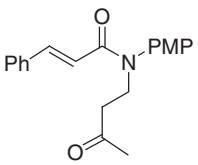
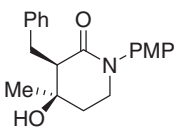
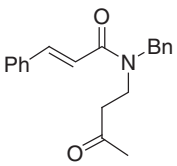
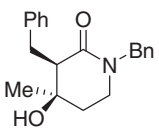
Scheme 67

Table 26 Enol-*endo* reductive cyclization (**Scheme 67**)

Entry	*Starting material* ***166***	*Method*	*Product* ***167***	*Yield (%)*	ds	ee *(%)*	*References*
1	 **166a**	A	 *rac*-**167a**	72	1:0	[a]	128
2	 **166b**	A	 *rac*-**167b**	65	1:0	[a]	128
3	 **166c**	B[b]	 **167c**	64	1:0	77	128
4		B[c]	*ent*-**167c**	62	1:0	74	128
5	 **166d**	D	 *rac*-**167d**	76	>19:1	[a]	131
6	 **166e**	C	 *rac*-**167e**	56	8:1	[a]	132
7	 **166f**	D	 *rac*-**167f**	42	5:1	[a]	131

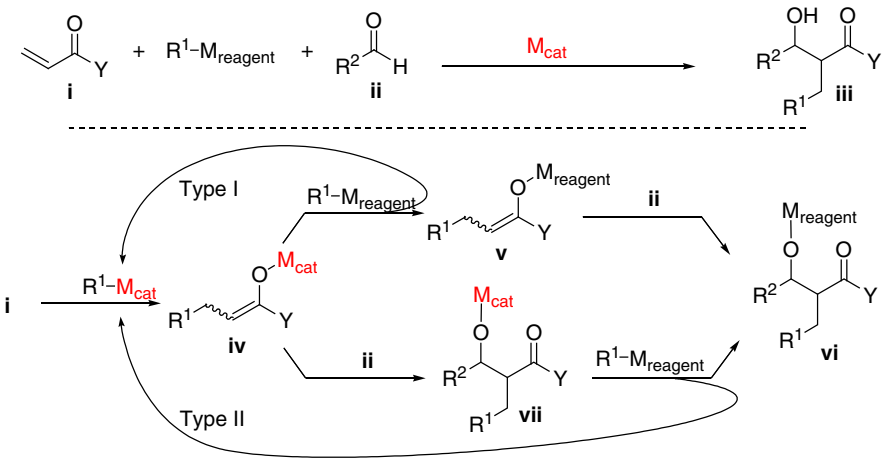
(*Continued*)

Table 26 Continued

Entry	*Starting material* ***166***	*Method*	*Product* ***167***	*Yield (%)*	ds	ee *(%)*	*References*
8	 **166g**	A	 *rac*-**167g**	66	1:0	[a]	129
9	 **166h**	A	 *rac*-**167h**	70	1:0	[a]	129
10	 **166i**	C	 *rac*-**167i**	88	9:1	[a]	132
11	 **166j**	A	 *rac*-**167j**	55	1:0	[a]	129
12	 **166k**	D	 *rac*-**167k**	97	>19:1	[a]	131
13	 **166l**	C	 *rac*-**167l**	89	12:1	[a]	132
14	 **166m**	D	 ***rac*-167m**	97	>19:1	[a]	131

[a]The product is racemic.
[b](*R*)-3,4-di-Pr^{i}-MeO-BIPHEP **168** was employed.
[c](*S*)-SEGPHOS **36b** was employed.

has been studied extensively.[133] Recent advances in transition metal enolates have made the reaction possible to be carried out in a catalytic manner, endowing diastereo- and/or enantioselectivity (Scheme 68).

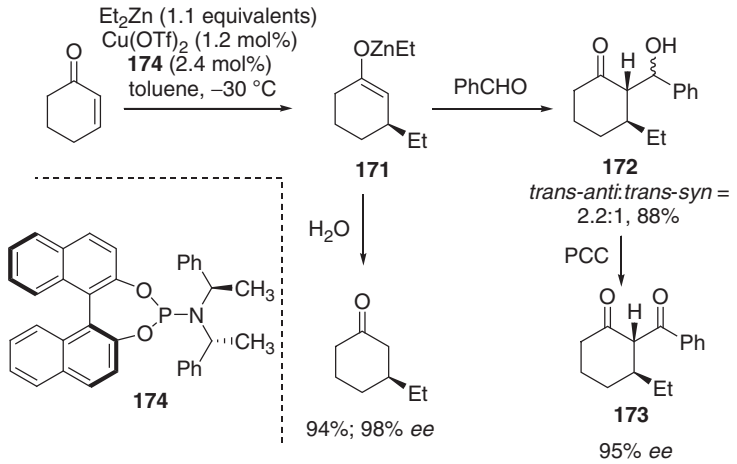


Scheme 68

In the catalytic alkylative aldol reaction, α,β-unsaturated carbonyl compounds **i**, organometallic reagents (R–$M_{reagent}$), and aldehydes **ii** (or ketones) were coupled together to give aldol product **iii**. The alkylative aldol reactions so far reported are classified into two types with respect to the mechanism. In a type-I reaction, an alkyl transition metal R–M_{cat} is first generated by the reaction of R–$M_{reagent}$ with a transition metal catalyst M_{cat} and then undergoes conjugate addition to form transition metal enolate **iv**, which participates in aldolization after being converted to enolate **v** with simultaneous regeneration of R–M_{cat} by transmetalation with R–$M_{reagent}$. This type of reaction can be carried out by a stepwise manner by adding aldehyde **ii** after generation of enolate **v**. Alternatively, in a type-II reaction, transition metal enolate **iv** is generated in the presence of carbonyl acceptor **ii**, undergoing aldolization before transmetalation to form **v** to furnish aldolate **vii**. The catalytic cycle is closed by the reaction of **vii** with R–$M_{reagent}$ to give aldolate **vi** and R–M_{cat}.

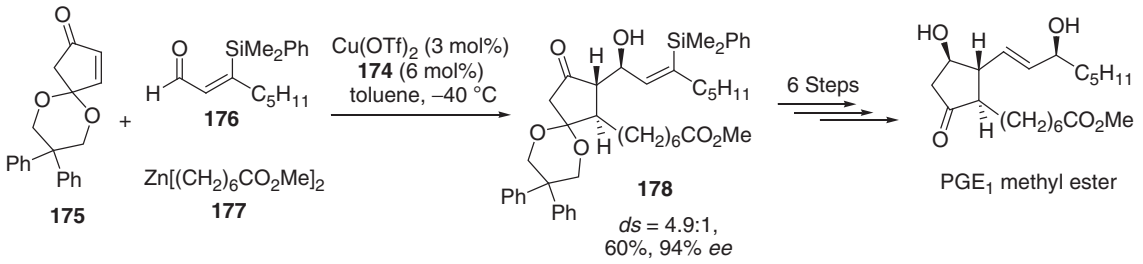
2.10.3.4.1 Cu-catalyzed reaction

In 1996, a catalytic enantioselective alkylative aldol reaction of type I was reported by Feringa et al. (Scheme 69).[134] A highly efficient chiral Cu catalyst system, derived from $Cu(OTf)_2$ and a chiral phosphoramidite **174**, was developed for an enantioselective conjugate addition of dialkylzinc reagents to cyclic enones.[135] For example, treatment of cyclohexenone with Et_2Zn (1.1 equivalents) in the presence of $Cu(OTf)_2$ (1.2 mol%) and **174** (2.4 mol%) afforded 3-ethylcyclohexanone in 98% *ee* and in high yield. When chiral Zn-enolate intermediate **171** was trapped with benzaldehyde, the aldolization occurred exclusively at a face opposite to the ethyl group to give alkylative aldol product **172** as a mixture of *trans–anti* and *trans–syn* diastereomer (2.2:1) in high yield.[136] Pyridinium chlorochromate (PCC) oxidation of the aldol afforded diketone **173** in 95% *ee*.



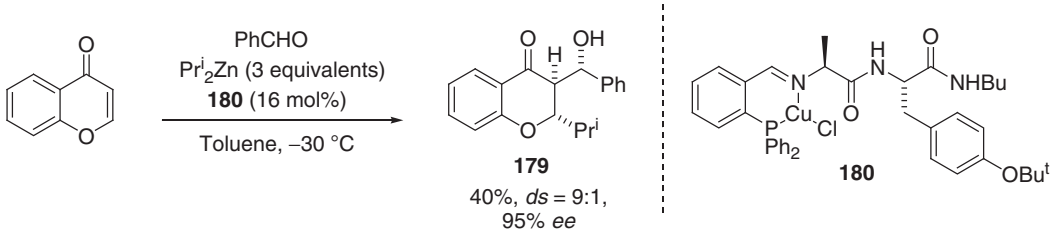
Scheme 69

The utility of the alkylative aldol reaction was demonstrated in a convergent asymmetric synthesis of PGE_1 methyl ester (Scheme 70).[137] Enantioselectivity of the conjugate addition to the cyclopentenones is relatively lower than cyclohexenones. However, the selectivity was found to be enhanced by the introduction of spiroacetal moiety at the γ position. Thus, the chiral Cu complex derived from $Cu(OTf)_2$ and phosphoramidite **174**-catalyzed reaction of zinc reagent **177** bearing a methoxycarbonyl group to **175**, followed by trapping with **176**, stereoselectively furnished the three-component coupling product **178** (*ds*=4.9:1, 94% *ee*), from which the PEG_1 derivative was synthesized with six additional steps.



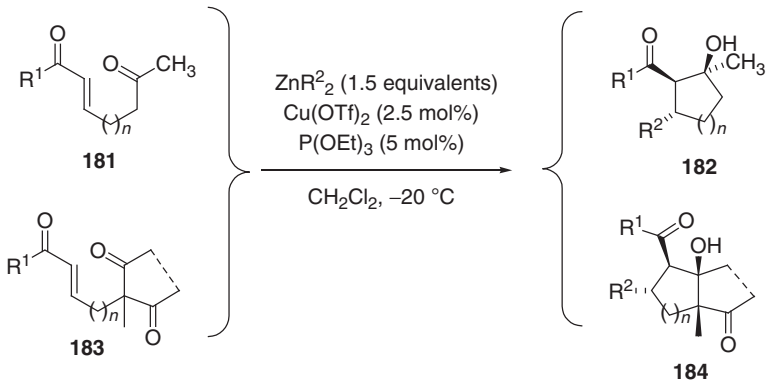
Scheme 70

Hoveyda and coworkers reported the alkylative aldol reaction of chromen-4-one and α,β-unsaturated lactones catalyzed by a chiral Cu(I)-peptide complex **180** (Scheme 71).[138] For example, in the presence of **180** (16 mol%) in toluene at −30 °C, a three-component coupling reaction of chromen-4-one, Pr^i_2Zn (3 equivalents), and benzaldehyde (2 equivalents) afforded aldol product **179** in 40% yield with high *anti*-selectivity and high enantioselectivity (95% *ee*). The catalytic system was also applicable to the alkylative aldol reaction of five-, six-, and seven-membered unsaturated lactones.



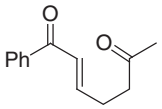
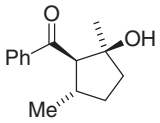
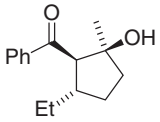
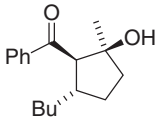
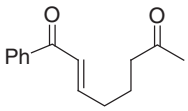
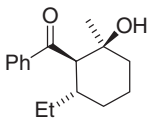
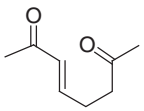
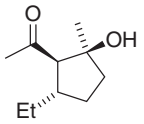
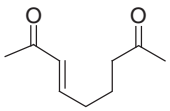
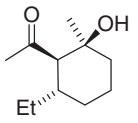
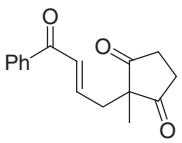
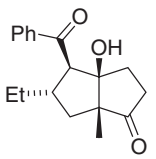
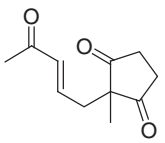
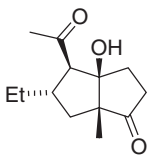
Scheme 71

A Cu(I)-catalyzed intramolecular alkylative aldol reaction of keto-enones **181** and diketo-enones **183** has been reported by Krische and coworkers (Scheme 72, Table 27, entries 1–6).[139] In the presence of catalyst precursors $Cu(OTf)_2$ (2.5 mol%) and $P(OEt)_3$ (5 mol%), the reaction of **181** and dialkylzinc reagents (1.5 equivalents) gave aldol products **182** diastereoselectively. Under these conditions, the reaction of **183** and Et_2Zn stereoselectively yielded bicyclic products **184** (entries 7 and 8). Interestingly, when chiral phosphoramidite **174** was employed in place of $P(OEt)_3$, a 2.3:1 mixture of **184a** and diastereomer *iso*-**184a** was formed both in high enantioselectivity (Scheme 73).

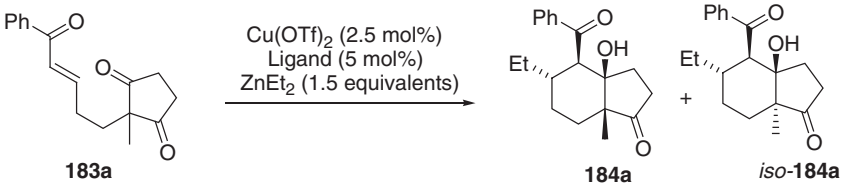


Scheme 72

Table 27 Cu-catalyzed intramolecular alkylative aldol reaction (**Scheme 72**)

Entry	*Keto-enone*	*R_2Zn*	*Product*[a]	*Yield (%)*	ds
1		Me_2Zn		83	>95:1
2		Et_2Zn		81	>95:1
3		Bu_2Zn		91	>95:1
4		Et_2Zn		98	>95:1
5		Et_2Zn		77	3:1
6		Et_2Zn		96	2.2:1
7		Et_2Zn		99	>95:1
8		Et_2Zn		96	2:1

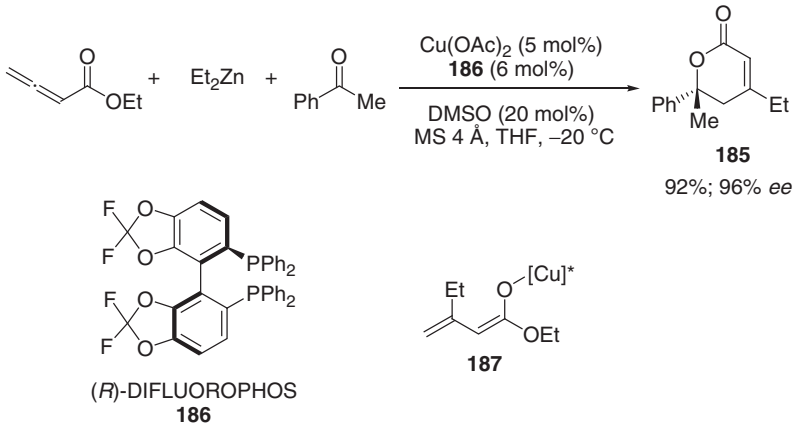
[a]The products are racemic.



Ligand	Yield (%)	*ds*	*ee*
$P(OEt)_3$	99	>19:1	NA
174	99	2.3:1	**184a** 80%, *iso*-**184a**, 98%

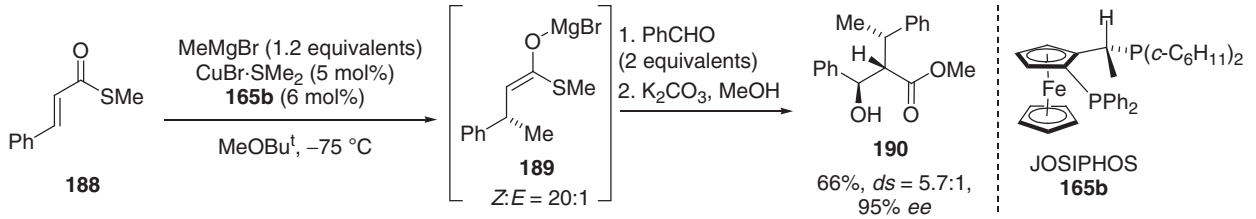
Scheme 73

The chiral Cu-catalyzed conjugate reduction of allenic esters with PinBH generates dienolate intermediates **155**, which undergo the tandem enantioselective aldol reaction with ketones either at the α or γ position (Scheme 61). Shibasaki and coworkers reported that a modified catalyst system, with employment of dialkylzinc reagents as nucleophiles, was valid for the enantioselective alkylative aldol reaction of allenic esters (Scheme 74).[140] In the presence of $Cu(OAc)_2$ (5 mol%) and (*R*)-DIFLUOROPHOS **186** (6 mol%), the reaction of an allenic ester, Et_2Zn, and acetophenone afforded lactone **185** in 96% *ee* and in 92% yield. The reaction was proposed to proceed through the intermediacy of a chiral Cu dienolate **187**, which underwent enantioselective addition to the ketones regioselectively at the γ position and subsequent cyclization to give **185**. It should be noted that the aldolization took place with a chiral Cu enolate before transmetalation to a Zn-enolate according to the type-II mechanism.



Scheme 74

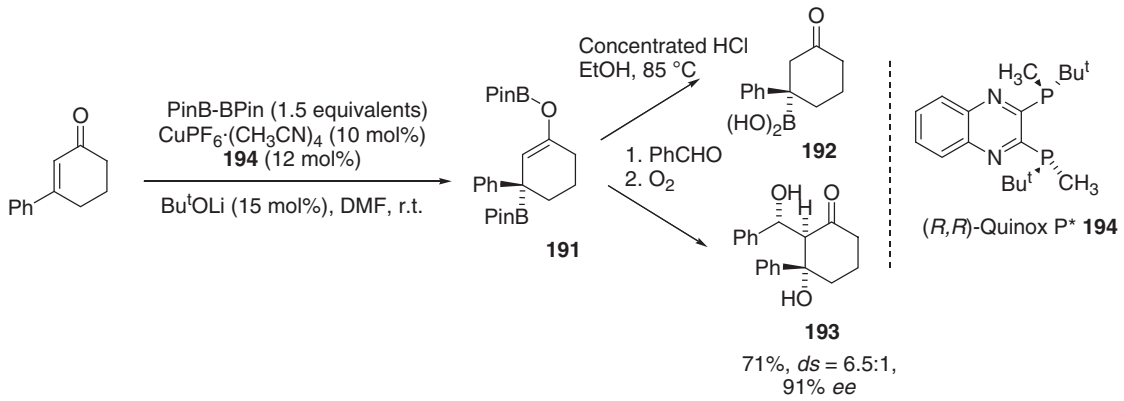
Feringa and coworkers reported asymmetric conjugate addition of methyl Grignard reagents to thiocinnamate **188** (Scheme 75).[141] In the presence of a chiral Cu(I) complex derived from $CuBr{\cdot}SMe_2$ (5 mol%) and JOSIPHOS **165b** (6 mol%), Mg (*Z*)-enolate **189** was generated diastereo- and enantioselectively by the reaction of **188** with MeMgBr. Subsequent treatment of **189** with benzaldehyde (2 equivalents) followed by methanolysis of the thiol ester moiety furnished the alkylative aldol product **190** diastereo- and enantioselectively.



Scheme 75

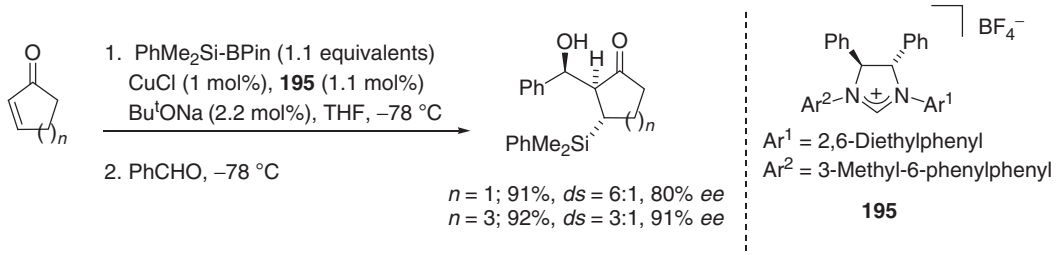
Recently, a variation of the alkylative aldol reactions was developed, in which boron and silicon nucleophiles participate in the conjugated addition step. Kanai and coworkers reported a tandem enantioselective conjugate borylation/aldolization of cyclic enones catalyzed by a chiral Cu(I) complex derived from $[Cu(CH_3CN)_4]PF_6$ (10 mol%) and (*R*,*R*)-QuinoxP* **194** (12 mol%) (Scheme 76).[142] As illustrated in the reaction of 3-phenylcyclohex-2-enone, bis(pinacolato)diboron (PinB–BPin) (1.5 equivalents) was employed as a precursor of the boron nucleophile in the presence of Bu^tOLi (15 mol%). It was proposed that, under these conditions, a chirally modified boryl-Cu species (PinB-Cu·**194**) was generated and underwent enantioselective conjugate addition. Transmetalation of the resulting Cu(I) enolate with the diboron produces a chiral boron-enolate **191**, which underwent hydrolysis under acidic conditions to give boronic acid **192**. However, subsequent treatment of enolate **191** with an aldehyde followed by the oxidation of the boryl moiety yielded aldol product **193** in 91% *ee* with good diastereoselectivity.[143]

A catalytic silylative aldol reaction of cyclic enones and aldehydes has been also developed based on the approach similar to the tandem borylation/aldolization (Scheme 77). Lee and Hoveyda reported that treatment of cyclic enones with $PhMe_2Si$–BPin (1.1 equivalents) in the presence of Cu(I) complex derived from CuCl (1 mol%), chiral imidazolinium salt **195** (a precursor of a chiral NHC ligand), and Bu^tONa (2.2 mol%) followed by the addition of an aldehyde afforded the corresponding silylative aldol product diastereo- and enantioselectively.[144] A chiral auxiliary-based approach to the silylative aldol reaction was reported by Riant and coworkers.[145] As illustrated in Scheme 78, three-component coupling of chiral alkenoyloxazolidinones **196**, aromatic

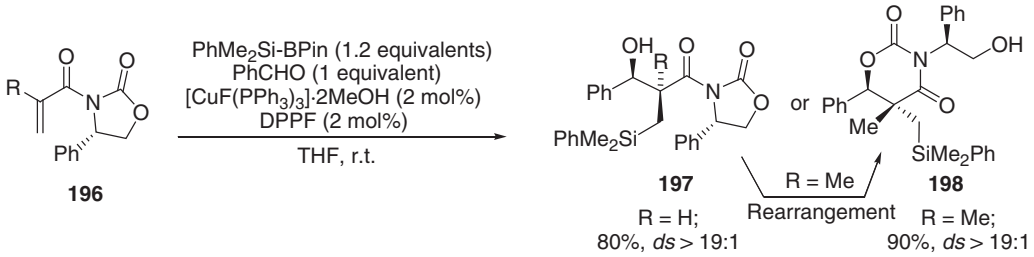


Scheme 76

aldehydes (1 equivalent), and $PhMe_2Si$–BPin (1.2 equivalents) proceeded efficiently in THF at room temperature in the presence of a Cu(I) catalyst derived from $[CuF(PPh_3)_3]\cdot 2MeOH$ (2 mol%) and DPPF (2 mol%) to furnish aldol product **197** or rearranged product **198**, depending on R=H or R=Me, respectively, with high diastereoselectivity (>19:1).



Scheme 77



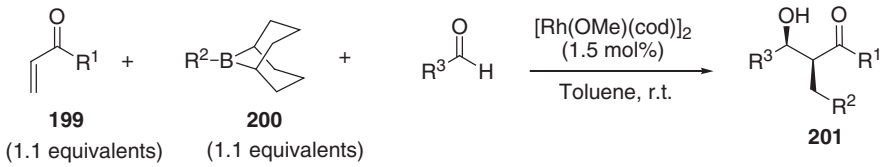
Scheme 78

2.10.3.4.2 Rh and relevant transition-metal-catalyzed reaction

In 1997, a Rh(I)-catalyzed conjugate addition of aryl and alkenyl boronic acids to α,β-unsaturated ketones was reported by Miyaura and coworkers.[146] In the following year, the enantioselective variant of this transformation was reported by Hayashi and coworkers.[147] Triggered by these seminal reports, the Rh-catalyzed enantioselective conjugate addition of organoboronic acids and other organometallic reagents has been extensively studied and now established as a reliable tool in asymmetric syntheses.[148] The conjugate addition of organoboron reagents is generally carried out in an aqueous solvent because water plays a key role in a catalytic cycle involving hydrolysis of a Rh(I)-enolate species to give Rh(OH) species and the hydrolyzed conjugate addition product.[148a,b,149] Therefore, it is difficult to trap enolate intermediates with an acceptor carbonyl compound in the presence of water to realize a Rh-catalyzed alkylative aldol reaction.

In 2002, Hayashi and coworkers reported that the Rh-catalyzed conjugate addition could be carried out in an aprotic solvent by using 9-BBN derivatives as nucleophiles.[150] In the presence of $[Rh(OMe)(cod)]_2$ (1.5 mol%) in toluene, vinyl ketones **199** (1.1 equivalents), 9-BBN derivatives **200** (1.1 equivalents), and aldehydes underwent efficient three-component coupling to give *syn*-aldol product **201** diastereoselectively (equation 29). The reaction exhibits a wide generality with respect to unsaturated ketones (R^1=Me, Bu^t, or Ph), boron reagents (R^2=aryl or 1-alkenyl), and aldehydes (R^3=Et, Pr^i, or Ph), allowing access to the range of *syn*-aldol products **201** (Table 28). When the reaction was carried out in the absence of an aldehyde under otherwise identical

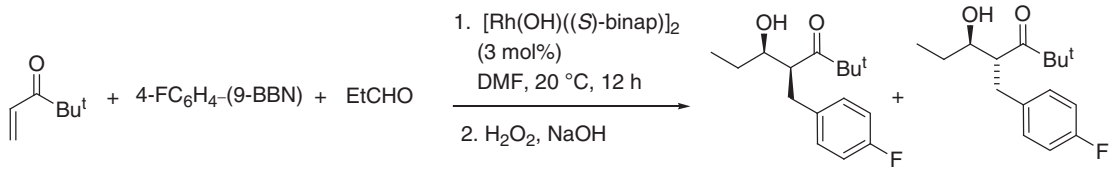
conditions, $[Rh(OMe)(cod)]_2$ did not catalyze the conjugate addition of the boron reagents to enones that would generate boron enolates. The observation suggested the participation of a Rh-enolate species in the aldolization step according to a type-II mechanism in Scheme 68. Concordant with the proposition, the use of chiral Rh complex $[Rh(OH)((S)\text{-binap})]_2$ (3 mol%) led to the formation of a 1:1.3 mixture of aldol adduct *syn*-(4*S*,5*R*)- and *anti*-(4*R*,5*R*)-**201a** in 41% *ee* and 94% *ee*, respectively (equation 30).



199 (1.1 equivalents) **200** (1.1 equivalents) **201** (29)

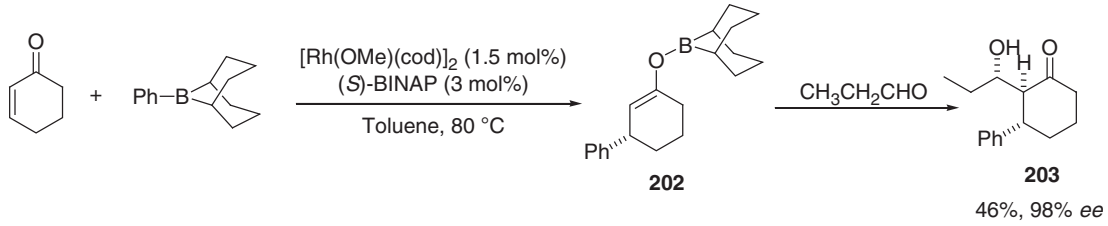
Table 28 Rhodiumcatalyzed alkylative aldol reaction (equation 29)

Entry	R^1	R^2	R^3	*Yield (%)*	ds
1	Me	4-FC_6H_4	Ph	99	5.7:1
2	Bu^t	Ph	Ph	97	11:1
3	Bu^t	4-FC_6H_4	Et	72	12:1
4	Bu^t	$C_5H_{11}CH{=}CH$	Ph	85	21:1
5	Ph	4-FC_6H_4	Pr^i	93	9:1



syn-(4*S*,5*R*)-**201a** 41% *ee* *anti*-(4*R*,5*R*)-**201a** 94% *ee* 44%, *syn*:*anti* = 1:1.3 (30)

Hayashi and coworkers also reported that, under more vigorous conditions, the enantioselective conjugate addition of aryl-9-BBN was catalyzed by a chiral Rh complex in the absence of aldehydes through a type-I mechanism.[151] Thus, at the higher temperature (80 °C) in toluene, aryl-9-BBN underwent addition to cyclohexenone in the presence of $[Rh(OMe)(cod)]_2$ (1.5 mol%) and (*S*)-BINAP (3 mol%) to give enantioenriched boron-enolate **202**. Subsequent treatment of **202** with propanal led to the formation of aldol product *trans*–*anti*-**203** as a single diastereomer in high enantioselectivity (98% *ee*) (Scheme 79).

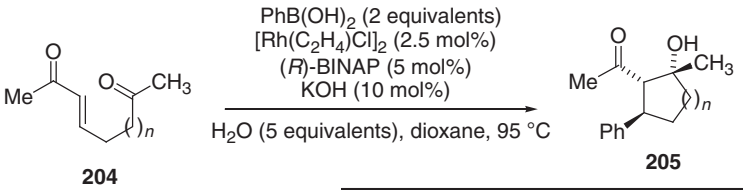


202 **203** 46%, 98% *ee*

Scheme 79

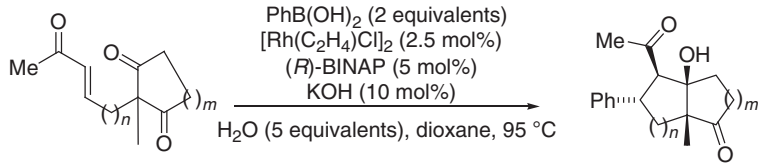
Intramolecular alkylative aldol reaction with phenylboronic acid was reported to occur even in the presence of water (Scheme 80).[152] In aqueous dioxane, the cyclization of Rh-enolate intermediates derived from keto-enones **204** and **206** was faster than protonation, affording the corresponding products **205** and **207**, respectively, with high efficiency as well as high enantioselectivity.

The Rh-catalyzed enantioselective three-component coupling reaction was successfully utilized by Nicolaou et al. in a convergent synthesis of spirocyclic structure motif present in vannusal A (Scheme 81).[153] Oct-1-enylzirconium reagent **208** was prepared by hydrozirconylation of 1-octyne and employed in the Rh-catalyzed tandem conjugate addition/aldol reaction to



204 **205**

n	Yield (%)	*ds*	*ee* (%)
1	88	>99:1	94
2	69	>99:1	95

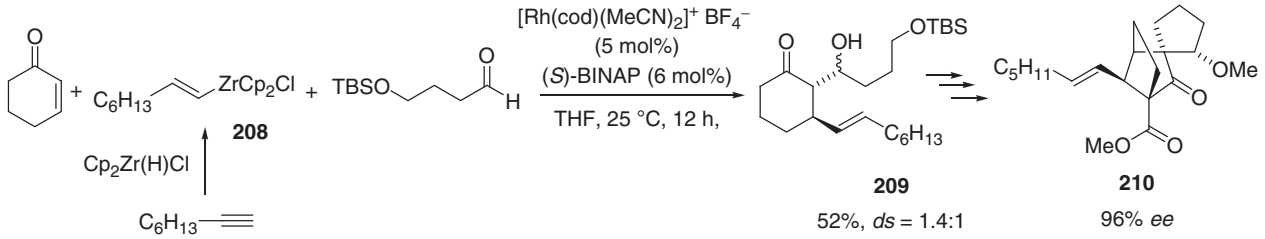


206 **207**

n	*m*	Yield (%)	*ds*	*ee* (%)
1	1	87	>99:1	90
1	2	86	>99:1	85
2	1	82	>99:1	85

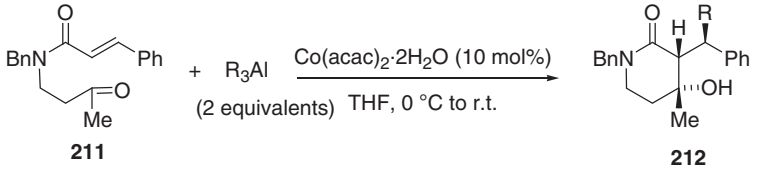
Scheme 80

provide enantioenriched product **209** as a mixture of *syn*- and *anti*-diastereomers, which was converted to the spirocyclic keto ester **210** (96% *ee*) in several steps.[154]



Scheme 81

Lam and coworkers reported a Co-catalyzed intramolecular alkylative aldol reaction of keto-enamides.[155] As illustrated in Scheme 82, treatment of **211** with trialkylaluminum (R_3Al) (2 equivalents) in the presence of $Co(acac)_2{\cdot}2H_2O$ (10 mol%) in THF

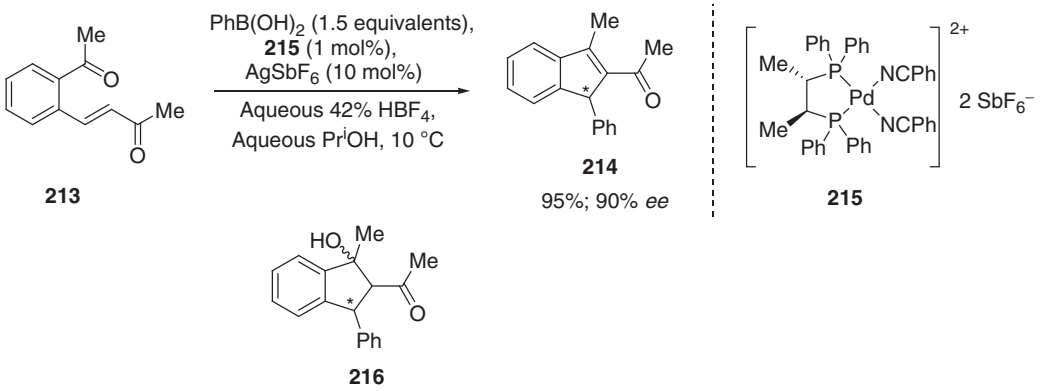


R	Yield (%)	*ds*
Me	43	>19:1
Et	98	>19:1
n-Hex	75	>19:1

Scheme 82

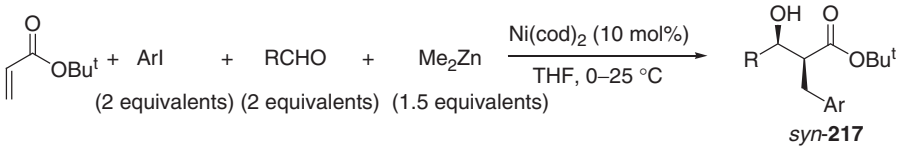
afforded β-hydroxylactam **212** with three-contiguous stereogenic carbons with high diastereoselectivity. The corresponding reductive aldol product was not observed even when alkylaluminum reagents possessing a β hydrogen were used, whereas the analogous reaction employing Et_2Zn under similar conditions led to the exclusive formation of reductive aldol product (Method C in Scheme 67).

Recently, a chiral Pd(II) complex-catalyzed enantioselective conjugate addition/aldol cyclization of ene-diones has been reported by Miyaura and coworkers (Scheme 83).[156] For example, the reaction of ene-dione **213** and phenylboronic acid was carried out with [Pd{(*S*,*S*)-chiraphos}$(PhCN)_2$][$(SbF_6)_2$ (**215**) (1 mol%) and $AgSbF_6$ (10 mol%) in acidic aqueous Pr^iOH to give indene derivative **214** in 95% yield and in 95% *ee*. It was proposed that the Brønsted acid facilitates both the conjugate addition of an Ar–Pd(II)$^+$ intermediate and subsequent aldol cyclization by protonation of the carbonyl groups. The acid might also catalyze the final dehydration of tertiary aldol intermediate **216**.



Scheme 83

Subburaj and Montgomery reported a unique tandem arylation/aldol reaction catalyzed by a Ni(0) complex (Scheme 84).[157] When a mixture of *t*-butyl acrylate, aryl iodides, and aldehydes was treated with Me_2Zn in the presence of $Ni(cod)_2$ (10 mol%) in THF, the aldol products *syn*-**217** were obtained in high yield with moderate-to-good diastereoselectivity. The authors proposed a mechanism involving oxidative addition of Ni(0) to Ar–I followed by the conjugate addition of the resulting aryl-Ni(II) species complexed with Me_2Zn.

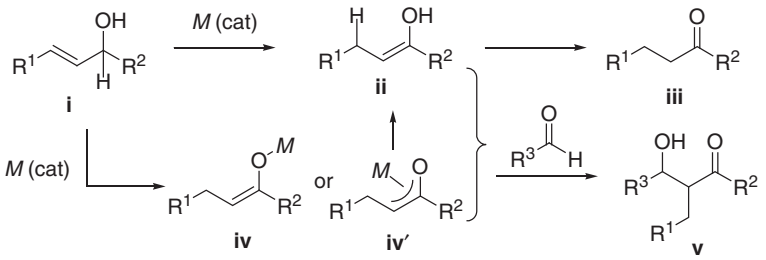


Ar	R	Yield (%)	*ds*
Ph	Ph	88	6.1:1
Ph	Et	75	5.7:1
3-(EtOCO)C_6H_4	Ph	54	6.7:1

Scheme 84

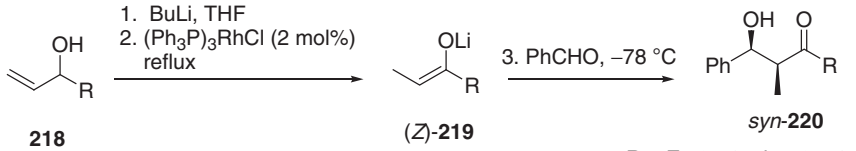
2.10.3.5 Tandem Isomerization/Aldol Reaction of Secondary Allylic Alcohols

The transition-metal-catalyzed isomerization of allylic alcohols to carbonyl compounds has been studied extensively as a useful synthetic process.[158] The isomerization proceeds through enols **ii** and/or enolates **iv** (or **iv′**), which undergo tautomerization to form the carbonyl compounds **iii**.[159] When the isomerization is performed in the presence of aldehydes, the intermediately generated species (**ii**, **iv**, and/or **iv′**) might undergo carbonyl addition to afford aldol products **v** (Scheme 85). In the reductive aldol reactions employing α,β-unsaturated carbonyl compounds, stoichiometric reductants, such as silanes, hydrogen, and diethylzinc, are necessary. However, in the tandem isomerization/aldolization reaction starting from allylic alcohols, no reductant is required because of an internal redox nature of the enolate formation step. Given the mild reaction conditions, regioselectivity, and full atom economy in generating enolates as well as the availability of the starting materials, the coupling reaction of allylic alcohols and aldehyde is a promising approach in aldol synthesis.[160]



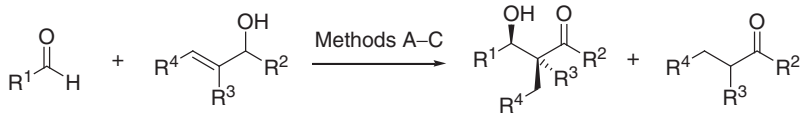
Scheme 85

In 1991, Sandham and coworkers reported the realization of this approach in the reaction of allylic alkoxides (Scheme 86).[161] In the presence of Wilkinson's catalyst (2 mol%), Li alkoxides derived from secondary allylic alcohols **218** underwent isomerization to form Li (*Z*)-enolate **219**. Subsequent reaction with benzaldehyde afforded *syn*-aldol product **220** with good diastereoselectivity.[162]



Scheme 86

The coupling reaction of allylic alcohols themselves was first reported in 2001 by Greé and coworkers (Scheme 87).[163] The reactions were catalyzed by $Fe(CO)_3$, generated *in situ* by irradiation of a precursor $Fe(CO)_5$. Later, it was shown that $Fe(CO)_3$(bda) (bda = benzylideneacetone) was a better precursor (Method A).[164] The reaction of hept-1-en-3-ol afforded the corresponding aldol adduct **221** in good yield with low *syn*-selectivity (Table 29, entries 1 and 11). Relatively high *syn*-selectivity was observed in the reaction of a sterically hindered functionalized alcohol (entry 6). The reaction was also applicable to disubstituted allylic alcohols as illustrated in entries 8 and 9. In these reactions, by-product formation of isomerized ketone **222** was observed.



Method A: $Fe(CO)_3$(bda) (2 mol%), allyl alcohol (1.2 equivalents), THF, hυ

Method B: $NiCl_2$(dppe) (3–7 mol%). $LiBHEt_3$ (3–7 mol%), $MgBr_2$ (3–7 mol%), allyl alcohol (1.1 equivalents), THF, rt

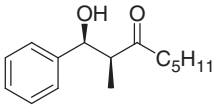
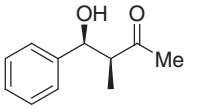
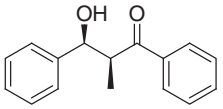
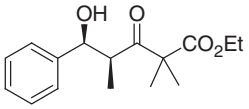
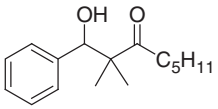
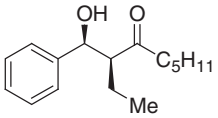
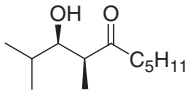
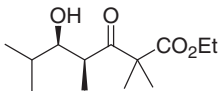
Method C: $RuCl_2(PPh_3)_3$ (3 mol%), allyl alcohol (1.25 equivalents), H_2O/toluene (4:1), 110 °C

Scheme 87

The isomerization to ketones was almost completely retarded by using Ni hydride-type catalysts developed by Greé and coworkers (Method B).[165,167] Under the optimized conditions employing *in situ*-prepared NiHCl(dppe) and cocatalyst $MgBr_2$ (3–7 mol% each) in THF at room temperature, the reaction afforded aldol products in good-to-excellent yield with moderate *syn*-selectivity (entries 2, 4, 7, 10, and 12). The tandem isomerization/aldolization catalyzed by $RuCl_2(PPh_3)_3$ (3 mol%) was reported by Wang et al. (Method C, entries 3 and 5).[166] Notably, the reaction could be carried out under air in a water/toluene mixture.[168]

In the above catalyst systems (Methods A–C), the aldolization step is thought to occur through a hydroxyl–carbonyl–ene type mechanism involving transition state **ix** (Scheme 88). For the Fe- and Ru-catalyzed reactions, a catalytic cycle-a involving an intramolecular 1,3-hydrogen shift via η^2 complex **iii**, π-allyl hydride intermediate **iv**, and π-enol complex **v** has been proposed.[164b,166b] For the Ni hydride-catalyzed reaction, a mechanism involving Ni alkoxide **vi** has been proposed (cycle-b).[165b] In the latter mechanism, alkoxide **vi** was first generated by the reaction of alcohol **i** with the Ni hydride. β-Hydride

Table 29 Tandem isomerization/aldolization of secondary allylic alcohols (Scheme 87)

Entry	R^1	R^2	R^3	R^4	Method	Product[a]	Yield (%)	ds	References
1	Ph	*n*-C_5H_{11}	H	H	A		86	1.1:1	164
2					B		99	1.5:1	165
3	Ph	Me	H	H	C		76	2.0:1	166
4	Ph	Ph	H	H	B		97	1.5:1	165
5[b]					C		80	2.1:1	166
6	Ph	$C(Me)_2CO_2Et$	H	H	A		83	6.1:1	164
7					B		93	>19:1	165
8	Ph	*n*-C_5H_{11}	Me	H	A		77	–	164
9	Ph	*n*-C_5H_{11}	H	Me	A		62	1.8:1	164
10					B		80	1.2:1	165
11	Pr^i	*n*-C_5H_{11}	H	H	A		58	1.9:1	164
12					B		93	1.9:1	165
13	Pr^i	$C(Me)_2CO_2Et$	H	H	A		70	6.1:1	164

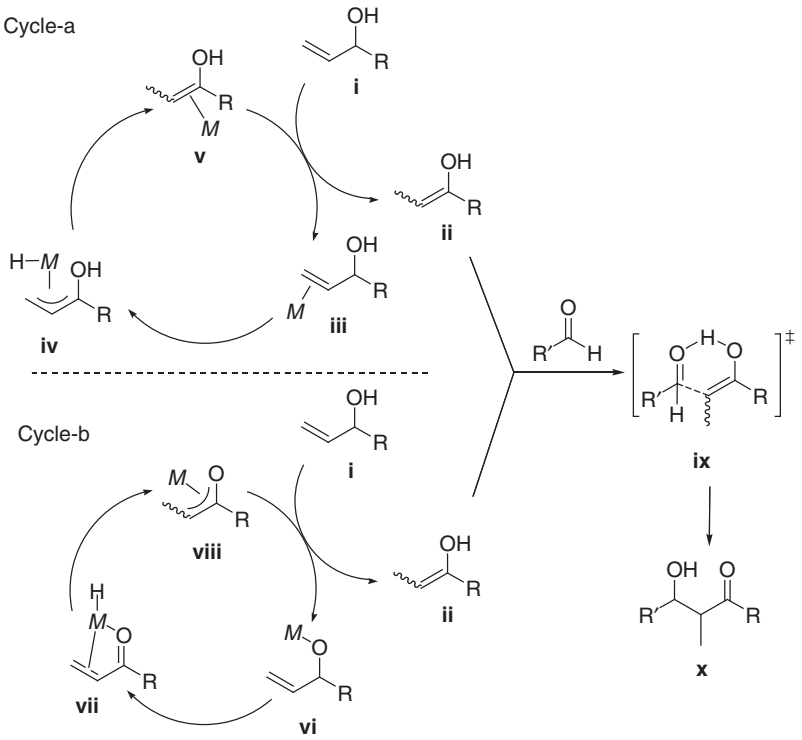
[a]Products are racemic.
[b]$In(OAc)_3$ (8 mol %) was used as a cocatalyst.

elimination/addition sequences lead to the formation of Ni-enolate **viii**, which then reacts with another molecule of allylic alcohol to regenerate alkoxide **vi** to liberate enol **ii**.

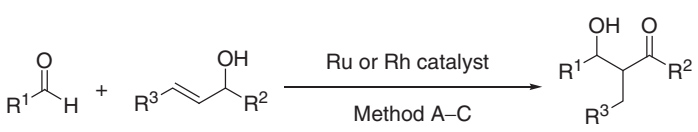
Recently, two catalytic systems have been developed in which transition metal enolates were thought to participate in the aldolization step before being transformed to enols. Martín-Matute et al. have reported that a Ru alkoxide complex, generated *in situ* from η^5-$(Ph_4MeCp)Ru(CO)_2Cl$ (**223b**) and Bu^tOK, catalyzes the isomerization of allylic alcohols to ketones efficiently at room temperature through a mechanism similar to catalytic cycle-b in Scheme 88.[169] They showed that, by employing a complex derived from sterically more congested complex η^5-$(Ph_5Cp)Ru(CO)_2Cl$ (**223a**), intermediately formed Ru-enolate **viii** was efficiently trapped by aldehydes to give aldol products (Scheme 89, Method A).[170] For example, in the presence of **223a** (5 mol%) and Bu^tOK (7 mol%), the reaction of α-vinylbenzyl alcohol and 4-chlorobenzaldehyde afforded the corresponding aldol product in 88% yield with moderate *syn*-selectivity (3.3:1) without by-product formation of isomerized propiophenone (Table 30, entry 1). Notably, in this reaction, high *syn*-selectivity (16:1) was observed at a lower conversion (*ca.* 5% conversion). However, the ratio was changed as the reaction proceeded, yielding higher amounts of the *anti*-diastereomer, likely through Ru-catalyzed red-ox epimerization at the carbinol carbon.[171] Formation of the kinetic *syn*-aldol product could be rationalized by a Zimmerman–Traxler six-membered transition state involving (*Z*)-enolate. In line with this supposition, 2-cyclohexen-1-ol of fixed configuration did not undergo tandem isomerization/aldolization under these conditions.

Ahlsten and Martín-Matute also reported a Rh-catalyzed tandem isomerization/aldolization reaction that proceeds through a similar mechanism involving a Rh-enolate.[172] Under the optimized conditions employing a catalyst prepared from $[Rh(cod)Cl]_2$ (2.5 mol%), PPh_3 (8 mol%), and Bu^tOK (5.5 mol%) (Method B), the reaction of allylic alcohols with aromatic aldehydes afforded the corresponding aldol products in high yield without diastereoselectivity (entries 3, 6, and 7).

The coupling reaction of primary allylic alcohols and aldehydes would afford β-hydroxy aldehydes, which could be employed successively as electrophiles for the second aldol reaction, thus, providing straightforward access to polyketides. Recently, Matsunaga and coworkers reported the first example of such a reaction by using a Rh catalyst system derived from $[Rh(cod)Cl]_2$



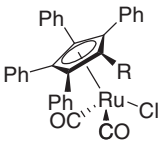
Scheme 88



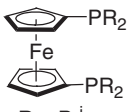
Method A: **223a** (5 mol%), Na_2CO_3 (1 equivalent), Bu^tOK (7 mol%), allyl alcohol (1.5 equivalents), toluene, 25–65 °C.

Method B: $[Rh(cod)Cl]_2$ (2.5 mol%), PPh_3 (8 mol%), Bu^tOK (5.5 mol%), allyl alcohol (1.2 equivalents), THF, 40 °C.

Method C: $[Rh(cod)Cl]_2$ (1.25 mol%), DIPPF (**224**) (2.5 mol%), allyl alcohol (2 equivalents), dioxane, r.t.



223a; R = Ph
223b; R = Me



R = Pr^i

DIPPF **224**

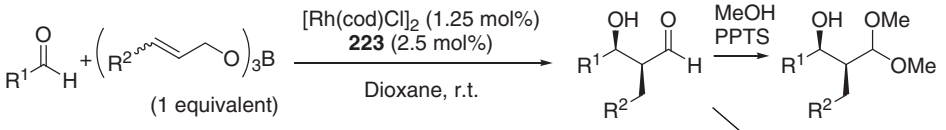
Scheme 89

Table 30 Ru- and Rh-catalyzed coupling of allyl alcohol and aldehydes (**Scheme 89**)

Entry	R^1	R^2	R^3	*Method*	*Yield (%)*	syn:anti	*References*
1	4-ClC_6H_4	Ph	H	A	88	3.3:1	170
2	Ph	Ph	H	A	84	2.2:1	170
3			H	B	92	1:1.2	172
4	4-CNC_6H_4	Ph	H	A	80	4.6:1	170
5	4-ClC_6H_4	Me	Ph	A	79	1:1.5	170
6	4-FC_6H_4	4-FC_6H_4	H	B	91	1:1.5	172
7	Ph	Me	Ph	B	79	1.3:1	172
8	Ph	H	H	C	73[a]	6.1:1	173
9	$PhCH_2CH_2$	H	H	C	72[a]	3:1	173
10	Ph	Me	H	C	90	6.1:1	173
11	*n*-C_5H_{11}	Me	H	C	96	4.9:1	173

[a]The yield was determined after conversion to dimethylacetal or 1,3-diol derivative.

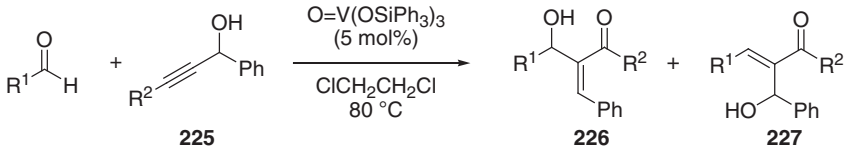
(1.25 mol%) and DIPPF **224** (2.5 mol%) (Method C).[173] The reaction of aldehydes and allyl alcohol (1 equivalent) afforded *syn*-aldol products (R^2 = H) diastereoselectively in good yield (entries 8 and 9). *Syn*-selective reactions were also observed for secondary allylic alcohols (entries 10 and 11). When allyloxyboranes were used instead of allylic alcohols with the Rh catalyst system, the tandem isomerization/aldolization proceeded with improved diastereoselectivity (Scheme 90). It is particularly noteworthy that the reaction was applicable to enolizable aliphatic aldehydes to give products which would be difficult to be synthesized by the direct cross-aldol reaction of two different enolizable aldehydes.



R^1	R^2	Yield (%)	*ds*
Ph	H	81	9:1
2-BrC_6H_4	H	83	16:1
$PhCH_2CH_2$	H	90	5.3:1
c-C_6H_{11}	H	62	2.8:1
Et	Me	71	3:1

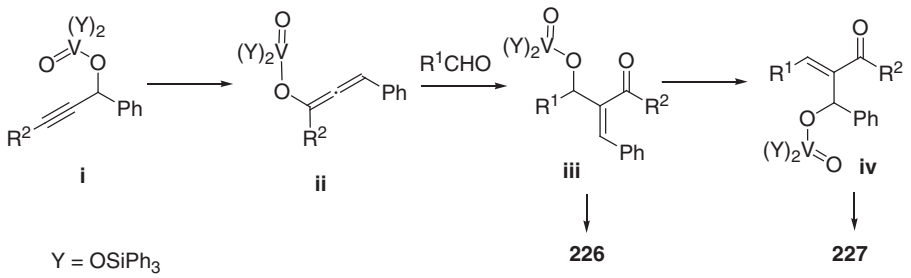
Scheme 90

As another type of atom-economical coupling reaction leading to aldol products, a vanadium-catalyzed coupling of secondary propargylic alcohols and aldehydes has been developed by Trost and Oi.[174] Treatment of alcohols **225** and aldehydes in the presence of $(Ph_3SiO)_3V(O)$ (5 mol%) in CH_2Cl_2 at 60 °C afforded the aldol-type coupling product **226** with high *Z*-selectivity (Scheme 91). The reaction was proposed to proceed through a mechanism involving 1,3-transposition of propargylic alkoxide **i** to form allenic derivative **ii**, which undergoes carbonyl addition to give **226**. For some instances, further 1,3-transposition of vanadium aldolate **iii** to **vi** occurs to form regioisomeric **227** as a minor by-product (Scheme 92).



R^1	R^2	Products	Yield (%)	*Z*:*E*
Ph	Bu^t	**226a** (= **227a**)	95	49:1
4-$CF_3C_6H_4$	Bu	**226b**+**227b** (19:1)	77	*Z* only
n-Pr	Bu	**226c**	55	8:1

Scheme 91



Scheme 92

The catalytic tandem isomerization/aldolization reaction is of high synthetic potential because of its full atom economy. In spite of the direct participation of the transition metal enolate under Ru and Rh alkoxide catalysis, the control of

diastereoselectivity and enantioselectivity remains a difficult, yet important, task owing to concurrent racemization at the carbinol carbon of the aldol products. The future development of the synthetically attractive reaction is awaited.

2.10.4 Conclusions

Over the past three decades, remarkable advances have been made in the transition-metal-catalyzed aldol reaction. Notably, transition metal catalysis has contributed to the significant expansion of the scope of donor components in the direct aldol reaction. The development of the reductive and alkylative aldol reaction has provided access to a wide variety of α-substituted β-hydroxy-carbonyl structures with high degree of diastereo- and/or enantio-control. The tandem isomerization/aldol reaction of allylic alcohols represents the high potential of transition metal catalysis in the future development of atom-economical aldol chemistry. Despite the progress, the potential of transition metal catalysis has not been fully exploited. Relatively high catalyst loadings are often required to obtain satisfactory product yields and selectivities. Tolerance of the reaction toward existing stereogenic centers and functional groups is another issue to be scrutinized for practical applications. The transition-metal-catalyzed aldol reaction will undoubtedly continue to be an area of intense research in the future.

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2.11 Aldolase-Catalyzed C–C Bond Formation of Carbohydrate Synthesis

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Glossary

Deoxyribose-5-phosphate aldolase (DERA) It is the enzyme responsible for the cleavage of deoxyribose 5-phosphate into glyceraldehyde 3-phosphate (G3P) and acetaldehyde in a reversible manner. The reverse, stereoselective aldol C–C bond formation reaction as well as the reaction by applying some substituted glyceraldehydes and acetaldehydes can be catalyzed by the same enzyme, which is now commercially available. As the reaction products further work in tandem as electrophile in the reaction mixture, enantiomerically pure 3,5-dihydroxypentanals and their intramolecular hemiacetal forms are obtained. This protocol is applied for the production of an active pharmaceutical ingredient (API), and it plays an important role in manufacturing of dihydroxy acid moiety in statins, which are antihyperlipidemic agents.

DHAP-dependent aldolase It is the enzyme responsible for the retroaldol and aldol reaction between phosphorylated ketoses and dihydroxyacetone phosphate. Representative examples with complementary stereoselectivity are D-fructose-1,6-diphosphate aldolase (FruA; RAMA originated from rabbit muscle), D-tagatose 1,6-diphosphate aldolase (TagA), L-fuculose 1-phosphatealdolase (FucA), and L-rhamnulose-1-phosphate aldolase (RhuA). Some of these are commercially available, and the synthetic reactions are intensively applied for the synthesis of glycosidase inhibitors with nitrogen-containing heterocyclic structures (azasugars).

Fructose-6-phosphate aldolase (FSA) It is an enzyme found in a recombinant *Escherichia coli*, catalyzing the cleavage of D-fructose-6-phosphate (F6P) into D-glyceraldehyde 3-phosphate (G3P) and dihydroxyacetone (DHA) in a reversible manner. This enzyme is a family of transaldolases, which originally works in interconversion of F6P plus D-erythorose 4-phosphate into G3P plus D-sedoheptulose 7-phosphate. The overexpressed enzyme is stable, and is promising, as nonphosphorylated nucleophile, DHA, is applicable instead of dihydroxyacetone phosphate (DHAP) for C–C bond formation. Some oxygen- and nitrogen-containing heterocycles were synthesized by combined chemoenzymatic procedure.

Hydroxynitrile lyase (HNL) It is a key enzyme in the catabolism of cyanogenic glycosides in higher plants. This enzyme catalyzes the decomposition of cyanohydrins, which are produced via the β-glucosidase-catalyzed cleavage of cyanogenic glycosides in plant, into corresponding aldehydes or ketones and HCN for defense against predators and microorganisms. The reverse reaction, asymmetric hydrocyanation, attracts the attention of scientists and industry because enantiomerically enriched forms of cyanohydrins are versatile building blocks in the fine chemical and pharmaceutical industries.

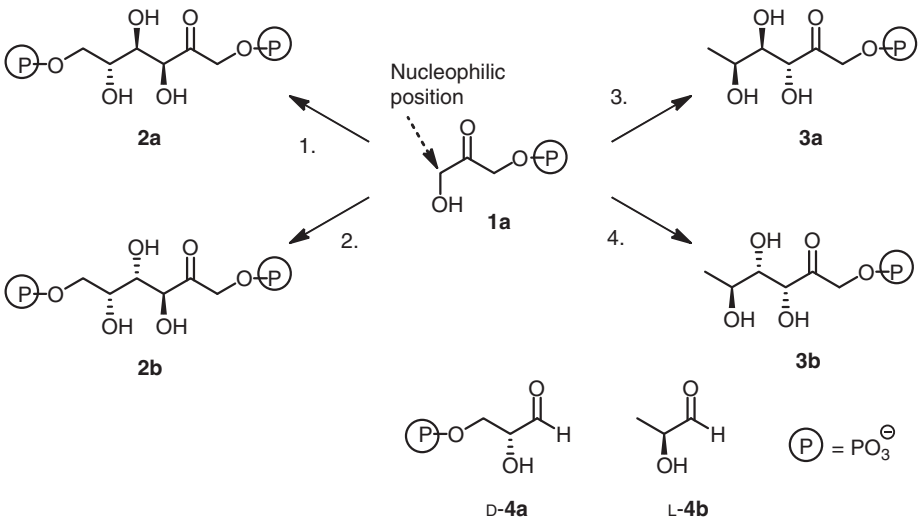
***N*-acetyl-D-mannosamine (ManNAc)** It is a 2-deoxy-2-aminosugar derivative involved in some oligosaccharides and a C-2 epimer of *N*-acetyl-D-glucosamine (GlcNAc). Compared with GlcNAc, which is a major component of peptidoglycan in Gram-positive bacteria and chitin, the availability of ManNAc from naturally occurring source is low. The major manufacturing depends on the aldolase-catalyzed degradation of sialic acid. It is also available by epimerization of GlcNAc and selective solvent extraction followed by microbial selective degradation of contaminating GlcNAc.

Sialic acid aldolase (*N*-acetylneuraminate lyase (NAL)) It is the enzyme responsible for degradation of sialic acid (*N*-acetylneuramic acid) into *N*-acetyl-D-mannosamine (ManNAc) and pyruvic acid. The reverse reaction can be catalyzed by the same enzyme, which is commercially available, and the reaction also works by applying some related mannosamines. This enzyme is applied for the synthesis of sialic acid from *N*-acetyl-D-glucosamine (GlcNAc) and pyruvic acid by combining it with *N*-acetyl-D-glucosamine epimerase. The enzyme-catalyzed production plays an important role in the manufacturing of inhibitors of sialidase, which are antiflu medicines such as zanamivir.

2.11.1 Introduction

Enzyme-catalyzed cross-aldol reaction proceeds with proper nonprotected hydroxy aldehydes and ketones in aqueous conditions. This protocol has been utilized for the *in vitro* chemoenzymatic synthesis of biologically relevant monosaccharides.[1] Since 2000, pertinent reviews have frequently been published,[2–7] which covers very wide variety and vast number of examples. Aldolases are classified into two types. In type I, aldolases aldehydes/ketones work as nuclephiles by activating through enamine formation and subsequent attack on other aldehydes for electrophiles. However, metal cations such as Zn^{2+} work as Lewis acids for activation of electrophiles in type II aldolases.

Regardless of the types, 'nucleophilic' aldehydes and ketones are further divided into two categories. The first ones are phosphorylated hydroxy aldehydes and hydroxy ketones, such as dihydroxyacetone phosphate (DHAP, **1a**). This type of reaction has intensively been studied, and by applying enzymes, DHAP-dependent aldolases, with complementary facial selectivity such as that of D-fructose-1,6-diphosphate (**2a**) aldolase (FruA; RAMA originated from rabbit muscle), D-tagatose 1,6-diphosphate (**2b**) aldolase (TagA), L-fuculose 1-phosphate (**3a**) aldolase (FucA), and L-rhamnulose-1-phosphate (**3b**) aldolase (RhuA), all possible kind of stereoisomers in regard to two stereogenic centers which can be produced as shown in Scheme 1.



Scheme 1 1., FruA, D-glyceraldehyde 3-phosphate (**4a**); 2., TagA, D-**4a**; 3., FucA, L-lactaldehyde (**4b**); 4., RhuA, L-**4b**.

In the second ones, the nucleophiles are nonphosphorylated, such as pyruvic acid (**5**), acetaldehyde (**6a**), and dihydroxyacetone (**1b**) as shown in Figure 1. In this chapter, the authors focus on the second category of three nucleophiles in Figure 1 and emphasizes especially on the examples which are promising not only for the practical synthesis of carbohydrates but also in active pharmaceutical ingredients manufacturing. For other important nucleophiles which have been developed in amino acid derivatives, the readers are requested to see the above-mentioned review.[6]

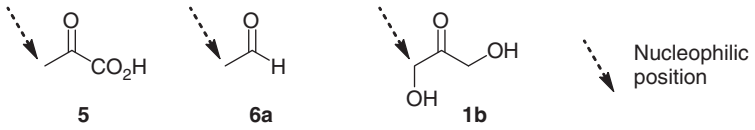
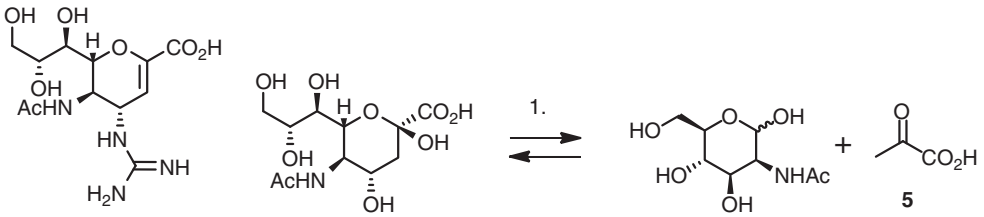


Figure 1 Nonphosphorylated nucleophiles in aldolase-catalyzed reactions.

2.11.2 Sialic Acid Aldolase-Catalyzed Synthesis

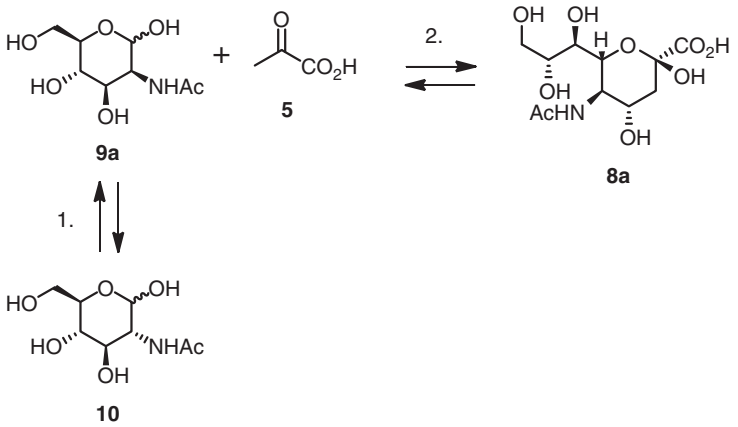
Sialic acid aldolase (*N*-acetylneuraminate lyase, NAL) has much attention of chemists, biochemists, and pharmaceutical industries as the manufacturing tool for sialidase inhibitors, which are antiflu medicines,[8,9] for example, zanamivir (**7a**). This enzyme was originally found as the enzyme responsible for the degradation of sialic acid (**8a**) into *N*-acetyl-D-mannosamine (ManNAc, **9a**) and pyruvic acid (**5**) as shown in Scheme 2; however, the reverse reaction toward the synthesis of sialic acid (**8a**) between **5** and **9a** was demonstrated more than 50 years ago.[10,11]



Scheme 2 1., Sialic acid aldolase.

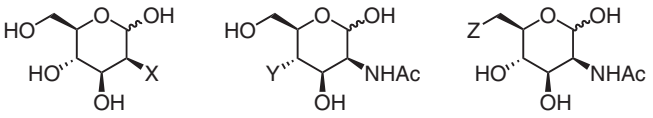
Since the pioneering work to find out the proper source of enzyme from *Escherichia coli* AKU0007 was published in 1984, aiming the commercial production,[12] until now, efforts for searching the microbial strain has been devoted.[13] The original aldolase was an enzyme induced by **8a** itself. The gene for the enzyme from *E. coli* was cloned[14,15] and a mutant with aldolase as constitutive enzyme, which is suitable for enzyme-catalyzed production, was established.[16]

As the availability of the starting material, ManNAc (**9a**) was low, the supply by the enzyme-catalyzed epimerization of naturally abundant *N*-acetyl-D-glucosamine (GlcNAc, **10**) at C-2 was studied. An enzyme for such purpose, *N*-acetyl-D-glucosamine epimerase from porcine kidney, was cloned and fully characterized.[17] After overexpression of this epimerase in *E. coli*, the above-mentioned epimerization of GlcNAc (**10**) to ManNAc (**9a**) was combined with the aldolase-catalyzed sialic acid synthesis. Important elaborations involving the portion-wise addition of pyruvic acid (**5**, as sodium salt), which has an inhibitory effect on the epimerase, divided into several small quantities established a large-scale production of sialic acid (**8a**), as shown in Scheme 3.[18] This procedure is an excellent example of multienzyme reaction system[19] and without doubt the basis of the commercial production of sialidase inhibitors such as zanamivir and related medicines. Whole cell-mediated production approaches, whose all necessary enzymes together with the cofactor recycling system are expressed in the common cell of microorganism, have also intensively been examined.[20–23]



Scheme 3 1., *N*-Acetyl-D-glucosamine epimerase, ATP, $MgCl_2$; 2., Sialic acid aldolase.

Sialic acid aldolase accepts a variety of mannosamine derivatives (**9a–r**) with substitution and protective groups[24–28] as shown in Figure 2, but the relative reaction rate depends on the structure of substrates. To widen the substrate specificity and enhance the catalytic activity, directed evolutional approaches in protein engineering have been examined.[29–33] Generally, highly active enzymes have such enzyme kinetic constants as high $1/K_m$ and high k_{cat} values. K_m is an approximation to the dissociation constant of enzyme–substrate complexes toward the substrates and enzymes and $1/K_m$ reflects the affinity between the substrates and enzymes. When the space of catalytic site becomes widen by the protein engineering, the wider range of substrates would be accepted; however, the result and the $1/K_m$ do not necessarily go together. K_{cat} is the rate of the decomposition of enzyme–substrate complexes toward the products and enzymes, and the shorter distance between catalytic functional group of enzyme and substrates would bring about the higher k_{cat}, but the property of the resulting engineered enzyme is not always consistent with the wider range of substrate specificity. Protein engineering aiming high $1/K_m$ and k_{cat} values often causes substantial loss of the stability of enzymes. Readers should carefully examine the properties of engineered enzymes that have appeared in the newly published paper, especially enzymes having 'inverted enantiofacial selectivity.' For industrial use, very sophisticated and robust enzymes are applied to each specific substrate, also under elaborated reaction conditions, but the general availability is not expected.



Substitutiion at C-2

9a X = NHAc
b H
c OH
d NHGc
e NHCbz
f N_3
g CH_2NHAc
h F

Substitutiion at C-4

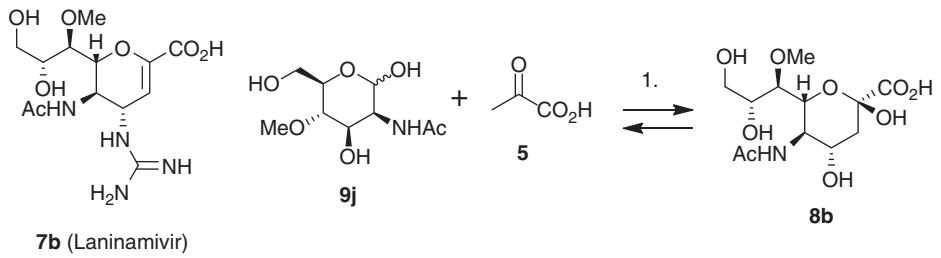
9i Y = H
j OMe
k $OCH{=}CH_2$
l N_3

Substitutiion at C-6

9m Z = OAc
n N_3
o OSO_2Ar
p O_2CCH_2NHBoc
q F
r OCOCH(OH)Me

Figure 2 Substrates of sialic acid aldolase-catalyzed reaction.

Among the mannosamines, 4-*O*-methyl derivative (**9j**) recently gains interests, as the product (**8b**) by sialic aldolase-catalyzed synthesis was the starting material for a newly developed inhibitor of sialidase, laninamivir (**7b**)[33], as shown in Scheme 4. In enzymatic synthesis, sialic acid aldolase is inhibited by gluco-isomer.[34] For example, K_i value of GlcNAc (0.85 M) was compatible with the K_m of ManNAc (0.7 M) in the synthetic direction, and pure manno-isomer without any contamination of gluco-isomer is desirable for a consistently efficient progress of aldolase-catalyzed synthesis.



7b (Laninamivir)

9j

5

8b

Scheme 4 1., Sialic acid aldolase.

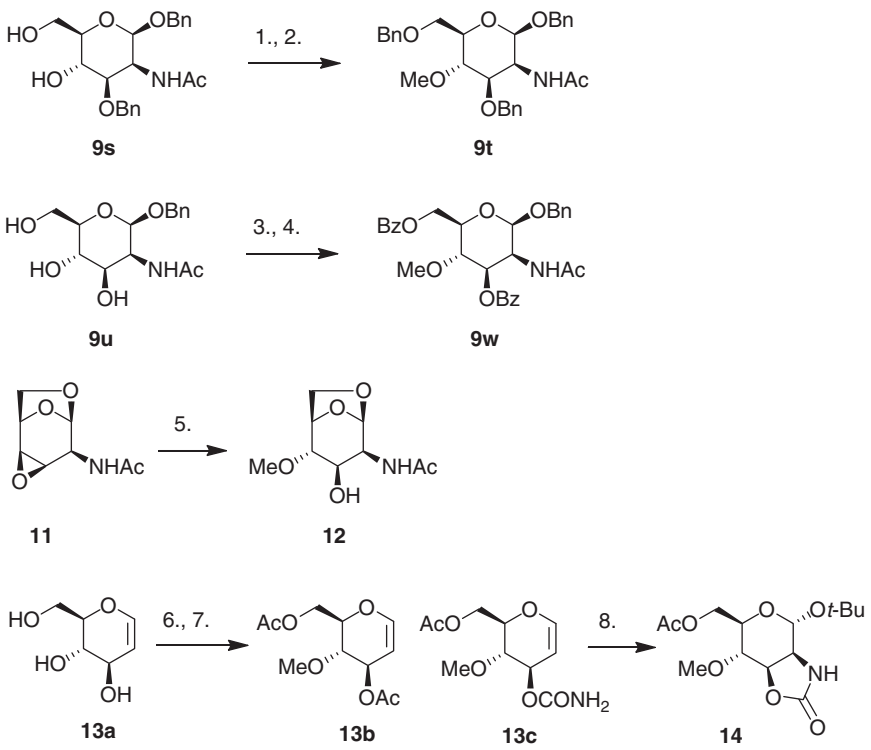
Under these circumstances, the syntheses of 4-*O*-methylManNAc (**9j**) started from ManNAc (**9a**) derivatives, with the natural origin or which had been synthesized by way of many steps from glucose. To introduce methyl group regioselectively onto C-4 hydroxy group, regioselective benzylation to **9s**,[35] regioselective benzoylation on **9u**,[36] and regioselective epoxide ring-opening reaction on bicyclic 1,6-anhydrosugar **11**[33] were the key reactions, as shown in Scheme 5.[37] However, lipase-catalyzed regioselective acetylation on **13a** combined with rhodium nitrenoid-mediated stereoselective cyclization of **13c** also provided pure manno-isomer.

si-Facial attack to aldehyde carbonyl group was predominant for sialic acid aldolase-catalyzed aldol reaction as shown in Scheme 6. For example, 3-deoxy-D-glycero-D-galacto-2-nonulosonic acid (D-KDN, **8c**) is prepared from D-mannose **9c**. Only in the limited cases, however, was the opposite *re*-facial attack observed.[38] Later, this phenomenon became understandable by isomerization of initially formed L-*epi*-**8c** with an axial hydroxy group to thermodynamically stable product, L-KDN (**8c**), with an equatorial hydroxy group in the reaction mixture,[39] as the aldolase-catalyzed reaction was reversible through the starting material L-**9c**.

Contrasting *re*-facial attack was shown by 3-deoxy-D-manno-2-octusolonic acid (KDO) aldolase. Stereochemically pure L-KDN (**8c**) was synthesized by using L-**9c** by the action of KDO aldolase.[40] L-Sialic acid (**8a**), however, could not be obtained by the combination of L-ManNAc (**9a**) and KDO aldolase, as KDO aldolase did not accept substrates such as L-**9a** with a bulkier acetamide substituent compared with hydroxy group at C-2 position in **9c**. Ten years later, this situation was overcome by the use of an engineered sialic acid aldolase with the mutation of Y98H, F115L, and V251I[41], as shown in Scheme 7.

A new artificial and diastereomeric substrate (**15**) as shown in Scheme 7, which is related to sialic acid (**8a**) but has the opposite stereochemistry at the stereogenic center (circled) in the direction of aldol addition, was designed and chemically synthesized. It was the powerful tool for the screening of properly engineered enzyme, as indexed by the activity to cleave C–C bond to give neutral aldose and pyruvic acid.[42]

By protein engineering, complete change of even the 'enantiofacial' selectivity was observed in the case of the reaction between pyruvic acid (**5**) as a nucleophile and acetaldehyde (**6a**) as an electrophile, catalyzed by aldolase BphI. The products were enantiomers of **16**[43], as shown in Scheme 8. Another representative example in which pyruvic acid works as a nucleophile is



Scheme 5 1., n-Bu_2SnO, BnBr; 2., MeI, Bu_4NBr; 3., BzCl, pyridine; 4., MeI, Ag_2O; 5., MeOH, Dowex 50W (H^+); 6., *Burkholderia cepacia* lipase, $CH_2{=}CHOAc$; 7., $PhI(OCOt\text{-}Bu)_2$, $Rh_2(OAc)_4$, t-BuOH, $ClCH_2CH_2Cl$.

2-keto-3-deoxygluconate (KDGlu) adolase-catalyzed reaction, which has been omitted here by the authors. The readers are requested to see the reviews for detailed information.[5]

2.11.3 Deoxyribose 5-Phosphate Aldolase-Catalyzed Synthesis

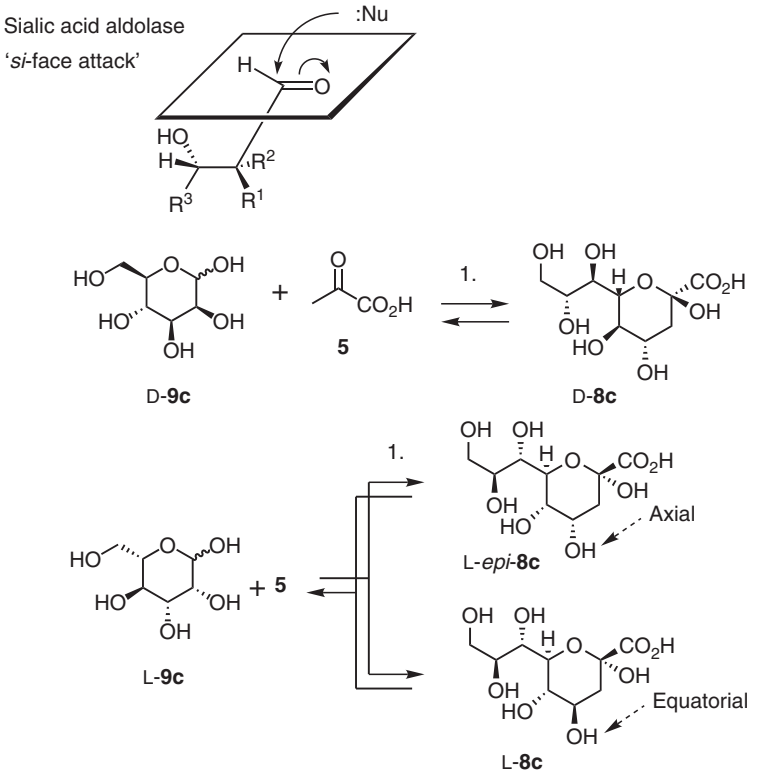
Studies on deoxyribose 5-phosphate aldolase (DERA) also have a long history of nearly 50 years. It was first characterized from *Lactobacillus plantarum*[44] as the enzyme responsible for the cleavage of deoxyribose 5-phosphate (**17a**) into glyceraldehyde 3-phosphate (G3P, **4a**) and acetaldehyde (**6a**) in a reversible manner, as shown in Scheme 9.

Synthetic applications using DERA, which was overexpressed in *E. coli*, were demonstrated, instead of G3P (**4a**), by applying various kinds of aldehydes (**4a–n**, **6a–m**) as electrophiles, as shown in Figure 3.[45–49] Despite propanal (**6n**), acetone (**1c**), and fluroacetone (**1d**) being weaker nucleophiles whose relative rates were less than 1% of **6a**, the aldol products were obtained. This enzyme became commercially available[48,50] by improvement of overexpression and purification conditions and was also effectively applied for the synthesis of labeled carbohydrate.[51]

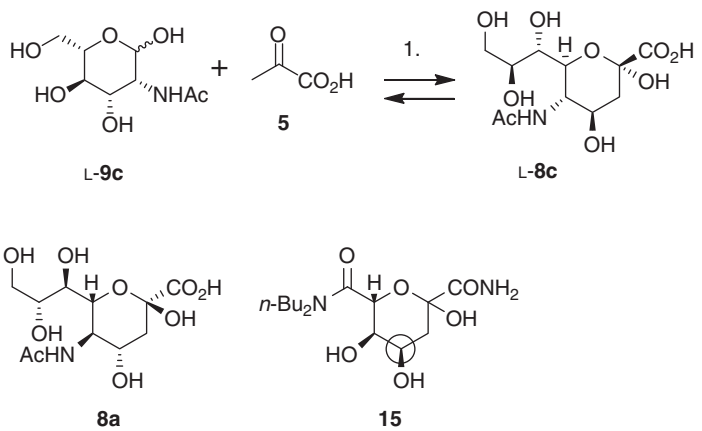
Three-dimensional structure of enzyme protein was fully characterized,[52] and it is advantageous to forecast the substrate specificity and selectivity. Until now, many efforts on the elaboration of enzyme production conditions[53] and screening from new sources[54,55] have been devoted.

The remarkable advantage of DERA-catalyzed reactions is the sequential aldol reaction as shown in Scheme 10.[47,48,56] The reason for the success of selective cross-aldol reaction was as follows. The products, substituted acetaldehydes, were weak nucleophiles, but at the same time worked further as electrophiles because of the presence of aldehyde carbonyl group. Not only homosequential addition by singly applying DERA, but also the combination with other aldolases such as FruA (RAMA) was effectively demonstrated.[56]

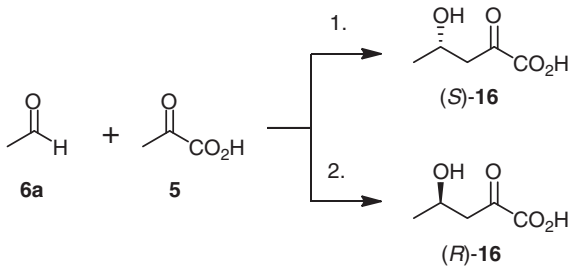
The excellent application of this protocol was enzyme-catalyzed manufacturing of **20a, d, e**, starting from substituted electrophiles (**6b**, **o**, **p**) under industrially improved conditions,[57–59] as shown in Scheme 11. The products are precursors for dihydroxylacid moiety in statins such as **22** and **23**,[60,61] the synthetic inhibitor for cholesterol biosynthesis developed as antihyperlipidemic agents. To explore enzymes with high activity, screening from environmental genes[58] and from hyperthermophilic microorganisms[62] as well as directed evolution technologies[30,63] have been studied. As the latter example, a mutant S238D[57] was applied to enhance the activity of DERA.



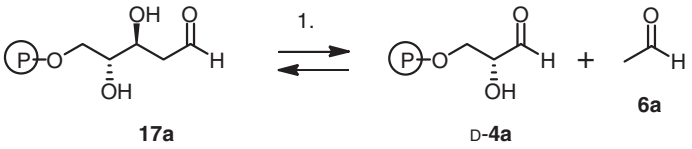
Scheme 6 1., Sialic acid aldolase; 2., KDO aldolase.



Scheme 7 1., Engineered sialic acid aldolase (Y98H, F115L, V251I).



Scheme 8 1., Aldolase BphI (wild type); 2., engineered aldolase BphI (L87N, Y290F).



Scheme 9 1., Deoxyribose 5-phosphate aldolase (DERA).

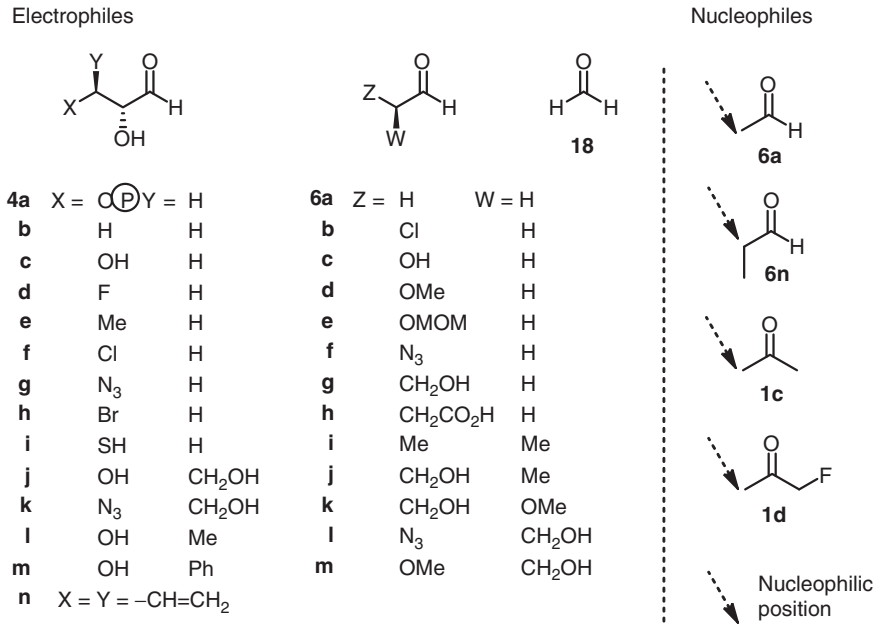
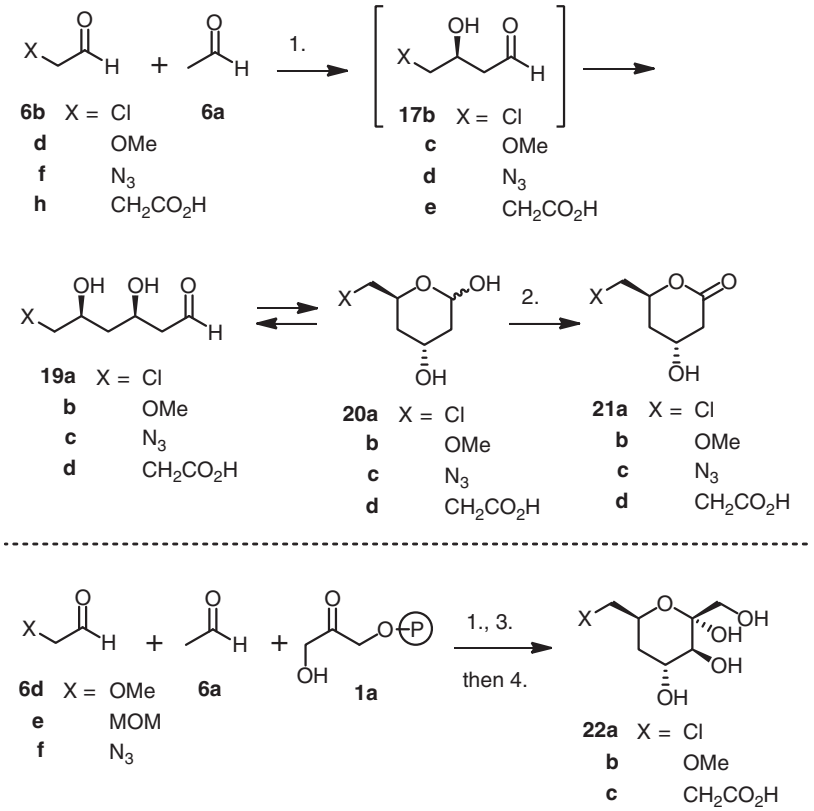


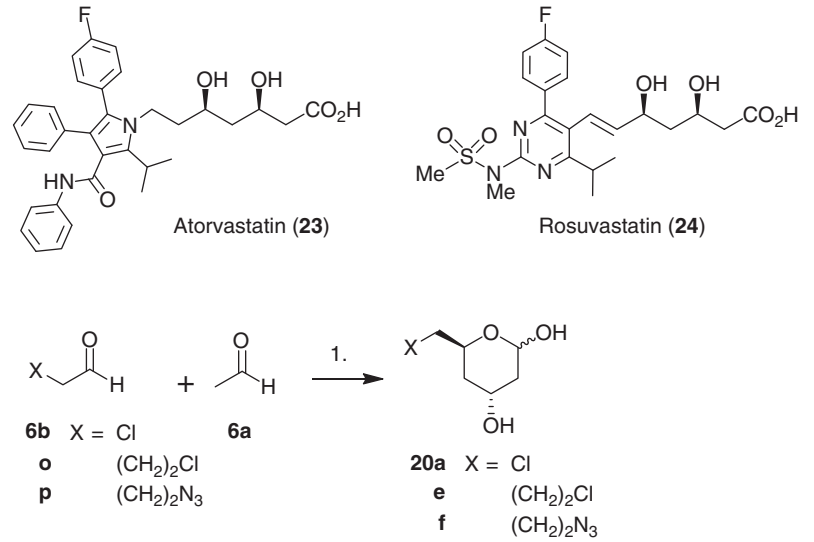
Figure 3 Substrates of DERA-catalyzed reaction.

2.11.4 Fructose-6-Phosphate Aldolase-Catalyzed Synthesis

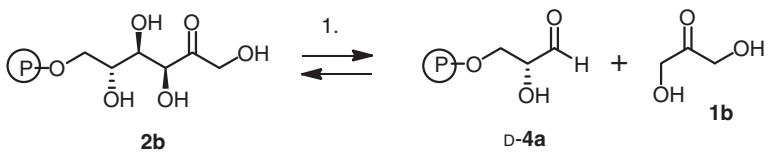
In contrast to the above-mentioned two aldolases, most of the study on fructose-6-phosphate (F6P, **2b**) aldolase (FSA) commenced in the twenty-first century.[64] This enzyme was found in a recombinant *E. coli* as a family of transaldolases, and its activity as aldolase which catalyzes the cleavage of F6P (**2b**) into G3P (**4a**) and dihydroxyacetone (**1b**) in a reversible manner was disclosed[65], as shown in Scheme 12. Advantage of FSA is that the enzyme can avoid the use of phosphorylated nucleophile such as DHAP (**1a**). The original enzyme was obtained from mesophilic bacteria[65] and later was fully characterized.[66] Its thermostable property was advantageous when this aldolase was used as immobilized forms in synthetic application.[67,68] Until now, the screening of new FSA has intensively been examined.[69,70]



Scheme 10 1., Deoxyribose 5-phosphate aldolase (DERA); 2., Br_2, $BaCO_3$, H_2O; 3., FruA (RAMA); 4., Phosphatase.



Scheme 11 1., DERA.



Scheme 12 1., Fructose-6-phosphate aldolase (FSA).

The substrate specificity toward the substances related to G3P (**4a**) as electrophile has been examined.[71,72] Hydroxyacetone (**1c**)[71] and glycolaldehyde (**6c**)[72] could also be accepted as the nucleophilic substrate instead of dihydroxyacetone (**1b**), as shown in Figure 4. The substrate specificity was substantially different from that covered by a related transaldolase (TalB).[73] For the aldol reaction with the phosphorylated electrophiles such as G3P (**4a**), in the synthetic standpoint, multienzyme system starting from readily available dihydroxyacetone (**1b**) was elaborated involving the use of dihydroxyacetone kinase and triose phosphate isomerase.[74]

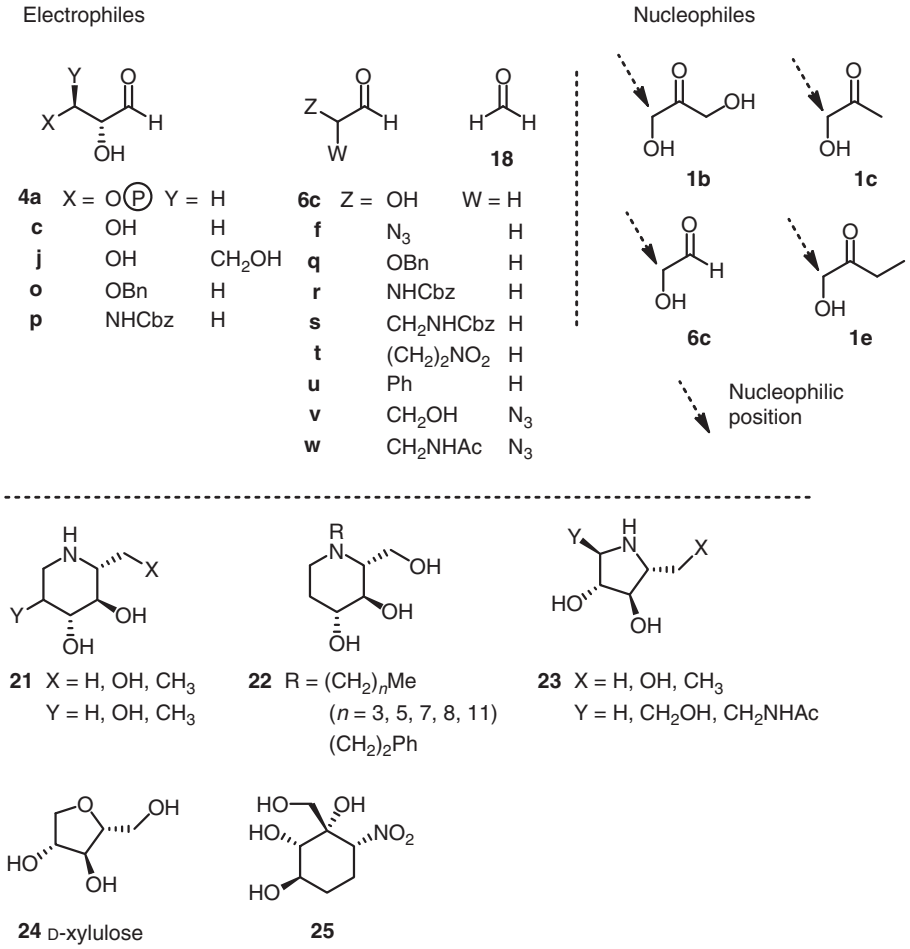
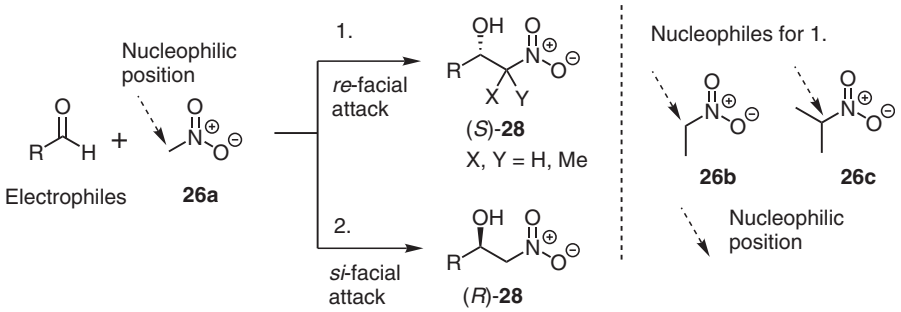


Figure 4 Substrates of FSA-catalyzed reaction and the application to the synthesis of nitrogen- and oxygen-containing heterocycles.

Hydrophobic electorophiles (**6q–w**), as shown in Figure 4, were also accepted by FSA, and this procedure was demonstrated in the synthesis of nitrogen- and oxygen-containing heterocycles, and a carbacycle.[75–77] To expand the substrate specificity and reactivity, protein engineering on the wide range of transaldolases involving this FSA is the continuing task.[78–80]

2.11.5 Promiscuous Enzyme Function – Hydroxynitrile Lyase-Catalyzed Nitroaldol Reaction

Nitroalkanes have acidic protons. For example, pK_a of nitromethane is approximately 10 in aqueous solution and it works as nucleophile like enolates in aldol reactions. There have not been known any enzymes whose native substrates are nitroalkanes. By taking advantage of promiscuous function of enzymes, especially the basicity of amino acid residues involved in catalytic center, however, recently, the nitroaldol (Henry) reactions became investigated.[81] Among many reported examples, only hydroxynitrile lyases (HNLs) catalyze the enantioselective C–C bond formation. Two plant-origin HNLs, whose native nucleophile is hydrogen cyanide, exhibited the complementary enantiofacial selectivity in the attack of nitromethane (**26a**). On the one hand, an enzyme from *Hevea brasiliensis* (*Hb*HNL) shows the *re*-facial selectivity,[82,83] on the other hand, the enzyme from *Arabidopsis thaliana* (*At*HNL) shows the *si*-facial attack,[84] with aromatic aldehydes as the electrophiles (**27**) as in Scheme 13. Some higher analogs (**26b** and **26c**) were accepted in the former enzyme. In both the cases, biphasic reaction system worked well to avoid the nonenzymatic reaction which causes the lowering of *ee* of the products.



Electrophiles for 1.

27a	R = Ph
b	$(C_6H_4)^{-3}$-OH
c	$(C_6H_4)^{-4}$-NO_2
d	2-furyl
e	$(CH_2)_5$Me
f	$(CH_2)_2$Ph
g	2-thienyl
h	3-furyl
i	$(C_6H_4)^{-2}$-Cl
j	$(C_6H_4)^{-3}$-Cl
k	$(C_6H_4)^{-4}$-Cl
l	$(C_6H_4)^{-4}$-OMe
m	Cyclohexyl

Electrophiles for 2.

27a	R = Ph
e	$(CH_2)_5$Me
i	$(C_6H_4)^{-2}$-Cl
j	$(C_6H_4)^{-3}$-Cl
k	$(C_6H_4)^{-4}$-Cl
l	$(C_6H_4)^{-4}$-OMe
n	$(C_6H_4)^{-4}$-F
o	$(C_6H_4)^{-4}$-Br
p	(C_6H_4)-2-Me
q	(C_6H_4)-3-Me
r	(C_6H_4)-4-Me
s	$(C_6H_4)^{-2}$-OMe
t	$(C_6H_4)^{-3}$-OMe
u	2-Naphthyl

Scheme 13 1., *Hevea brasiliensis* hydroxynitrile lyase (*Hb*HNL). 2., *Arabidopsis thaliana* hydroxynitrile lyase (*At*HNL).

2.11.6 Conclusion

In this chapter, the authors introduced three types of aldolase-catalyzed reactions, which are promising for C–C bond formation. Screening of new enzymes, characterization, docking study with substrates, and protein engineering are very important to develop improved biocatalysts. Toward an ideal design and diagram for target compounds of fine chemicals from biomass, complementary use of chemical and biochemical synthesis would be the best solution. For that, 'substrate molecular technology' is a very important partnership contributable by synthetic organic chemists to meet the advances made by molecular biologists.

Acknowledgments

This chapter is dedicated to Prof. Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol reaction. The authors thank Prof. Pere Clapés of Institute for Chemical and Environmental Research (IIQAB)-CSIC, Spain and Prof. Chun-Hung Lin of Institute of Biological Chemistry, Academia Sinica, Taiwan for providing valuable information.

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2.12 Zinc Enolates: The Reformatsky and Blaise Reactions

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This chapter is a revision of the previous edition chapter by Michael W. Rathke, Paul Weipert, Vol. 2, pp 277–299, © 1991, Elsevier Ltd.

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Glossary

Activated zinc The zinc removed from a surface oxide film by treatments such as washing with acid.

Asymmetric induction Preferential formation in a chemical reaction of 1 enantiomer or diastereoisomer over another as a result of the influence of a chiral feature present in the substrate, reagent, catalyst, or environment.

BINOL derivatives 1,1′-Bi-2-naphthol-based derivatives.

Bioactive molecules A molecule having beneficial or adverse effects on living matter.

Chemotherapeutic agents An agent for the treatment of cancer with an antineoplastic drug, or with a combination of such drugs, into a standardized treatment regimen.

Chiral auxiliary A chemical compound or unit that is temporarily incorporated into an organic synthesis so that it can be carried out asymmetrically with the selective formation of 1 of 2 enantiomers.

Organozinc species Chemical compounds containing a carbon–zinc bond.

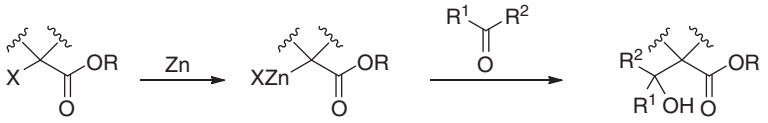
Salen complex A complex between a metal and an *N*,*N*′-ethylenebis(salicylimine)-derived ligand.

Spiro compound A bicyclic organic compound with rings connected through only 1 atom.

Zinciocarbonyl compound Chemical compounds possessing zinc at the α-position of a carbonyl group.

2.12.1 Introduction

Reformatsky reaction is one of the most important transformations of organic compounds and includes the creation of new carbon–carbon bonds. This reaction differs from the Grignard reaction as it includes carbonyl groups in the starting organic reagents. An organozinc species effectively works in the reaction with compatible reactive functional groups. In general, the Reformatsky reaction is performed with the treatment of an α-halo ester with a carbonyl compound in the presence of metallic zinc to produce a β-hydroxyl ester (**Scheme 1**). In 1887, Sergey Reformatsky, a Russian chemist, reported the reaction,[1] and it has been applied to various types of substrates to achieve stereoselective reactions, asymmetric syntheses, practical protocols, and total syntheses.[2,3] The previous edition of this comprehensive study well-summarized the Reformatsky reaction before 1990,[4] and, therefore, this chapter is focused mainly on the recent development of the Reformatsky reaction (and the Blaise reaction described later).

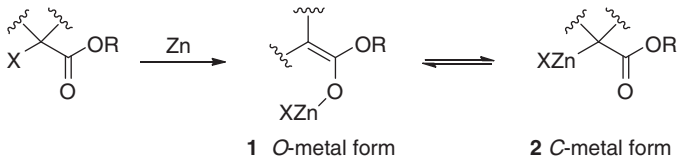


Scheme 1

2.12.2 Reformatsky Reagent

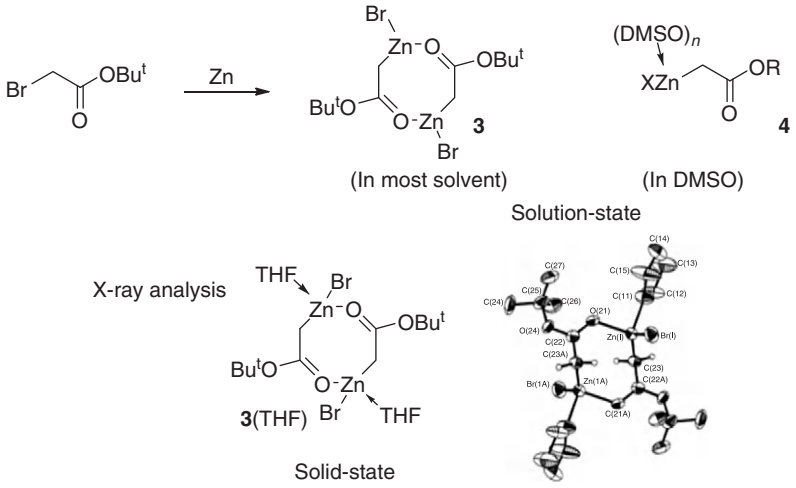
2.12.2.1 Structure of Zinc Enolates

The Reformatsky reaction is generally promoted by employing an α-halo ester, a carbonyl compound, and zinc metal in a suitable solvent. The reaction is considered to start with the formation of a zinc enolate prepared from an α-halo ester and a metallic zinc (Scheme 2), and therefore the structural analysis of the zinc species is undoubtedly important for the design of the reaction. The structure is considered to be either a zinc enolate (**1**; *O*-metal form) or a zinciocarbonyl compound (**2**; *C*-metal form).



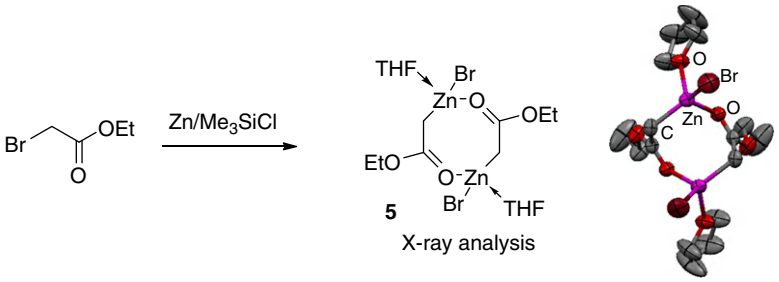
Scheme 2

The first crystallographic analysis of a Reformatsky reagent was reported in 1983 by Boesrsma.[5,6] The treatment of 2-bromo *tert*-butyl acetate with zinc afforded a suitable crystal for X-ray analysis to show a dimeric structure **3** with a *C,O*-bridging, 8-membered ring that did not include an *O*-metal form but did include a *C*-metal form (Scheme 3). Nuclear magnetic resonance (NMR) studies for analyzing a solution-state revealed that the dimeric structure was also found in nonpolar solvents. In the very polar dimethyl sulfoxide (DMSO), the reagents, however, existed as a monomeric *C*-metalated species **4**.

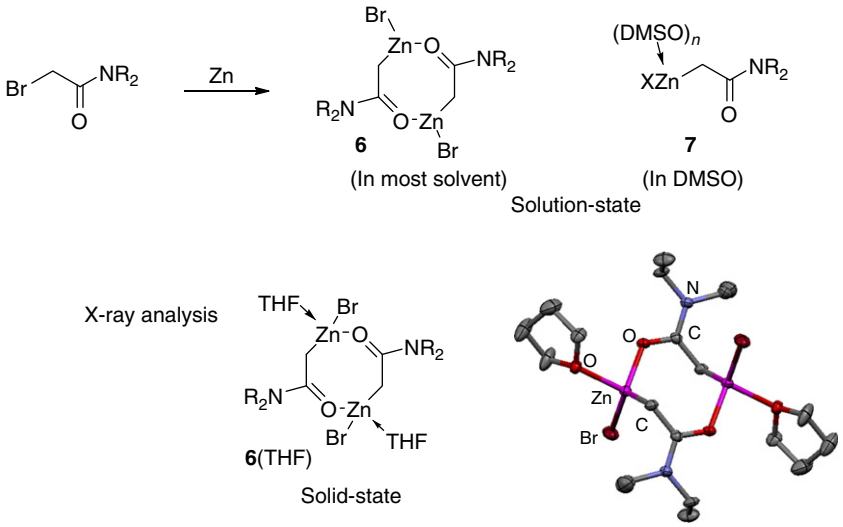


Scheme 3

Ethyl (bromozinc) acetate is a classic and typical Reformatsky reagent and it has been analyzed by X-ray crystallography by Miki (Scheme 4).[7] The species **5** crystallized from tetrahydrofuran (THF) had the same degree of aggregation – an 8-membered dimeric structure. However, the stereochemistry of the 8-membered ring was different from the *tert*-butyl derivative. The two bromides in **5** had a *cis*-configuration, in contrast to the *trans*-configuration of the *tert*-butyl derivative **3**. The conformation of the 8-membered ring in **5** was boat-like, in contrast to the chair-like conformation in the *tert*-butyl derivative **3**. The amide enolates were also analyzed and showed similar dimeric structures **6** with a *C,O*-bridging zinc (Scheme 5). In solution, the dimeric forms were observed, but coordinative solvents like DMSO gave the monomeric species **7**.[8]

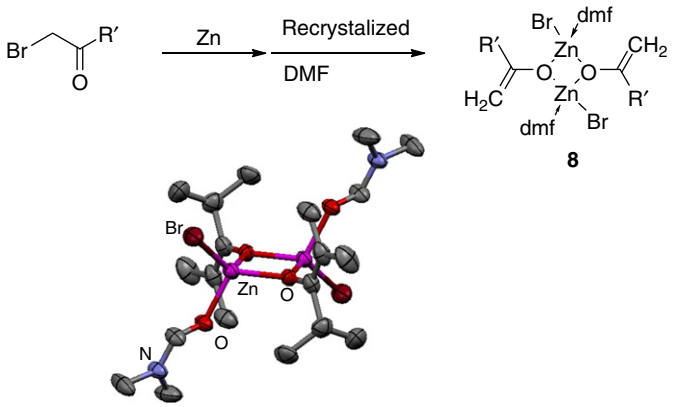


Scheme 4



Scheme 5

The ketone enolate generated from α-bromoketone with zinc had a different dimeric structure **8** in the solid phase, with *O*-bridging enolate ligands consisting of a 4-membered ring (Scheme 6).[8] This marked the first crystallographic analysis of the *O*-metalated form of Reformatsky reagents.

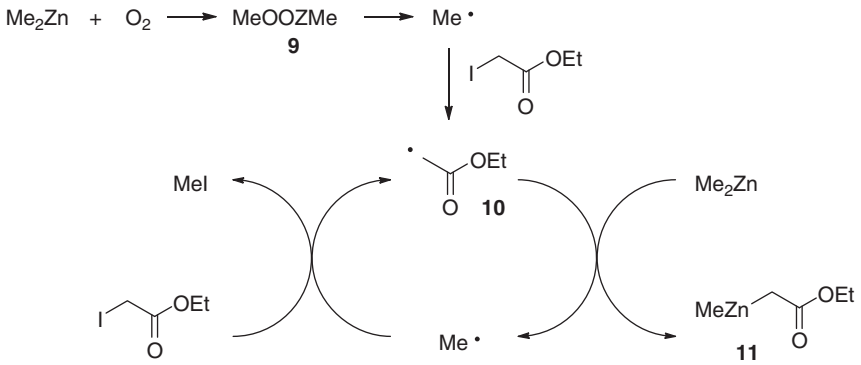


Scheme 6

The structures of the Reformatsky reagents depend on the starting substrates and solvents. The solid-state structures are thermodynamically favorable and are not necessary for the real species in the Reformatsky reaction. However, the structural analysis would be quite useful in the design of synthetic strategies.

2.12.2.2 Generation of Zinc Enolate from Dialkylzinc

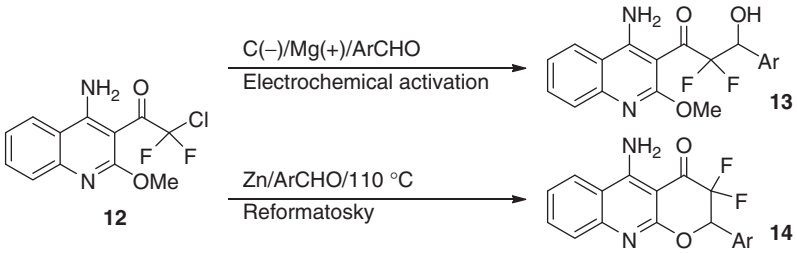
Dialkyl zincs are sometimes used for the generation of zinc enolates from α-halocarbonyl compounds. The mechanism was investigated by chemical transformation and spectroscopy.[9] Me_2Zn is often used as a transmetalating reagent with iodoacetate. The reaction between Me_2Zn and air provides an unstable peroxo species **9**, which releases one methyl radical to abstract iodine from iodoacetate, giving the α-radical ester **10**. The resulting radical **10** gives Reformatsky reagent **11** by Me_2Zn to generate a methyl radical (Scheme 7). This radical process was confirmed by Cozzi during an experiment that trapped the radical using phenyl *tert*-butyl nitrone (PBN).[9] The radical species was observed by electron paramagnetic resonance spectroscopy.



Scheme 7

2.12.2.3 Generation of Zinc Enolate by Electrochemistry

The electrochemical activation of a C–Cl bond of 4-amino-3-chlorodifluoroacetyl-2-methoxyquinoline (**12**) was employed to give a normal Reformatsky-type product, the aldol adduct **13**.[10] However, under Reformatsky reaction conditions using activated zinc (2.2 equivalents), the cyclized product **14** was obtained (Scheme 8). Although the reason was not clearly shown, the requisite high temperature of a normal Reformatsky reaction promoted successive cyclization.

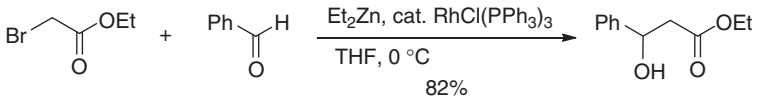


Scheme 8

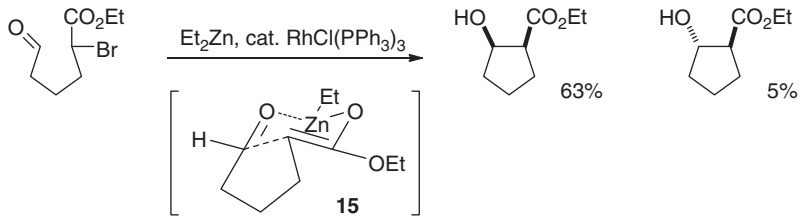
2.12.3 Reaction with Aldehyde and Ketone Substrates

2.12.3.1 Effect of Metal Catalysts

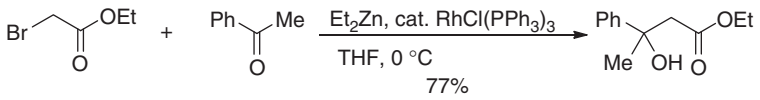
A classical Reformatsky reaction often requires preactivation of the zinc metal. Ideally, freshly prepared zinc should be used because of instability up on exposure to air and moisture. To overcome tedious preoperations, an appropriate catalyst is loaded into the system. A catalytic amount of transition metal will effectively promote this reaction. In 2000, a very important discovery was made concerning the use of a rhodium catalyst.[11] The reaction involved the use of Wilkinson's catalyst, $RhCl(PPh_3)_3$, and diethylzinc (equation 1), in which inter- and intramolecular Reformatsky reactions with aldehydes were achieved under mild conditions to give *β*-hydroxyl esters. The intramolecular reaction was accomplished with high stereoselectivity. The cyclic transition state with a chair-like conformation **15** was proposed for the predominant formation of a *cis* isomer (equation 2). Ketones also are applicable to give the products in high yields (equation 3).



(1)

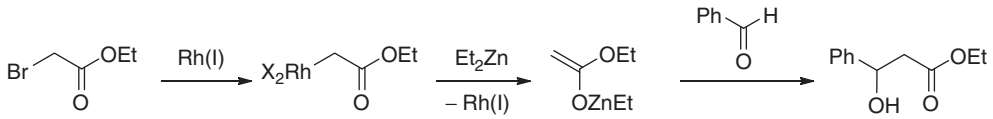


(2)



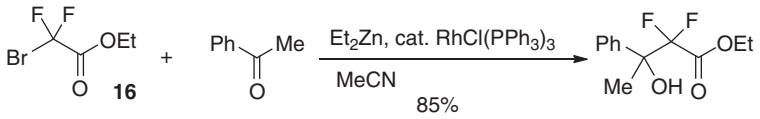
(3)

The oxidative addition of an α-halo ester into Rh(I) initiates the reaction (Scheme 9). After formation of a rhodium(III) complex, its transmetalation with diethylzinc produces ethylzinc enolate, and the regeneration of Rh(I) catalyzed the activation step of the C–halogen bond (Scheme 9).



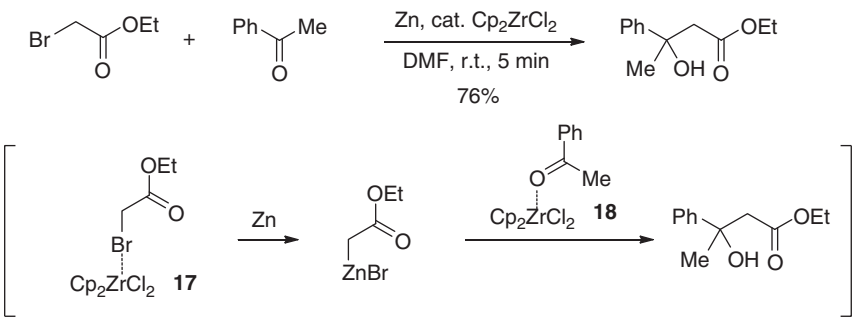
Scheme 9

The Rh-catalyzed Reformatsky reaction of the fluoro-substituted compound **16** was also accomplished with the use of Et_2Zn (equation 4).[12,13] The use of acetonitrile as solvent was critical for the reaction, although the details are not clear.



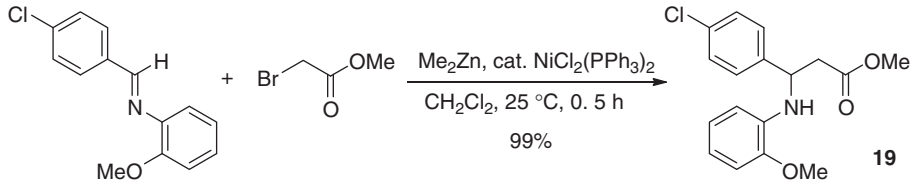
(4)

A mild and rapid process for the Reformatsky reaction was developed using a catalytic amount of Cp_2ZrCl_2 as a promoter and zinc as a terminal reductant at room temperature in a very short amount of time (Scheme 10).[14] The Lewis acid Cp_2ZrCl_2 was expected to function as a dual activator by increasing the feasibility of the insertion of zinc into the carbon–halogen bond through coordination (**17**). Additionally, the electrophilicity of carbonyl groups **18** may also be enhanced by the coordination of Cp_2ZrCl_2.



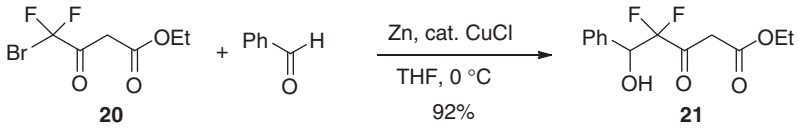
Scheme 10

A Reformatsky reaction with imines often gives lactams that are cyclized products from the β-aminocarbonyl adducts. The nickel complex catalyst, however, effectively promoted the imino-Reformatsky reaction to give an open-form adduct, the β-aminoesters **19**.[15,16] Mild reaction conditions probably avoided the formation of cyclization (equation 5).



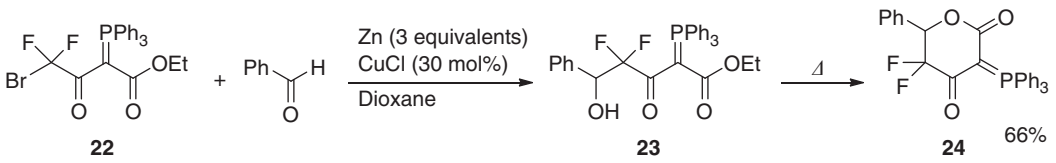
(5)

In the presence of zinc dust and a catalytic amount of CuCl, 4-bromo-4,4-difluoroacetoacetate (**20**) was reacted with aromatic aldehydes and aryl alkyl ketones to give the corresponding δ-hydroxyl-γ,γ-difluoro-β-ketoesters **21** (equation 6).[17] Zinc dust was plausibly activated by copper(I) chloride. No adduct **21** was obtained without CuCl.



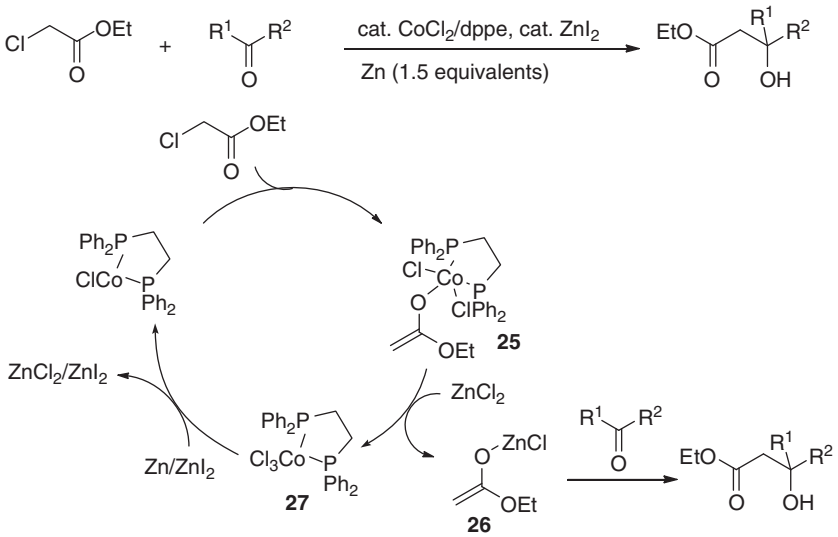
(6)

The bromodifluoromethylcarbonylylide compound **22** was reacted with carbonyl compounds to give the *gem*-difluoromethylenated product **23**, which can lead to the formation of heterocyclic ylide **24** in a high yield (Scheme 11).[18]



Scheme 11

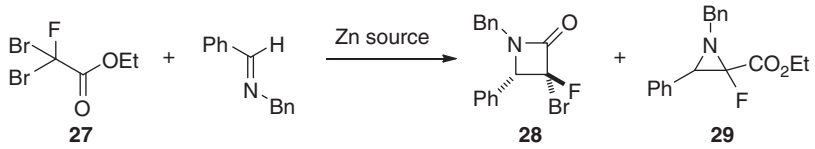
The Reformatsky reaction presented several problems in terms of yield, reproducibility, and competing reactions such as ester- or aldehyde- self-condensation or dehydration of the aldol adducts. The metal was previously identified as the main factor responsible for the somewhat erratic performance of Reformatsky reactions. The cobalt-mediated reaction overcame the problem because of its high reactivity with the C–Cl bond; the oxidative addition of α-chlorocarbonyl to cobalt(I) gave cobalt enolate **25** that led to Reformatsky reagent **26** by transmetalation. The generated Co(III) species **27** was reduced by Zn and the Co(I) was regenerated (Scheme 12).[19]



Scheme 12

2.12.3.2 Reaction with Functionalized Substrates

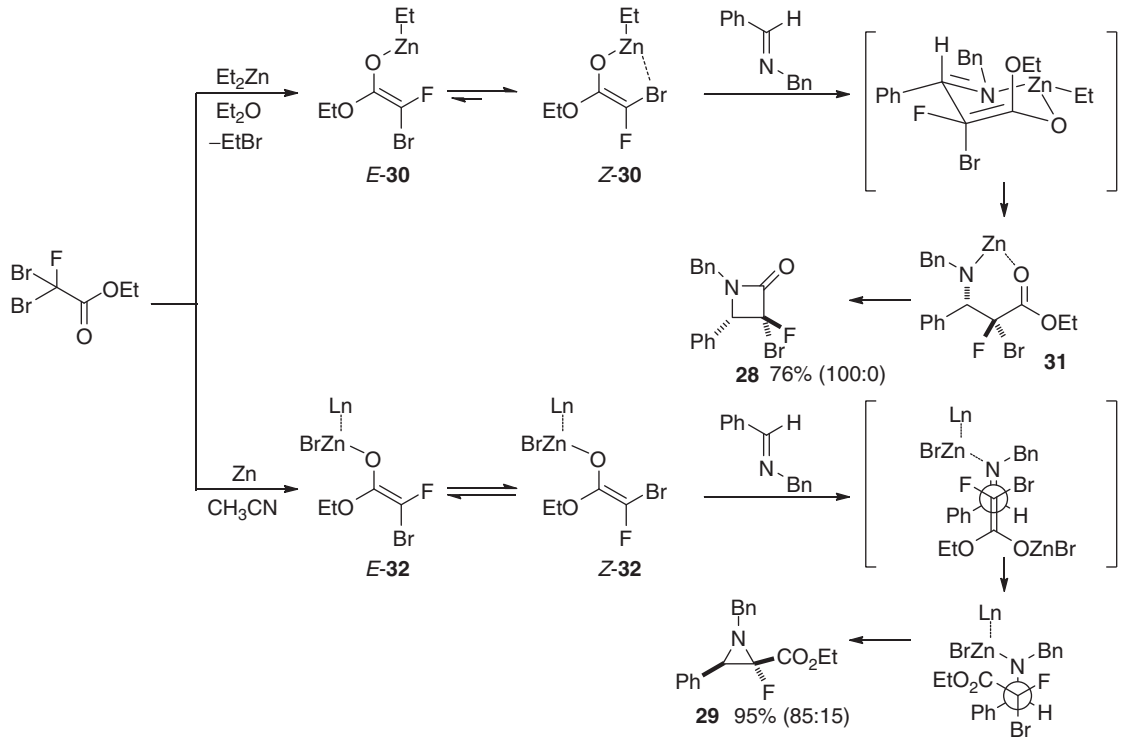
The introduction of fluorine atoms into bio-organic and bioactive molecules often induces modifications of chemical, physical, and biological properties and as a consequence leads to the generation of novel and potent pharmacological and chemotherapeutic agents.[20] The Reformatsky reaction is a powerful method for the synthesis of fluorine-containing β-lactams and β-aminocarboxylic acids using fluorine-containing building blocks like ethyl dibromofluoroacetate. The Reformatsky-type reaction of ethyl dibromofluoroacetate (**27**) with imines using Et_2Zn gave the *syn*-α-bromo-α-fluoro-β-lactams **28** in good yields with ether (equation 7). The products were dramatically changed by using a cetonitrile as a solvent to give 2-fluoroaziridine-2-carboxylate **29** selectively. Zinc metal also led to the selective formation of aziridine **29** in acetonitrile.[21,22]



Et_2Zn	Et_2O	76% (100:0)	8% (0:100)
Et_2Zn	CH_3CN	ND	91% (82:18)
Zn	CH_3CN	ND	95% (85:15)

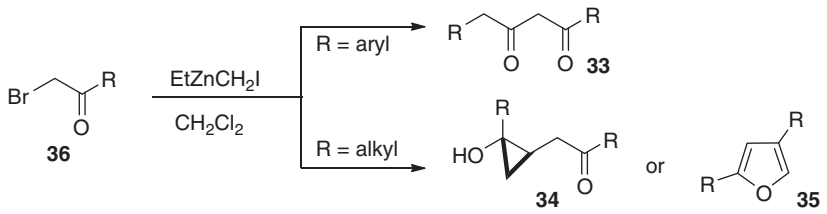
(7)

In the reaction system using Et_2Zn/Et_2O, chemo- and diastereoselective formation of lactam **28** was achieved by the addition of stable (*Z*)-zinc bromofluoro enolate *Z*-**30** to imine, where the low coordination power of Et_2O made the generation of the chair-like cyclic transition state favorable (Scheme 13). The predominant formation of *Z*-enolate can be ascribed to the high affinity between Zn and Br in **30**. The further intramolecular cyclization of intermediate zinc amide **31** was promoted by the coordination of the carbonyl moiety to zinc. The strong coordinating solvent CH_3CN reacted with the Zn of the enolate leading to a reversible equilibrium for the *E*/*Z* isomers of **32**. The solvent coordination could lead to an open-chain transition state rather than the chair-like transition state. The adduct was cyclized to give the *syn*-aziridine **29** stereoselectively through an *anti*-elimination.

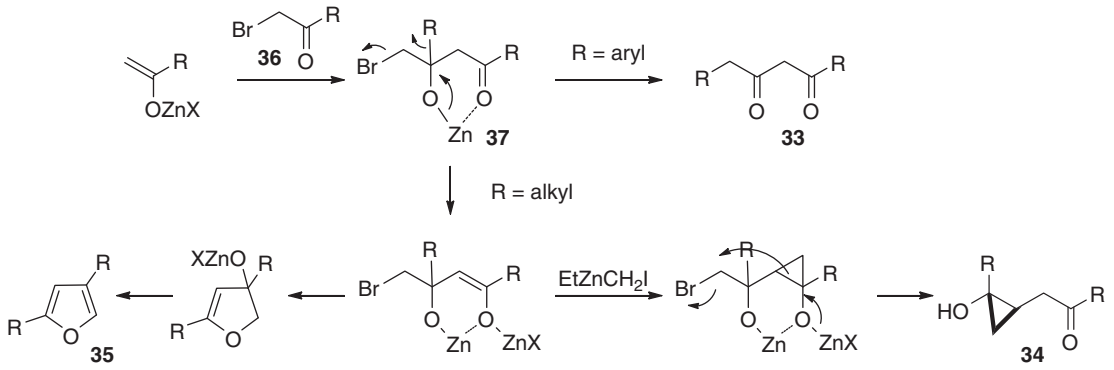


Scheme 13

When a zinc enolate reacted with functionalized compounds, unique structural compounds were formed. The reaction with $EtZnCH_2I$ generated zinc enolate by the insertion of organozinc into the C–Br bond. The Reformatsky-type self-condensation of aromatic α-bromoketones **36** was followed by C–C bond sigmatropic rearrangement of the aldolate intermediate **37** to give β-diketones **33**.[23] Aliphatic α-bromomethyl ketones resulted in the formation of 2,4-disubstituted furans **35** or *cis*-1,2-disubstituted cyclopropanols **34** via Simmons–Smith reaction. In this case, the alkyl group R had a low migratory aptitude (Schemes 14 and 15).

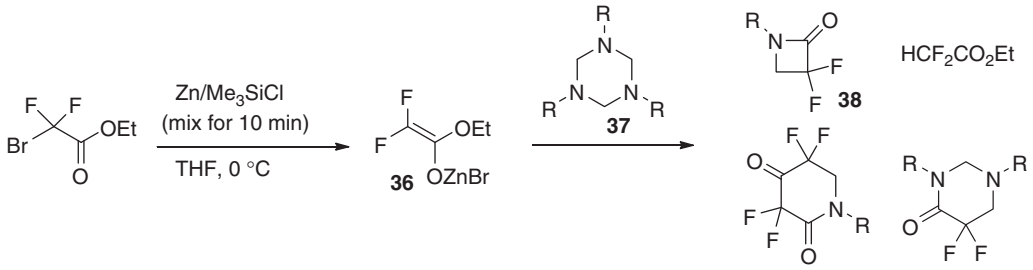


Scheme 14



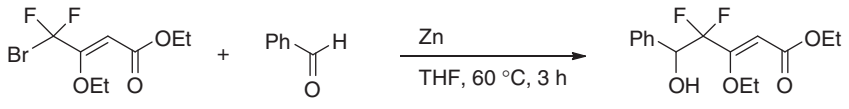
Scheme 15

N-Protected 3,3-difluorozetidin-2-ones **38** were obtained by the cyclization of *N*-substituted 3-amino-2,2-difluoropropanoates prepared from a Reformatsky reaction between *N*,*N*′,*N*″-trisubstituted(hexahydro)-1,3,5-triazinanes **37** and zinc enolate **36** derived from ethyl bromodifluoroacetate. The triazinanes **37** were engaged because they were in equilibrium with the corresponding monomeric imines in solution (Scheme 16). The mixing of Zn with Me_3SiCl was crucial for preparing Reformatsky reagents in this reaction.[24]



Scheme 16

Ethyl 4,4-difluoro-3-ethoxy-4-bromocrotonate (**39**) was reacted with carbonyl compounds in the presence of zinc, giving 4,4-difluorocrotonate derivatives **40**. Prolonging the reaction time resulted in the formation of 4,4-difluoro-2-lactenones **41** (equations 8 and 9).[25]



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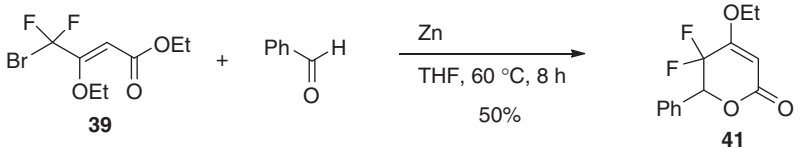
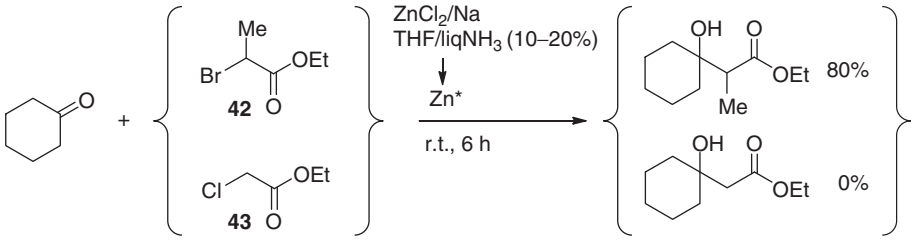


(9)

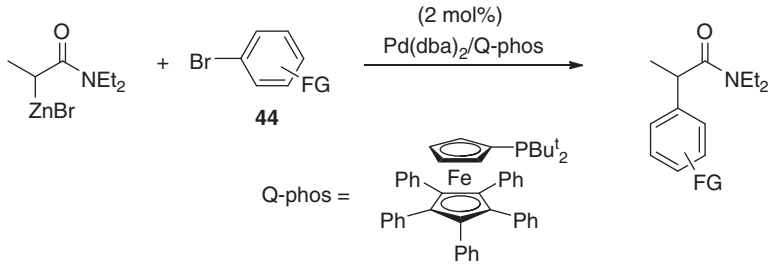
For Reformatsky reactions, the activation of zinc is crucial. Makosza examined two methods; the former was the preparation of active zinc by the reduction of $ZnCl_2$ with sodium in THF-liquid ammonia mixture, and the latter was a treatment in THF containing a 10–20 volume % of liquid ammonia. The latter method gave a higher yield than the former, and showed a selectivity in the competitive reaction between chloroester **43** and bromoester **42** (equation 10). Bromoester **42** was exclusively introduced to the Reformatsky reaction.[26]



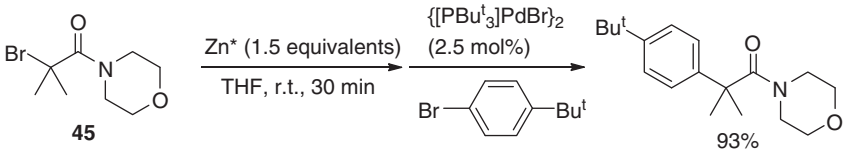
(10)

2.12.3.3 Cross-Coupling Reaction

The Reformatsky reagent generated from amides can react with aryl bromides.[27] Aryl bromides **44** can have various types of functional moieties such as cyano, nitro, ester, keto, fluoro, hydroxyl, or amino groups. The hindered pentaphenylferrocenyl di-*tert*-butylphosphine (Q-phos) was effective as a ligand for this catalytic system (equation 11). The reaction was developed with morphorine amides **45**, the products of which were precursors to ketones and aldehydes (equation 12). The highly reactive, dimeric, Pd(I) complex $\{[PBu^t_3]PdBr\}_2$ was an effective catalyst for this reaction (equation 12).



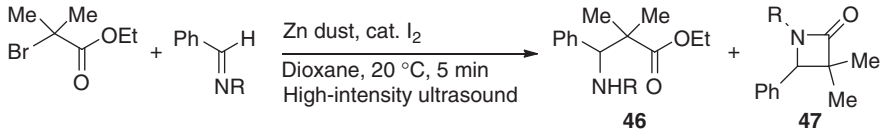
(11)



(12)

2.12.3.4 High-Intensity Ultrasound Method

An underlying problem with the classic protocol of using zinc dust for a Reformatsky reaction has been its low reactivity. It is necessary to activate the zinc dust to initiate the reaction. Control of the resulting exothermic reaction has also been a problem. In some cases, ultrasonic irradiation can be utilized as an alternative energy source for organic reactions ordinarily accomplished by heating. High-intensity ultrasound irradiation (HIU) was applied to the Reformatsky reaction of imine, α-bromoester, zinc dust, and a catalytic amount of iodine in dioxane.[28] The HIU method was successful for both enolizable and nonenolizable imines affording in short reaction times to give high yields of β-lactam **47**. The corresponding β-aminoester **46** or a mixture of the 2 products **46** and **47** depended on the imine and bromoester that was used. The sulfonyl group on nitrogen decreased the nucleophilicity for cyclization to give the β-aminoester (equation 13).

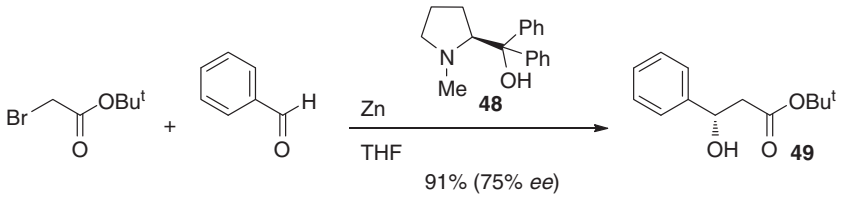


R = Ph	0%	94%
R = SO_2Ph	98%	0%

(13)

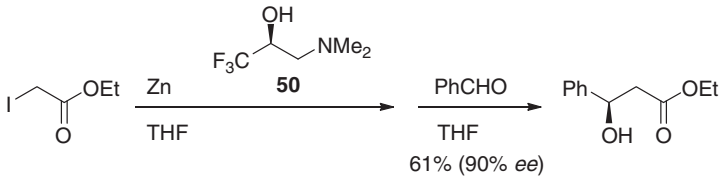
2.12.3.5 Asymmetric Reaction

In 1973, the first example of an enantioselective synthesis employed with a Reformatsky reagent appeared with the use of (–)-sparteine.[29,30] Soai presented the first application of chiral aminoalcohols to an enantioselective Reformatsky reaction in 1991,[31] where in the presence of an equivalent of (*S*)-(+)-diphenyl(1-methylpyrrolidin-2-yl)methanol (**48**) in THF at 0 °C, (*S*)-(–)-*tert*-butyl 3-hydroxy-3-phenylpropanoate (**49**) with 75% *ee*, was obtained in a 91% yield (equation 14). The Reformatsky reagent attacked from the *Si*-face of the aldehyde in the presence of **48**. Other types of chiral aminoalcohols have been widely studied and showed an enantioselective reaction with aldehydes. Pedrosa reported that one example, acetophenone, gave 68% *ee*.[32]



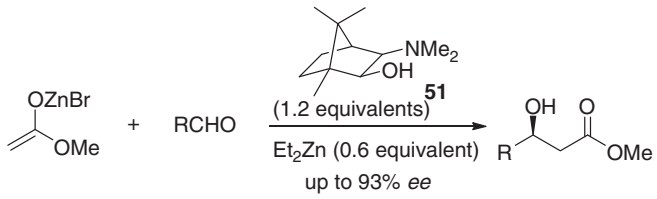
(14)

Trifluoromethylaminoalcohol **50** has been a useful ligand for an asymmetric Reformatsky reaction with benzaldehyde and has afforded the product enantioselectively at up to 90% *ee* (equation 15).[33]

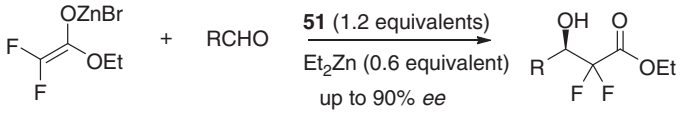


(15)

The amino alcohol, (–)-*N*,*N*-dimethylaminoisoborneol ((–)-DAIB) (**51**), was an excellent ligand for the enantioselective addition of zinc enolates to aromatic and aliphatic aldehydes (equations 16 and 17).[34] The zinc enolates were generated by Me_3SiCl-activated zinc and bromoesters. The addition of Et_2Zn was crucial and it was used for the deprotonation of the amino alcohol in order to avoid the use of an excess of the Reformatsky reagent. Other bases such as BuLi or MeMgCl gave low selectivity.



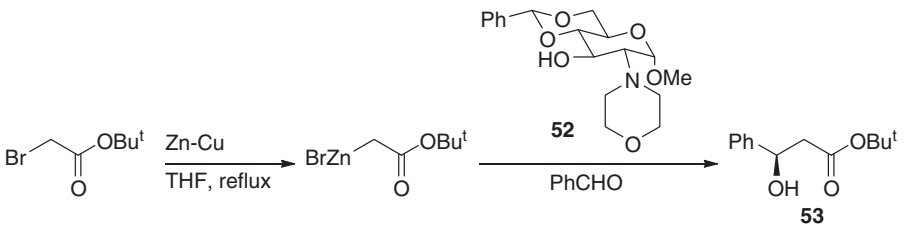
(16)



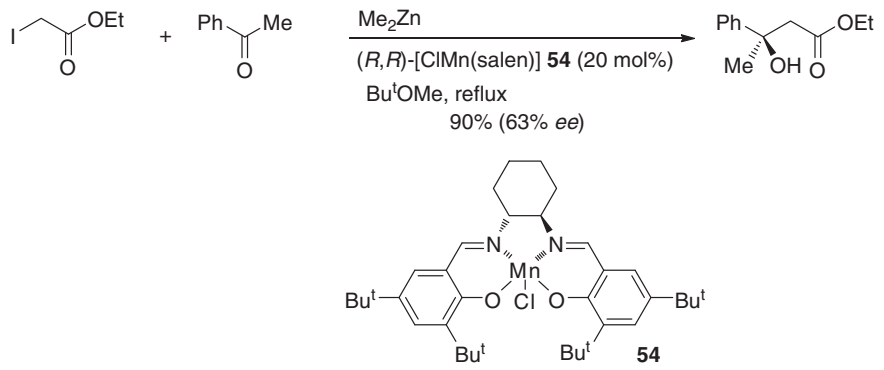
(17)

Members of a family of functionally and stereochemically diverse D-glucosamine-derived tertiary aminoalcohol ligands **52** have been used to promote the asymmetric Reformatsky reaction.[35] The *β*-hydroxyester product, *tert*-butyl 3-phenyl-3-hydroxypropanoate **53** was obtained enantioselectively (up to 74% *ee*) (**Scheme 17**). A secondary binding mode between the ligand and zinc was proposed in addition to the expected N-2, O-3 coordination in an ^1H NMR study.

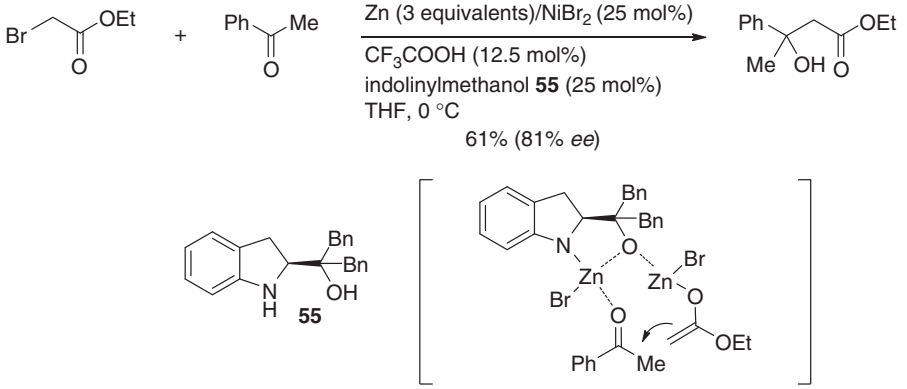
The first enantioselective Reformatsky reaction with ketones was accomplished by Cozzi using a manganese–salen complex catalyst **54** (equation 18).[36] Chiral indolinylmethanol ligands **55** have been applied in the asymmetric reaction of an α-bromoester with ketones. In the presence of $NiBr_2$ and zinc powder, yields of up to 75% and 87% *ee* were obtained for a variety of aromatic and aliphatic ketones in the manner proposed in **Scheme 18**.[37]



Scheme 17

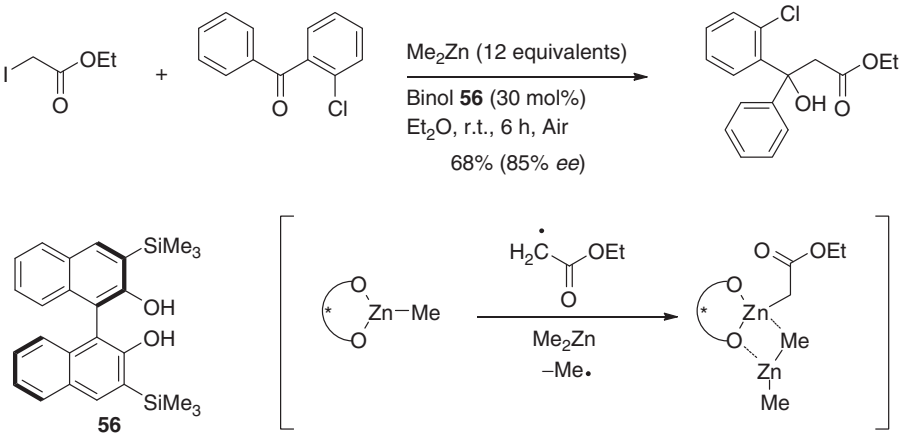


(18)



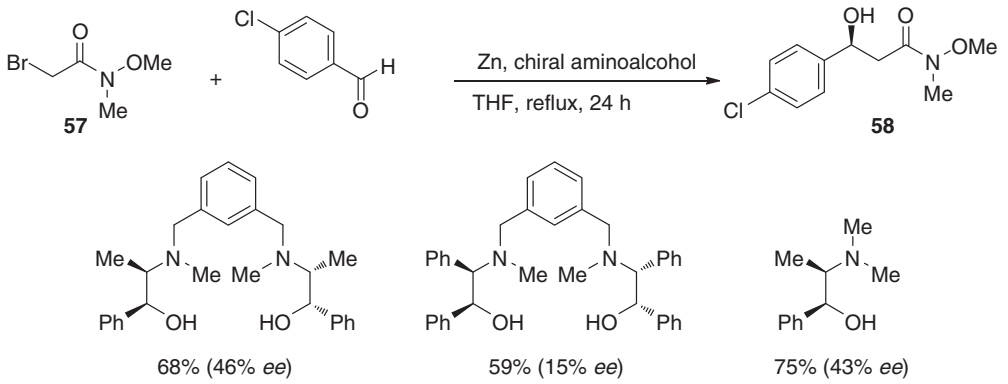
Scheme 18

A catalytic enantioselective Reformatsky reaction with *ortho*-substituted diarylketones was accomplished using BINOL derivative **56**. The presence of air was crucial to achieving an effective coupling reaction, which proceeded in a radical manner. Dinuclear zinc complex with a chiral ligand was proposed for the active reagent (Scheme 19).[38]

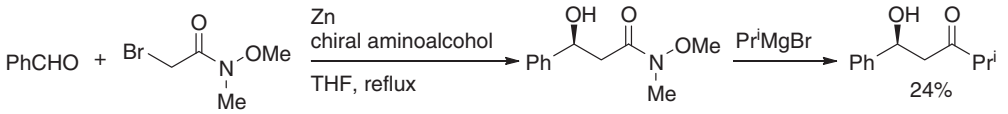


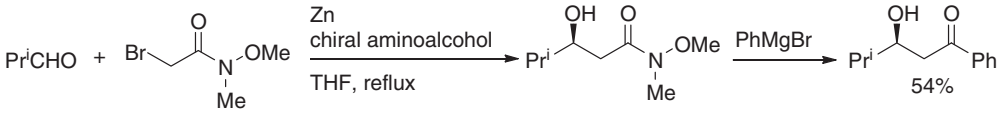
Scheme 19

Chiral 1,2-aminoalcohols catalyzed the enantioselective addition of a zinc derivative from α-bromo Weinreb amides **57** (Scheme 20). The reaction of the resulting β-hydroxy *N*-methoxy *N*-methyl amides with a Grignard reagent allowed the preparation of chiral β-hydroxy ketones. When the starting aldehyde and Grignard reagent were chosen, the product had different substituent patterns (equations 19 and 20) (Scheme 20).[39]

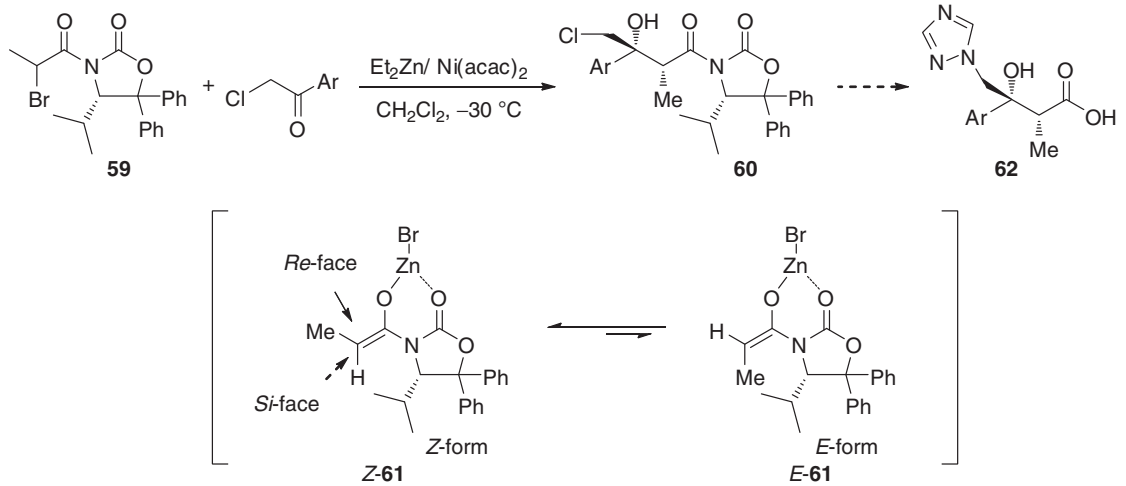


Scheme 20





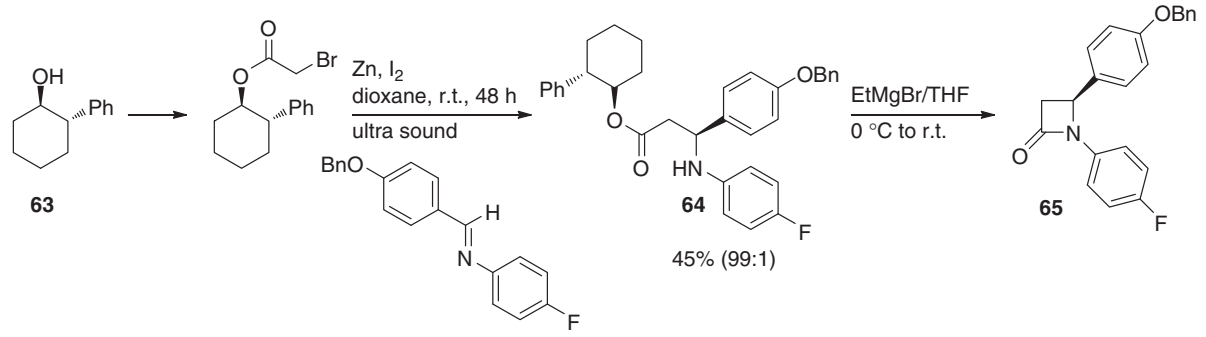
For reliable asymmetric syntheses, the employment of chiral auxiliaries is undoubtedly an important protocol. Evans chiral imide was applied to the generation of Reformatsky reagents using a nickel catalyst and Et_2Zn (Scheme 21).[40] The chiral imido zinc enolate, which was formed through the metal–halogen exchange reaction of chiral α-bromopropionyl-2-oxoazolidinones **59** with diethylzinc under a $Ni(acac)_2$ catalyst, performed the asymmetric zinc-Reformatsky reaction with activated



Scheme 21

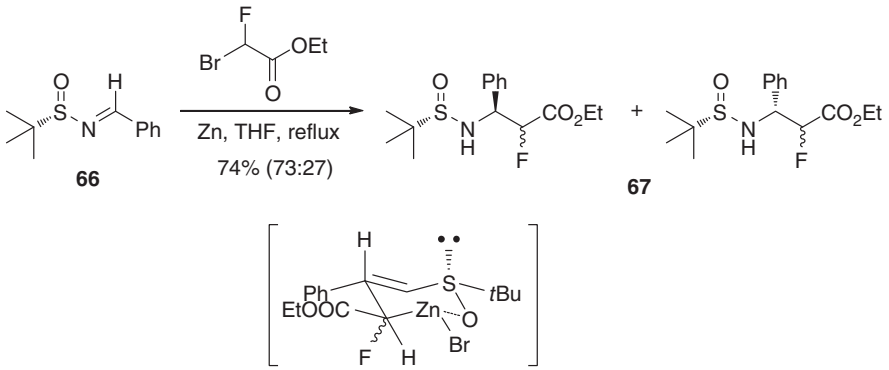
α-haloacetophenones to give the chiral β-hydroxyamides **60** with high selectivity. The zinc enolate *Z*-**61** was preferable to the *E*-form probably for steric reasons. As the isopropyl group of the chiral auxiliary moiety blocked the *Re*-face of the zinc enolate, the carbonyl molecule preferably approached the *Si*-face of the zinc enolate. The produced chiral β-hydroxyamides were transformed to versatile chiral building blocks for triazole antifungal agents **62**.

Asymmetric induction by several chiral alcohols in bromoacetate reactions with imines was studied (Scheme 22). *Trans*-2-phenylcyclohexanol **63** was introduced to bromoester as a starting material. The diastereoisomeric β-aminoesters **64** obtained from the reaction with imine was cyclized by an ethyl Grignard reagent to give β-lactam **65**.[41]



Scheme 22

Reformatsky reactions have been effectively applied to asymmetric syntheses because of the tolerance of many functional groups. The treatment of chiral *N*-(*tert*-butylsulfinyl)imines **66** with ethyl bromofluoroacetate in the presence of activated Zn dust in THF afforded the α-fluoro-β-amino acid derivatives **67** in good yields with moderate diastereoselectivity.[42] A possible mechanism was proposed based on the 6-membered chair-like transition state (equation 21).

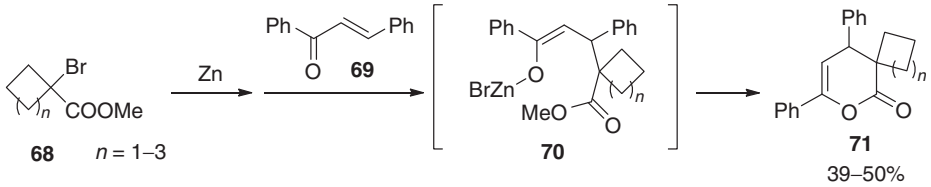


(21)

2.12.4 Reaction with Other Substrates

2.12.4.1 Michael Addition

The cyclic bromoesters **68** reacted with zinc and chalcone (**69**) to form spiro compounds **71**. The Michael-type addition of a Reformatsky reagent to an unsaturated carbonyl gave zinc enolate intermediates **70**, which were cyclized intramolecularly. Cyclobutane, cyclopentane, or cyclohexane derivatives were used for starting α-bromoesters (Scheme 23).[43]

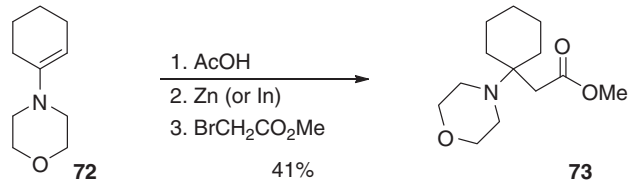


Scheme 23

The Michael-type addition of acyclic halides with unsaturated nitriles or esters was also reported.[44] The reaction with α,β-unsaturated α-cyanoamide compounds gave the lactams via a Michael-type addition.

2.12.4.2 Reaction with Enamines

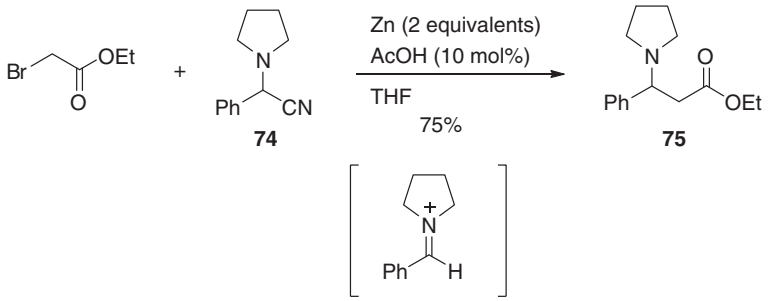
The reaction of enamine **72** with bromoacetate in the presence of Zn gave β-aminoester **73** (equation 22). The addition of acetic acid was crucial for acceleration of the reaction. An indium metal was also used instead of zinc. The choice of a reductant was dependent on the enamine that was used. Allylic halides were also used for the precursor of the nucleophile.[45]



(22)

2.12.4.3 Reaction with Aminonitriles

N,N-Disubstituted α-aminonitriles **74** underwent a Bruylants reaction under Reformatsky conditions with bromoesters and zinc in the presence of 10 mol% AcOH. The reaction proceeded through the formation of a highly reactive iminium ion to give β-aminoesters **75** (equation 23).[46] The role of AcOH may have activated the metal surface and facilitated the subsequent formation of the organozinc species. Acetic acid could have been used for the generation of reactive iminium salt. This reaction has been applied not only to bromoesters, but also to allylic bromides.

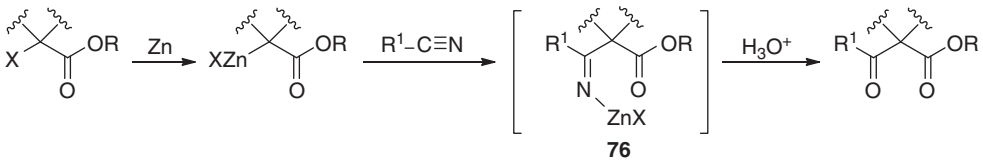


(23)

2.12.5 Blaise Reaction

2.12.5.1 Introduction, Reaction with Nitriles

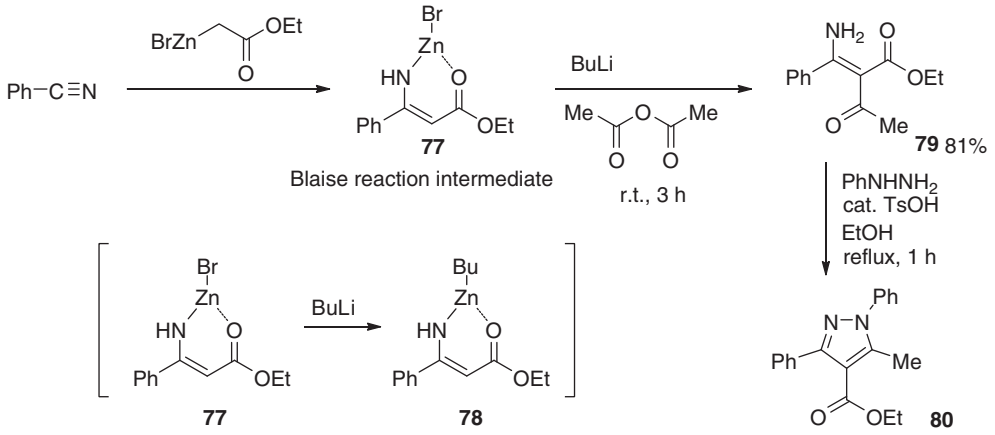
In 1901, Blaise discovered the first example of the reaction of a nitrile with the zinc enolate derived from bromoesters to give the corresponding β-ketoester (Scheme 24).[47] The reaction intermediate was zinc β-imino ester **76**. A review of the Blaise reaction was recently published.[48]



Scheme 24

2.12.5.2 Utility of the Reaction Intermediate from a Blaise Reaction

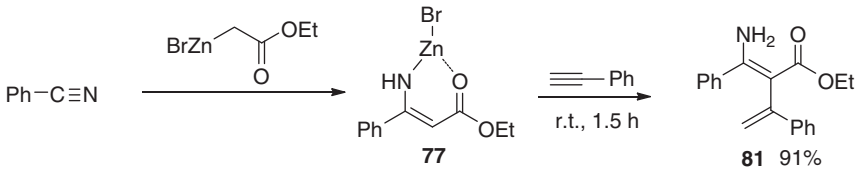
Lee has widely developed the scope of Blaise reaction for various types of products. The Blaise reaction intermediate **77**, a zinc bromide complex of the β-enamino ester, was activated by a stoichiometric or catalytic amount of *n*-BuLi to allow chemoselective tandem C2-acylation, providing α-acyl-β-enamino esters **79** (Scheme 25).[49] The addition of BuLi led to a ligand exchange on zinc to afford the ZnBu-intermediate **78** which had a higher nucleophilicity toward acetic anhydride. The formed β-enaminoketoesters



Scheme 25

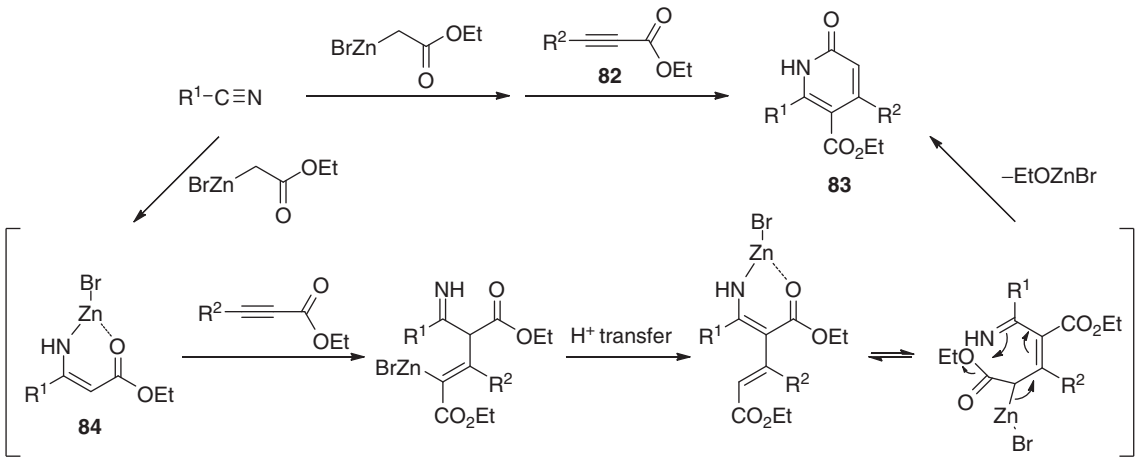
79 reacted with phenyl hydrazine in the presence of a catalytic amount of *p*-toluenesulfonic acid to afford the corresponding 1,3-diphenyl-5-mehtyl pyrazole **80** regioselectively.[50]

The Blaise reaction intermediate **77** reacted with various unactivated terminal alkynes and an internal alkyne under mild conditions to afford α-vinylated β-enaminoesters **81** (Scheme 26).[51] In this system, the ligand exchange of Br to Bu retarded the reaction because the Lewis acidity of zinc was important for the course of the reaction.



Scheme 26

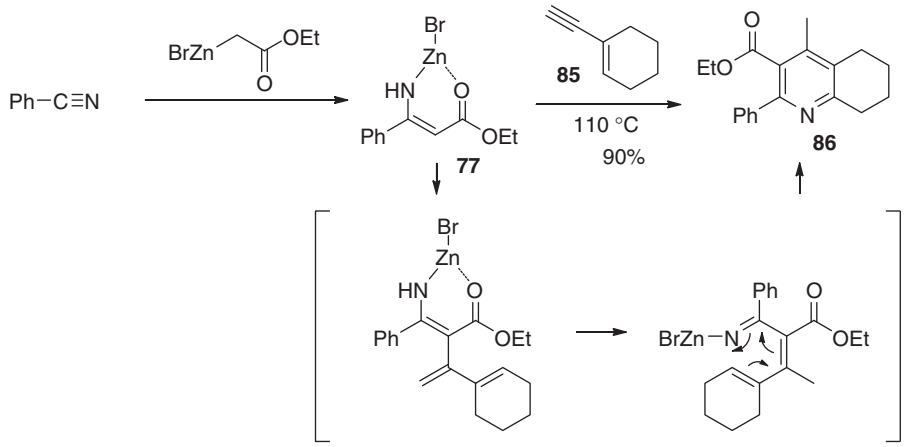
Functionalized alkynes have shown interesting reactions because of a potent further reaction course. The reaction with propiolates **82** gave an interesting cyclic compound **83** and 2-pyridone derivatives.[52] The intermediate **84** was added to the alkyne moiety in a carbozincation manner, followed by H transfer and cyclization (Scheme 27).



Scheme 27

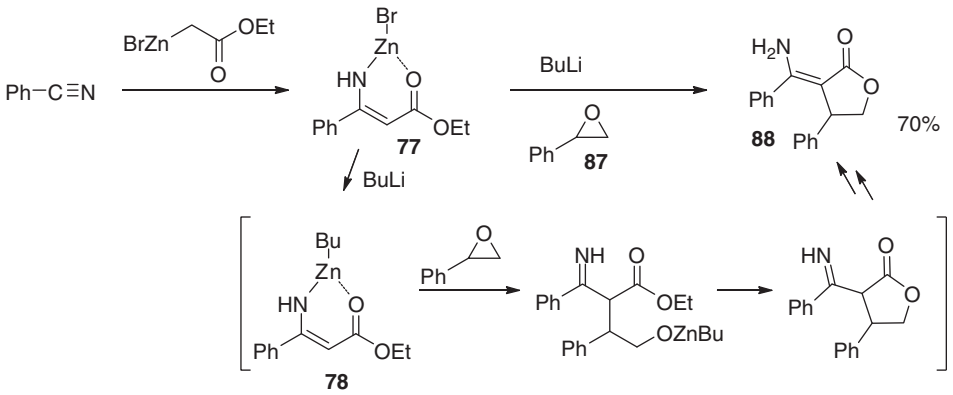
A tandem one-pot method for the construction of a pyridine moiety was accomplished with the reaction of enyne compounds **85**.[53] A cyclization effectively gave the substituted pyridine **86** (Scheme 28).

The Blaise reaction intermediate **77** reacted with epoxide **87** to give α-(aminomethylene)-γ-butyrolactone **88**. A regioselective ring opening proceeded in the course of the reaction. The addition of a stoichiometric amount of BuLi to the Blaise reaction



Scheme 28

intermediate **77** increased its nucleophilicity toward the epoxide opening reaction and lactonization, where Bu–Zn species **78** was generated (Scheme 29).[54]



Scheme 29

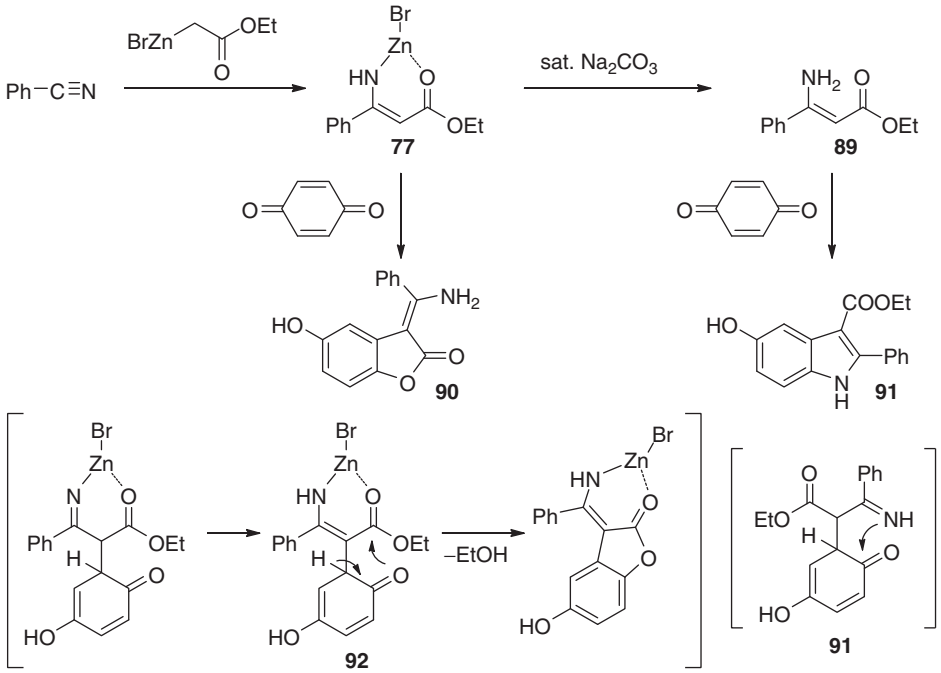
In general, the reaction of *β*-enaminoesters **89** with quinoline provided indols **91** (Nenitzescu reaction) through intramolecular cyclization from the N atom to the benzoquinone carbonyl in **92**. On the contrary, the tandem one-pot reaction of the Blaise reaction intermediate **77**, a zinc bromide complex of *β*-enaminoesters, with benzoquinone afforded 5-hydroxy-α-(aminomethylene)benzofuran-2(3*H*)-ones **90** (tandem Blaise–Nenitzescu reaction).[55] In the course of the reaction, the zinc bromide complex of the Blaise reaction intermediate **92** activated the ester carbonyl group, and favored the formation of benzofuranone **90** (Scheme 30).

The palladium-catalyzed intramolecular *N*-arylative trapping of the intermediate **93** afforded indol derivative **94** in a tandem one-pot manner from nitriles.[56] A palladium catalyst with a base effectively promoted the cyclization (Scheme 31).

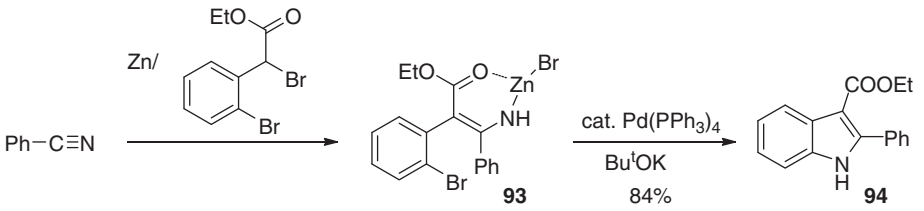
The reaction of the nitrile **94** bearing a Cl moiety with a Reformatsky reagent gave chloro-substituted Blaise intermediate **95**. In this case, the selectivity of either *N*- or *C*-alkylation was a problem. Heating conditions exclusively gave the *C*-alkylative product **97**, a cyclopentene derivative. The addition of sodium hexamethyldisilazide (NaHMDS) dramatically increased not only the reactivity, but also the chemoselectivity to give *N*-alkylative product **96** in a high yield (Scheme 32).[57] Other bases such as LiHMDS, BuLi, K_2CO_3, Na_2CO_3, DBU, DIEA, and triethylamine were not effective. NaHMDS abstracted the proton on nitrogen from the Blaise intermediate to give a dianionic species and the generated species had a unique chemoselectivity, although the details were not clear.

2.12.5.3 Blaise Reaction of Functionalized Substrates

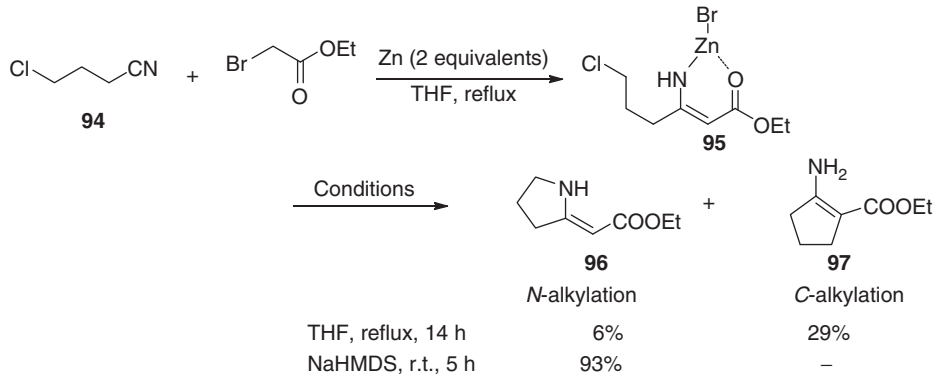
In general, the Blaise reaction has some disadvantages such as a narrow scope and competing side reactions. The functionalized substrate is sometimes difficult to use. However, sonication has been used to effectively promote the Blaise reaction and give δ-hydroxy-*β*-oxo esters from *β*-hydroxynitriles (equation 24).[58]



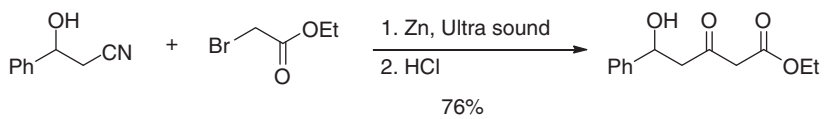
Scheme 30



Scheme 31

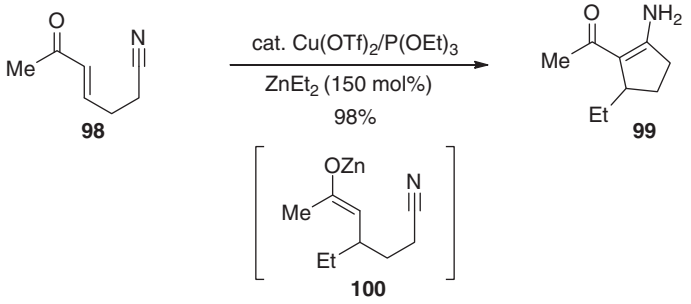


Scheme 32



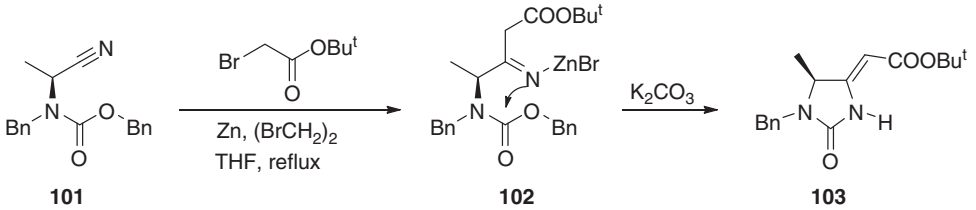
(24)

Tandem C–C bond formations are attractive methodological targets. Krische reported a tandem Blaise reaction using conjugated carbonyl compounds bearing electrophilic moieties such as ketone, ester, or cyano groups. The reaction of cyano-substituted conjugated carbonyl **98** provided an addition-electrophilic trapping process that effectively yielded cyclized compound **99**. Zinc enolate **100** generated by the conjugate addition of Et_2Zn to the unsaturated carbonyl moiety reacted with the cyano group in a Blaise reaction manner (equation 25).[59]



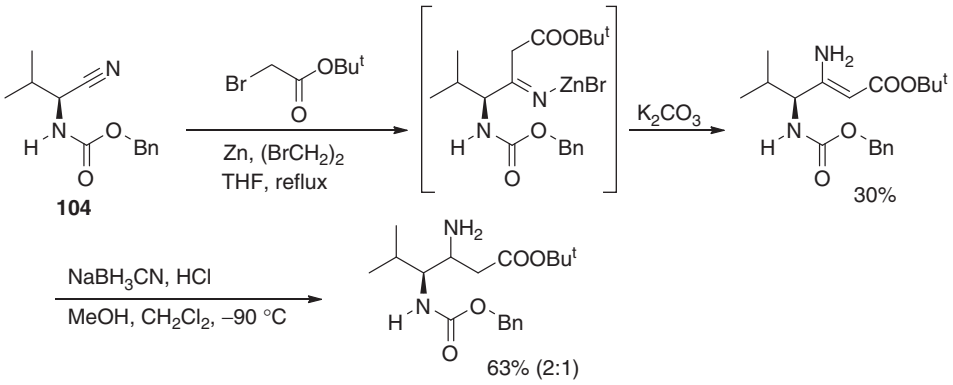
(25)

The Blaise reaction of bromoacetate with α-aminonitriles **101** followed by intramolecular cyclization of the intermediate **102** gave imidazolidines-2-ones **103** (Scheme 33).[60] Since the starting nitrile **101** derived from an amino acid was optically active, the product **103** was homochiral. The reliable retention of stereochemistry is very useful for organic synthesis under Blaise reaction conditions.



Scheme 33

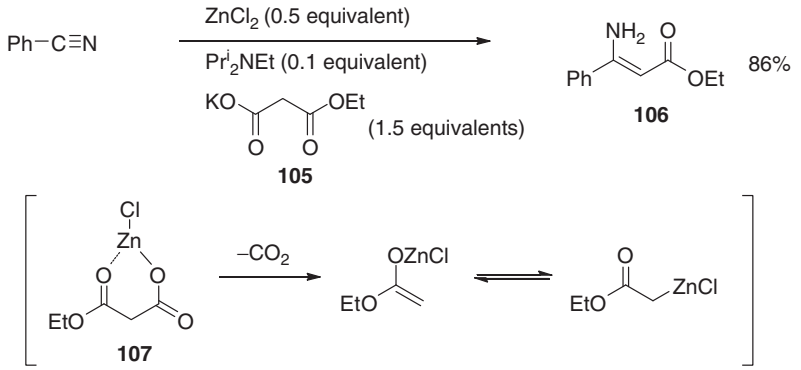
Kouklovsky also reported a reaction with nitrile **104** bearing an NH amino group where intramolecular cyclization was retarded to give an acyclic product. In this case, the chiral center was retained in the reaction course, although the derivatization step of reduction confused the stereochemistry and generated a chiral center (Scheme 34).[61]



Scheme 34

2.12.5.4 Generation of Zinc Enolate from Carboxylate

Reactions of aryl nitriles with potassium ethyl malonate **105** in the presence of zinc chloride and a catalytic amount of Hunig's base provided β-amino acrylates **106** in a moderate to good yields.[62] Under these conditions, the decarboxylative process generated zinc enolate from **107** (Scheme 35). Compared to the classic Blaise reaction, this reaction was safer (endothermic), devoid of lachrymatory reagent, and was possible using a 0.5–1.0 equivalent of zinc chloride.



Scheme 35

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2.13 The Henry (Nitroaldol) Reaction

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This article is a revision of the previous edition chapter by Goffredo Rosini, Vol. 2, pp 321–340, © 1991, Elsevier Ltd.

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Glossary

1,1′-Bi-2-naphthol (BINOL) BINOL is an axially chiral molecule and widely used in chiral ligands and organocatalysts.

aza-Henry reaction Homologous reaction of Henry reaction starting from imines instead of carbonyl compounds. Same as nitro-Mannich reaction.

Nef reaction Conversion reaction of a nitroalkane into a corresponding carbonyl compound.

Nitroaldol A β-nitro alcohol produced by an addition of a carbonyl compound with a nitroalkane.

Nitronate An enolate form of a nitroalkane.

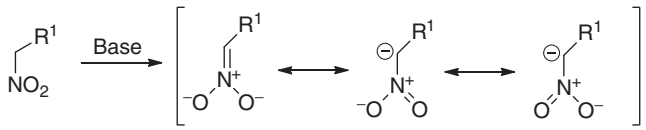
Organocatalyst Metal-free catalyst consisting entirely of organic molecules.

Quinuclidine Bicyclic amine moiety found in cinchona alkaloids, 1-Azabicyclo[2.2.2]octane.

Rare earth The group 3 elements, Sc, Y, and lanthanoids are designated as rare earth metals.

2.13.1 Introduction

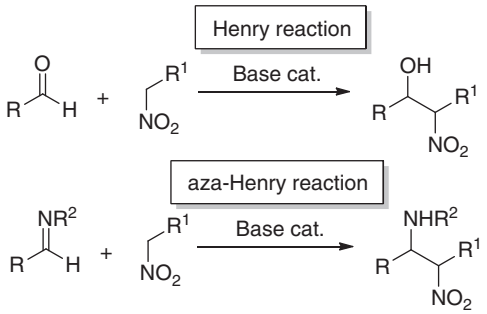
The nitro group is a versatile and useful functionality which can be readily introduced to organic molecules. Due to its strong electron-withdrawing nature, a proton at the α-position of the nitro group (pK_a is approximately 10) is easily abstracted even by a weak base (Scheme 1).



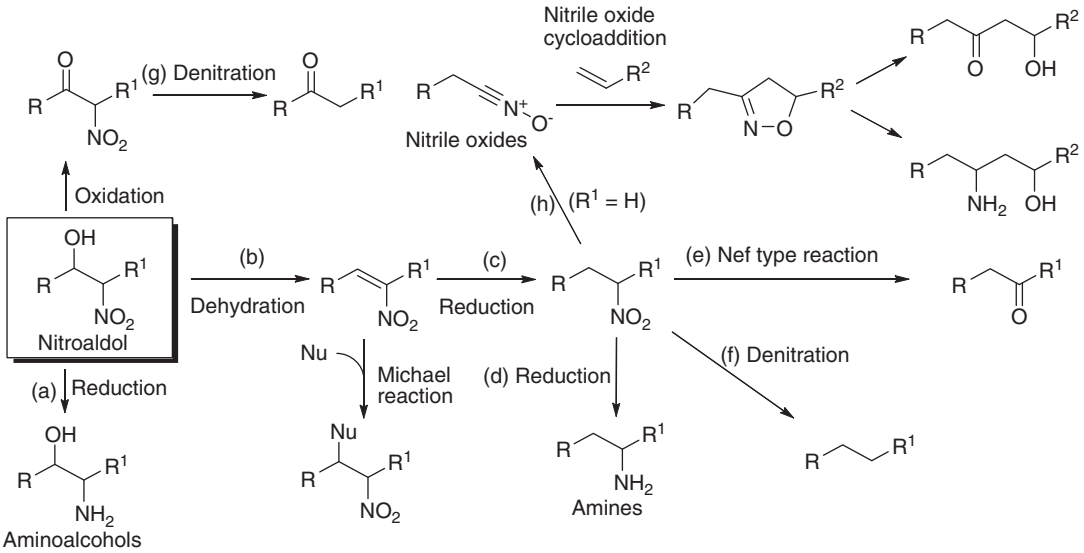
Scheme 1 Generation of nitronate anion.

The nucleophilic attack of the nitronate anion thus generated to a carbonyl compound to give β-nitro alcohol (nitroaldol) is designated the Henry reaction or nitroaldol reaction, as shown in Scheme 2.[1] When the electrophile is an imine (Schiff base) instead of a carbonyl compound, the reaction is called an aza-Henry reaction (or nitro-Mannich reaction).

A wide range of basic reagents such as sodium methoxide, triethylamine, potassium fluoride, and so on can promote the Henry reaction. Some Lewis acids such as trimethylsilyl chloride also catalyze the Henry reaction by activating the carbonyl compounds under mild acidic conditions. Inexpensive nitromethane is the most commonly used nitroalkane in the Henry reaction. Usually the Henry reaction is an equilibrium reaction, and nitromethane is often used in excess amount to obtain the nitroaldols in satisfactory yield. The nitroaldol can be converted into a variety of important functional groups, as shown in Scheme 3. For instance, the nitro group is readily reduced to amino group (path a and d). Dehydration of nitroaldol generates a nitroolefin, which is a good Michael acceptor often used in domino reactions and total synthesis of natural products (path b). Nitroolefins are readily reduced to nitroalkanes (path c). The Nef-type reaction is useful to convert nitroalkanes into carbonyl compounds (path e),[2] and radical conditions are often utilized for the replacement of a nitro group to hydrogen (path f and g).[3,4] The primary



Scheme 2 Henry reaction and aza-Henry reaction.



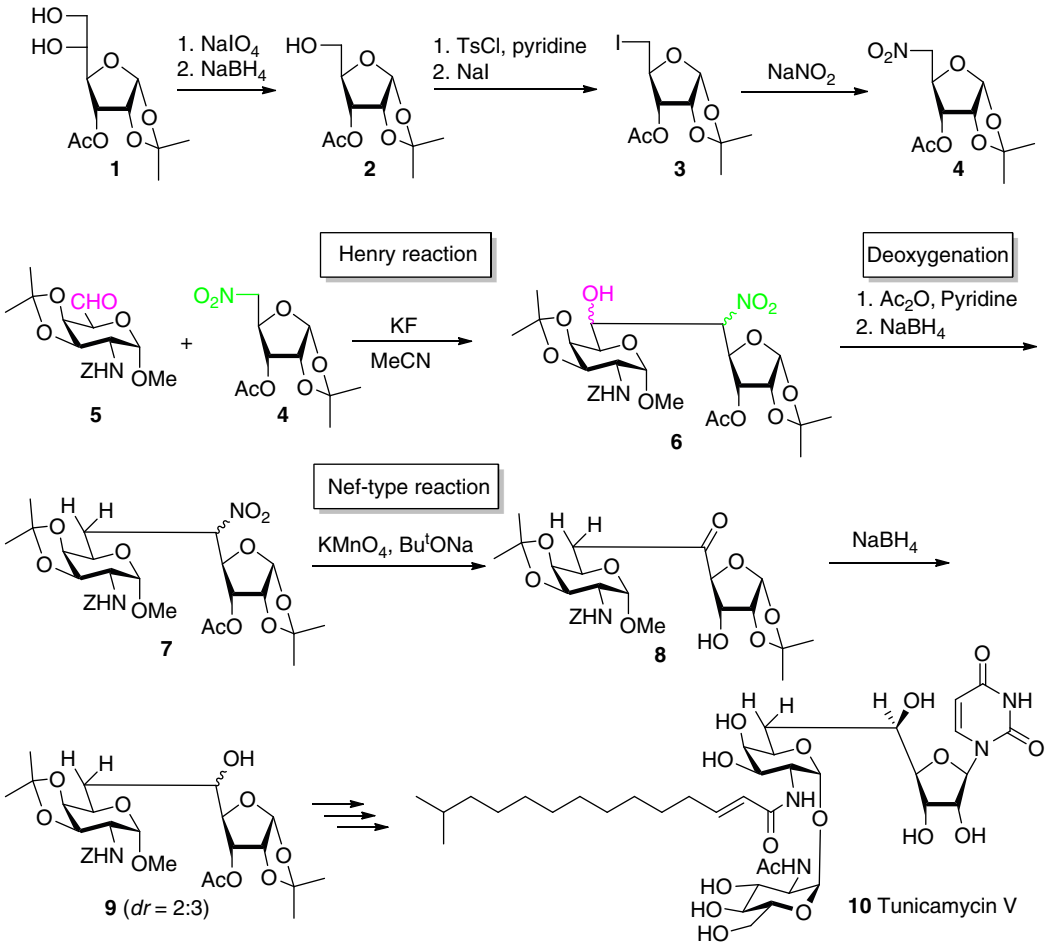
Scheme 3 Conversion of nitroaldols.

nitro compound can be converted into nitrile oxide, which is a good precursor of isoxazoline derivative via nitrile oxide cycloaddition (path h). The isoxazoline derivatives are further converted into *β*-hydroxy ketones or *β*-amino alcohols. These conversion methods are utilized in a number of syntheses of natural products and biologically important molecules. Several concrete examples of the application of the Henry reaction and conversion methods for the nitro group are shown in the next section.

2.13.2 Synthetic Application of Henry Reaction

2.13.2.1 Total Synthesis of Tunicamycines[5–7]

The Henry reaction has been used in carbohydrate chemistry to prepare natural and unnatural sugars, since the Henry reaction can be carried out without the protection of hydroxy group under mild reaction conditions. In addition, Henry reactions have been applied to the synthesis of complex natural products. Nucleoside antibiotic tunicamycins (**10**) consist of a novel higher carbon carbohydrate called tunicamine, a fatty acid, *N*-acetyl-D-glucosamine, and uracil, synthesized by Suami, Sasai and coworkers for the first time in 1984 (Scheme 4). In this total synthesis, the tunicamine unit was constructed by Henry reaction of hexose derivative **5** with a small excess of nitro-substituted pentose derivative **4**. The nitro sugar **4** was synthesized by nucleophilic substitution of corresponding iodide **3** using sodium nitrite. In the presence of dried potassium fluoride as a catalyst, the undecose derivative **6** (nitroaldol) was obtained in 51% yield. Deoxygenation of the nitroaldol **6** was performed by dehydration followed by reduction with $NaBH_4$ to give **7**. The nitro group was converted into a hydroxy group via a modified Nef reaction,[8] followed by reduction of the resulting carbonyl group of **8** to give **9** as a mixture of diastereomers in 2:3 ratio. The total synthesis of tunicamycins has been achieved by introduction of uracil, *N*-acetyl glucosamine unit, and an *α*,*β*-unsaturated carboxylic acid to **9** in eight steps. Synthesis of higher carbon carbohydrates using a Henry reaction was further reported by Suami and coworkers.[9]



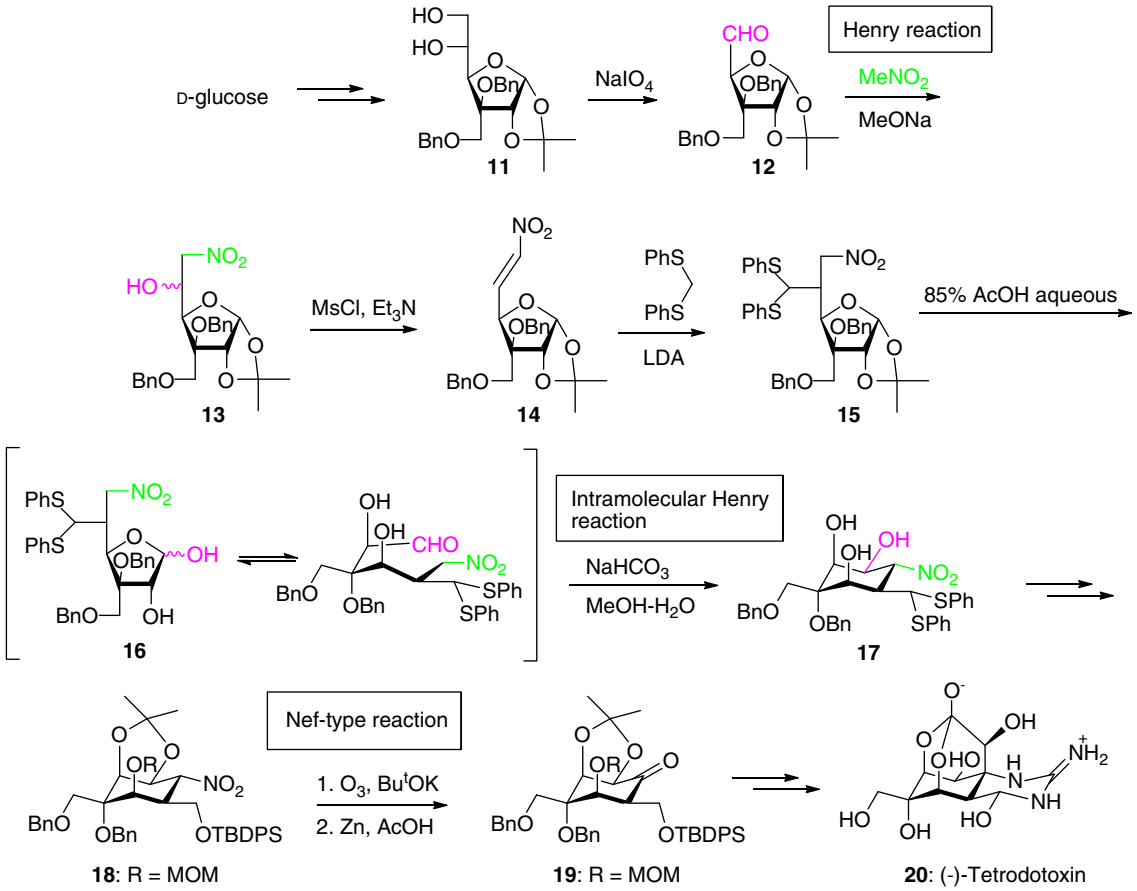
Scheme 4 Total synthesis of tunicamycin V.

2.13.2.2 Total Synthesis of Tetrodotoxin from D-Glucose

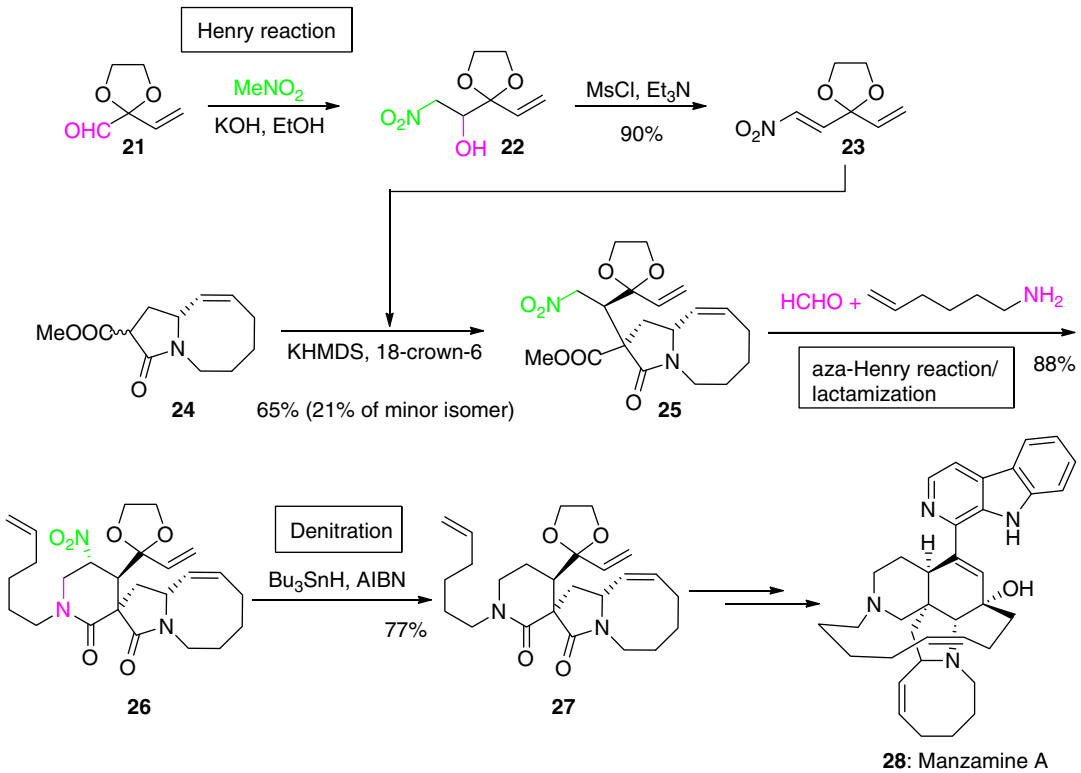
Tetrodotoxin (**20**, Scheme 5) is a well-known marine toxin originally isolated from puffer fish. Several groups have succeeded in the total synthesis of tetrodotoxin. Sato et al. reported a synthesis of tetrodotoxin employing the Henry reaction as a key step.[10] Staring from D-glucose, they prepared nitro sugar **13** via a conventional Henry reaction, and the resulting nitro sugar **13** was dehydrated to afford the nitroolefin **14** as a Michael acceptor, which was further reacted with bis(phenylthio)methane in the presence of lithium diisopropylamide (LDA). The Michael adduct **15** was converted into a hemiacetal **16** followed by an intramolecular Henry reaction to give the cyclohexane derivative **17**. Nef-type conversion of the intermediary nitro compound **18** into carbonyl compound **19** was achieved by ozonolysis of the corresponding nitronate, which was generated by Bu^{t}OK.

2.13.2.3 Total Synthesis of Manzamine A

Manzamine A (**28**) is a marine alkaloid which exhibits a range of potent biological activities such as anticancer, antimalarial, anti-inflammatory, and so on. Recently, Dixon and coworkers reported an efficient synthesis of manzamine A and related alkaloids using Henry and aza-Henry reactions as the key step.[11] As shown in Scheme 6, they prepared the nitroolefin **23** as a Michael acceptor utilizing Henry reaction of the aldehyde **21** with nitromethane. After the diastereoselective Michael reaction of the nitroolefin **23** with known β-ketoester **24**[12] under basic conditions (diastereomer ratio = 73:27:0:0), the resulting major Michael adduct **25** was treated with formaldehyde and hex-5-en-1-amine in refluxing methanol to give 4-nitro-piperidin-2-one derivative **26** as a single diastereomer. In this reaction sequence, aza-Henry reaction of *in situ*-generated imine with nitroalkane moiety takes place followed by lactamization to afford **26**.[13] The nitro group was efficiently removed under modified Ono's radical conditions to produce the key intermediate **27** in good yield.[4]



Scheme 5 Total synthesis of (−)-tetrodotoxin.

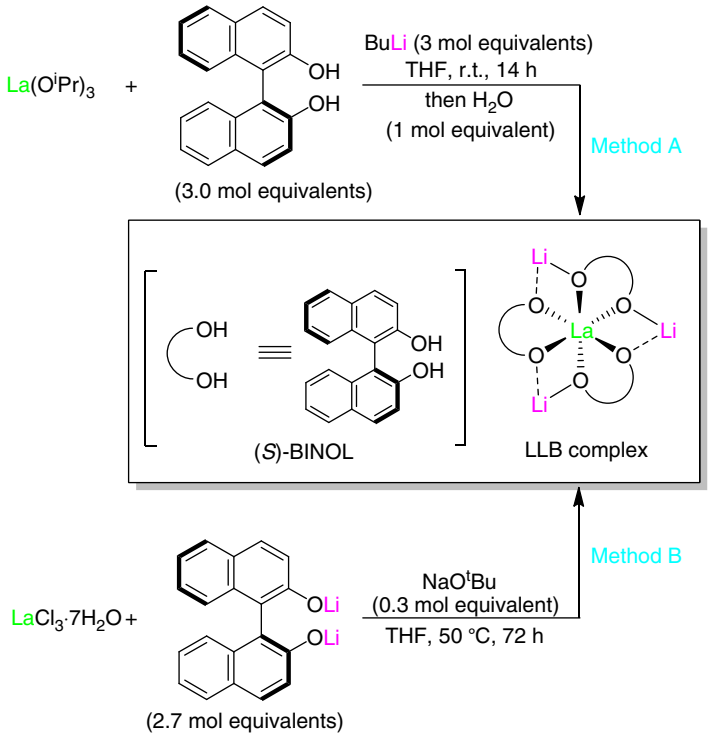


Scheme 6 Total synthesis of manzamine A by Dixon.

2.13.3 Stereoselective Henry Reaction

2.13.3.1 Enantioselective Catalysis

In addition to the conventional catalysts, enantio- and diastereoselective catalysts have been developed. The first enantioselective Henry reaction was realized by Shibasaki, Sasai, and coworkers in 1992.[14,15] They developed rare earth–lithium–BINOL catalysts such as $LaLi_3$tris((*S*)-binaphthoxide)((*S*)-LLB) and achieved highly enantioselective Henry reaction. The LLB catalyst can be readily prepared by mixing with lanthanum tri(2-propoxide) with 3 equivalents of optically pure BINOL monolithium salt in tetrahydrofuran (THF) (Scheme 7, method A). The LLB catalyst is prepared more practically from lanthanum trichloride and BINOL dilithium salt in the presence of a small amount of water (Scheme 7, method B).[16,17] LLB catalyzes the Henry reaction of various aliphatic and aromatic aldehydes with nitroalkane to give nitroaldols in high efficiency (Figure 1). Other rare earth–lithium–BINOL catalysts (LnLB, where Ln = rare earth) have been prepared in a similar manner and showed pronounced differences in the reactivity and enantioselectivity in Henry reactions, as shown in Figure 2.[18] For the aromatic aldehydes, LnLB consisting of a rare earth element with smaller ionic radius than lanthanum, such as gadolinium and europium, showed higher enantioselectivity.



Scheme 7 Preparation of LLB catalyst.

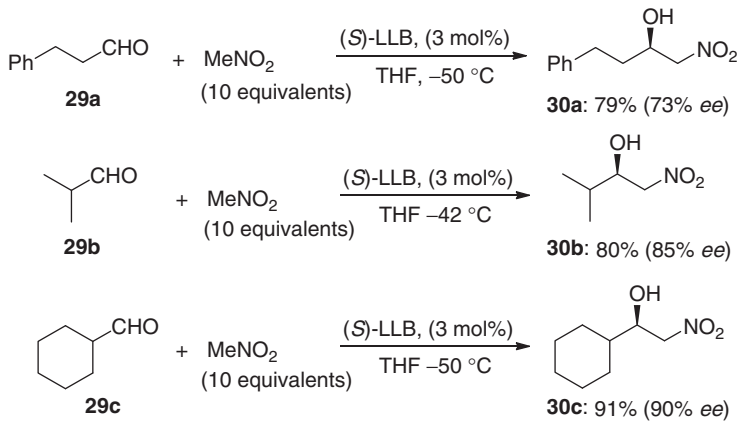


Figure 1 LLB-catalyzed enantioselective Henry reaction.

The structures of the LnLB catalysts have been determined by a combination of X-ray crystallographic analysis of their crystalline analogues, which contain sodium instead of lithium (Figure 3), and laser desorption/ionization time-of-flight mass spectroscopy.[19] Later, the structures of LnLB complexes have been unequivocally determined by X-ray crystallography.[20,21]

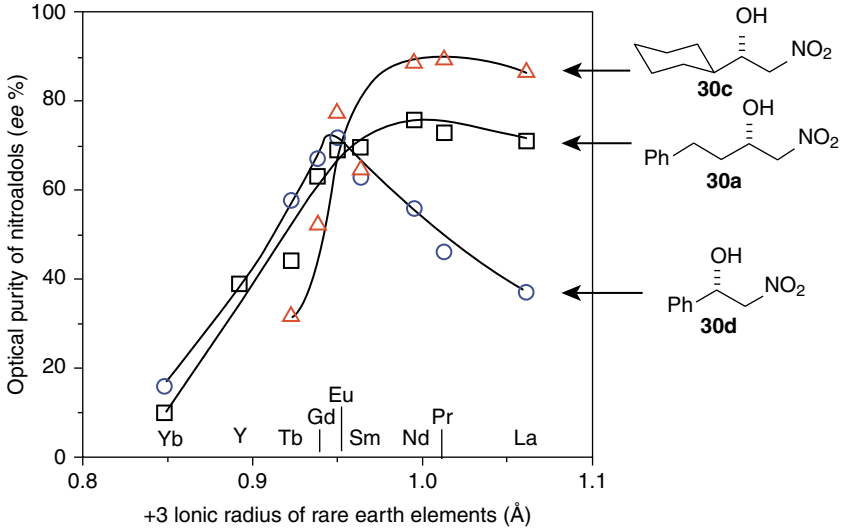


Figure 2 Effects of the ionic radii of rare earth elements on the optical purities of nitroaldol derivaties.

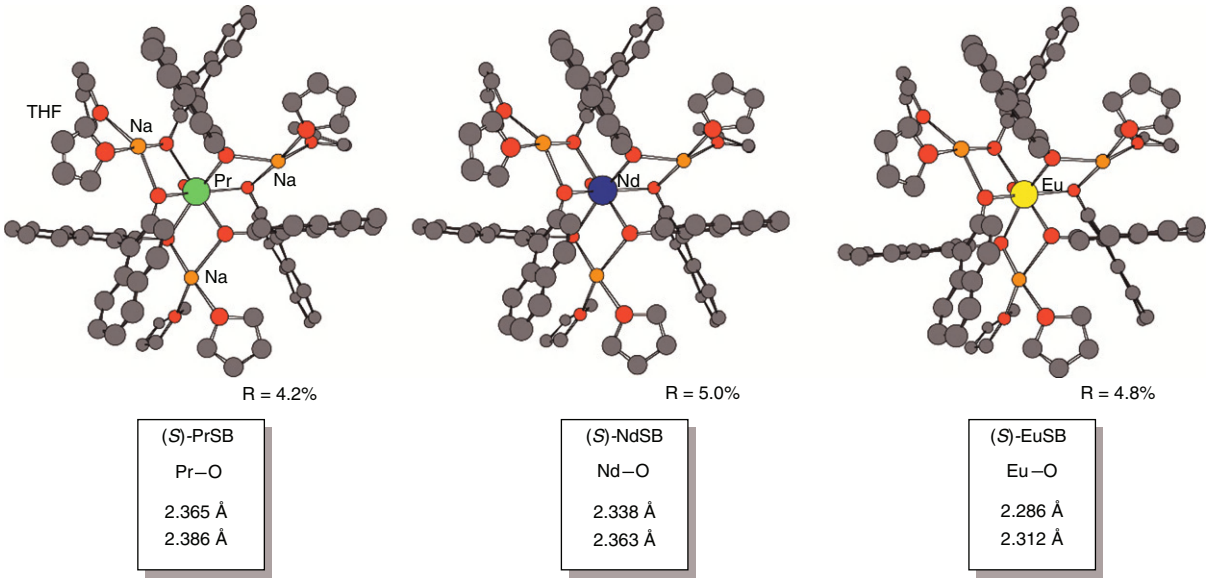


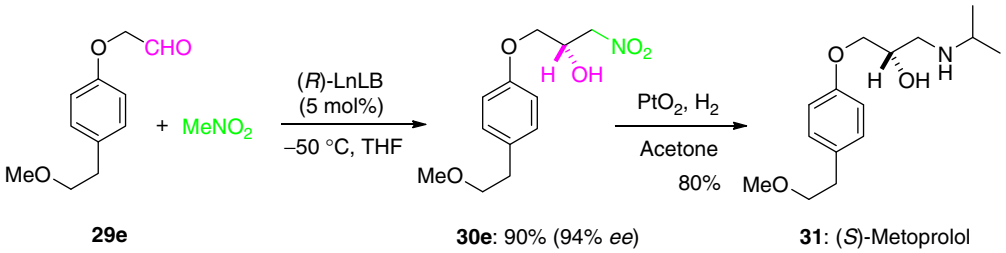
Figure 3 Structure of LnSB complexes (Ln, rare earth; S, sodium; B, BINOL).

The LnLB catalysts are stable against oxygen and moisture, and can be stored without loss of catalytic activity. LnLB catalysts have been applied to the synthesis of useful biologically active molecules.[22,23] A synthetic application for the synthesis of a *β*-blocker (*S*)-(−)-metoprolol **31** is shown in Scheme 8.[24]

After the discovery of the LnLB catalyst, a number of metal catalysts and organocatalysts for enantioselective Henry reaction have been developed.

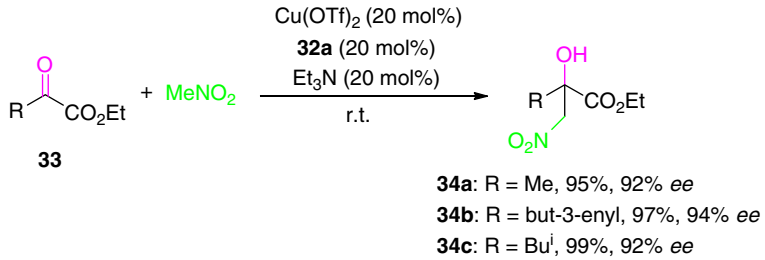
Jørgensen reported an efficient asymmetric Henry reaction of nitoromethane with *α*-ketoesters catalyzed by copper(II)–bisoxazoline (Cu(II)–box) complex in the presence of triethylamine (Scheme 9).[25,26] Among the box ligands they examined, (*S*)-Bu^t-box **32a** shows the highest performance, giving the nitroaldols **34** in up to 94% *ee* in high yields.

Jørgensen also examined enantioselective Henry reaction of silylnitronate **35** with aromatic aldehydes **29** utilizing Cu(II)–box catalysis.[27] By the application of Cu(II)–DiPh–box complex **36** as the catalyst, moderate enantioselectivities (up to 66% *ee*) were



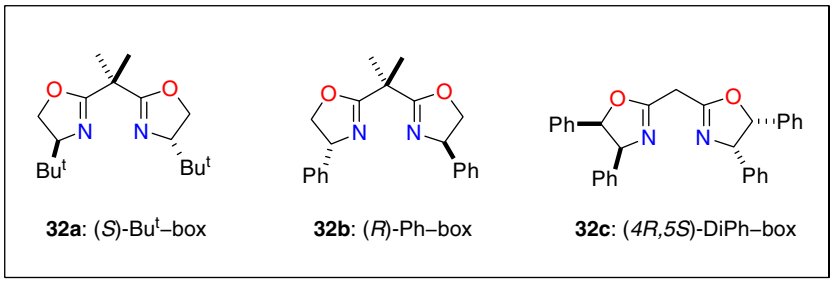
29e **30e**: 90% (94% *ee*) **31**: (*S*)-Metoprolol

Scheme 8 Catalytic enantioselective synthesis of a β-blocker.



33

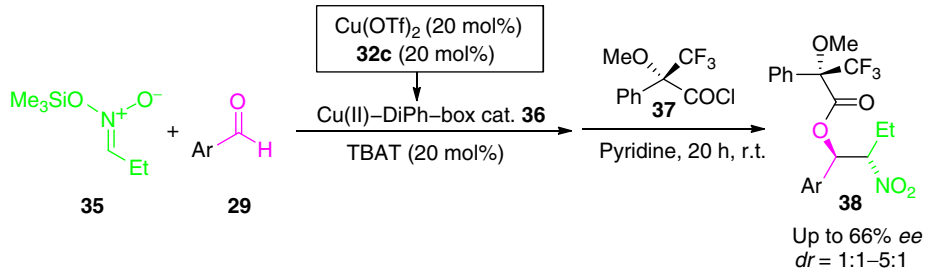
34a: R = Me, 95%, 92% *ee*
34b: R = but-3-enyl, 97%, 94% *ee*
34c: R = Bu^{i}, 99%, 92% *ee*



32a: (*S*)-Bu^{t}–box **32b**: (*R*)-Ph–box **32c**: (*4R,5S*)-DiPh–box

Scheme 9 Cu–box-catalyzed enentioselective Henry reaction of α-ketoesters.

observed in the presence of tetrabutylammonium triphenylsilyldifluorosilicate (TBAT), as shown in Scheme 10. Enantioselectivity of the nitroaldols was determined after the derivatization into the corresponding Mosher esters **38** using **37** and pyridine.



35 **29** **38**

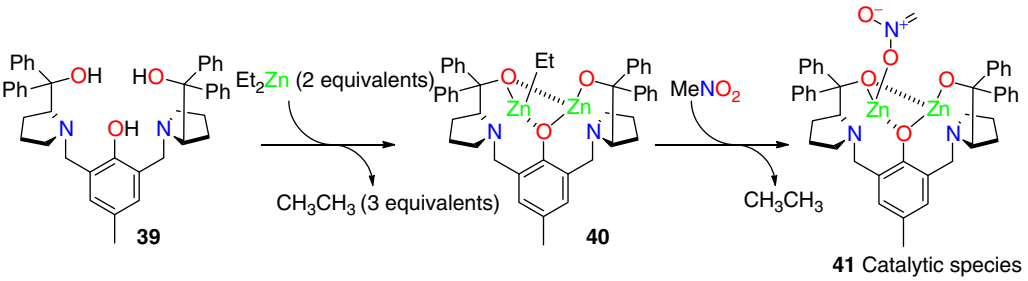
Up to 66% *ee*
dr = 1:1–5:1

Scheme 10 Cu–box-catalyzed Henry reaction of silyl nitronate with aromatic aldehydes.

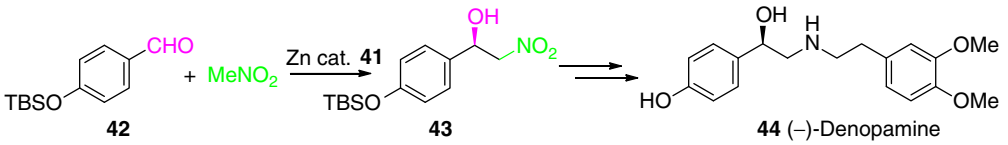
Despite the common enantioselective aldol reactions which utilize silylenolates, most of the enantioselective Henry reaction can use nitroalkanes without the conversion into their silylnitronates. Trost developed a dinuclear zinc catalyst and achieved efficient enantioselective Henry reaction.[28] The dinuclear zinc complex **40** was prepared by treating phenol derivative **39** with 2 equivalents of diethylzinc. When the precatalyst **40** was reacted with nitromethane, the nitronate catalyst **41** was evolved (Scheme 11). The catalyst **41** showed high reactivity and enantioselectivity for both aromatic and aliphatic aldehydes.[29] Scheme 12 shows the application of the dinuclear zinc catalyst **41** for the synthesis of (−)-denopamine.

Gao et al. reported that a trinuclear zinc complex (Figure 4) catalyzed enantioselective Henry reaction and direct aldol reaction. Using 1 mol% of the complex, they achieved high catalytic efficiency (89% yield; 92% *ee*) in the Henry reaction of benzaldehyde with nitromethane.[30]

Evans et al. have greatly improved the copper(II)–box-catalyzed enantioselective Henry reaction. They prepared the catalyst from $Cu(OAc)_2 \cdot H_2O$ and indabox ligand **47** (Figure 5) and achieved direct Henry reaction of nitroalkanes with either aliphatic or



Scheme 11 Preparation of the dinuclear zinc catalyst.



Scheme 12 Application of dinuclear zinc catalyst.

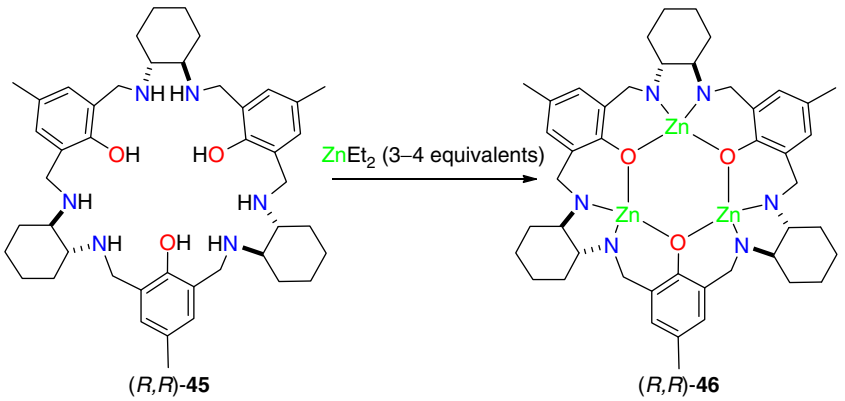


Figure 4 Trimetallic zinc complex reported by Gao.

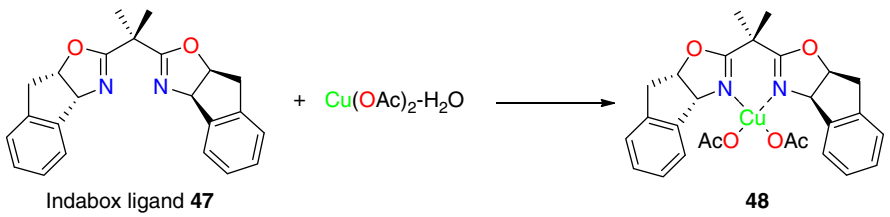


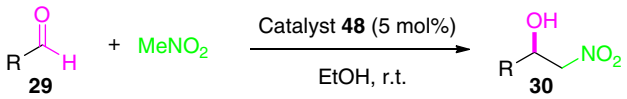
Figure 5 Cu(II)–box catalyst reported by Evans.

aromatic aldehydes in high enantiocontrol even at room temperature, as shown in Table 1.[31] Contrary to the above-mentioned Jørgensen's catalysis, this system does not require the addition of basic reagent. The mode of enantioselection was rationalized based on Jahn–Teller effect, in which a weakly coordinated nucleophile (shown in green) should position perpendicular to the ligand plane as shown in Figure 6.

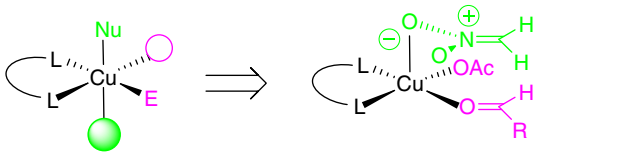
A number of chiral ligands have been investigated in Cu(II)-catalyzed Henry reactions.[32] Figure 7 shows the variety of chiral ligands which indicate high enantioselectivity in Henry reaction.[33,34] Zakarian et al. applied the highly enantioselective Henry reaction developed by Wan to the total synthesis of (+)-brevisamide as depicted in Scheme 13.[35]

In addition to the copper(II) catalysis, copper(I)-catalyzed Henry reactions have been reported. Figure 8 summarizes the representative Cu(I)-mediated enantioselective Henry reactions.[36]

Table 1 Enantioselective Henry reaction developed by Evans



Entry	*R*	*Product **30***	*Time (h)*	*Yield (%)*	ee *(%)*
1	$PhCH_2CH_2$	**30a**	24	81	90
2	Cyclohexyl	**30c**	48	95	93
3	Ph	**30d**	22	76	94
4	Bu^i	**30e**	48	86	92
5	Bu^t	**30f**	96	83	94
6	Bu^n	**30g**	48	87	93



Proposed most reactive transition state

Figure 6 Plausible transition state to explain the mode of enentioselection.

Metal catalysts other than rare earth, zinc, and copper are also reported. Yamada found a ketoiminatocobalt catalysts and a salen–cobalt catalyst for the enantioselective Henry reaction in the presence of diisopropylethylamine (Figures 9(a) and (b)).[37] The similar salen ligands are also effective in chromium catalyses.[38] Hong reported a self-assembled dinuclear cobalt(II)–salen catalyst (Figure 9(c)) through complementary hydrogen bonding interactions, which results in significant enhancement of catalytic activity and enantioselectivity of Henry reaction in the presence of diisopropylethylamine.[39] The self-assembly through hydrogen bonding was confirmed by X-ray crystallography and ^{1}H-NMR analysis. The corresponding monomeric catalysts gave nitroaldols in lower yields and enantioselectivities.

A number of metal-free organocatalysts are also reported to promote enantioselective Henry reactions. Unlike the common metal catalysts, organocatalysts are usually stable under air and moisture, and the products thus obtained are free from metal contamination. Thus, organocatalysis attracts much attention in the field of green chemistry. Several kinds of bifunctional organocatalysts are found to be effective in promoting enantioselective Henry reaction. Due to the weak interaction between a functional group of organocatalysts and substrates, cooperative activation with the two functionalities is able to achieve not only high catalytic activity but also high enantiocontrol.

Cinchona alkaloids have been applied to various kinds of asymmetric reactions.[40] Deng et al. reported C6′-OH *Cinchona* alkaloid derivatives **80** and **81** as efficient catalysts for various enantioselective reactions, in which the C6′-OH group and quinuclidine nitrogen act as an acidic and a basic group, respectively (Figure 10).[41] The highly enantioselective Henry reaction of α-ketoester **33** with nitromethane proceeds smoothly using C6′-OH *Cinchona* derivative as a catalyst (Table 2).[42] The quinidine catalyst **80** and quinine catalyst **81** act as a pseudoenantiomer to each other. The *Cinchona* alkaloid-derived catalysts **81** also promote enantioselective Henry reaction of α-ketophosphonates with nitromethane (Scheme 14(a)).[43] Similar *Cinchona* alkaloid-based catalysts such as **84** were applied to the enantioselective Henry reaction of fluoromethyl ketones with nitromethane by Bandini et al. (Scheme 14(b)).[44]

Thiourea-based catalysts are also effective in promoting asymmetric Henry reactions, especially aza-Henry reactions (*vide infra*). In 1998, Jacobsen and coworkers utilized the thiourea unit as a linker to construct a library of 132 compounds based on a combinatorial approach and realized an asymmetric Strecker reaction, as shown in Scheme 15.[45] After the discovery of the importance of the urea unit, they have successfully found various efficient enantioselective reactions such as the aza-Henry reaction (Table 3; nitro-Mannich reaction)[46] and acyl-Pictet–Spengler reaction.[45–47]

Takemoto et al. also reported efficient bifunctional thiourea-based organocatalyses for enantioselective reactions, including the Michael reaction and aza-Henry reaction.[48,49] Representative results on aza-Henry reaction utilizing organocatalyst **92** are shown in Table 4. In this case *N*-phosphinoylimines gave the best results among the protective group they employed. The plausible mode of activation of the imine and nitroalkane by the thiourea–amine catalyst is proposed as depicted in Figure 11.[49,50] The amino group activates the nitroalkane while the thiourea unit enhances the reactivity of imine via hydrogen bonding. In addition to the above-mentioned thiourea-based organocatalysts, several groups reported bifunctional thiourea catalysts for Henry and/or aza-Henry reactions.[51]

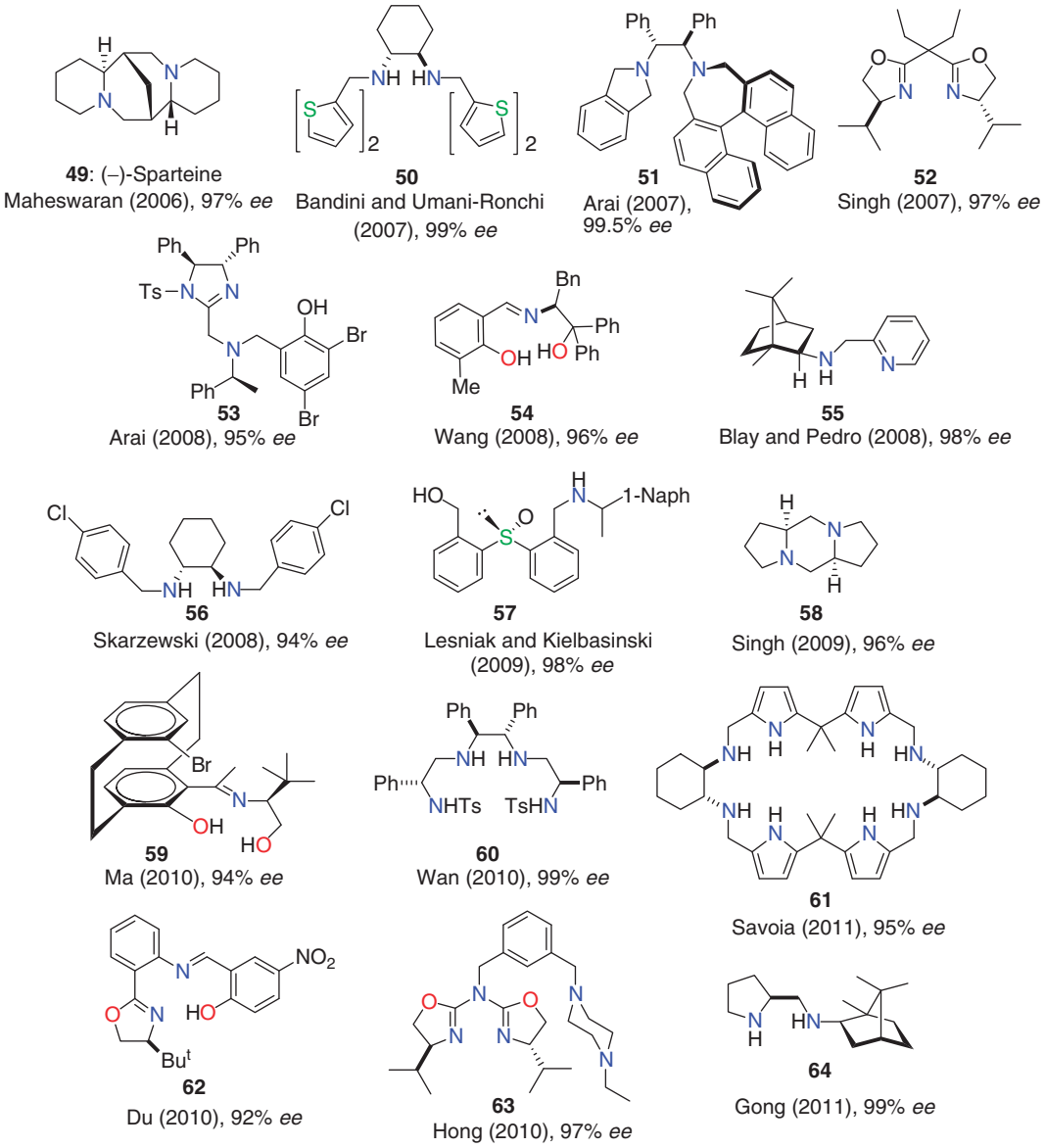
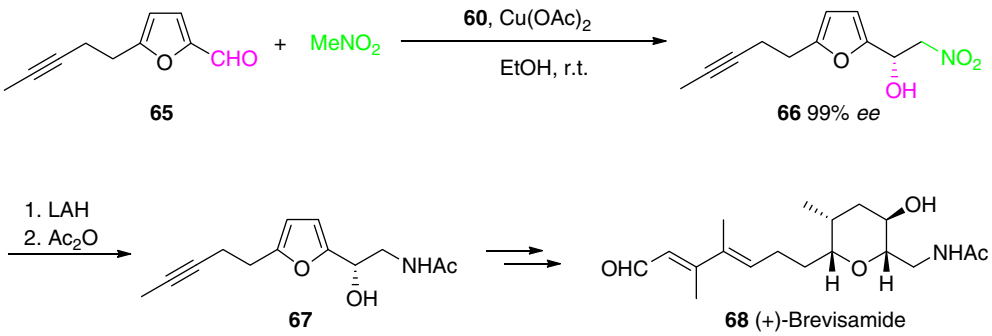


Figure 7 Some successful examples of chiral ligands in Cu(II) catalyses.



Scheme 13 Application of highly enantioselective Cu(II)-catalyzed Henry reaction.

Since the thiourea unit is a versatile functionality to combine different type organic molecules, some important classes of combined organocatalysts such as *Cinchona*–thiourea and guanidine–thiourea-type organocatalyst have been developed. Hiemstra prepared a 6′-thiourea-substituted *cinchona* alkaloid derivative **95**, which promotes enantioselective Henry reaction of

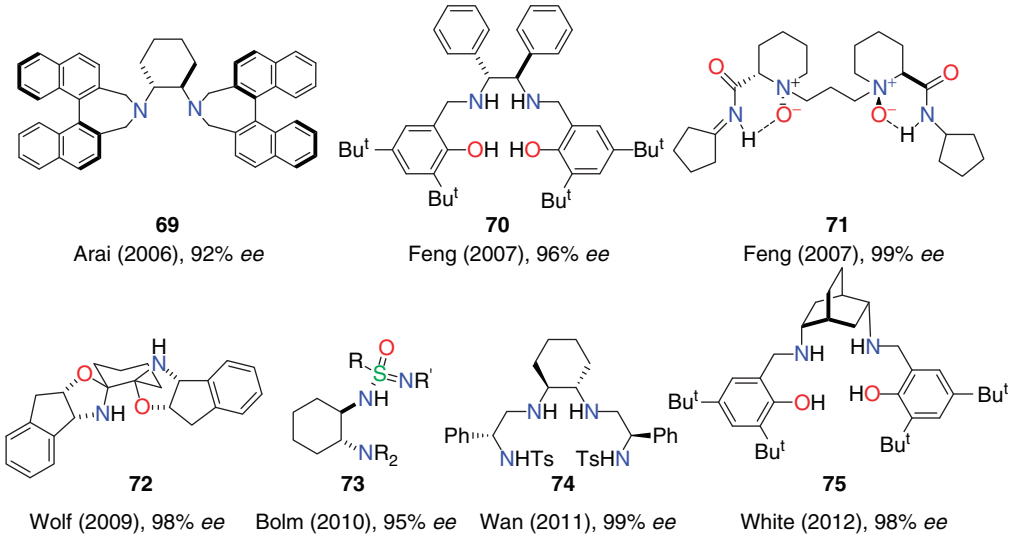


Figure 8 Reresentative chiral ligands for Cu(I) catalyses.

nitromethane with aromatic aldehydes (Table 5).[52] Ricci reported an enantioselective aza-Henry reaction catalyzed by a *Cinchona*–thiourea-type organocatalyst as shown in Scheme 16.[53]

Nagasawa and coworkers developed an organocatalyst having two thiourea units and a guanidine moiety based on their study on chiral guanidines.[54] The catalyst structure and representative results are depicted in Scheme 17.[55] The catalyst **97c** bearing a long alkyl chain on the guanidine moiety showed much higher catalytic activity and enantioselectivity than **97a** and **97b**. In these bifunctional catalysts, the guanidine moiety would generate a nitronate anion while the thiourea unit would activate the carbonyl group to facilitate the enantioselective Henry reaction (Figure 12). The similar guanidinium–thiourea catalyst **66d** gave aza-Henry products in high enantiocontrol (Scheme 18).[56]

Catalytic efficiency of chiral guanidines themselves has been studied. Although the early attempts using the chiral guanidines as organocatalysts had been limited to moderate enantioselectivity in Henry reaction,[57] Terada developed an axially chiral guanidine catalyst **100**, which gave the nitroaldols in good to high enantioselectivities based on the complexation between guanidinium unit and nitronate through two hydrogen bondings (Figure 13). Fairly good *anti*-selectivity was observed when nitroethane and/or nitropropane were used as a starting material.

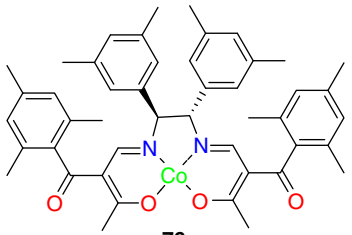
Ooi et al. reported that a unique chiral tetraaminophosphonium salt-mediated highly enantioselective Henry reaction.[58,59] The structure of the tetraaminophosphonium salt **101**-Cl and catalytic cycle proposed by Ooi are shown in Figure 14. An application for a synthesis of (−)-codonopsinine starting from an ynal **102** and nitroethane is shown in Scheme 19, in which excellent *anti*-selectivity (>20:1) was observed.[59] The nitroaldol adduct **103** was chemoselectively reduced to the corresponding aminoalcohol **104** using indium metal, leaving the triple bond intact.

2.13.3.2 Diastereoselective Henry Reaction Using Chiral Aldehyde

Various enantioselective catalysts have been utilized in diastereoselective Henry reactions starting from chiral aldehydes. Kinetically controlled nitroaldols and/or thermodynamically controlled products were obtained, depending on the reaction conditions. In general, a long reaction period under strong basic conditions is prone to generate thermodynamically stable nitroaldols since the usual Henry reaction is an equilibrium reaction. As shown in the following examples, choice of matched pairs of appropriate enantiomer of the catalyst to the substrate is able to achieve high diastereoselectivity.

LnLB catalysts are effective in obtaining the products in high diastereoselectivity. Phenylnorstatine (**109**), a component of the HIV protease inhibitors KNI-227 (**110a**) and KNI-272 (**110b**), was synthesized starting from a chiral aldehyde **107**.[60] As shown in Scheme 20, (*R*)-LLB, which was prepared from (*R*)-BINOL, is the matched pair to obtain the product in high *erythro*-selectivity (99:1). The opposite enantiomeric catalyst, (*S*)-LLB, and an achiral basic reagent, lanthanum tri(2-propoxide), failed to obtain the nitroaldol in high diastereoselectivity (74:26 and 89:11, respectively).

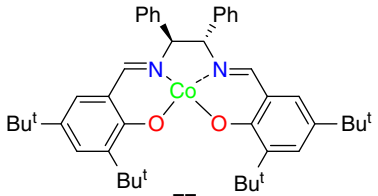
The salen–cobalt complex **111** developed by Yamada was applied in the total synthesis of (+)-(5*R*,4′*R*)-K01-0509 B (**118**), which is a potent selective inhibitor of type III secretion systems.[61] As shown in Scheme 21, Omura et al. prepared the chiral aldehyde **114** via enantioselective epoxidation of allylic alcohol **112** (sharpless epoxidation) as the key step. The Henry reaction of **114** with nitromethane proceeds in a manner of 'catalyst control' to give the *anti*-adducts depending on the chirality of the catalyst employed. *anti*-Adduct **115**, obtained by use of (*R*,*R*)-**111** as a catalyst, was converted to the desired product **118** via guanidine derivative **116**. Meanwhile, 4-*epi*-K01-0509B was synthesized in a similar manner from the *syn*-adduct **119**, which was obtained in 78% diastereoselectivity using (*S*,*S*)-**111**.



76

Yamada (2004), 92% *ee*

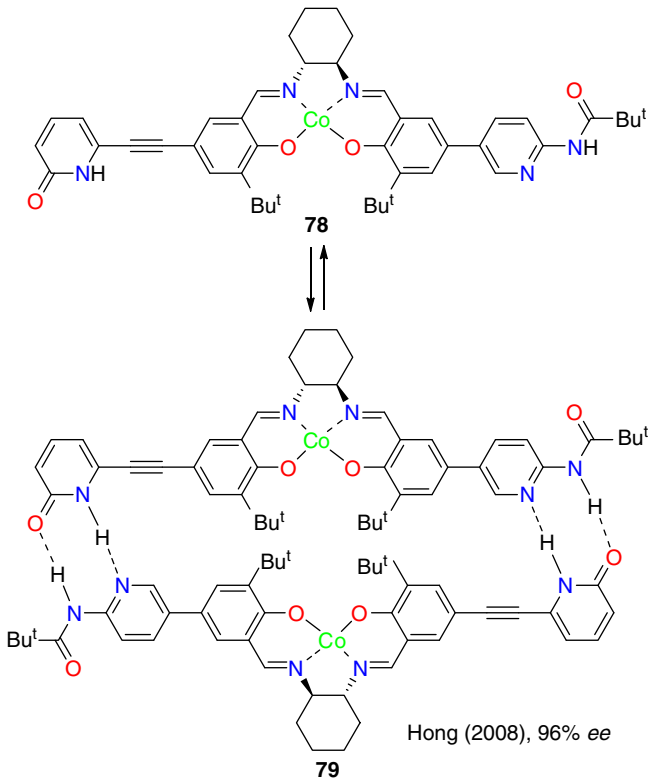
(a) Ketoiminatocobalt catalyst



77

Yamada (2004), 98% *ee*

(b) Salen cobalt catalyst

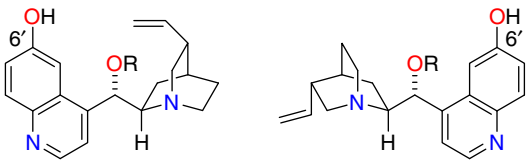


78 ⇌ **79**

Hong (2008), 96% *ee*

(c) Self-assembled dinuclear cobalt catalyst

Figure 9 Enantioselective cobalt catalysts for Henry reaction.



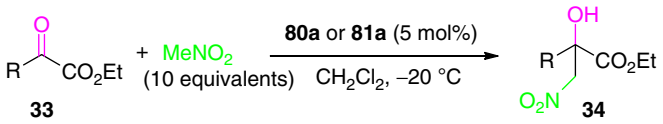
80a: R = Bz
80b: R = H
80c: R = Bn

81a: R = Bz
81b: R = H
81c: R = Bn

Figure 10 Cinchona alkaloid-derived catalyst developed by Deng.

Corey et al. applied *Cinchona* alkaloid-derived quaternary ammonium salt[62] as a phase-transfer catalyst for the synthesis of HIV protease inhibitor amprenavir **124** (Scheme 22).[63] Treatment of optically pure *N*,*N*-dibenzyl-(*S*)-phenylalaninal (**121**) and nitromethane by finely powdered potassium fluoride (12.5 equivalents) and quaternary ammonium fluoride **120** (10 mol%) gave nitroaldol **122** with a 17:1 diastereomer ratio. In contrast, Henry reaction of **121** in the presence of tetra-*n*-butylammonium

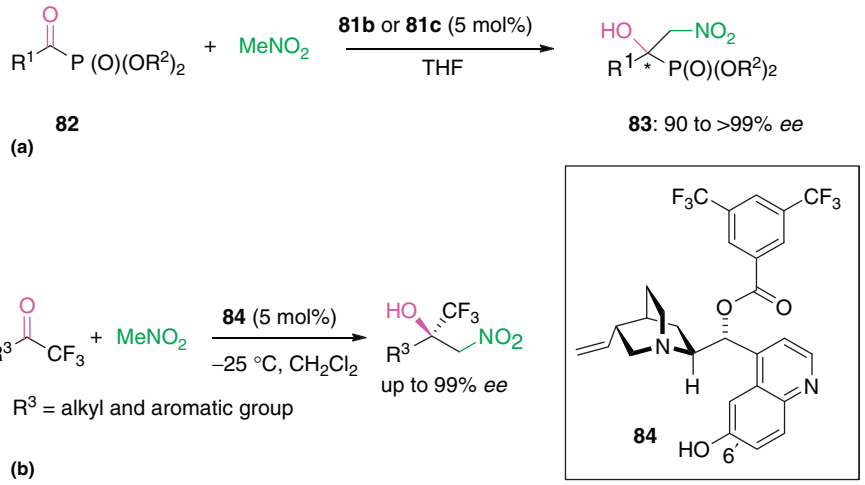
Table 2 *Cinchona* alkaloid catalysis developed by Deng



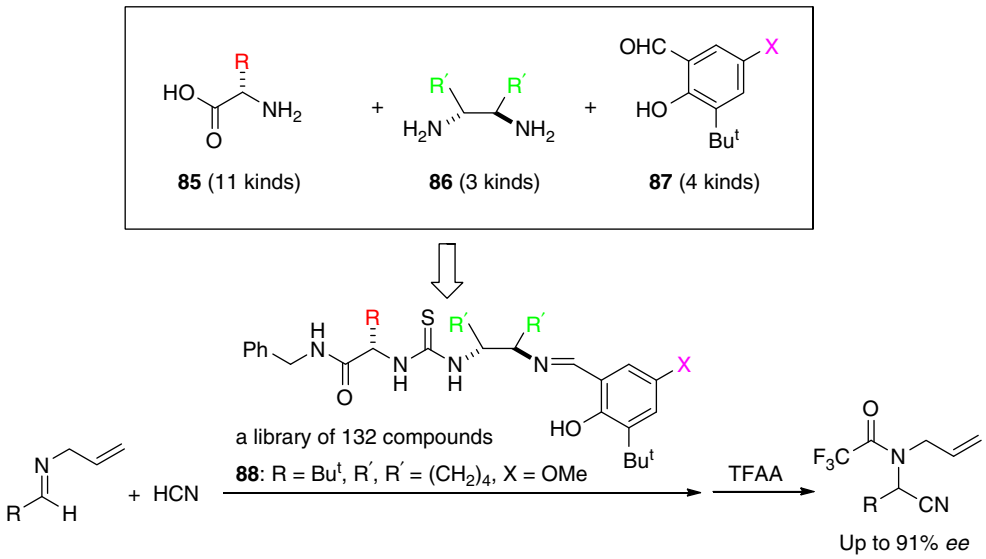
33 **34**

Entry	*R*	*Product* ***34***	*Time (h)*	*Yield (%)*	ee *(%)*
1	Me	**34a**	12 (12)	89 (90)	95 (95)
2	Ph	**35d**	35 (46)	96 (96)	95 (93)
3	Pr^n	**35e**	17 (15)	90 (90)	93 (93)
4	4-Cl-C_6H_4	**35f**	12 (12)	98 (96)	97 (96)
5	3-Cl-C_6H_4	**35g**	11 (11)	91 (96)	95 (95)
6	4-MeO-C_6H_4	**35h**	96 (96)	86 (84)	94 (97)
7	$PhCH_2CH_2$	**34i**	14 (11)	88 (89)	95 (94)

The results in parentheses were obtained with **81a** to give opposite enantiomer.

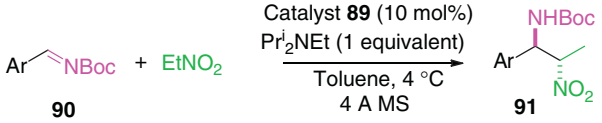


Scheme 14 Various enantioselective Henry reactions promoted by *Cinchona*-based organocatalysts.

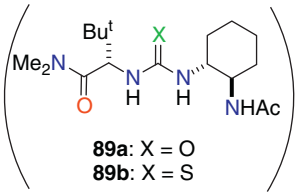


Scheme 15 Chiral thiourea-catalyzed Strecker reaction developed by Jacobsen.

Table 3 Thiourea-catalyzed aza-Henry reaction developed by Jacobsen

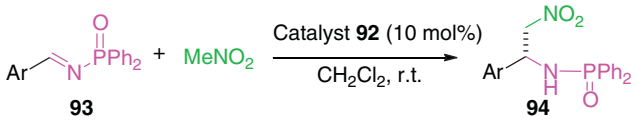


Entry	*Ar*	*Catalyst*	*Product **91***	*Yield (%)*	dr	ee *(%)*
1[a]	Ph	**89a**	**91a**	36	11:1	91
2[a]	Ph	**89b**	**91a**	>95	15:1	92
3	4-Cl-C_6H_4	**89b**	**91b**	98	7:1	95
4	*p*-Tolyl	**89b**	**91c**	90	12:1	96
5	2-Furyl	**89b**	**91d**	95	6:1	93
6	4-MeO-C_6H_4	**89b**	**91e**	95	16:1	96
7[b]	3-Pyridyl	**89b**	**91f**	79	7:1	97

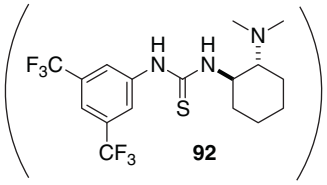


[a]At 0 °C.
[b]Reaction performed by using 5 equivalents of nitroethane and 2 equivalents of Pr^i_2NEt.

Table 4 Catalytic asymmetric aza-Henry reaction developed by Takemoto



Entry	*Ar*	*Product **94***	*Yield (%)*	ee *(%)*
1	Ph	**94a**	87	67
2	4-Cl-C_6H_4	**94b**	76	67
3	*p*-Tolyl	**94c**	72	63
4	2-Furyl	**94d**	85	76
5	2-Thienyl	**94e**	57	64



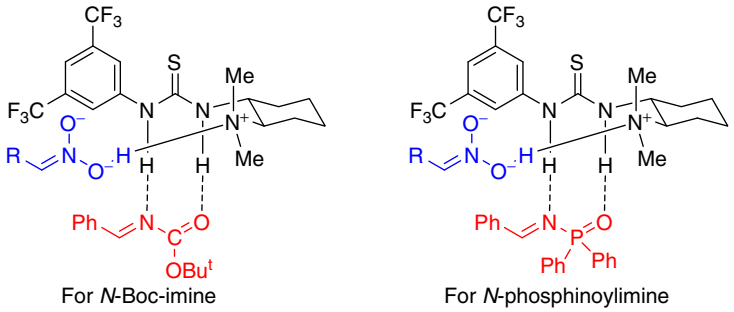
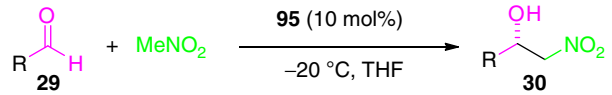


Figure 11 Plausible mode of activation of the substrates using thiourea–amine catalyst.

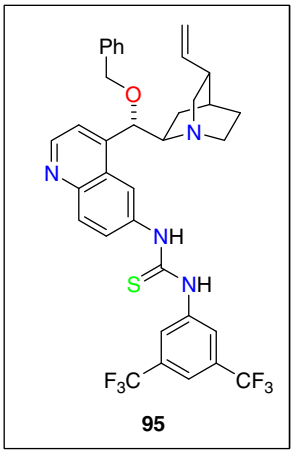
fluoride afforded a mixture of **122** and its C2 diastereomer with only 4:1 diastereoselectivity. The Henry reaction promoted by chiral quaternary ammonium salt was also applied to the stereoselective synthesis of the 2-*epi*-amprenavir. As shown in Scheme 23, starting from the *N*-Boc-protected chiral aldehyde **126**, the quaternary ammonium bromide **125** gave **127** in 9:1 diastereomer ratio. In these reactions, high *si*- and *re*-face selectivities are observed by careful tuning of the quaternary ammonium salts and protective group of chiral aldehydes. The *si*-face selectivity was accounted for by a contact ion pair of the formyl oxygen with the ammonium nitrogen.

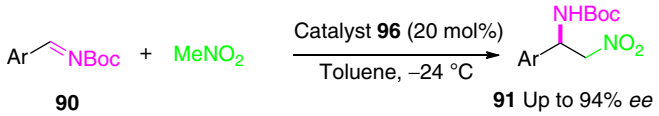
Paintner utilized the Evans' Cu(II)-(+)-indabox catalyst **48** for the total synthesis of sperabillin A and C. As shown in Scheme 24, high diastereoselectivity (95% *de*) is observed to control the newly created stereogenic center at C-5. Using a mismatched pair of chiral catalyst (−)-**48** and without using chiral catalyst resulted in lower diastereoselectivities (91% *de* and 0–50% *de*, respectively)[64] A Cu(II)–indabox catalyst was also utilized in the total synthesis of malyngamide U.[65]

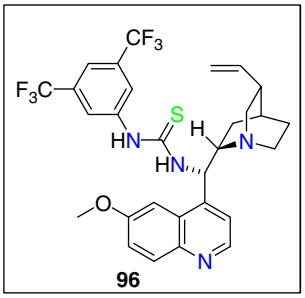
Table 5 Cinchonin–thiourea catalysis developed by Hiemstra



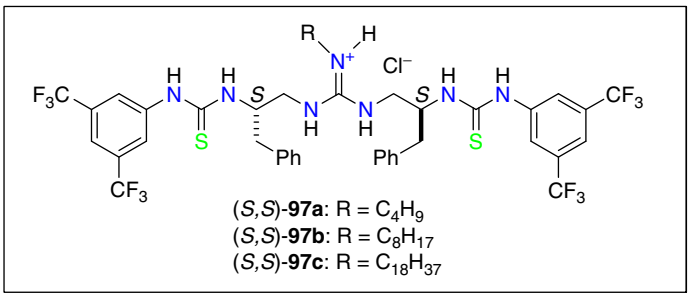
Entry	*R*	*Product* ***30***	*Yield (%)*	ee *(%)*
1	Ph	**30d**	90	92
2	2-Me-C_6H_4	**30h**	97	91
3	4-MeO-C_6H_4	**30i**	94	89
4	4-NO_2-C_6H_4	**30j**	91	86
5	3-Pyridyl	**30k**	91	86

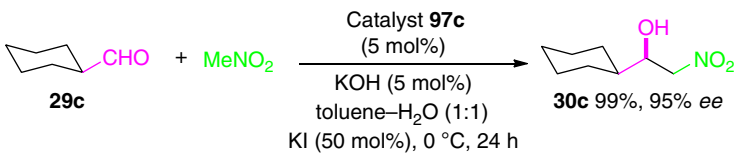






Scheme 16 Cinchonin–thiourea catalysis developed by Ricci.





Scheme 17 Guanidinium–thiourea-catalyzed Henry reaction reported by Nagasawa.

2.13.3.3 *Syn*-Selective Henry and aza-Henry Reaction

Starting from nitroalkanes such as nitroethane or nitroethanol, enantioselective, and diastereoselective Henry reactions can be performed. The LnLB complexes show high *syn*-selectivity in Henry reaction. The *syn*-selectivities are enhanced by the introduction of trialkylsilylethynyl substituents at the 6,6′-position of BINOL.[66] The structures of the improved LLB-type catalyst LLB* is

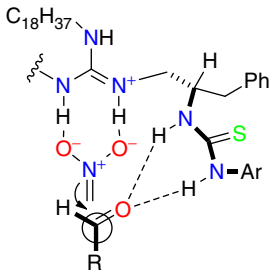
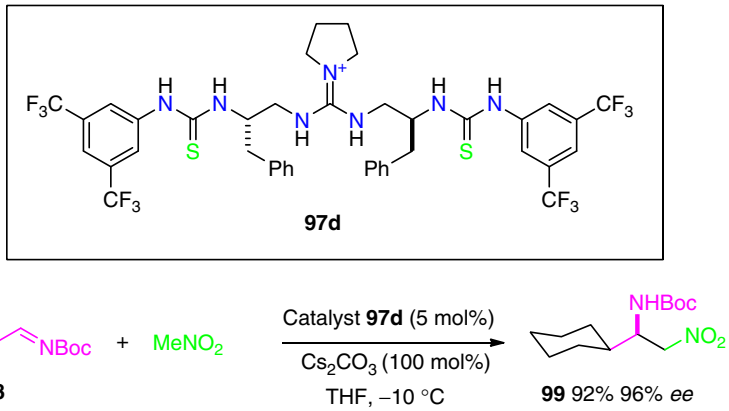


Figure 12 Synergistic mode of activation by the guanidine–thiourea bifunctional catalyst.



Scheme 18 Guanidinium–thiourea-catalyzed aza-Henry reaction.

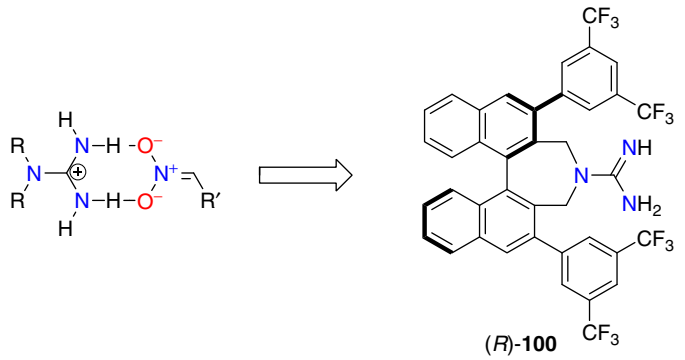


Figure 13 Mode of activation of nitroalkanes by guanidine derivative and the axially chiral guanidine developed by Terada.

depicted in Figure 15. A synthetic application for the synthesis of *threo*-dihydrosphingosine by LLB* is shown in Scheme 25. The *syn*-selectivity is increased from 86:14 using LLB to 91:9 using LLB*.

The *syn*-selectivity using an LLB-type catalyst is accounted for by a transition state model, as shown in Figure 16. Due to the strong oxophilicity of rare earth metals, the bicyclic transition state with less steric repulsion to give a *syn*-adduct seems to be favorable.

Barua and coworkers also applied the LLB-catalyzed *syn*-selective Henry reaction for the synthesis of several biologically important molecules.[67] The representative results for the synthesis of C-13 side-chain of taxol and (−)-bestatin are shown in Scheme 26.

The catalytic activity of LnLB was greatly increased by an addition of catalytic amount of basic reagent such as butyllithium.[68] The activated catalyst is designated LLB-II (second-generation LLB). The comparison of the catalytic activities of LLB with LLB-II is shown in Table 6. It is noteworthy that only 1 mol% of LLB-II promotes the Henry reaction in good yield and enantioselectivity

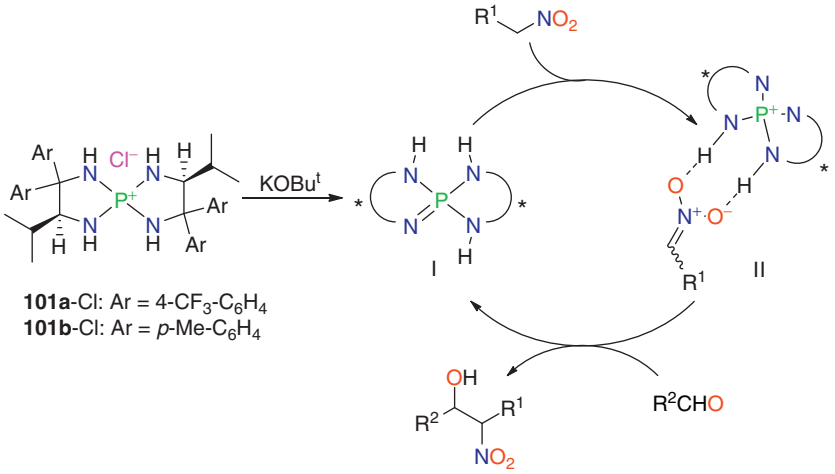
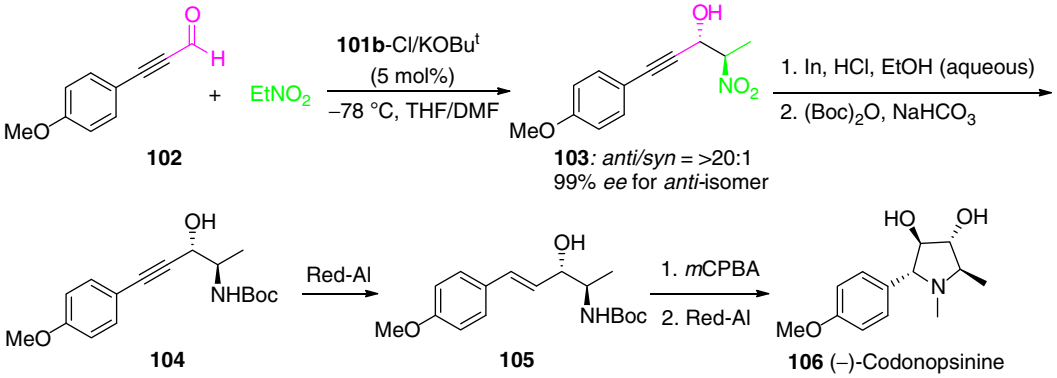
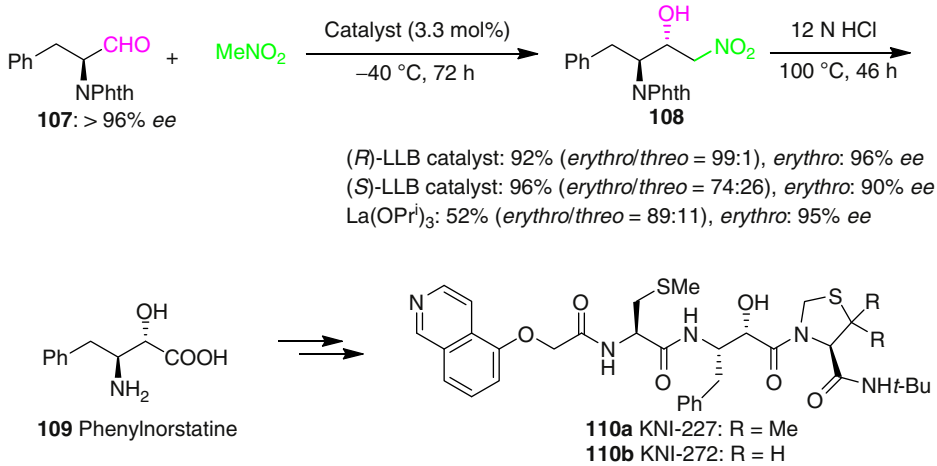


Figure 14 Tetraaminophosphonium salt-mediated Henry reaction.

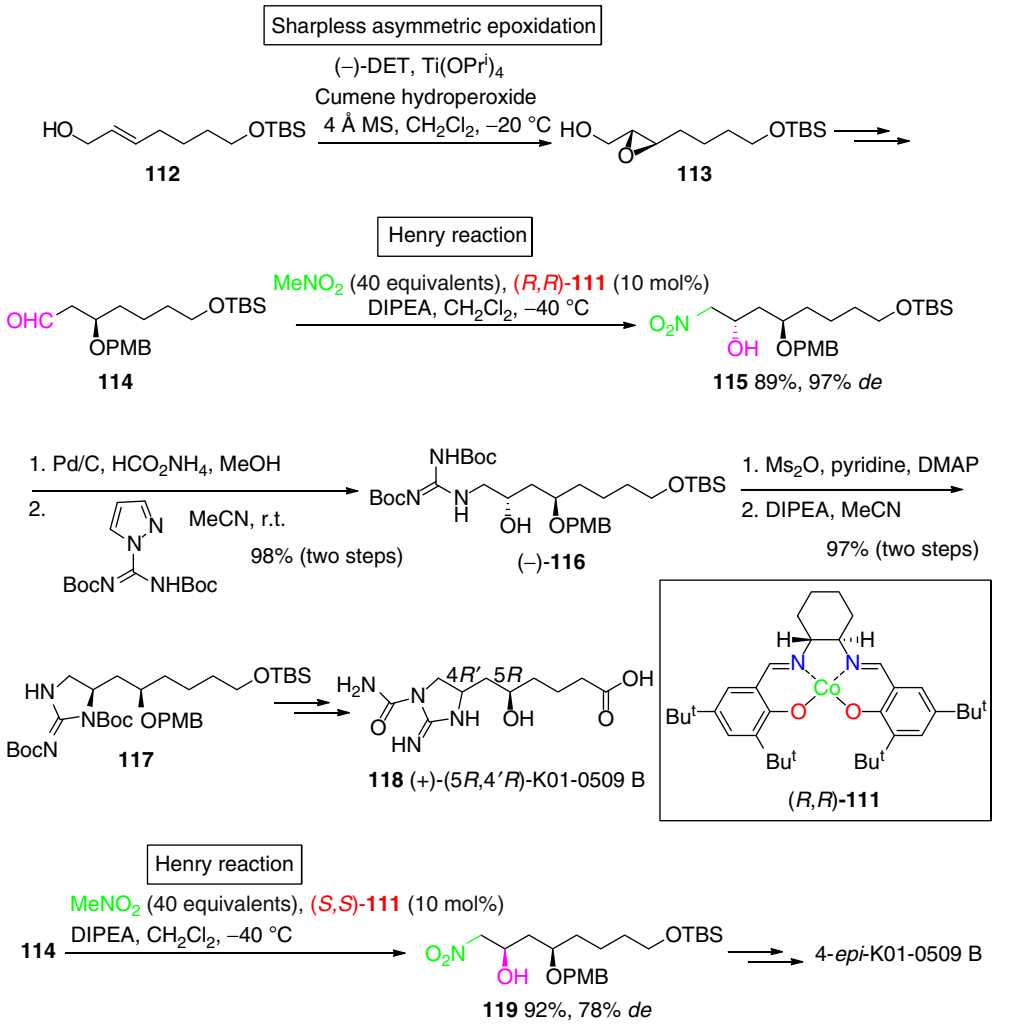


Scheme 19 Synthesis of codonopsinine using Ooi's catalyst.

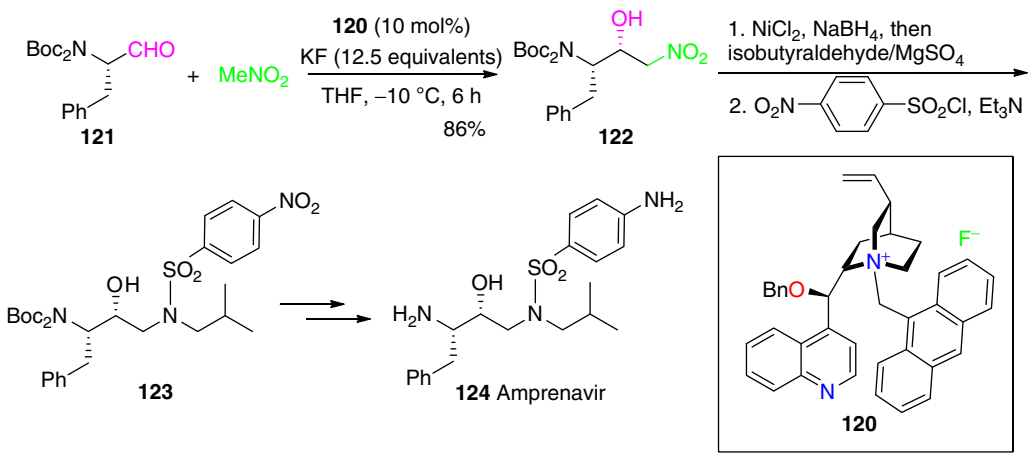


Scheme 20 Diastereoselective synthesis of phenylnorstatine(*erythro*-AHPA).

(entry 3) at −50 °C. The enhancement of catalytic activity in LLB-II catalysis is rationalized by an exchange of a proton with a lithium ion to form the self-assembled intermediate II (Scheme 27, path c). In the case of the first generation LLB catalysis, the nitronate intermediate I, bearing a proton (shown in green color), would be formed (path a). The intermediate I is prone to regenerate parent LLB and nitroalkane by an intramolecular protonation.

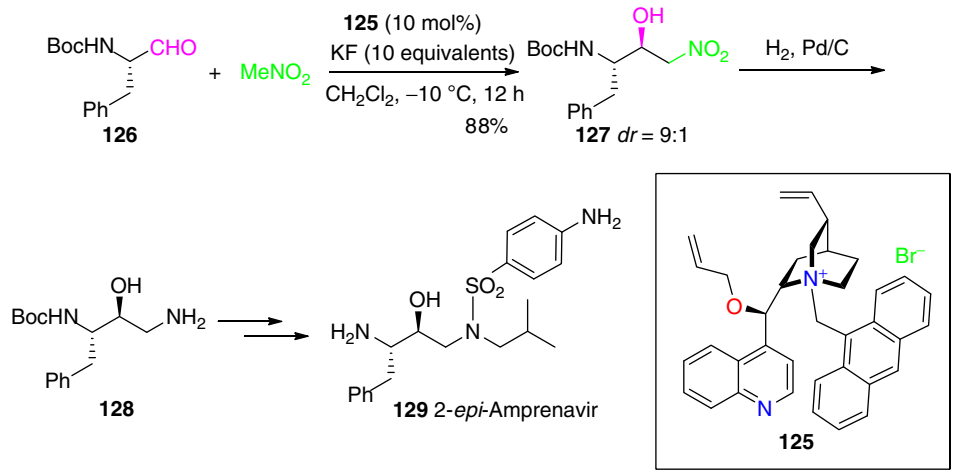


Scheme 21 Total synthesis of K01-0509 B reported by Omura using salen–cobalt catalyst.

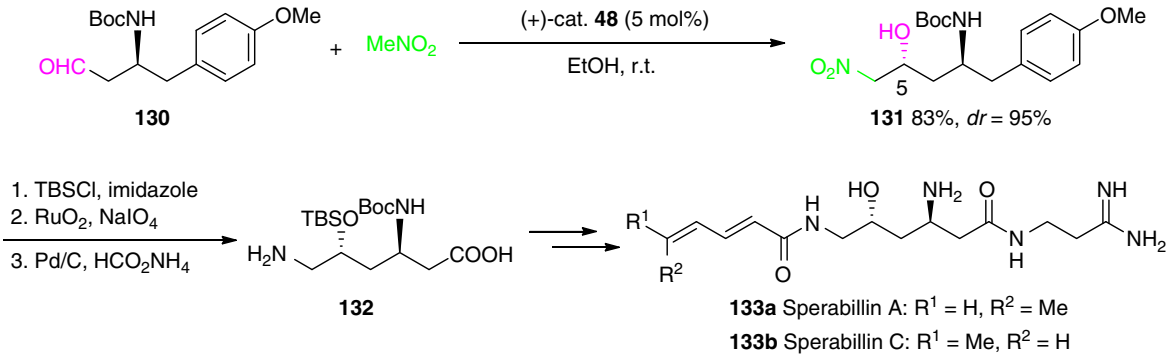


Scheme 22 Diastereoselective Henry reaction promoted by chiral quaternary ammonium fluoride.

High *syn*-selectivity was also achieved in Cu catalysis. Arai reported a *syn*-selective enantioselective Henry reaction utilizing CuCl and various kinds of ligands.[69] Gong reported Cu(II) catalysis for *syn*-selective Henry reaction.[34] The organocatalyst **97c** reported by Nagasawa is efficient in promoting *syn*-selective Henry reactions. The structure of the chiral ligands or organocatalysts



Scheme 23 Synthesis of 2-*epi*-amprenavir.



Scheme 24 Application of Evans' catalyst in the total synthesis of sperabillin A and C.

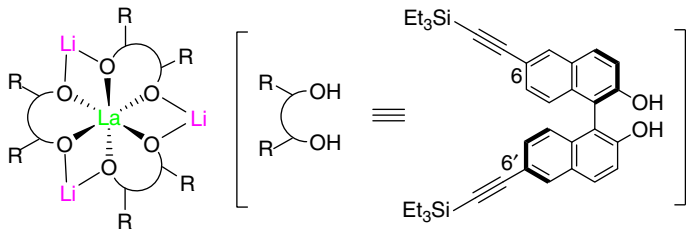
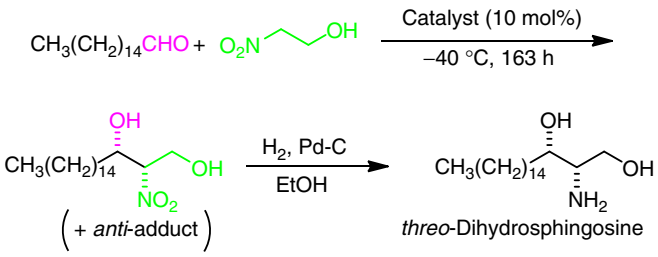


Figure 15 Structure of LLB*.



LLB* catalyst: 78% (*syn*/*anti* = 91:9), *syn*: 97% *ee*
LLB catalyst: 31% (*syn*/*anti* = 86:14), *syn*: 83% *ee*

Scheme 25 Catalytic asymmetric synthesis of *threo*-dihydrosphingosine.

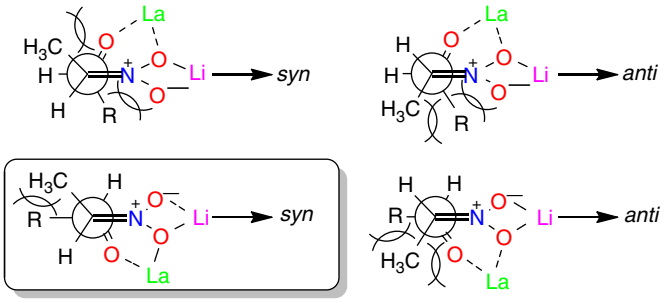
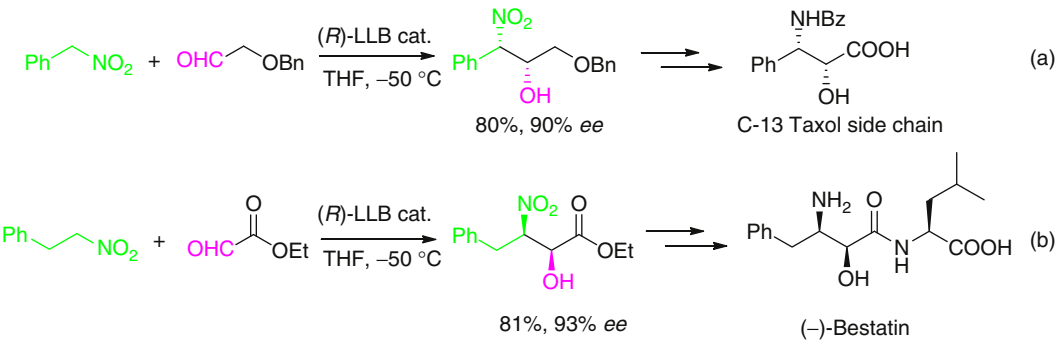
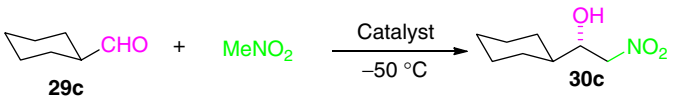


Figure 16 Proposed transition states of diastereoselective and enentioselective nitroaldol reactions promoted by LLB-type catalyst.



Scheme 26 *Syn*-selective Henry reaction promoted by LLB catalyst.

Table 6 Catalytic activity of LLB and LLB-II

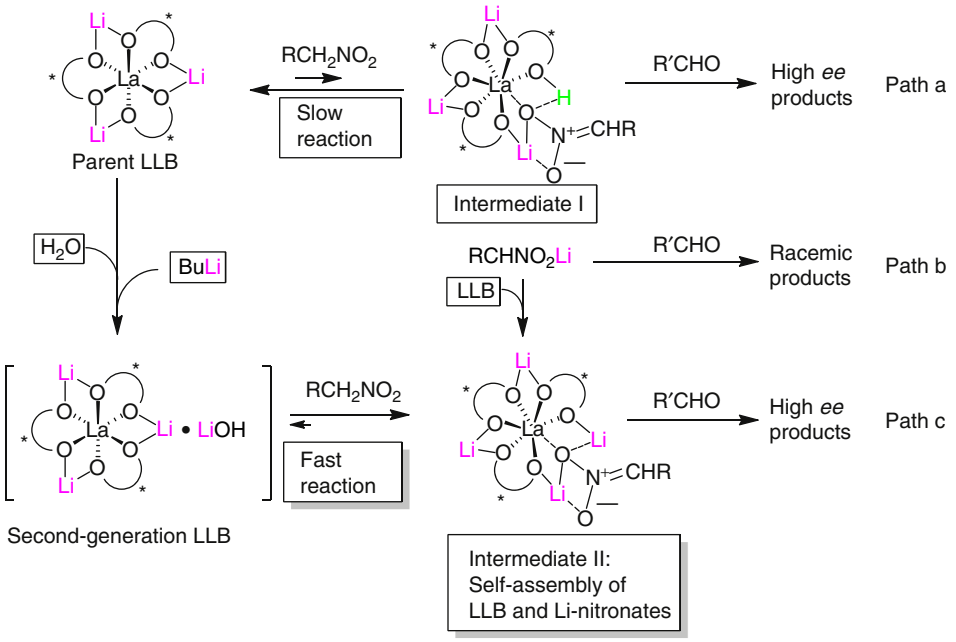


Entry	*Catalyst (mol%)*	*Time (h)*	*Yield (%)*	ee *(%)*
1	LLB	24	5.6	88
2	LLB-II (3.3)	4	70	90
3	LLB-II (1)	24	73	89

and representative results are shown in Figure 17. For *syn*-selective aza-Henry reactions, Shibasaki et al. reported a highly efficient transition metal/rare earth metal heterobimetallic catalyst.[70,71] The most effective Cu/Sm/Schiff base catalyst **135** (Figure 18), which showed good substrate scope, was prepared from $Sm_5O(OPr^i)_{13}$ as a samarium source. The catalyst **135** has to be prepared *in situ*, and the structure was proposed based on electrospray ionization-mass spectra of the catalyst solution and some experimental observations. The utility of catalyst **135** was demonstrated in the catalytic enantioselective synthesis of nemonapride (Scheme 28), which is used clinically as an antipsychotic agent.[71]

2.13.3.4 *anti*-Selective Henry and aza-Henry Reaction

An *anti*-selective asymmetric catalysis for Henry reaction was reported by Jørgensen and coworkers for the first time in 2003 (Scheme 10). [27] They found that Cu(II)–bisoxazoline complex promotes the reaction of silylnitronates **35** with aromatic or *α,β*-unsaturated aldehydes **29** to give nitroaldol derivatives with up to 10/1 *anti*-selectivity. Maruoka and coworkers also reported *anti*-selective Henry reaction in 2003. High *anti*-selectivity (*anti*/*syn* = 94:6) was observed using chiral quaternary ammonium bifluoride catalyst **142** (Scheme 29).[72]



Scheme 27 Proposed mechanism of catalytic asymmetric nitroaldol reaction promoted by LLB, LLB-II, or LLB–Li nitronate.

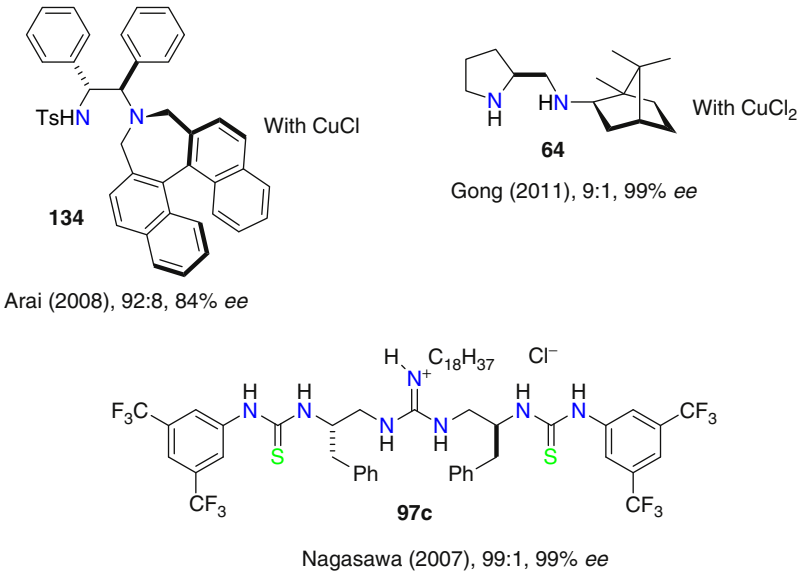
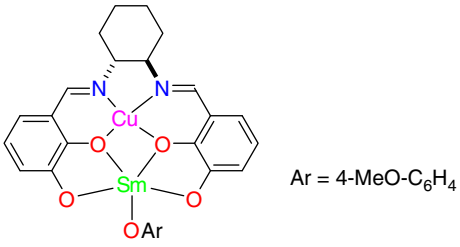


Figure 17 Representative chiral catalysts for *syn*-selective Henry reaction.

Direct-type *anti*-selective Henry reactions utilizing unprotected nitroalkane are favorable to realize an environmentally benign process. The organocatalyst, tetraaminophosphonium-derived catalyst (**101a**-Cl+KOBu^t),[58] and axially chiral guanidine catalyst **100**[73] showed high *anti*-selectivity (Figure 19).

Shibasaki et al. also developed *anti*-selective Henry reactions promoted by novel heterobimetallic catalysts. As shown in Figure 20, they postulated that each distinct metal activates a nitroalkane and an aldehyde independently (path b). Based on this consideration, they developed Pd/La/Schiff base complex **143**[74] and Nd/Na/amido complex **145**,[75,76] which gave nitroaldols in high *anti*-selectivities (Figure 21).

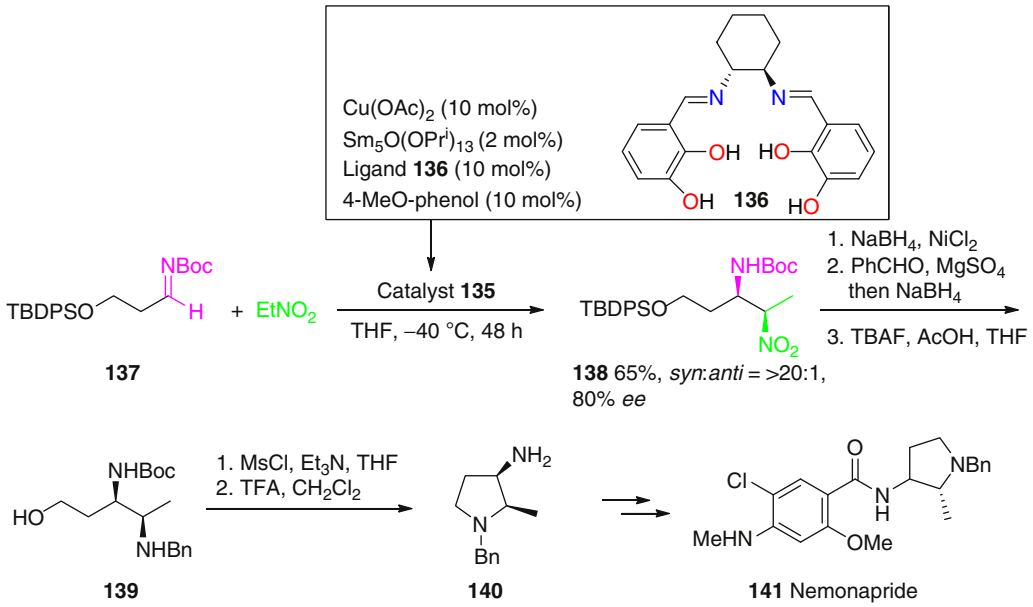
For *anti*-selective aza-Henry reactions, various metal catalysts and organocatalysts have been reported. As shown in Table 3, thiourea catalyst **89** developed by Jacobsen showed high *anti*-selectivity. Representative results on *anti*-selective aza-Henry reactions, including Jacobsen's catalysis, are shown in Figure 22.



135

Shibasaki and Matsunaga
(2007, 2010), >20:1, 97% *ee*

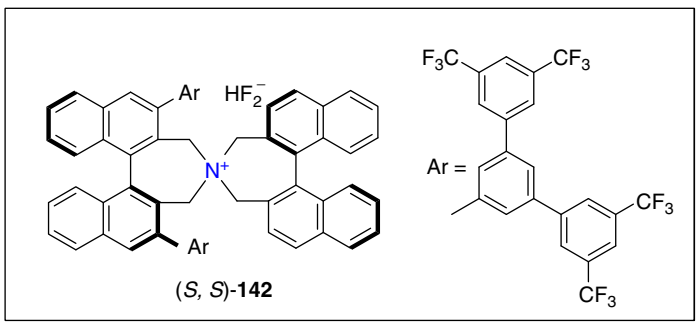
Figure 18 *syn*-Selective catalyst for aza-Henry reaction developed by Shibasaki et al.

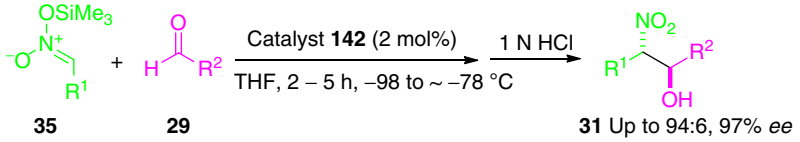


137 **138** 65%, *syn*:*anti* = >20:1, 80% *ee*

139 **140** **141** Nemonapride

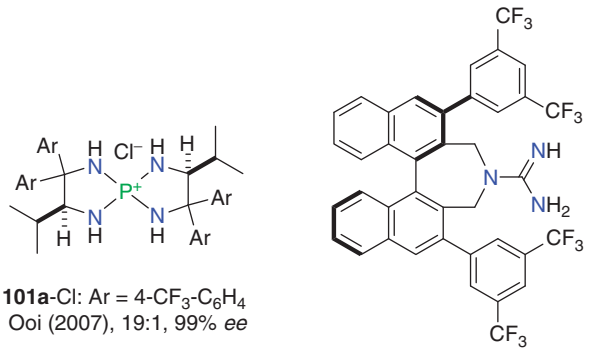
Scheme 28 Synthesis of nemonapride using *syn*-selective aza-Henry reaction.





35 **29** **31** Up to 94:6, 97% *ee*

Scheme 29 *anti*-Selective Henry reaction reported by Maruoka.



101a-Cl: Ar = 4-CF_3-C_6H_4
Ooi (2007), 19:1, 99% *ee*

(*R*)-**100**
Terada (2009), 94:6, 69% *ee*

Figure 19 Effective organocatalysts for *anti*- and enantioselective Henry reaction.

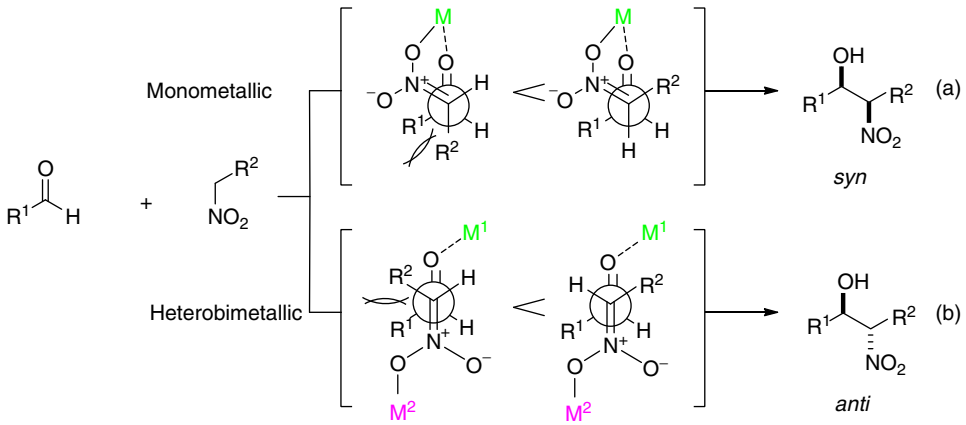
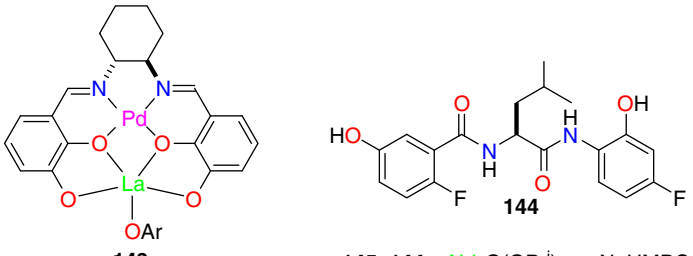


Figure 20 Diastereocontrol in Henry reaction.



143

145: **144** + $Nd_5O(OPr^i)_{13}$ + NaHMDS

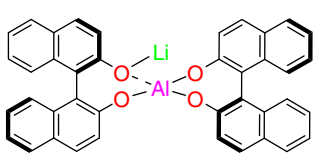
Shibasaki and Matsunaga
(2008), 19:1, 87% *ee*

Shibasaki and Kumagai
(2009), >40:1, 97% *ee*

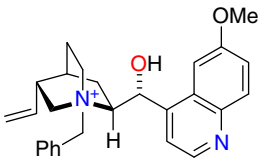
Figure 21 *anti*-Selective heterobimetallic catalysts for Henry reaction.

2.13.4 Synthetic Application in Domino Reactions

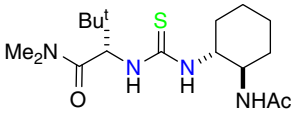
Since Henry reactions can be carried out without the formation of silyl nitronate and the resulting nitroaldols are readily converted into various nucleophilic and electrophilic substrates (Scheme 3), the Henry reaction is often incorporated in domino reactions. In the view of green chemistry, domino reactions can save natural resources to be consumed for the isolation and purification of the intermediate, as well as time and labor. The first enantioselective domino reaction was reported by Sasai et al. utilizing two sequential Henry reaction catalyzed by LnLB.[77] Usually, Henry reaction requires an activating functional group for ketones.



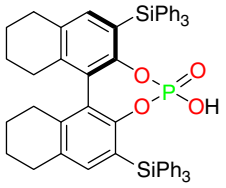
146 ALB + KOBu^t (ALB-II)
Shibasaki (2001), 7:1, 82% *ee*



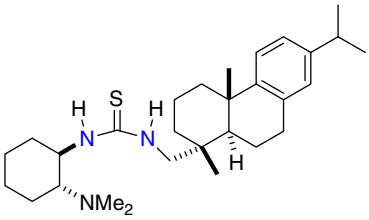
147
Palomo (2005), 93:7, 94% *ee*



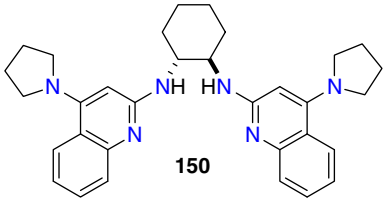
89b Jacobsen (2005), 15:1, 92% *ee*



148 For α-imino ester
Rueping (2008), 13:1, 91% *ee*



149
Wang (2009), 98:2, 85–95% *ee*

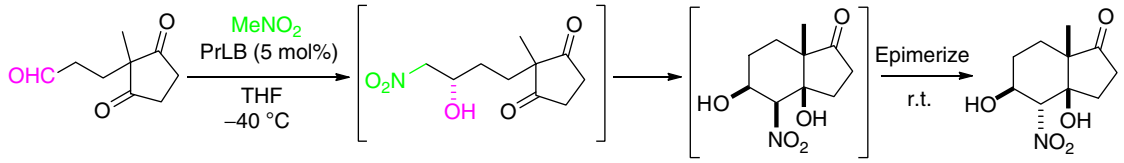


150

150 + TfOH (2:3)
Johnston (2010), 35:1, 91% *ee*

Figure 22 Representative catalyses for *anti*-selectve aza-Henry reaction.

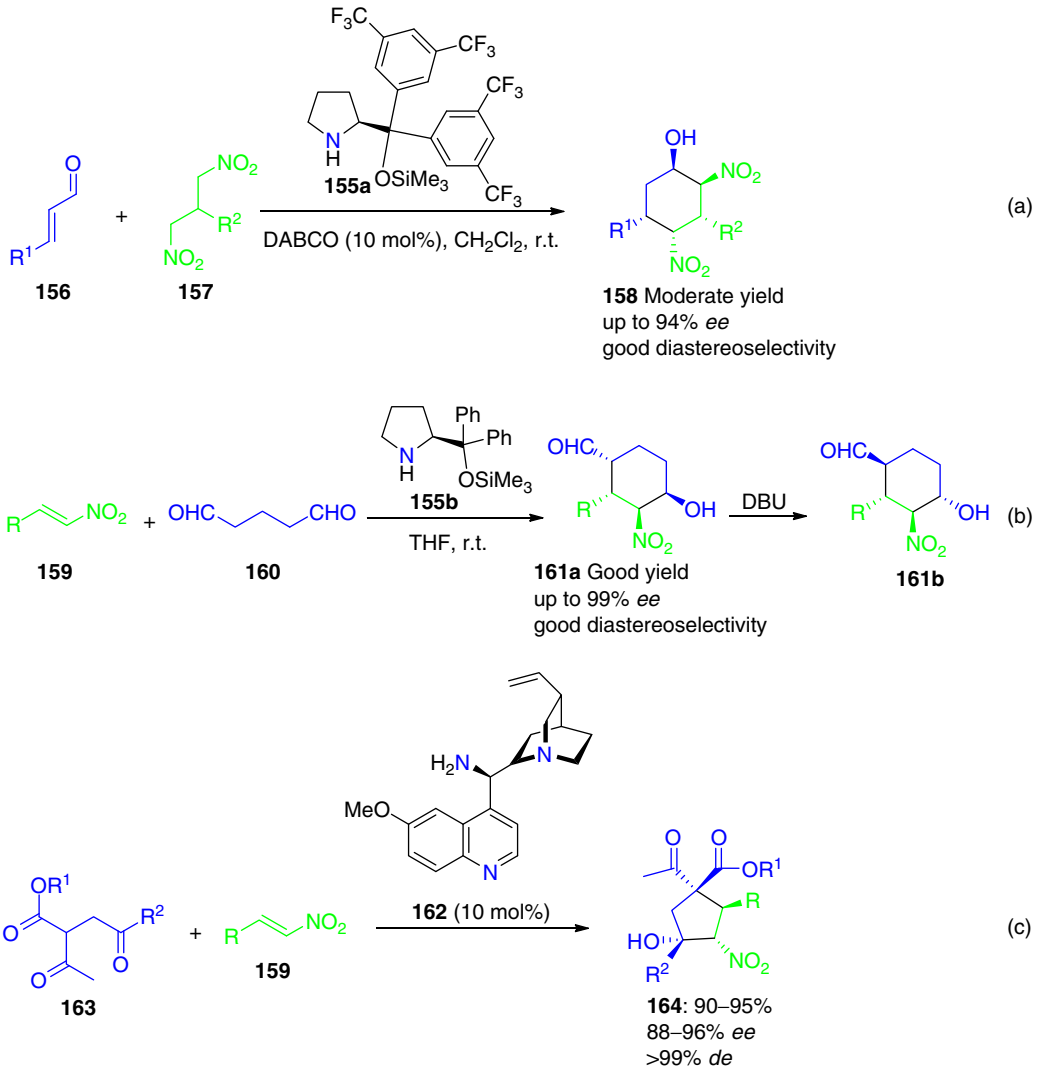
Therefore, α-ketoesters **33** (cf. Scheme 9 and Table 2) and fluoromethyl ketones (cf. Scheme 14) are often used as the substrate. However, intramolecular Henry reaction takes place smoothly when thermodynamically stable products are generated. As shown in Scheme 30, after the enantioselective Henry reaction, the nitroalkane unit in **152** reacted with the ketone carbonyl group intramolecularly and formed the stable six-membered cyclic intermediate **153**. The nitro group on the cyclic intermediate was epimerized to the more stable product **154** at room temperature.



151 **152** **153** 58% *ee* **154**

Scheme 30 Domino-type reaction promoted by PrLB catalyst.

Jørgensen and Hayashi independently developed diarylprolinol silyl ether catalyst **155**, and reported its application in a catalytic enantioselective domino Michael–Henry reaction as shown in Scheme 31 (equations a and b, respectively).[78] Although the Jørgensen's product **158** has five contiguous stereocenters, only a couple of products are observed for alkyl substituent R^1 and aryl substituent R^2. In general, a good diastereomer ratio (approximately 4:2:1) was observed in the presence of 10 mol% of 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base additive. In the case of the Michael–Henry reaction developed by Hayashi, no base additive was required and high enantioselectivities were achieved for various nitroalkenes. The major isomer **161a** (13:1 for R=Ph, 99% *ee*) was isomerized by the treatment of 10 mol% of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford more stable **161b**, which has all equatorial substituents without loss of high optical purity of **161a** (95% *ee*). A plausible mechanism for Hayashi's domino reaction is shown in Scheme 32. After the enamine intermediate **I** was formed from the catalyst **155b** and the substrate **160**, a Michael reaction proceeds with the nitroalkene to give the zwitterion **II**. Then an intramolecular Henry reaction takes place to give **III**, which would be hydrolyzed to provide substituted nitrocyclohexanecarbaldehyde **161**. Zhong et al. also reported a highly efficient domino Michael–Henry reaction of diketoester **163** with nitroalkene **159** using a *cinchona* alkaloid-derived diamine catalyst **162** (Scheme 31(c)).[79]



Scheme 31 Representative results on catalytic enentioselective domino Michael–Henry reactions.

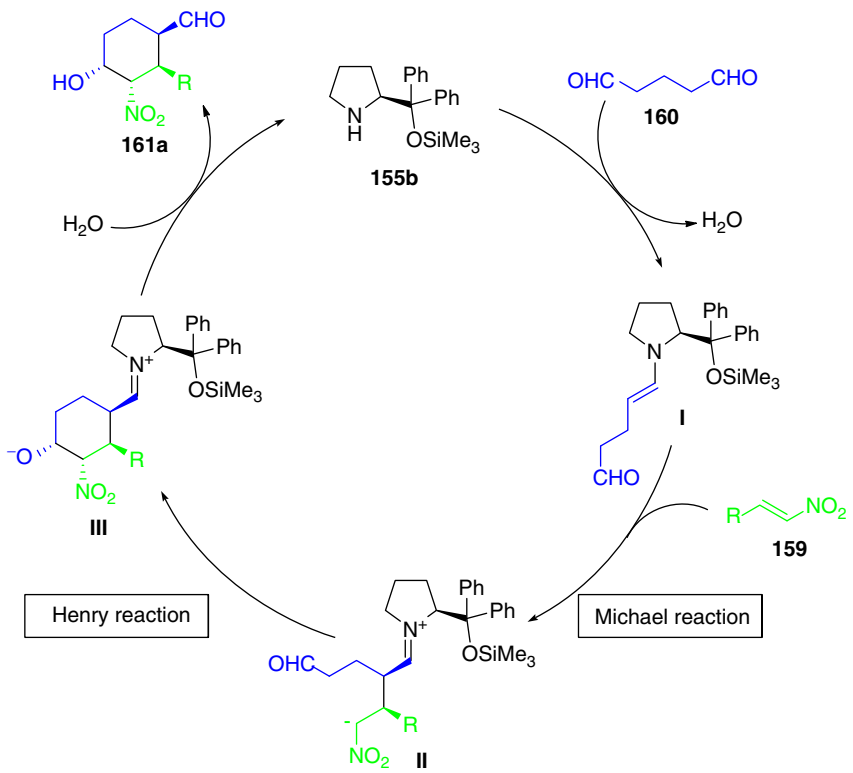
Rueping and coworkers investigated domino Michael–Henry reaction using an organocatalyst. As shown in Table 7, among the chiral organocatalysts they examined, bifunctional organocatalysts gave the bicyclic domino products **167** in good optical purity. In particular, cinchonine-based thiourea catalyst **172** and cinchonidine-based thiourea catalyst **173** afforded **167** in high enantioselectivity.[80] When the α-position of the nitro group is substituted (R^1 = Me), very high diastereoselectivities (up to 1:33) are achieved due to the slow epimerization.

Hayashi extended the domino reaction to an excellent four-component, one-pot coupling process which involves Michael/aza-Henry/acetalization/allylation or cyanation reactions (Scheme 33).[81] Although three sequential reactions are carried out in one pot, the catalyst **155b** which promoted the first Michael reaction did not interfere with the following reactions. In many cases, almost a single diastereomer was obtained. Representative results are also shown in Scheme 33.

2.13.5 Outlook

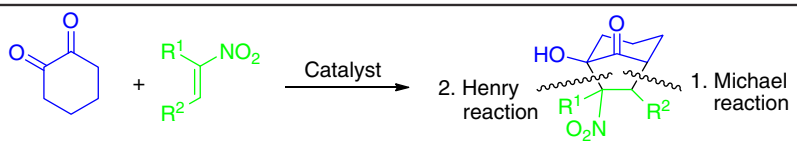
Recent progress in catalytic enantio- and diastereoselective Henry and aza-Henry reactions has enabled an efficient synthesis of biologically and pharmaceutically important compounds. In the next decade, development of robust organocatalysts that can promote the requisite reaction with less than 0.1 mol% will be required. Recycling and reuse of an expensive catalyst are also issues to be considered. Several heterogeneous catalysts have been developed so far. Quite recently, Shibasaki has succeeded in recycling and reusing their heterogeneous neodymium catalyst **145**[75] by mixing with a multiwalled carbon nanotube.[82]

For related chapters in this Comprehensive, you can refer to – Chapters 4.22, 8.13, and 6.03.



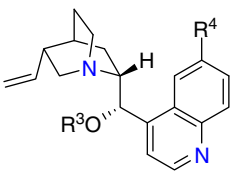
Scheme 32 Plausible reaction mechanism for domino Michael–Henry reaction promoted by the prolinol catalyst.

Table 7 Catalytic asymmetric domino Michael–Henry reaction reported by Rueping

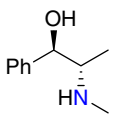


165 **166**: R^1 = H, R^2 = Ph **167**

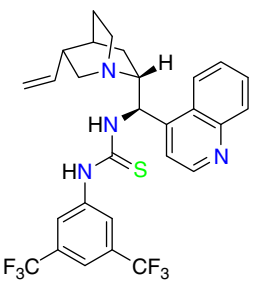
Entry	*Catalyst*	*Time (h)*	*Yield (%)*	dr	ee *(%)*
1	**168**	3	85	3:1	45, 24
2	**169**	1.5	86	9:1	rac, rac
3	**170**	24	80	8.3:1	rac, rac
4	**171**	6	82	5:1	–36, –30
5	**172**	<1	92	2:1	–83, –80
6	**173**	<1	91	3:1	87, 92



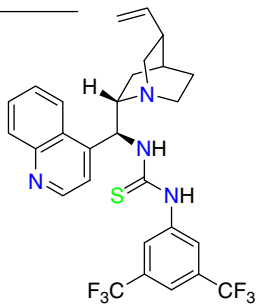
168 $R^3 = R^4 = H$
169 $R^3 = H$, $R^4 = OH$
170 $R^3 = Me_3Si$, $R^4 = H$



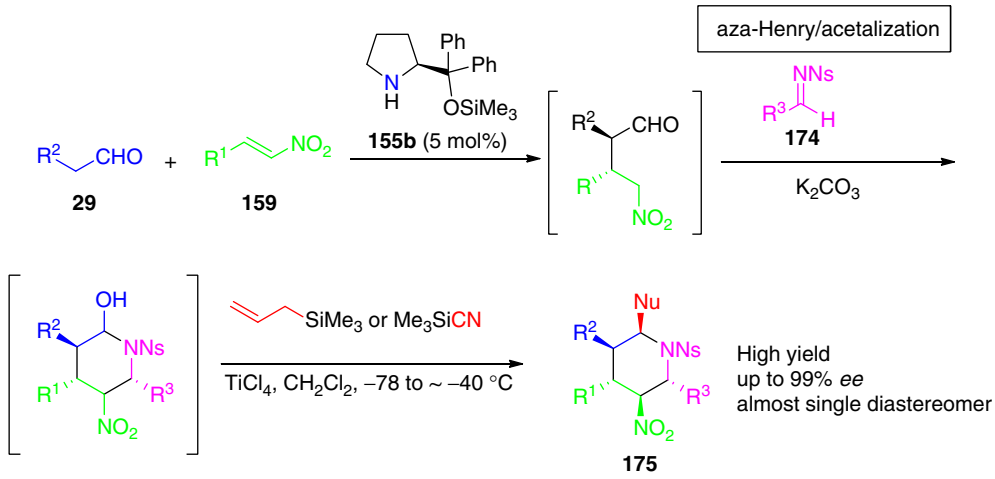
171 Ephedrine



172 *epi*-TUCN



173 *epi*-TUCD



175a R^1 = Ph, R^2 = Me, R^3 = Ph, Nu = allyl, 79%, 99% *ee*
175b R^1 = *p*-MeO-C_6H_4, R^2 = Me, R^3 = Ph, Nu = allyl, 72%, 98% *ee*
175c R^1 = Ph, R^2 = Et, R^3 = Ph, Nu = allyl, 88%, 96% *ee*
175d R^1 = Ph, R^2 = Me, R^3 = Ph, Nu = CN, 80%, 99% *ee*

Scheme 33 One-pot synthesis of chiral piperidine derivative based on Michael/aza-Henry/acetalization/allylation or cyanation.

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2.14 Other Condensation Reactions (Knoevenagel, Perkin, Darzens)

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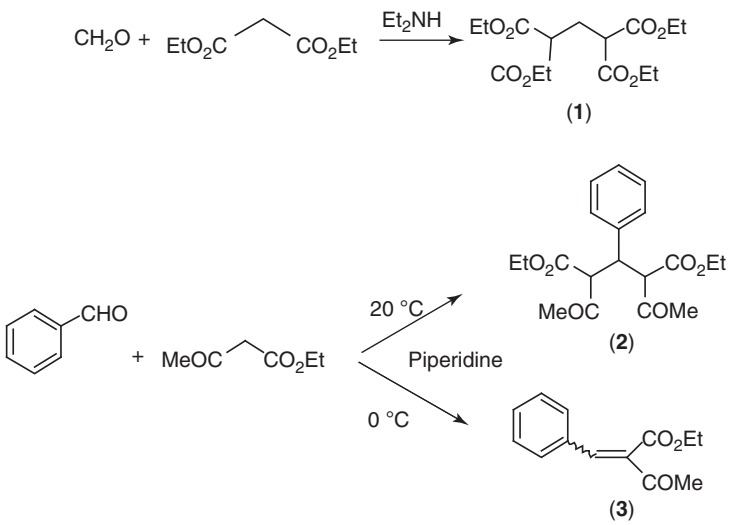
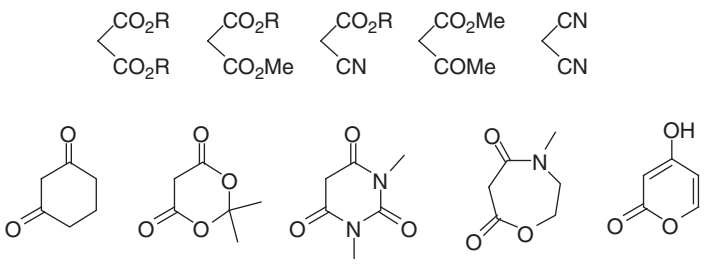
2.14.1 Introduction

Emil Knoevenagel discovered a new type of carbon–carbon bond-forming reaction, which was published in Chemische Berichte in 1894, in the reaction of formaldehyde with diethyl malonate in the presence of diethylamine as a catalyst to form the bis adduct (**1**).[1] Two years later, he found that the reaction of benzaldehyde with ethyl acetoacetate in the presence of piperidine at room temperature afforded the bis adduct (**2**), whereas the reaction at 0 °C gave benzylidene-1,3-dicarbonyl compound (**3**) (Scheme 1).[2]



Scheme 1

The Knoevenagel condensation covers reactions of carbonyl compounds (aldehydes and ketones) with active methylene compounds in the presence of a weak base, for example, amine, to give alkylidene- or benzylidene-dicarbonyls or analogous compounds (Knoevenagel products).[3–6] Methylene groups activated by two electron-withdrawing moieties are usually employed as active methylene compounds; the reaction of an aldehyde or a ketone with nitroalkanes in the presence of a weak base is also considered a variant of the Knoevenagel condensation (*see* Chapter 2.13). Most frequently used methylene compounds are acyclic 1,3-dicarbonyls and analogous substances such as malonates, acetoacetates, acetonitriles, acetylacetone, and malonodinitrile. Cyclic compounds such as 1,3-cyclohexanediones, Meldrum's acid, barbituric acids, oxazepanediones, and 4-hydroxycoumarins are also employed (Scheme 2). With the latter compounds, it is often difficult to isolate the Knoevenagel product because a fast Michael addition with a second molecule of the methylene component takes place to give a *bis* adduct. Isomerization of the initial α,β-unsaturated dicarbonyl to α,β,γ-unsaturated system should also be noted. In the case of unsymmetrical 1,3-dicarbonyls, two diastereomeric products can be formed.



Scheme 2

Variation of active methylene and carbonyl compounds has already been mentioned in the previous text.[3] For example, malonic esters; Meldrum's acid derivatives; malonic acids; mono- and di-amides of 1,3-diacids; 1,3-diketones; malondialdehyde; malononitrile; β-keto esters and β-keto acids; cyanoacetic esters, cyanoacetic acid, and isocyanoacetic esters; cyanoacetamides, thiocyanoacetamides, and β-keto nitriles; derivatives of arylacetic acid; methylenes activated by sulfur-containing functional groups; pyrazolones and isoxazolones; and methylenes activated by heterocycles can be used for the Knoevenagel condensation as activated methylene compounds.[3] Aldehydes, ketones, thioketones, imines, enamines, and acetals have been frequently used as electrophiles in the Knoevenagel condensation.

General aspects such as reaction conditions, spectroscopy, and physical properties of Knoevenagel products to determine the configuration and conformation, reaction mechanism involving addition of a carbanion to a carbonyl or heterocarbonyl group, the retro-Knoevenagel reaction, stereochemistry, competitive reaction (vs. the Michael addition), and analytic applications were comprehensively described in the previous text.[3] The previous edition covers the scope and limitation, sequential reactions, and synthetic application for carbocycles and heterocycles, natural products and biologically active compounds, transformation of sugars, and dyes and polymers until 1990. The present edition is intended to cover recent progresses in the Knoevenagel condensation during 1990–2011, particularly on new catalytic systems (reagents), one-pot sequential (domino) reactions, and synthetic applications. The history of organoaminocatalysis toward the Knoevenagel condensation has recently been reviewed.[7]

This chapter also covers recent progress of the Perkin[8] and Darzens[9] condensations.

2.14.2 Knoevenagel Condensation

2.14.2.1 Reaction Systems

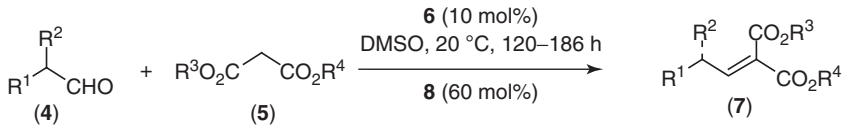
An asymmetric Knoevenagel condensation of α-branched aldehydes such as hydratropaldehyde (**4a**) with diethyl malonate (**5a**) has been conducted by cinchona-derived primary amine catalyst (**6**) to afford the compound **7a**.[10] Addition of benzene-1,3,5-tricarboxylic acid (**8**) improved the enantioselectivity of the product. Racemic α-branched aldehydes can be converted in a dynamic kinetic resolution into the corresponding enantiomerically enriched products with enantiometric ratios of up to >95:5 (Table 1; Scheme 3).

The Knoevenagel condensation of aromatic aldehydes **12** with malonic acid (**13**) proceeded in the presence of tetra butyl ammonium bromide (TBAB) and K_2CO_3 under microwave irradiation in water, affording cinnamic acids **14**.[11] This method was extended for other aromatic aldehydes as well as acetophenones substituted with electron-donating and -withdrawing groups (Scheme 4).

Inorganic zinc salts such as $Zn(OAc)_2 \cdot 2H_2O$, $ZnCl_2$, and $ZnBr_2$ were found to act as a catalyst for the Knoevenagel condensation of aromatic aldehydes with active methylene compounds (malononitrile or ethyl cyanoacetate, **10**) under solvent-free conditions.[12] *p*-Methoxy-phenyltellurium trichloride has been shown to be an efficient catalysis in the solvent-free Knoevenagel condensation of nonenolizable aldehydes with active methylene compound to yield the corresponding olefinic products in high yields and high purities.[13] *p*-Methoxy-phenyltellurium trichloride has been prepared by condensation of tellurium tetrachloride with anisole.

Ionic liquids have been used as a catalyst for organic syntheses including the Knoevenagel condensation.[14] 1-Hexyl-3-methylimidazolium hexafluorophosphate ([hmin][PF_6]) promoted the Knoevenagel condensation of aldehydes with malononitrile in the presence of glycine as a promotor.[15] This reaction system can be recycled multiple times affording the desired product in excess of 90% conversion. Amino-functionalized ionic liquid acted as an efficient and recyclable catalyst for the Knoevenagel condensation of aromatic aldehydes with malononitrile and ethyl cyanoacetate (**10**) in water.[16] It was found that the ionic liquid 1,3-dimethylimidazolium methyl sulfate, [MMIm][MSO_4], together with small amount of water acts efficiently as both solvent and catalyst of the Knoevenagel condensation of 4-substituted benzaldehydes with malononitrile.[17] When L-proline was used as an additional promoter, 3-(methoxycarbonyl)coumarins (**16**) were obtained from *o*-hydroxybenzaldehydes (**15**) in high yields (Scheme 5). Task-specific ionic liquid,[18] [NH_3N^+-CH_2-CH_2-OH][CH_3COO^-], also acted as a recyclable catalyst in the Knoevenagel condensation of aromatic aldehydes with ethyl cyanoacetate **10** or malononitrile under solvent-free conditions.[19] The above task-specific ionic liquid was obtained by the reaction between ethanolamine and acetic acid at room temperature.

Table 1 Primary amine-catalyzed asymmetric Knoevenagel condensation of α-branched aldehydes with dialkyl malonates in the presence of **6** and **8**

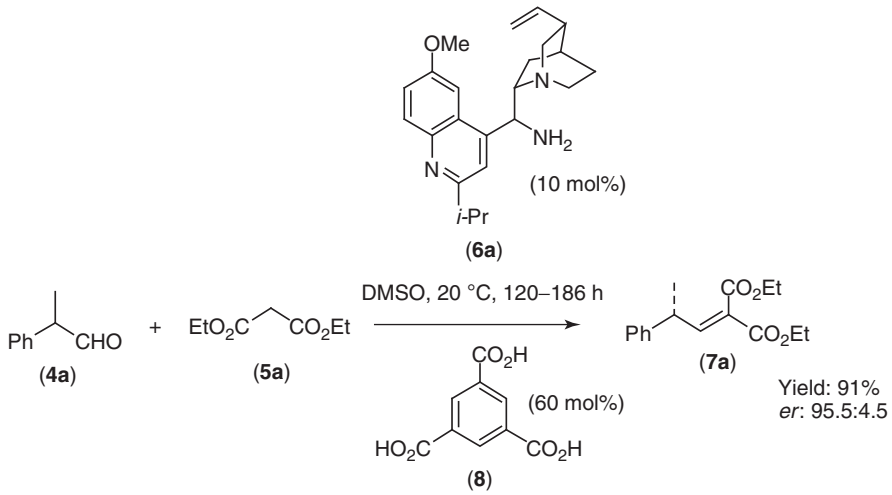


No.	R^1	R^2	R^3	R^4	*Product*	*Yield (%)*[a]	*e.r.*[b]
1	Ph	Me	Et	Et	**7a**	91	95.5:4.5
2	4-$OMeC_6H_4$	Me	Et	Et	**7b**	81	87.0:13.0
3	4-MeC_6H_4	Me	Et	Et	**7c**	87	93.5:6.5
4	4-ClC_6H_4	Me	Et	Et	**7d**	86	93.5:6.5
5	2-FC_6H_4	Me	Et	Et	**7e**	90	89.5:10.5
6	3-FC_6H_4	Me	Et	Et	**7f**	91	93.5:6.5
7	4-FC_6H_4	Me	Et	Et	**7g**	92	94.5:5.5
8	3-MeC_6H_4	Me	Et	Et	**7h**	90	95.0:5.0
9	Ph	Et	Et	Et	**7i**	91	91.5:8.5
10	*c*-C_6H_{11}	Me	Et	Et	**7j**	92	60.0:40.0
11	4-*i*Pr$C_6H_4CH_2$	Me	Et	Et	**7k**	90	52.5:47.5
12	Ph	Me	Me	Me	**7l**	97	94.5:5.5
13	Ph	Me	*n*Pr	*n*Pr	**7m**	96	95.0:5.0
14	Ph	Me	*n*Bu	*n*Bu	**7n**	96	94.5:5.5
15	Ph	Me	Bn	Et	**7o**	94	93.5:5.5
16	Ph	Me	Bn	Bn	**7p**	84	90.5:9.5

[a]Yield of isolated product.

[b]Determined by HPLC analysis on a chiral stationary phase.

Reaction conditions: **4** (0.2 mmol), **5** (10.0 mmol), catalyst **6** (0.02 mmol), additive **8** (0.12 mmol), DMSO (2.0 ml), 20 °C, 120–168 h.

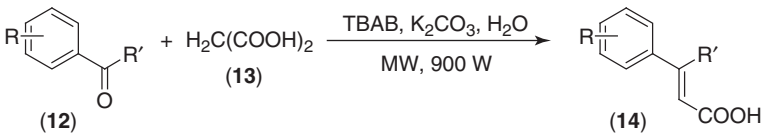


Scheme 3

In a basic ionic liquid, with 1-(2′-diisopropylamino)ethyl-3methylimidazolium bis(trifluoromethanesulfonyl) amide as solvent, the Knoevenagel condensation of aromatic aldehydes with malononitrile proceeded efficiently.[20]

2.14.2.2 Solid Reagents and Catalysts

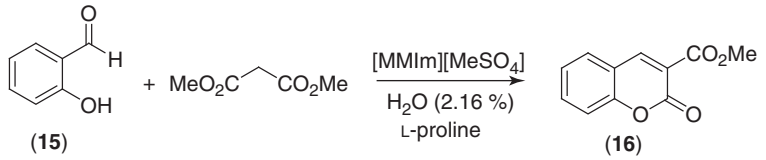
Silica gel-catalyzed the Knoevenagel condensation of aromatic aldehydes and ketones with peptidyl cyanomethyl ketone derivatives (**19**) to new benzylidene and alkylidene derivative of peptides such as *N*-acetylphenylalanine and *N*-acetylleucylphenylalanine (Table 2).[21] Malononitrile, benzoylacetonitrile, and nitroacetonitrile were also reactive in this reaction system. These transformations were brought about without significant epimerization. Preparation of cyanomethyl ketone derivatives (**19**) was achieved in two steps. First, enol **18** was generated by allowing carboxylic acid **17** to react with



(12) (14)

	yield (%)		yield (%)
14a: R = R′ = H	85	14f: R = 3-Br, R′ = H	70
14b: R = 4-OMe, R′= H	65	14g: R = 2,4-Cl_2, R′= H	73
14c: R = 4-Cl, R′ = H	80	14h: R = 4-OH, R′ = H	72
14d: R = 4-NO_2, R′ = H	75	14i: R = H, R′ = CH_3	86
14e: R = 3-NO_2, R′ = H	80	14j: R = 4-Br, R′ = CH_3	85
		14k: R = 4-NO_2, R′ = CH_3	90

Scheme 4

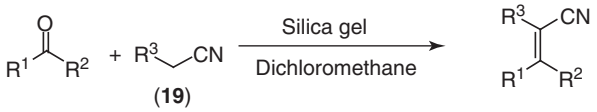


(15) (16)

Yield: 98%

Scheme 5

Table 2 Silica gel-catalyzed Knoevenagel condensation

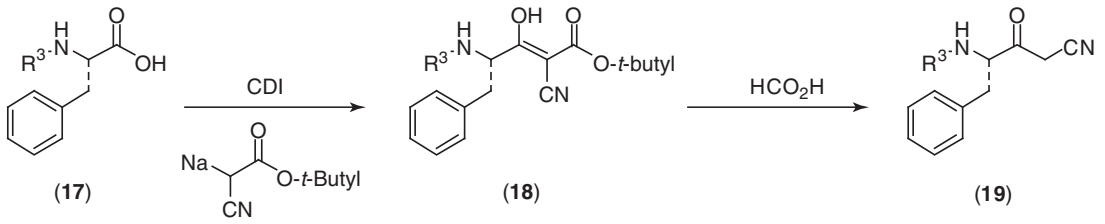


No.	R^1	R^2	R^3	*Yield (%)*[a]
1	H	4-$MeOC_6H_4$	CN	91
2	H	4-$MeOC_6H_4$	O_2N	81
3	H	4-$MeOC_6H_4$	C_6H_5CO	87
4	H	4-$MeOC_6H_4$	*N*-Ac-L-Phe	86
5	H	C_6H_5	*N*-Ac-L-Phe	90
6	H	4-$Me_2NC_6H_4$	*N*-Ac-L-Phe	91
7	H	4-$NO_2C_6H_4$	*N*-Ac-L-Phe	92
8	H	2-$CO_2HC_6H_4$	*N*-Ac-L-Phe	90
9	H	3-MeO(4-OH)C_6H_3	*N*-Ac-L-Phe	91
10	–	$(CH_2)_5$	*N*-Ac-L-Phe	92
11	–	$(CH_2)_4$	*N*-Ac-L-Phe	90
12	Me	Me	*N*-Ac-L-Phe	97
13	Me	$HOCH_2$	*N*-Ac-L-Phe	96[b]
14	Me	Me(OH)CH	*N*-Ac-L-Phe	96[b]
15	H	4-$MeOC_6H_4$	*N*-Ac-L-Leu-L-Phe	94
16	H	4-$MeOC_6H_4$	*N*-Ac-L-Leu-D-Phe	84

[a]All yields are for chromatographically purified materials.
[b]Product is a 56:44 mixture of geometrical isomers.

1,1′-carbonyldiimidazole (CDI), resulting in an acylimidazole intermediate solution, and then adding the preformed sodium salt of *tert*-butyl cyanoacetate generated by using sodium hydride. In the second step, the crude enol **18** was treated with 96% formic acid to proceed hydrolysis and decarboxylation of the *tert*-butyl ester group to give the corresponding cyanomethyl ketones **19** (Scheme 6).

A solid Brönsted base catalyst with a uniform distribution of basic sites with high base strength was prepared by anchoring tetraalkylammonium hydroxide on the surface of MCM-41.[22] It was highly active and selective for the Knoevenagel condensation of benzaldehyde with ethyl cyanoacetate **10** under an N_2 in ethanol solvent. Only a very small decrease of activity was observed on



Scheme 6

recycling experiments, and the leaching of the active component was practically negligible. Silica-supported bases could be operated within electroosmotic flow reactors for the Knoevenagel condensation of aldehydes with activated methylene compounds to obtain the product with high yields (>99%) and purity.[23]

Aminopropylsilyl-tethered mesoporous silicate such as MCM-41 also catalyzed Knoevenagel condensation of benzaldehyde with ethyl cyanoacetate in toluene solvent.[24] Mesoporous alumina acted as a base catalyst for the Knoevenagel condensation of benzaldehyde with ethyl cyanoacetate (**10**).[25]

Fluorapatite, activated by water and benzyltriethylammonium chloride, acted as a new solid catalyst for the Knoevenagel condensation of aldehydes with nitriles without solvent.[26] The Knoevenagel reaction of aldehydes and nitriles was assisted by sodium nitrate/fluoroapatite in heterogenous media under solvent-less conditions.[27] The activity of the sodium nitrate/fluoroapatite system was equivalent to that of MgO[28] and superior to those of KF/Al_2O_3[29] and $ZnCl_2$.[30]

Enolatorhenium(I) complexes *cis*-$Re(NCCR^1CO_2R^2)(NCCHR^1CO_2R^2)(PMe_2Ph)_4$ (R^1 = H, Me, R^2 = Me, Et, *n*Bu), prepared by the reaction of $ReH(N_2)(PMe_2Ph)_4$ with alkyl cyanoalkyl carboxylate, have an octahedral Re geometry, where *cis* enolate and ester ligand mutually bind to the rhenium via cyano groups.[31] These rhenium(I) complexes catalyze the Knoevenagel condensation of aromatic aldehydes with active methylene compounds under mild conditions. A possible mechanism for the condensation has been proposed. Addition of methyl (*E*)-4-bromo-3-methoxycrotonate to aldehydes in the presence of indium and water delivers *β*-hydroxy ester, acidic hydrolysis of which leads to Knoevenagel-like adducts.[32]

Sodium carbonate modified form of natural clinoptilolite (NC), a variation of heulandite (natural zeolite), showed catalytic activity for the Knoevenagel condensation of benzaldehyde with methyl cyanoacetate.[33] The normalized activity per surface area of NC was higher than that of faujasite zeolites. Competing Michael and Knoevenagel reactions of terpenoids with malononitrile on basic Cs-exchanged beta zeolite were investigated.[34] It was found that chemoselectivity depends on steric crowdedness of both the *β*-position of C=C bond lying near the carbonyl group and of the carbonyl group itself. New basic zeolite obtained by grafting amino groups onto CsNaX zeolite showed excellent catalytic activity for the Knoevenagel condensation of benzaldehyde and cyanoacetate, ethyl acetoacetonate, and diethyl malonate in multichannel microreactor.[35] Removal of water by NaX membrane led to a 25% improvement in reaction conversion.

Reconstructed hydrotalcite also catalyzed the Knoevenagel condensation of various aldehydes with nitriles in the presence of water. Reconstructed hydrotalcite also showed aqueous Michael reaction of nitriles with *α*,*β*-unsaturated compounds.[36] The layered double hydroxides-supported diisopropylamine catalyzed the Knoevenagel condensation of aromatic carbonyl compounds with malononitrile or ethyl cyanoacetate.[37] This solid base could be recycled at least four times and exhibited the activity for aldol, Henry, Michael, transesterification, and epoxidation of alkenes.

Highly thermal stable three-dimensional spongelike mesoporous $Ce_xZr_{1-x}O_2$ nanocrystalline acted as acid–base bifunctional solid solutions for the Knoevenagel condensation of aldehydes with active methylene compounds.[38] This catalyst can be recycled at least twice for the reaction of benzaldehyde with malononitrile. Highly stable $CoFe_2O_4$ nanoparticles were synthesized as magnetically separable catalyst for the Knoevenagel condensation of aldehydes with ethyl cyanoacetates in aqueous medium.[39] The $CoFe_2O_4$ nanoparticles were stable during the reaction; therefore, the particles were recycled at least three times. A bifunctional polystyrene bearing both DMAP and piperidine groups was an effective organocatalyst for decarboxylative Doebner–Knoevenagel reactions of arylaldehydes and monoethyl malonate to give *E*-cinnamates in high yields. A synergistic effect obtained by colocating the two different catalytic amine groups on the same polymer backbone has been observed.[40] Crystalline zeolite imidazolate framework acted as reusable heterogenous catalyst for the Knoevenagel reaction of benzaldehyde with malononitrile.[41]

2.14.2.2.1 Microwave-assisted Knoevenagel condensation

Triphenylphosphane (Ph_3P) catalyzed the Knoevenagel condensation of aldehydes with acidic methylene compounds such as ethyl cyanoacetate and malononitrile to afford substituted olefins under solvent-less conditions.[42] In this method, heterocyclic *α*-cyanoacrylates and *α*-cyanoacrylonitriles were obtained in high yields. Microwave irradiation enhanced the reaction rates and improved the yields.

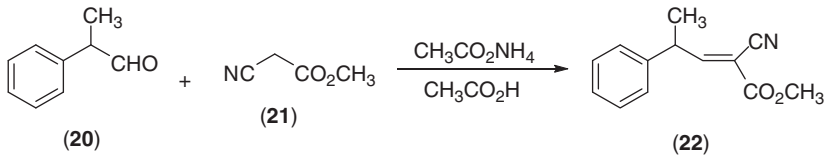
The Knoevenagel condensation of substituted aromatic aldehydes with ethyl cyanoacetate, cyanoacetamide, malononitrile, and malonic acid in the presence of ammonium acetate was assisted by microwave irradiation.[43] A combination of microwave activation and hydroxyapatite promoted the Knoevenagel condensation of a series of aldehydes with malononitrile under

solvent-less conditions.[44] Hydroxyapatite showed high thermal stability and can be recovered by simple filtration and reused for at least ten times without the loss of activity.

2.14.2.3 One-pot Sequential Reactions

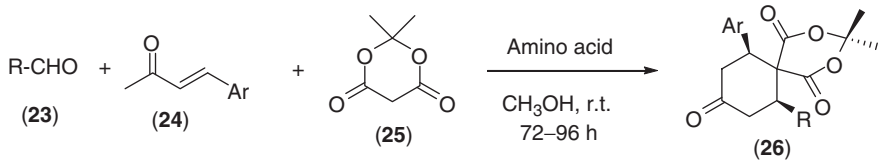
From the viewpoint of Green and Sustainable Chemistry,[45] organic syntheses should be ecological and economical. Domino reactions are one of the powerful synthetic methods to avoid isolation of intermediates and purification, which minimizes waste production.[46] In this part, one-pot sequential domino reaction using the Knoevenagel condensation is described.

The Cope–Knoevenagel reaction of 2-phenylpropionaldehyde (**20**) with methyl cyanoacetate (**21**) in the presence of ammonium acetate produced methyl (*E*)-2-cyano-4-phenylpent-2-enoate (**22**) (Scheme 7).[47]



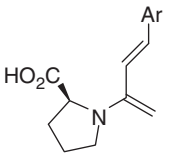
Scheme 7

Highly substituted spiro[5,5]undecane-1,5,9-triones (**26**) were successfully synthesized from the three-component reaction of 4-nitrobenzaldehyde (**23**), *trans*-4-phenyl-3-buten-2-one (**24**), and Meldrum's acid (**25**) with a catalytic amount of L-proline in methanol at ambient temperature through domino Knoevenagel/Diels–Alder reaction (Scheme 8).[48] The Knoevenagel condensation of aldehyde with Meldrum's acid provides the alkylidene derivative of Meldrum's acid, which then undergoes a concerted [4 + 2] cycloaddition with a 2-amino-1,3-butadiene (**27**) generated *in situ* from enone and amino acid to form spiro[5,5]undecane-1,5,9-triones in a highly enantioselective and diastereospecific manner. Solvent had a significant effect on the rate, yield, and *ee* value. The rate of both the Knoevenagel and Diels–Alder reactions catalyzed by L-proline were faster in protic/polar solvents than in aprotic/nonpolar solvents.



23a: R = 4-$NO_2C_6H_4$
23b: R = 4-CNC_6H_4
23c: R = C_6H_5
23d: R = 3,4-$(OCH_2O)C_6H_3$

24a: Ar = Phenyl
24b: Ar = Piperonyl
24c: Ar = 1-Naphthalenyl
24d: Ar = 2-Furanyl
24e: Ar = 2-Thiophenyl



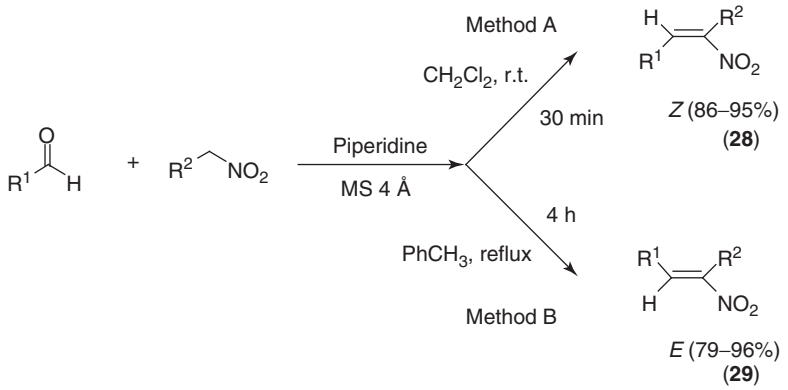
(**27**)

No.	Aldehyde	Enone	Yield (%)[a]
1	23a	24a	95
2	23a	24c	93
3	23a	24d	92
4	23a	24e	80
5	23b	24a	85
6	23c	24a	85
7	23d	24b	99

[a]Isolated yield.

Scheme 8

The reaction of aliphatic aldehydes with nitroalkanes in the presence of catalytic amount of piperidine over 4 Å molecular sieves afforded nitroalkenes. By changing the solvent and temperature, it was possible to control the stereochemical outcomes of the reactions. The reaction at room temperature in CH_2Cl_2 for 30 min gave (*Z*)-nitro alkenes (**28**), whereas reaction in toluene at reflux temperature for 4 h afforded (*E*)-nitro alkenes (**29**) (Scheme 9).[49] The most common two-step preparation of nitro alkenes is the Henry reaction[50] between a carbonyl compound and a nitro alkene, followed by the dehydration of the resulting *β*-nitro alcohol. With this two-step method, *E*-isomer is obtained as the only or the major product.[51] Conjugated nitro alkenes have proved to be versatile compounds that have widespread use as powerful electrophiles that readily undergo Diels–Alder reaction or Michael addition with many nucleophiles (Scheme 10).



No.	R^1	R^2	Yield (%) *Z* (method A)[a]	Yield (%) *E* (method B)[a]
1	Et	Me	93	*b*
2	Et	Et	86	86
3	Bu	Me	90	92
4	Bu	Et	89	83
5	Pentyl	Me	95	81
6	Pentyl	Et	90	87
7	*i*-Bu	Me	*c*	96
8	*i*-Bu	Me	*c*	79

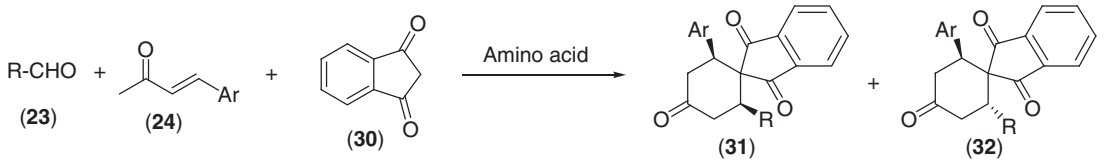
[a]After filtration of the crude mixture on celite.
[b]Boiling point of nitro compound is too low.
[c]No nitro alkenes were detected.

Scheme 9

Highly substituted symmetrical and nonsymmetrical spiro[cyclohexane-1,2′-indan]-1′,3′,4-triones (**31**) were synthesized by amino acid and amines-catalyzed three-component (aldehydes, enones, and 1,3-indandione **30**) heterodomino Knoevenagel/Diels–Alder/epimerization reactions.[52] This domino reaction involves amino acid- and amine-catalyzed epimerization reactions of *trans*-spiranes (**32**) to *cis*-spiranes (**31**) through retro-Michael reaction. The *cis*/*trans* ratios were found to be 99:1.

A new domino process using Knoevenagel/1,6-heteroelectrocyclization sequence was conducted to synthesize 5-phosphono-substituted 2*H*-thiopyrans (**35**) from the reaction between *α*,*β*-unsaturated aldehydes (**33**) and phosphonodithioacetate (**34**) (Scheme 11).[53] Highly substituted 2-alkyl-cyclohexa-1,3-diones (**39**) and Wieland–Miescher ketone analogs (**40**) were obtained in good to high yields with excellent enantioselectivity by a direct combination of L-proline-catalyzed cascade Knoevenagel/hydrogenation and cascade Robinson annulation of acid (1,3-cyclohexanedione **37**), benzaldehydes (**36**), Hantzsch ester (**38**), and methyl vinyl ketone (Scheme 12).[54] 2-Alkyl-cyclohexa-1,3-diones (**39**) and Wieland–Miescher ketone analogs (**40**) are attractive intermediates in the synthesis of natural product and in medicinal chemistry.

One-flask tandem Knoevenagel–Michael addition reaction of sulfonimines (**41**) with diethyl malonate in the presence of catalytic amount of base afforded the corresponding arylidene dimalonates (**42**) in good yield (Scheme 13).[55] Arylidene dimalonate has the potential to serve as a bone-affinity agent in the treatment of bone disease and as the precursor for the synthesis of 3-Ar-glutaric acid.

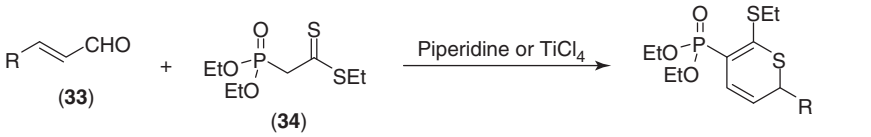


23a: R = 4-$NO_2C_6H_4$
23b: R = 4-CNC_6H_4
23c: R = C_6H_5
23d: R = 3,4-$(OCH_2O)C_6H_3$
23e: R = 4-$MeOC_6H_4$
23f: R = 4-$NMe_2C_6H_4$
23g: R = 4-OHC_6H_4
23h: R = 4-ClC_6H_4
23i: R = 2-$NO_2C_6H_4$
23j: R = 4-$CO_2MeC_6H_4$
23k: R = 1-Naphthalenyl
23l: R = 2-Furanyl
23m: R = *trans*-$C_6H_5CH{=}CH$-

24a: Ar = C_6H_5
24b: Ar = 1-Naphthalenyl
24c: Ar = 4-$MeOC_6H_4$
24d: Ar = 3,4-$(OCH_2O)C_6H_3$
24e: Ar = 4-$NMe_2C_6H_4$
24f: Ar = 4-OHC_6H_4
24g: Ar = 4-ClC_6H_4
24h: Ar = 4-$NO_2C_6H_4$

No.	Aldehyde	Butenone	Yield (%)
1	23a	24a	98
2	23b	24a	99
3	23c	24a	96
4	23e	24a	71
5	23g	24a	99
6	23h	24a	99
7	23i	24a	80
8	23j	24a	99
9	23k	24a	99
10	23l	24a	99
11	23m	24a	74
12	23k	24b	95
13	23e	24c	95
14	23d	24d	98
15	23f	24e	90
16	23g	24f	95
17	23h	24g	98
18	23a	24h	98

Scheme 10



33a: R = Ph
33b: R = Me

35a: R = Ph, yield: 74%
35b: R = Me, yield: 67%

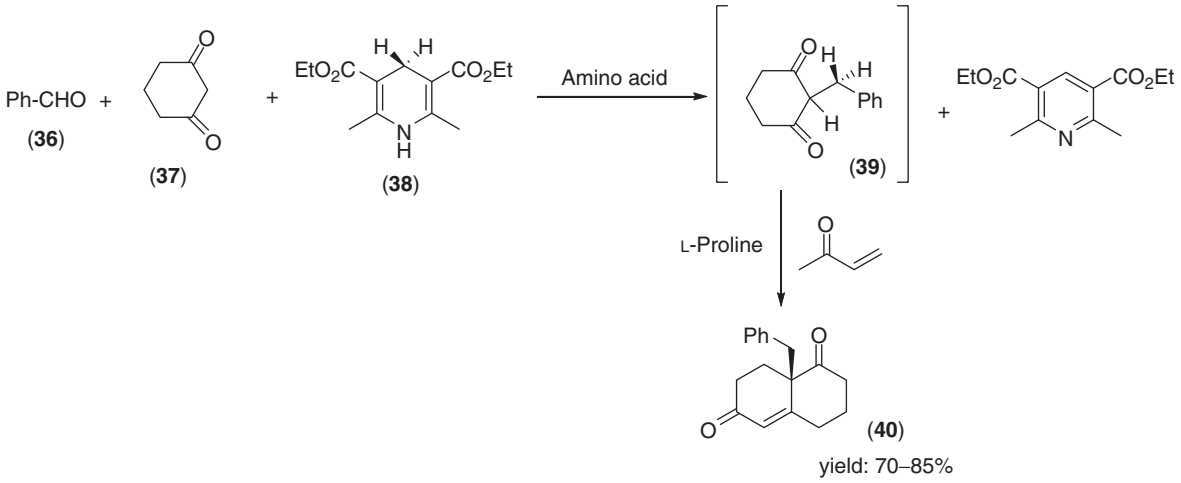
Scheme 11

The methodology using organocatalytic domino Michael–Knoevenagel condensation reaction was presented for the synthesis of optically active 3-diethoxyphosphoryl-2-oxocyclohex-3-enecarboxylates (**45**).[56] This method involves a Michael–Knoevenagel reaction sequence of ethyl 4-diethoxyphosphoryl-3-oxobutanoate (**43**) and α,β-unsaturated aldehydes catalyzed by a chiral diarylprolinol ether **44** (Scheme 14). The cyclohexenecarboxylates are particularly well suited for the preparation of highly functionalized cyclohexene and cyclohexane derivatives, with up to four chiral centers and high level of stereocontrol.

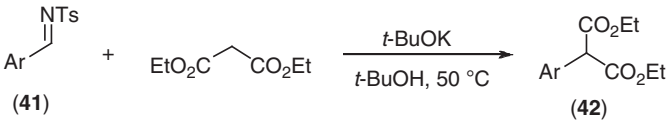
One-pot tandem process involving a proline-catalyzed Knoevenagel condensation, a Michael addition, and an electrophilic fluorination by *N*-fluorobenzenesulfonimide (NFSI) afforded fluorinated flavanone derivatives (**46**) in moderate to good yields with excellent diastereoselectivities under mild reaction conditions (Scheme 15).[57]

Combining the regioselective hydroformylation and a decarboxylative Knoevenagel reaction allowed for the development of an efficient, one-pot procedure for the synthesis of (*E*)-α,β-unsaturated carboxylic acid (**47**) (Scheme 16).[58]

Substituted 2-aminothiophenes (**49**) are synthesized by the Knoevenagel condensation of ketones (**48**) with malononitrile followed by the solid base-promoted Gewald reaction (Scheme 17).[59]



Scheme 12



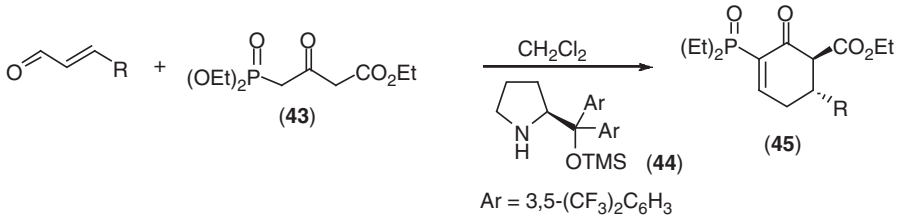
No.	Ar	Yield of **42** (%)
1	Ph	91
2	*p*-$CH_3OC_6H_4$	80
3	*p*-$CH_3C_6H_4$	78
4	*o,m*-$(CH_3O)_2C_6H_3$	75
5	*p*-FC_6H_4	88
6	*p*-$NO_2C_6H_4$	92
7	*p*-IC_6H_4	86
8	*o*-$CF_3C_6H_4$	89
9	*o*-ClC_6H_4	93
10	1-Naphthyl	88
11	2-Furan	92
12	2-Thiophe	93

Scheme 13

The reaction of 2-(*N*-alkenyl-*N*-aryl)amino-4-oxo-4*H*-1-benzopyran-3-carbaldehyde (**50**) with dimedone by heating in ethanol in the presence of catalytic amount of pyridine produces cyclic heterocycles (**51**) bearing both pyridine and pyran rings via the Knoevenagel-hetero Diels–Alder domino sequence reaction (Scheme 18).[60]

The Knoevenagel condensation of cyclic ketones (**52**) with benzylonitrile (**53**) and *N,N′*-dimethylbarbituric acid (**54**) afforded heterodynes (2-cycloalkylidene-3-oxo-3-phenyl-propionitriles **55** and 5-cycloalkylidene-1,3-dimethylpyrimidine-2,4,6-triones **56**), which underwent hetero-Diels–Alder cycloaddition reaction with enol ethers (**57** and **58**) giving sterically hindered dispiropyrans (**59**, **60**) (Scheme 19 and Table 3).[61]

Basic conditions of the Suzuki–Miyaura coupling using SiO_2-supported Pd catalyst[62] could operate in the Knoevenagel condensation under aqueous conditions without the use of amine catalyst.[63] This situation allowed for a combination of the Suzuki–Miyaura coupling of aryl halides **61** and phenylboronic acid (**62**) with the Knoevenagel condensation with malononitrile and ethyl cyanoacetate to afford the corresponding compound (**63**) (Scheme 20).



No.	R	Yield of **45** (%)	*ee* (%)[a]	*dr*[b]
1	C_6H_5	79	98	>95:5
2	4-$NO_2C_6H_4$	95	98	87:13
3	4-$CF_3C_6H_4$	81	98	>95:5
4	2-$CH_3OC_6H_4$	94	97	92:8
5	3-$CH_3OC_6H_4$	76	97	>95:5
6	Biphenyl	78	98	>95:5
7	2-Furyl	71	97	90:10

[a]Determined by HPLC on a chiral stationary phase.
[b]Determined by ^{31}P-NMR spectroscopy.

Scheme 14

A multicomponent reaction between aromatic aldehydes (**64**), 2-nitromethylenethiazolidine (**65**), and nitriles **66** in the presence of Et_3N afforded a series of 5-amino-7-aryl-8-nitrothiazolo[3,2-α]pyridines (**67**) (Scheme 21, Table 4).[64] This one-pot multicomponent reaction was initiated by the Knoevenagel reaction of aldehyde with nitrile compound, followed by conjugated addition of enamine and cyclization.

Library of multifunctional biphenyl methyl-C-β-D-glycosides (**73**) was obtained by the Knoevenagel condensation of butenonyl-C-β-D-glycosides (**68**) with malononitrile in the presence of K_2CO_3 in water with a one-pot manner (Scheme 22).[65] The most probable mechanism as depicted in Figure 1 involves initially a Michael addition of malononitrile to the double bond of glycosyl butanone (**68**) resulting in an adduct (**69**). The latter, on the Knoevenagel condensation with another malononitrile in the presence of base B, gives an intermediate **70**. The base abstracts a proton from **70** to generate carbanion, which makes a nucleophilic attack onto one of the nitriles to give cycloaddition product **71**. The base-catalyzed elimination of HCN gave an intermediate imine **72**, which on oxidation afforded the biphenyl methyl glycosides **73** through an aromatization. These kinds of compound are of interest as antitumor, antibiotics, or anti-inflammatory agents.

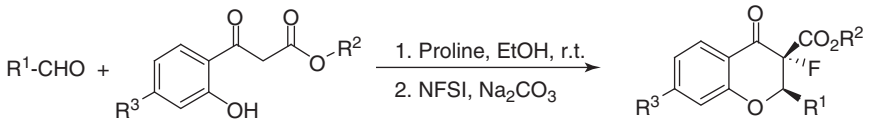
2.14.2.4 Synthetic Applications

When the Knoevenagel condensation of aliphatic aldehydes with 1,3-diketones was carried out in the presence of thiophenol in dichloromethane containing silica gel, the precursors (**77**) of monoprotected succinaldehydes (**77**) were obtained.[66] For example, the three-component reaction of bifunctional electrophilic aldehyde (**74**) with dimenone (**75**) in the presence of thiophenol (**76**) gave the adduct (**77**) (Scheme 23). Deblocking the Knoevenagel product (**77**) to release a new aldehyde functional group was to be followed immediately by deprotonation and intramolecular aldol cyclization to afford spirocycles (**79**).

Ethyl 3-aryl-2-(perfluoroalkanesulfonyl)propenoates **81** were prepared by the Knoevenagel condensation of various aldehydes with ethyl (trifluoromethanesulfonyl)acetate (**80**) or ethyl (nonafluorobutanesulfonyl)acetate in the presence of piperidine (Scheme 24).[67] The compound **80** was prepared by the reaction of sodium triflate (**82**) with ethyl bromoacetate (**83**) (Scheme 25). These deactivated olefins were used in Diels–Alder cycloaddition with cyclopentadiene.

2-(2,3,4,9-Tetrahydro-1*H*-β-carbolin-1-yl)aldehyde (**85**), synthesized from tryptamine (**84**) in five steps, is easily homologated by the Knoevenagel condensation to substituted acrylate (**86**) (Scheme 26).[68] Removal of Boc group by trifluoroacetic acid (TFA) affords the ester lactam (**87**). This compound is highly active and a key intermediate in the synthesis of natural indol alkaloid ajmalicine.

A highly functionalized four-carbon unit, 4-hydroxyalk-2-en-1-one functionality [$R^1CH(OH)CH{=}CHCOR^2$](**89**), was prepared by the Knoevenagel reaction of aldehyde (R^1CH_2CHO) with a 1-(arylsulfinyl)alkan-2-one [$ArS(O)CH_2COR^2$](**88**) in the presence of diethylamine (Scheme 27, Table 5).[69] This type of carbon chain elongation method was used in the synthesis of (+)-(11*E*)-13-hydroxy-10-oxooctadec-11-enoic acid (**91**), having cytotoxic activity, from undec-10-enoic acid (**90**) (Scheme 28).

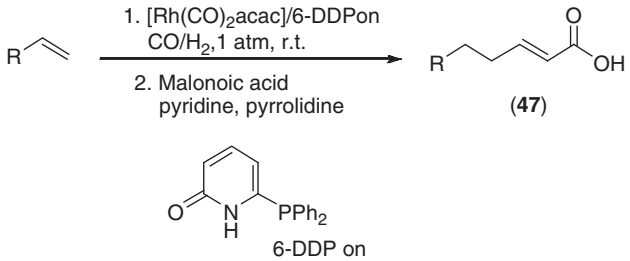


(**46**)

No.	R^1	R^2	R^3	Yield of **46** (%)[a]
1	C_6H_5	Et	H	88
2	*p*-FC_6H_4	Et	H	50
3	*p*-ClC_6H_4	Et	H	52
4	*p*-BrC_6H_4	Et	H	79
5	*p*-MeC_6H_4	Et	H	63
6	*p*-PhC_6H_4	Et	H	81
7	*p*-$MeOC_6H_4$	Et	H	74
8	*p*-$BnOC_6H_4$	Et	H	57
9	*p*-$NO_2C_6H_4$	Et	H	64
10	*o*-BrC_6H_4	Et	H	74
11	*m*-BrC_6H_4	Et	H	73
12	3-BnO-4-$MeOC_6H_3$	Et	H	57
13	Furan-2-yl	Et	H	85
14	Pentyl	Et	H	67
15	*p*-MeC_6H_4	*t*-Bu	H	40
16	*p*-BrC_6H_4	*t*-Bu	H	58
17	*p*-$MeOC_6H_4$	*t*-Bu	H	50
18	*p*-MeC_6H_4	*t*-Bu	Me	61

[a]Isolated yield after flash chromatography.

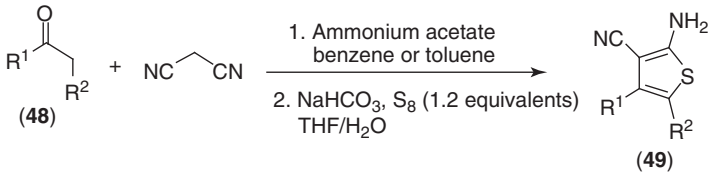
Scheme 15



(**47**)

Scheme 16

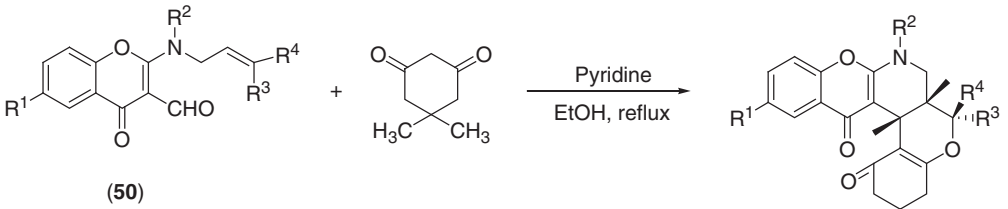
Decarboxylative Knoevenagel condensation has been used for the synthesis of (*E*)-α,β-unsaturated esters (**93**) from aliphatic and aromatic aldehydes and half-ester of malonates **92** in the presence of 4-dimethylaminopyridine (DMAP) (Scheme 29).[70] This methodology is advantageous over previous synthetic methods for (*E*)-α,β-unsaturated esters such as the Horner–Wadsworth–Emmons and the Wittig reactions because by-products formed are only water and carbon dioxide. Half-ester malonates **92** are as inexpensive as the corresponding phosphorus-based reagents and can be obtained from inexpensive dialkyl malonates.



(**48**) (**49**)

No.	R^1	R^2	Yield of **49** (%)
1	4-$NO_2C_6H_4$	H	80
2	Ph	H	40
3	3-$NO_2C_6H_4$	H	81
4	4-$MeSO_2C_6H_4$	H	58
5	4-BrC_6H_4	H	73
6	2,6-$F_2C_6H_3$	H	58
7	4-$MeOC_6H_4$	H	80
8	2-Thiophene	H	46
9	Ph	Ph	78

Scheme 17



(**50**) (**51**)

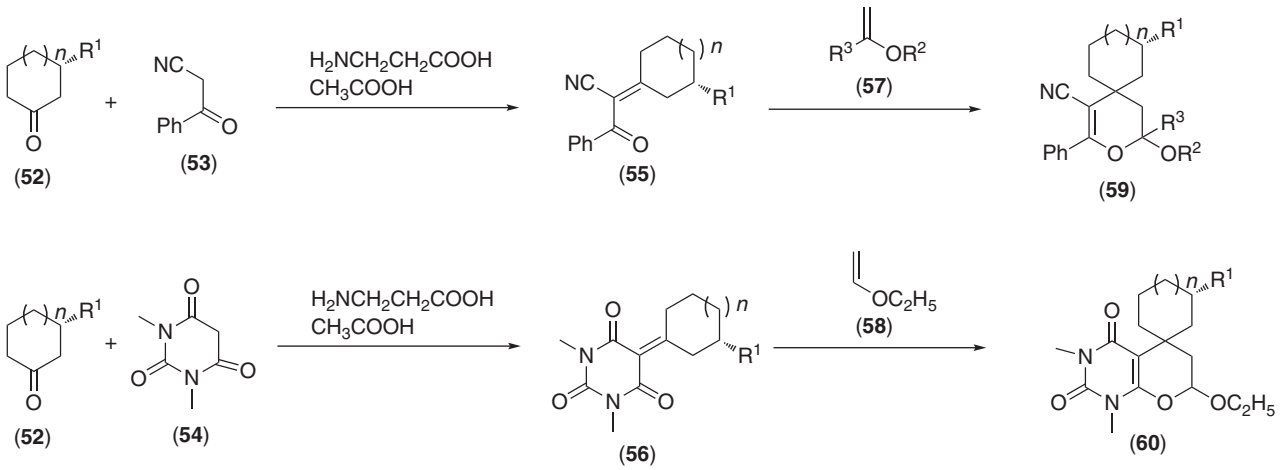
	Yield (%)
51a: $R^1 = R^3 = H$; $R^2 = R^4 = Ph$	58
51b: $R^1 = R^3 = R^3 = Me$, $R^2 = Ph$	74
51c: $R^1 = H$; $R^2 = Ph$; $R^3 = R^4 = Me$	72
51d: $R^1 = R^4 = Me$; $R^2 = Ph$; $R^3 = H$	55
51e: $R^1 = R^3 = H$; $R^2 = Ph$; $R^4 = Me$	60
51f: $R^1 = R^3 = R^4 = H$; $R^2 = Me$	50
51g: $R^1 = Me$; $R^2 = Et$; $R^3 = R^4 = H$	55

Scheme 18

The Knoevenagel condensation of ethylmalonate with butyraldehyde was used to synthesize highly functionalized five-membered nitrogen heterocycles (**94–96**) (Scheme 30).[71] Use of chlorotrimethylsilane, $(CH_3)_3SiCl$, as a promoter and water scavenger enables the Knoevenagel condensation of aromatic aldehydes with various methylene compounds. Intermediate **96** can be viewed as a possible synthon for further work that involves the synthesis of sarin A because it possesses the same ring junction as the natural alkaloid.

The Knoevenagel condensation of aldehydes substituted with an electron-withdrawing group such as aromatic and hetero-aromatic ones with *O*-acetoacetyl TEMPOs (2,2,6,6-tetramethylpiperidine-1-oxyl) (**97**) led preferentially to *E*-adducts (**98**), whereas acylacetoamides including Weinreb amides (**99**) exclusively produced *Z*-adducts (**100**) (Scheme 31).[72] These *E*- and *Z*-adducts were selectively converted into the corresponding (2*E*)- and (2*Z*)-2-hydroxyalkyl-2-alkenals, respectively, by stepwise reductions of the acyl group with DIBALH and then carboxylic functions after protection of hydroxyl group.

Light-emitting donor–acceptor conjugated polymers were synthesized using the Knoevenagel condensation of (*N*,*N*-diphenylamino)benzaldehyde (**101**) with 3,5-dicyano-2,4,6-tristyrylpyridine (**102**) using piperidine in *n*-propanol (Scheme 32).[73] Further Knoevenagel condensation of the product with aromatic dialdehydes using piperidine in DMF affords conjugated polymers.

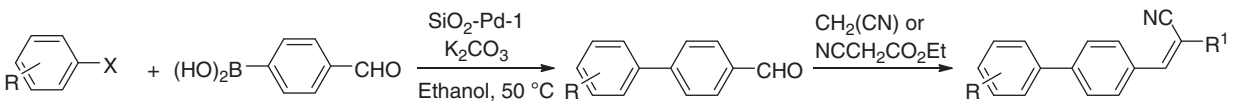


Scheme 19

Table 3 Synthesis of spiropiranes **57** and **58** by Diels–Alder reactions

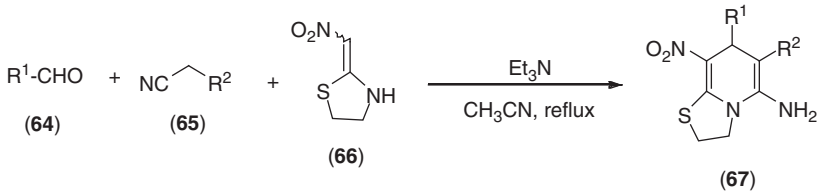
No.	*Diene*	*n*	R^1	R^2	R^3	*Yield (%)*[a]
1	53a	1	H	C_2H_5	H	89
2	53a	1	H	*i*-Bu	H	91
3	53a	1	H	CH_3	CH_3	84
4	53b	0	H	C_2H_5	H	87
5	53c	2	H	C_2H_5	H	86
6	53d	3	H	C_2H_5	H	83
7	53e	1	CH_3	C_2H_5	H	87
8	54a	1	H	C_2H_5	H	79
9	54b	0	H	C_2H_5	H	93
10	54c	2	H	C_2H_5	H	91
11	54d	3	H	C_2H_5	H	88
12	54e	1	CH_3	C_2H_5	H	78

[a]Isolated yields after column chromatography.



R = 4-NO_2, X = Br
R = 4-OMe, X = I
R = 4-Me, X = I
R = 3-OMe, X = Br

Scheme 20

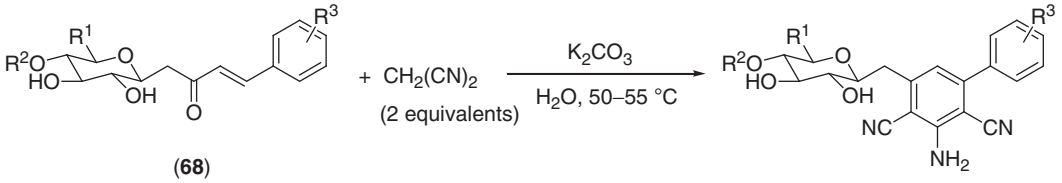


Scheme 21

Table 4 Reactions of aldehydes with nitriles and 2-nitromethylenethiazoline (**66**)

No.	R^1	R^2	*Yield of* ***67*** *(%)*[a]
1	C_6H_5	CN	95
2	4-FC_6H_4	CN	90
3	4-ClC_6H_4	CN	94
4	4-BrC_6H_4	CN	79
5	2-FC_6H_4	CN	93
6	2,4-$Cl_2C_6H_3$	CN	99
7	2,6-$Cl_2C_6H_3$	CN	97
8	2-BrC_6H_4	CN	97
9	2-HO-5-BrC_6H_3	CN	82
10	4-$NO_2C_6H_4$	CN	99
11	4-$MeNC_6H_4$	CN	90
12	4-ClC_6H_4	CO_2Et	78 (88)
13	4-BrC_6H_4	CO_2Et	73
14	4-$NO_2C_6H_4$	CO_2Et	70 (79)

[a]Yields in parentheses refer to reactions carried out under solvent-free conditions brought about by grinding with a pestle and a mortar.



	Compounds	Yield (%)
68a, **73a**: $R^1 = R^2 = R^3 = H$	**73a**	76
68b, **73b**: $R^1 = R^2 = H$, R^3 = 4-Cl	**73b**	73
68c, **73c**: $R^1 = R^2 = H$, R^3 = 3-NO_2	**73c**	73
68d, **73d**: $R^1 = R^2 = H$, R^3 = 4-OMe	**73d**	75
68e, **73e**: $R^1 = CH_2OH$, R^2 = β-D-glucopyranos-1-yl, $R^3 = H$	**73e**	61

Scheme 22

Combinatorial libraries comprising 11 000 benzylidene compounds of high structural and functional diversity have been generated through the Knoevenagel condensation of aldehydes with methylene-active compounds using chlorotrimethylsilane as efficient promoter and water scavenger.[74]

A series of conjugated, bispyridyl and tetrapyridyl compounds (**104–108**) were synthesized using either terephthalaldehyde or isophthalaldehyde and activated pyridyl compounds by the Knoevenagel condensation on heating in acetic anhydride in the presence of acetic acid (Scheme 33), and their optical and thermal properties were examined.[75] All of the products exhibited photoluminescence in chloroform, THF, and DMSO as well as in solid state.

gem-Dibromobenzenes (**109–116**) are employed for the first time in the Knoevenagel–Doebner condensation as aldehyde equivalent for the efficient synthesis of α,β-unsaturated carboxylic acids (**117**).[76] The reaction of *gem*-dibromobenzenes with dicarboxylic acid (malonic acid) in the presence of catalytic amount of piperidine afforded α,β-unsaturated carboxylic acids (Scheme 34), which are important reagents in organic synthesis both as intermediates and final products. For example, they have been used to prepare compounds of biological relevance, such as tetrahydromyricoid or antibacterial reutericyclin.

The Knoevenagel condensation is employed in the synthesis of 3-ethyl 5-methyl 2-[(2-(2-(2-aminoethoxy)ethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (**120**) (Scheme 35).[77] The Knoevenagel condensation is used in the formation of ethyl 4-{[2-[2-(2-azidoethoxy)ethoxy]ethoxy]-acetyl}-3-(2-chlorophenyl)acrylate (**119**) from ethyl 4-{2-[2-(2-azidoethoxy)ethoxy]ethoxy}-3-oxobutanoate (**118**).

Cyanovinyl-substituted branched copolymer having 1,3,5-triphenylbenzene as core and *p*-phenylenevinylene as connecting groups (**123**) were synthesized via the Knoevenagel condensation of 1,3,5-tri(4-formylphenyl)benzene (**121**) with aromatic dinitrile derivatives (**122**) in the presence of sodium methoxide in the mixture of anhydrous chloroform and ethanol at room temperature (Scheme 36).[78] The redox activity of the polymers was investigated.

New through-space cyano-substituted poly(*p*-arylenevinylene)s containing a [2.2]paracyclophane (**126**) unit were synthesized by the Knoevenagel condensation of *p*-diformyl[2.2]paracyclophane monomer (**124**) with 2,5-bis(hexyloxy)benzene-1,4-diacetonitrile

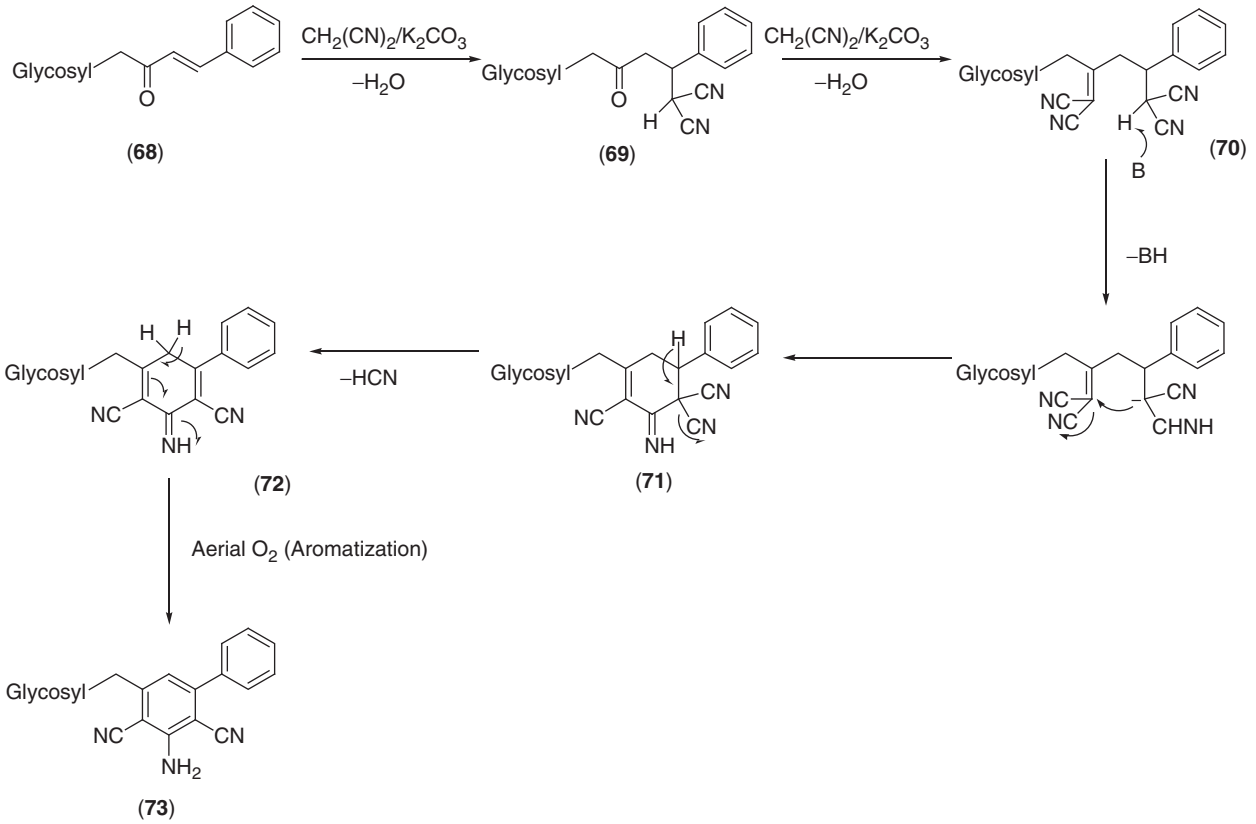
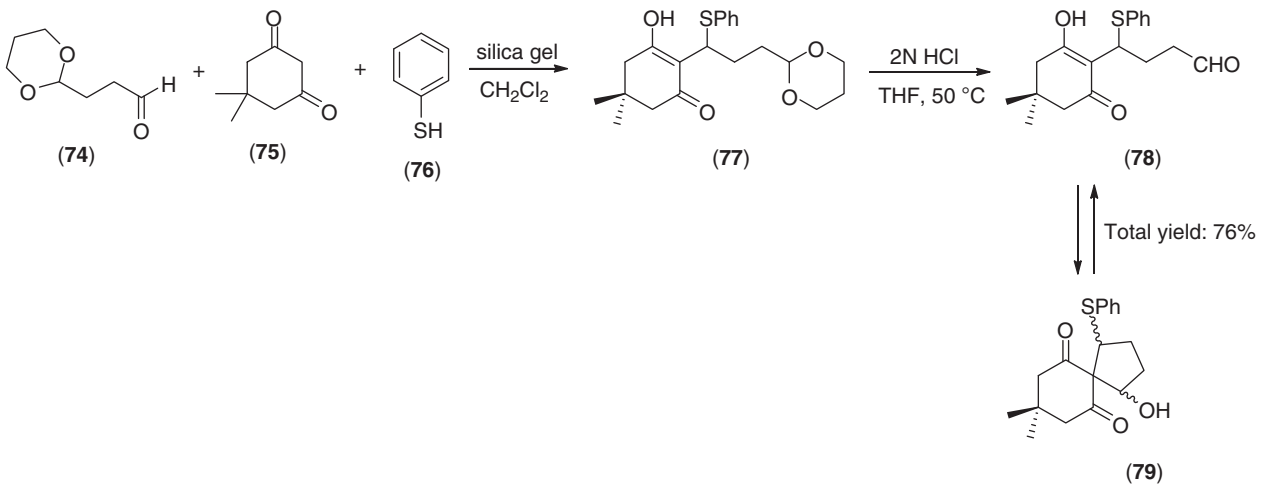


Figure 1 A plausible route to multifunctional biphenyl methyl-C-β-D-glycoside (**73**).

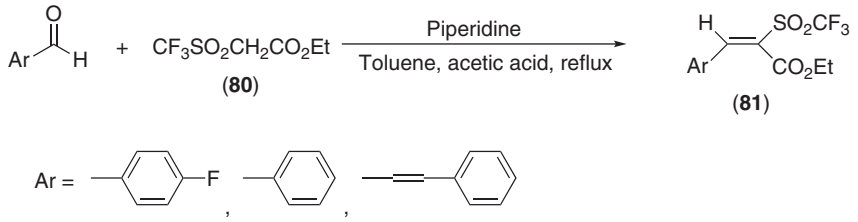


Scheme 23

(**125**) (Scheme 37).[79] The number average of molecular weight (M_n) and the molecular weight distribution (M_w/M_n) of **126** were 6600 and 3.0, respectively. The optical and electrochemical properties were investigated.

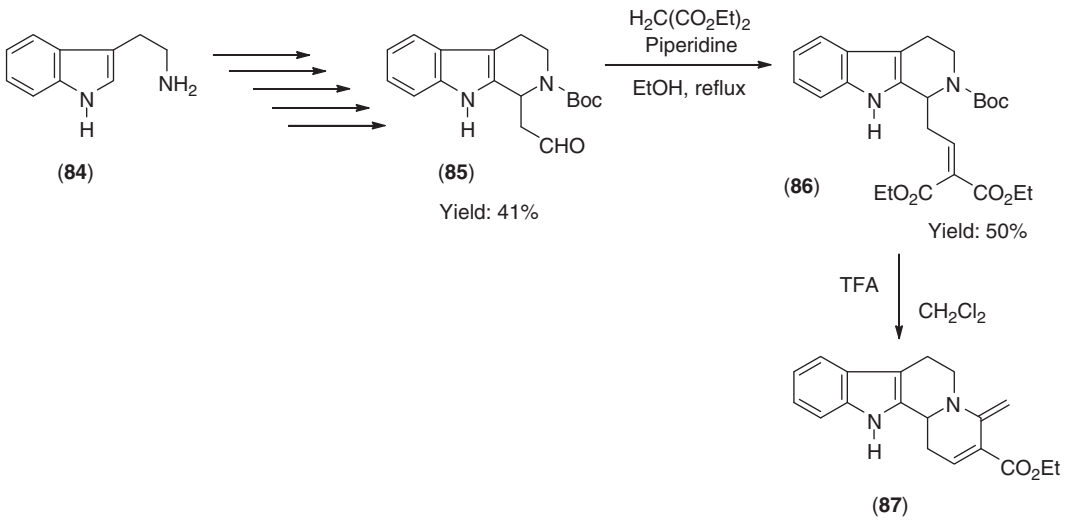
Asymmetrically disubstituted malonamide (*r*AA-mGly-AA′, **127**), obtained from Meldrum's acid, was considered as methylene-active compound.[80] Short malonyl dehydro peptide (*r*AA-*m*Δ^2AA″-AA′, **128**) can be obtained efficiently. One example is shown in Scheme 38. Chiral aldehydes can also be used to synthesize multifunctional malonyl dehydro peptides.

Two symmetrical and one unsymmetrical 'push-pull' amphiphilic 2,2′-bipyridine chromophore (**132**) has been synthesized through the Knoevenagel condensation of the aldehyde (**129**) with 4,4′-dimethyl-2,2′-bipyridine (**130**) (Scheme 39).[81] Linear optical property and thermal stability were investigated.

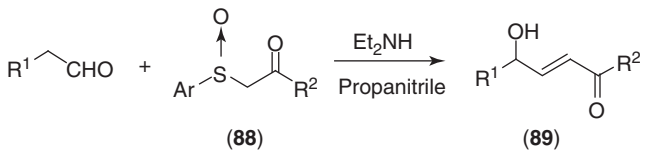


Scheme 24

Scheme 25



Scheme 26

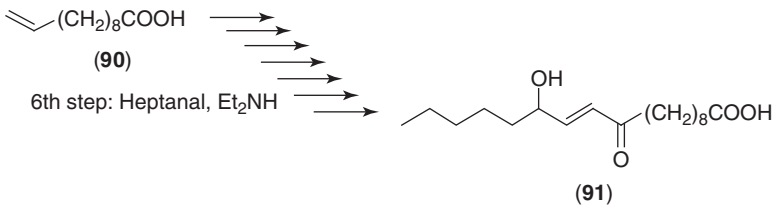


Scheme 27

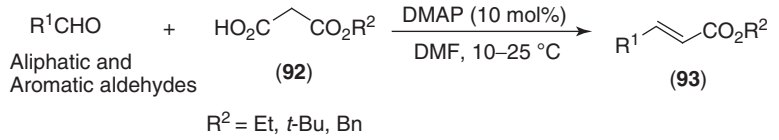
The Knoevenagel condensation was applied for the synthesis of 3-cyano-2-pyridones derivatives (**136**).[82] The reaction of aromatic ketones (**133**) with ethyl cyanoacetate in the presence of ammonium acetate at 100 °C afforded ethyl 2-cyano-3-arylbut-2-enoate (**134**) (Scheme 40i). The compound **134** was converted into enaminonitriles (**135**) using DMSO–dimethylacetal (DMA) at room temperature (Scheme 40ii).[82] Cyclization of enaminonitriles with primary nucleophile amines afforded 3-cyano-2-pyridones (**136**) (Scheme 40iii). All reactions were performed under solvent-less condition.

Table 5 Formation of 4-hydroxy-2-alkenones unit by the Knoevenagel reaction of aldehydes with **88**

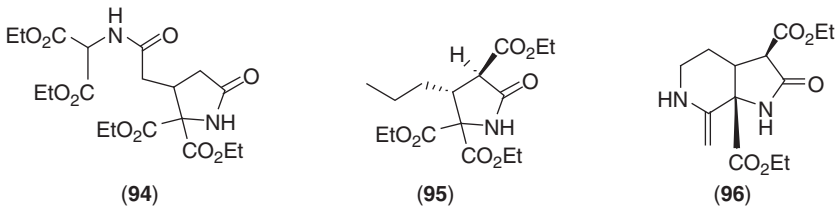
No.	*R^1 [or aldehyde]*	*Ar*	*R^2*	*Yield of **89** (%)*
1	n-C_4H_9	C_6H_5	CH_3	82
2	n-C_4H_9	p-ClC_6H_4	CH_3	76
3	(Citronellal)	p-ClC_6H_4	CH_3	84
4	n-$C_5H_{11}CO(CH_2)_2$	p-ClC_6H_4	CH_3	66
5	$CH_3O_2C(CH_2)_7$	p-ClC_6H_4	CH_3	51
6	n-C_4H_9	p-ClC_6H_4	$(CH_2)_6CH_3$	64
7	n-C_4H_9	p-ClC_6H_4	$(CH_2)_2CH=CH_2$	68
8	n-C_5H_{11}	C_6H_5	$(CH_2)CH(OH)(CH_2)_5(CH_3)$	63
9	n-C_4H_9	C_6H_5	$CH_2C_6H_5$	54
10	n-C_4H_9	C_6H_5	$(CH_2)_2CO_2CH_3$	64



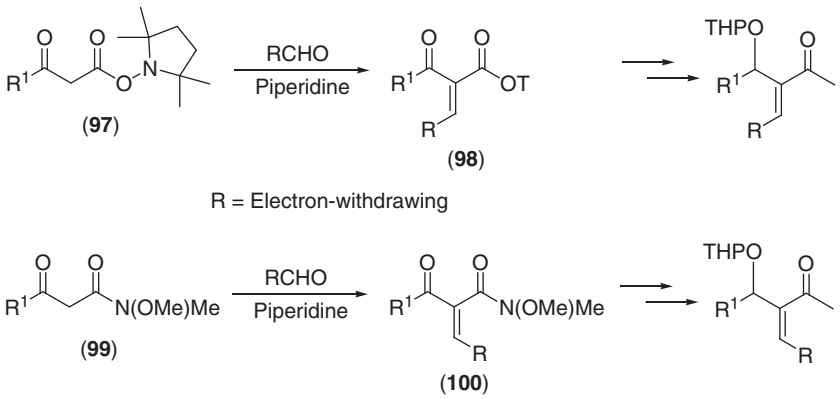
Scheme 28



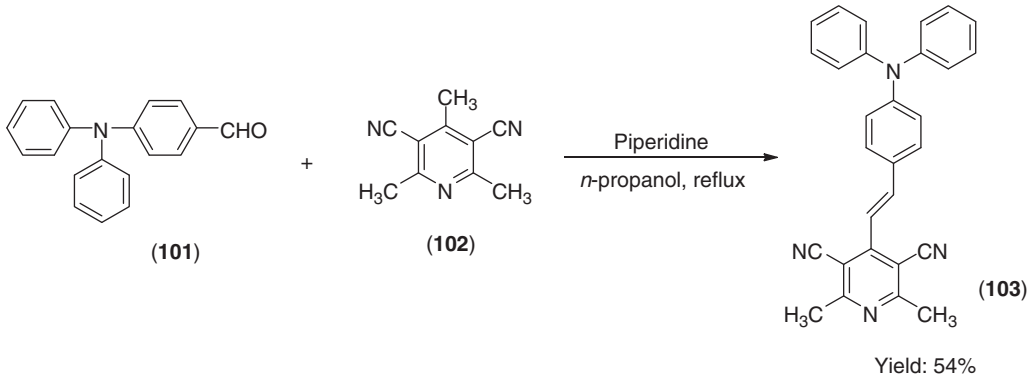
Scheme 29



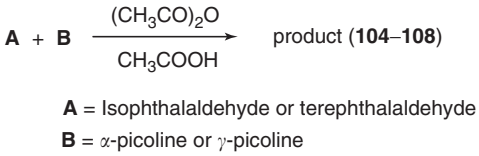
Scheme 30



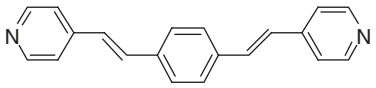
Scheme 31



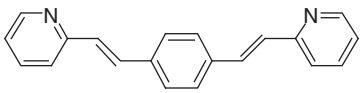
Scheme 32



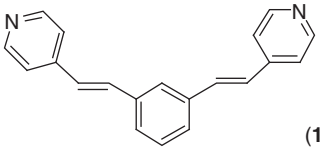
A = Isophthalaldehyde or terephthalaldehyde
B = α-picoline or γ-picoline



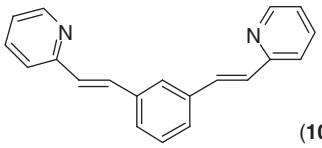
(**104**)



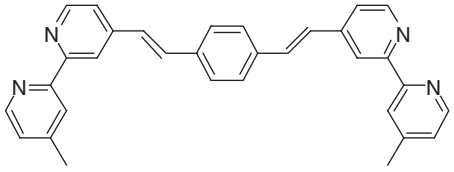
(**105**)



(**106**)

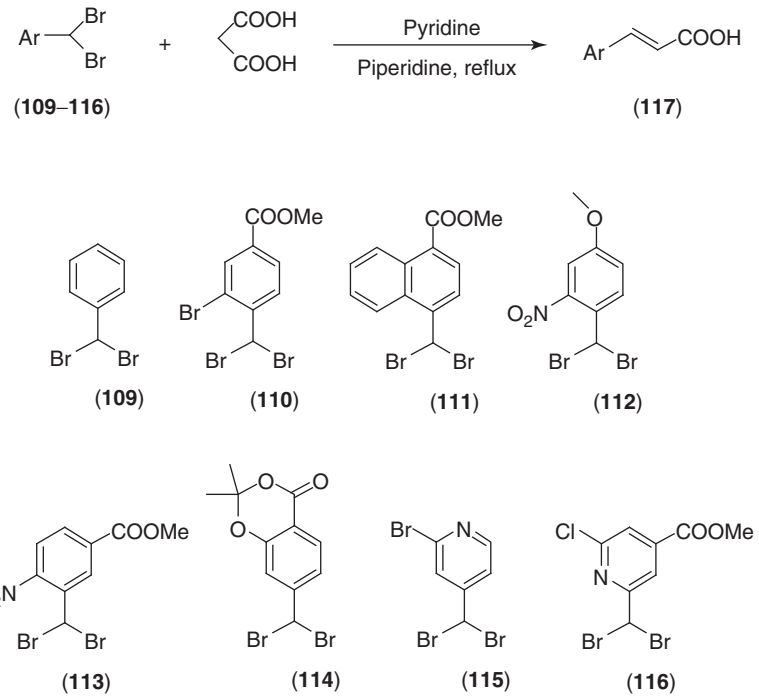


(**107**)

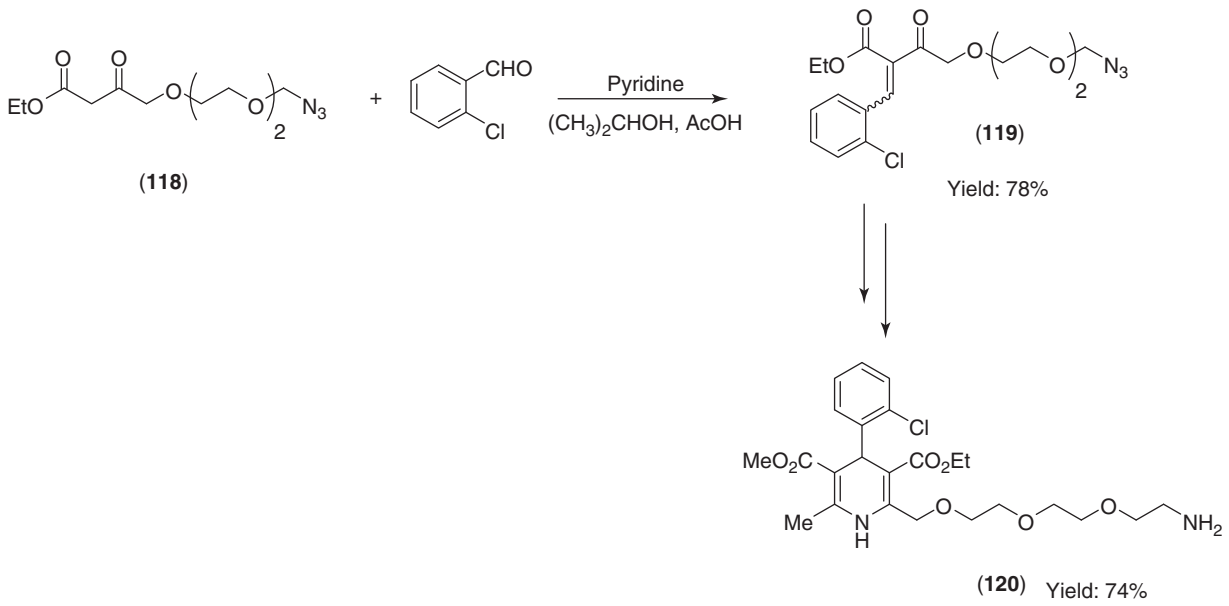


(**108**)

Scheme 33



Scheme 34

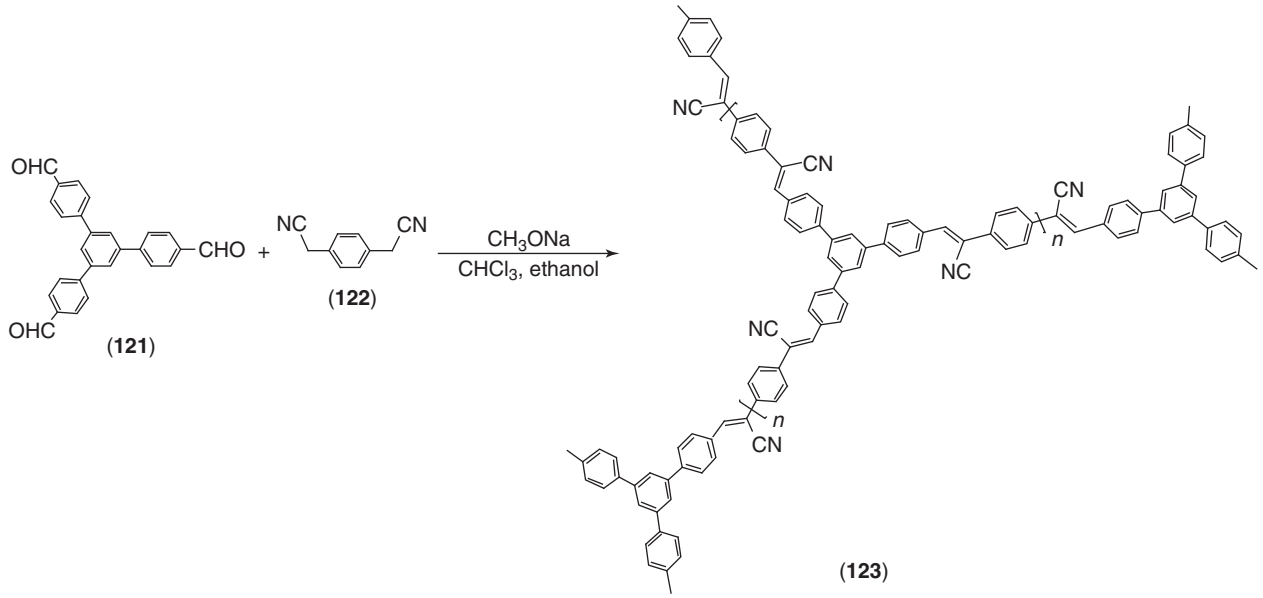


Scheme 35

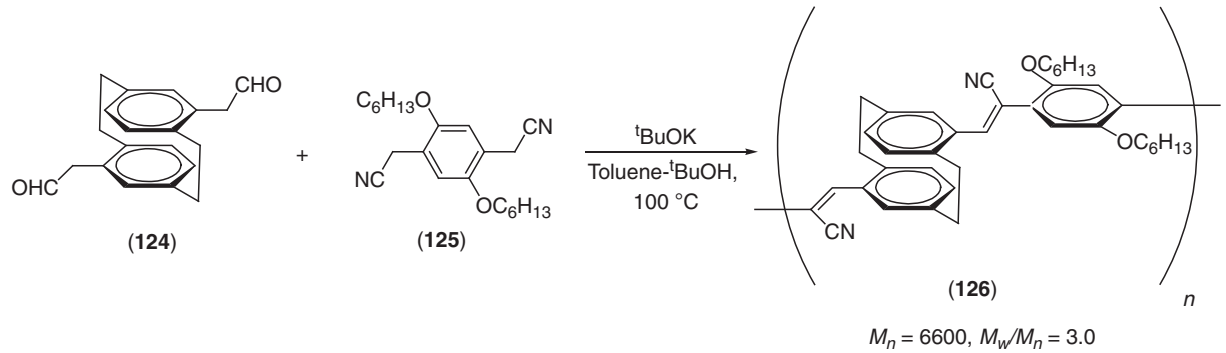
2.14.3 Perkin Condensation

The reaction of aromatic aldehydes **137** with carboxylic acids having active methylene at α-position of **138**, affording β-aryl acrylic acids **139**, in the presence of base is called as Perkin condensation (Scheme 41). The Perkin condensation is a key step for the synthesis of stilbenes.

The Perkin condensation of 3-hydroxy-4-methoxybenzaldehyde (**140**) with 3,4,5-trimethoxyphenylacetic acid (**141**) followed by decarboxylation of the product, cinnamic acid (**142**), using copper and quinoline gave (*Z*)-combretastatin A-4 (**143**) as an anticancer drug (Scheme 42).[83] The iodine-catalyzed isomerization of (*Z*)-combretastatin A-4 (**143**) results in complete conversion to the *E*-isomer (**144**).

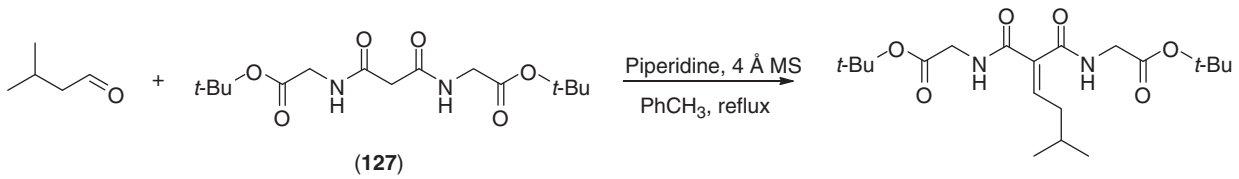


Scheme 36



M_n = 6600, M_w/M_n = 3.0

Scheme 37



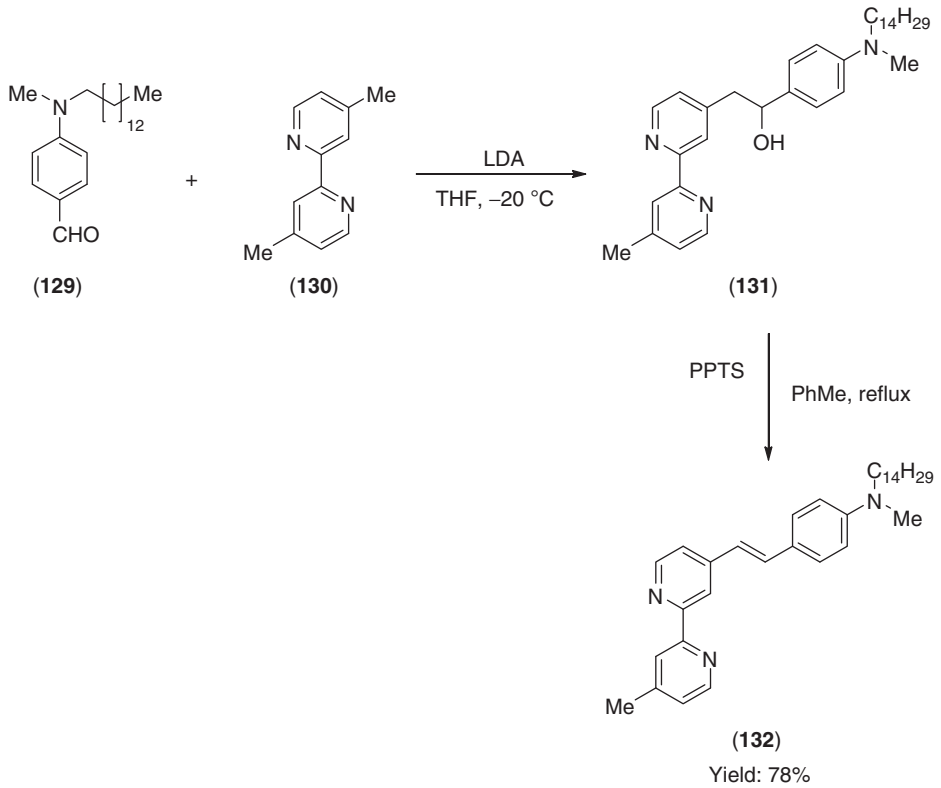
γGly(O-*t*-Bu)-*m*Gly-Gly(O-*t*-Bu)

γGly(O-*t*-Bu)-*m*Δ^{2}Leu-Gly(O-*t*-Bu)

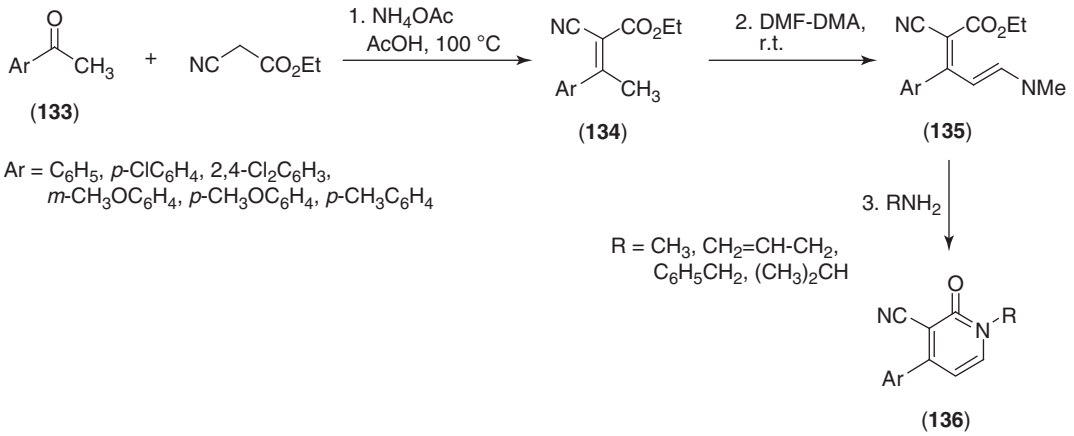
Yield: 95%

Scheme 38

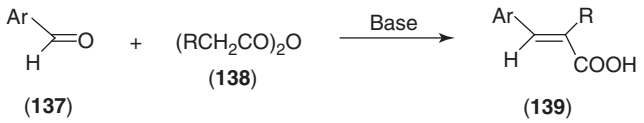
Unusually, hydroxylated (*E*)-stilbenes (**147**) can be obtained by the Perkin condensation of benzaldehydes (**145**) with phenylacetic acids (**146**) bearing 4-hydroxy substitution at the aromatic ring in the presence of piperidine–methylimidazole (MIm) and polyethylene glycol (PEG) under microwave irradiation and subsequent decarboxylation (Scheme 43).[84] It was hypothesized that MIm initially forms a carboxylate salt with the aryl acid intermediate obtained by the piperidine-induced condensation between hydroxyl-substituted benzaldehydes and phenylacetic acid.



Scheme 39

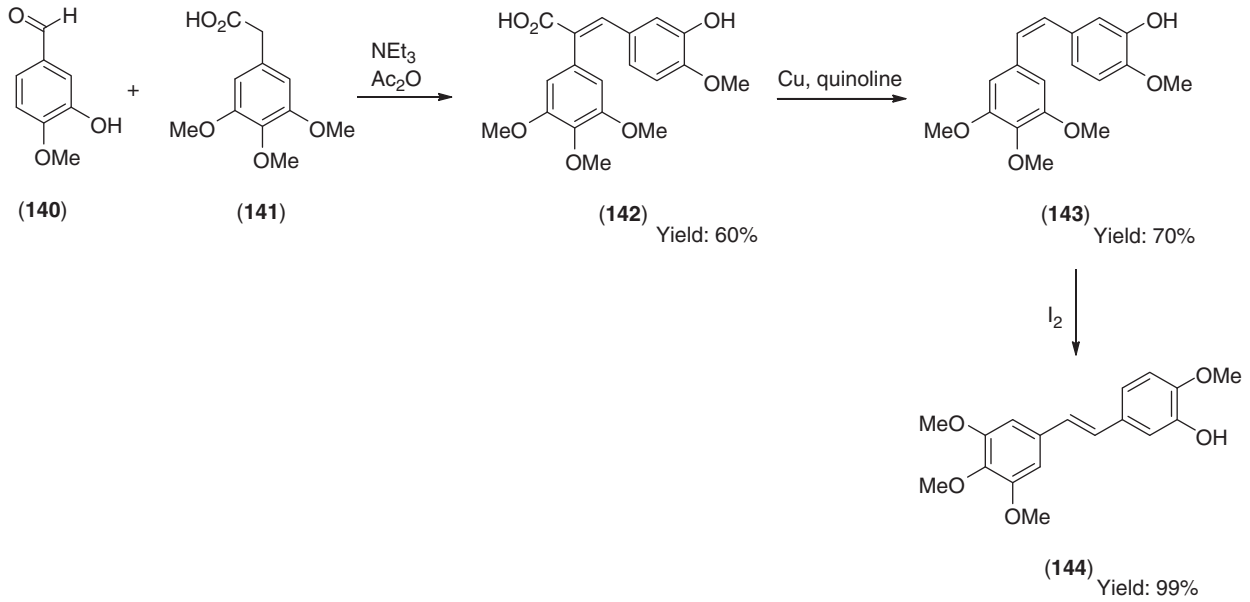


Scheme 40

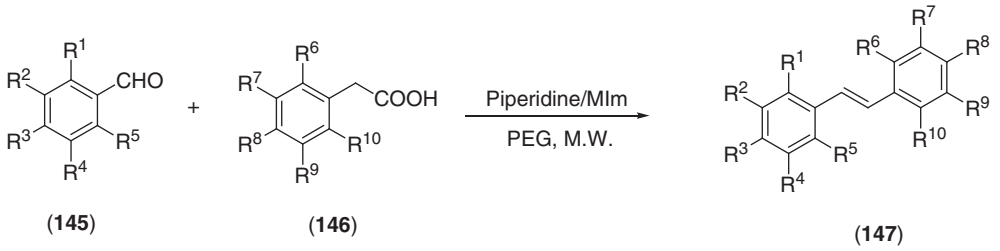


Scheme 41

Coumarin-resveratrol hybrid compounds (**151**), which shows tyrosinase inhibitory activity, were obtained via the Perkin condensation of methoxy-substituted *o*-hydroxybenzaldehydes (**149**) with arylacetic acids (**150**) in the presence of dicyclohexylcarbodiimide, followed by the hydrolysis of methoxy groups with HI (Scheme 44).[85]



Scheme 42

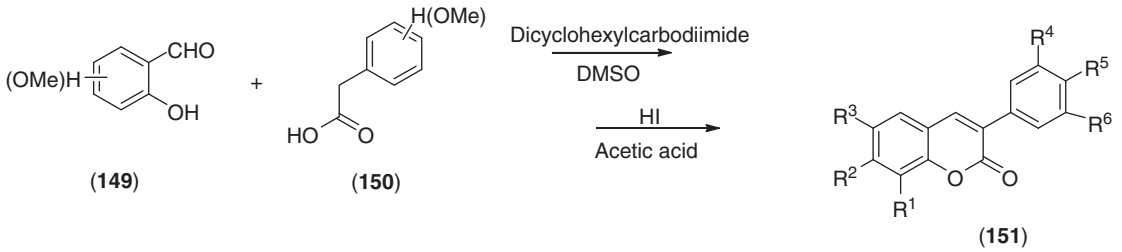


	Yield (%)
147a: $R^1 = R^2 = R^5 = R^6 = R^7 = R^8 = R^9 = R^{10} = H$; $R^3 = OH$; $R^4 = OMe$	56
147b: $R^1 = R^2 = R^4 = R^5 = R^6 = R^7 = R^8 = R^9 = R^{10} = H$; $R^3 = OH$	54
147c: $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = R^7 = R^9 = R^{10} = H$; $R^8 = OH$	44
147d: $R^1 = R^2 = R^5 = R^6 = R^7 = R^9 = R^{10} = H$; $R^3 = OH$; $R^4 = OMe$; $R^8 = Cl$	71
147e: $R^1 = R^2 = R^5 = R^6 = R^7 = R^9 = R^{10} = H$; $R^3 = OH$; $R^4 = OMe$; $R^8 = OMe$	53
147f: $R^1 = R^2 = R^5 = R^6 = R^{10} = H$; $R^3 = R^7 = R^9 = OH$	51
147g: $R^1 = R^4 = R^5 = R^6 = R^7 = R^8 = R^{10} = H$; $R^2 = R^3 = OH$; $R^9 = OMe$	54
147h: $R^1 = R^2 = R^4 = R^5 = R^6 = R^7 = R^8 = R^{10} = H$; $R^3 = OH$; $R^9 = OMe$	56
147i: $R^1 = R^2 = R^4 = R^5 = R^6 = R^{10} = H$; $R^3 = OH$; $R^7 = R^9 = OMe$	64
147j: $R^1 = R^4 = R^5 = R^6 = R^7 = R^9 = R^{10} = H$; $R^2 = R^3 = OMe$; $R^8 = OH$	46
147k: $R^1 = R^2 = R^4 = R^5 = R^6 = R^7 = R^9 = R^{10} = H$; $R^3 = R^8 = OH$	41
147l: $R^1 = R^2 = R^3 = R^6 = R^7 = R^8 = R^9 = R^{10} = H$; $R^4 = OMe$, $R^5 = OH$	41
147m: $R^1 = R^2 = R^3 = R^6 = R^7 = R^9 = R^{10} = H$; $R^4 = OMe$, $R^5 = OH$; $R^8 = OMe$	43
147n: $R^1 = R^4 = R^5 = R^6 = R^7 = R^9 = R^{10} = H$; $R^3 = OH$; $R^2 = R^8 = OMe$	42

Scheme 43

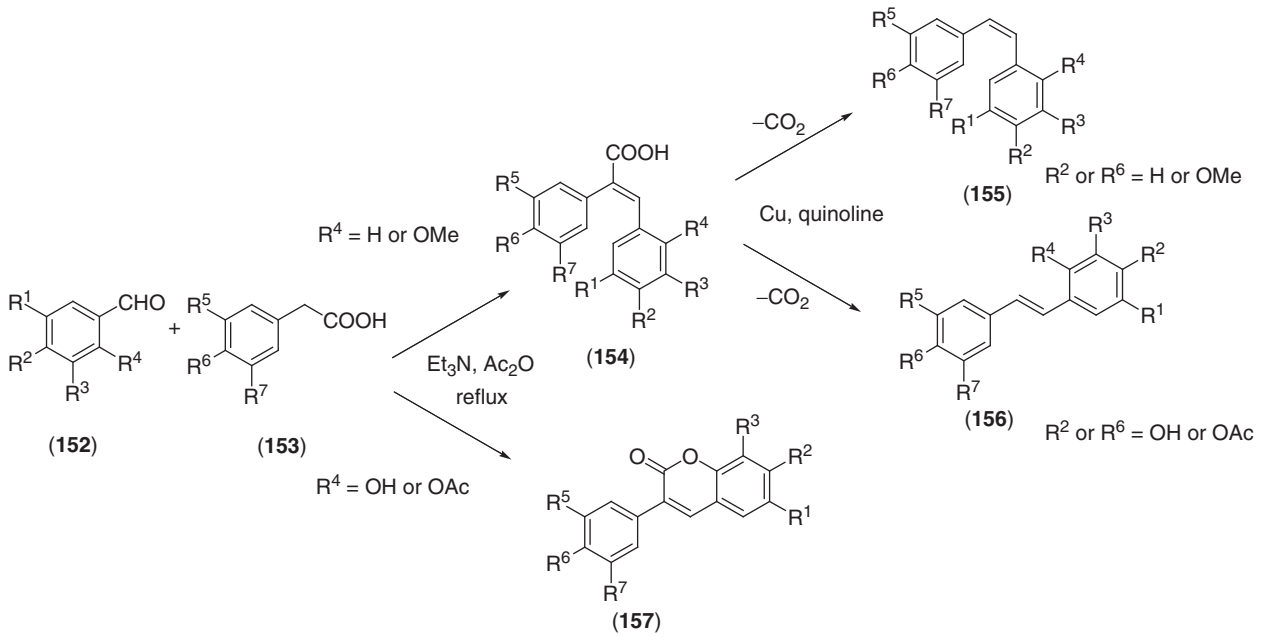
The substitutional effect in the selective synthesis of *cis*, *trans* stilbenes and 3-arylcoumarine was investigated (Scheme 45).[86] The regio- and geometrical selectivity for synthesis of stilbene derivatives under the Perkin strategy strongly depends on the presence and absence of hydroxyl group as well as their positions in the phenyl ring. When R^4 group is H or OMe, treatment of aldehyde **152** with carboxylic acid **153** affords *E*-2,3-diarylacrylic acid **154**, which undergoes decarboxylation into *cis*-stilbene (**155**) (when R^2 and R^6 group is H or OMe) and *trans*-stilbene (**156**) (when R^2 and R^6 is OH or OAc), respectively. When using aldehyde having R^4 group with OH or OAc, cyclic stilbene (**157**) was formed.

2-Alkyl-7-methoxy-5-nitrobenzo[*b*]furans (**159**) can be obtained by an intramolecular Perkin cyclization of 2-(2-formyl-6-methoxy-7-nitrophenoxy)alkanoic acid (**158**) in the presence of AcONa in Ac_2O (Scheme 46).[87]



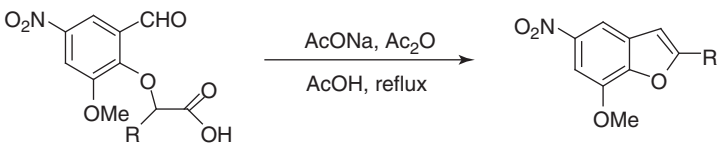
(**149**) (**150**) (**151**)

Scheme 44



	Yield (%)
154a: $R^1 = R^4 = H$; $R^2 = R^5 = R^6 = R^7 = OMe$; $R^3 = OH$	80
154b: $R^1 = R^4 = R^6 = H$; $R^2 = R^5 = R^7 = OMe$; $R^3 = OH$	79
154c: $R^2 = R^4 = R^5 = H$; $R^1 = R^3 = R^6 = OMe$	87
154d: $R^1 = R^3 = R^4 = R^6 = H$; $R^2 = R^5 = R^6 = R^7 = OMe$	84
154e: $R^1 = R^5 = H$; $R^2 = R^3 = R^4 = R^6 = OMe$; $R^7 = OH$	78
154f: $R^1 = R^3 = OMe$; $R^2 = R^4 = R^5 = R^7 = H$; $R^6 = OH$	85
154g: $R^1 = R^3 = R^6 = OH$; $R^2 = R^4 = R^5 = R^7 = H$	81
154h: $R^1 = R^2 = R^3 = OMe$; $R^4 = R^5 = R^7 = H$; $R^6 = OH$	82

Scheme 45



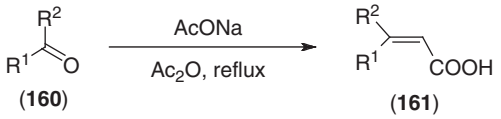
(**158**) (**159**)

R = C_2H_5, C_3H_7, C_4H_9

Scheme 46

The Perkin-type reaction of fluoroalkyl–arylketone (**160**) as a carbonyl component in the presence of sodium acetate exclusively leads to 3-polyfluoroalkylated *E*-cinnamic acids (**161**) (Table 6).[88]

Table 6 Synthesis of *E*-cinnamic acids **161**



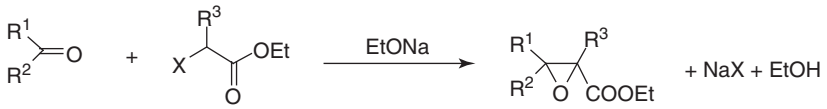
(**160**) (**161**)

No.	R^1	R^2	*Yield (%)*[a]	*E:Z ratio*
1	CF_3	3-$CF_3C_6H_4$	75	91:9
2	CF_3	4-ClC_6H_4	78	95:5
3	CF_3	Ph	67	93:7
4	CF_3	4-MeC_6H_4	81	93:7
5	CF_2Cl	Ph	46	100:0

[a]Yield of isolated product.

2.14.4 Darzens Condensation

The finding by Erlenmeyer in 1904 was generalized as Darzens condensation. Generally, the Darzens condensation represents the reaction of carbonyl compounds with α-halo carbonyl acids **162** as a carbon nucleophile in the presence of base to construct α,β-epoxy esters **163** via cyclic transition state[89] (Scheme 47). Dehydration and decarboxylation of compound **163** gives ketones **164** or aldehydes **165** with larger carbon numbers (Figure 2).



(**162**) (**163**)

Scheme 47

(**164**) (**165**)

Figure 2 Aldehydes and ketones from α,β-epoxy esters (**163**).

2.14.4.1 New Reagents

Stannylcarbamate **166** proved to be a selective reagent for generating organotin(IV) enolates (**167**) (Figure 3) from α-halo ketones. Reaction of aldehydes **168** with α-halo ketones **169** in the presence of an equimolar tin reagent **166** gave the corresponding α,β-epoxy ketones **170** (Scheme 48).[90] This tin-promoted Darzens reaction takes place without any side reaction and even with aliphatic α-halo ketones bearing enolizable α′-hydrogens.

The method of phase-transfer catalysts[91] has also been used for the Darzens condensation. Quaternary ammonium salt (**171**), derived from cinchonine, is used for asymmetric Darzens condensation of aldehydes (**172**) with α-chloroketone (**173**) to the corresponding coupling product (**174**) (Table 7).[92]

When aldehydes was reacted with α-chloro cyclic ketone **175**, the corresponding Darzens product **176** was obtained diastereoselectively (Table 8).[93]

The same Darzens reaction system using phase-transfer reagent can be applied for the asymmetric synthesis of α,β-epoxysulfones **179** from aromatic aldehydes **177** and chloromethyl phenylsulfone **178** (Table 9).[94] It has been reported that the addition of 10 mol% $Sn(OTf)_4$ significantly improves the enantiopurity of **170**.[95]

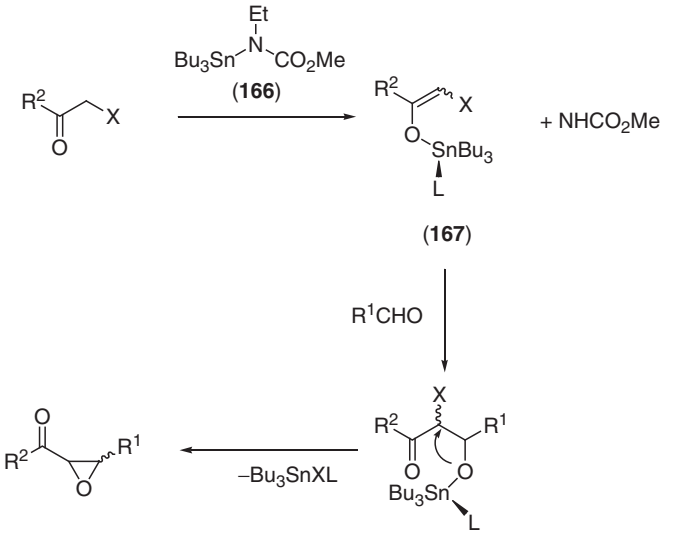
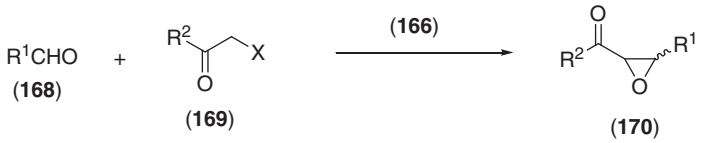


Figure 3 Generation of organotin(IV) enolates (**167**) for Darzens condensation.



	Yield (%)
170a: R^1 = Ph; R^2 = CH_3; X = Cl	66
170b: R^1 = CH_3Ph; R^2 = CH_3; X = Br	40
170c: R^1 = CH_2CH_3Ph; R^2 = CH_3; X = Br	81
170d: R^1 = Ph; R^2 = *t*-Bu; X = Br	63

Scheme 48

The scope of employability of sulfones in asymmetric organocatalysis has been recently reviewed. Sulfones can act as activators of both nucleophiles and electrophiles.[96]

The Darzens condensation of 4-*tert*-butylbenzaldehyde (**180**) with *N*,*N*-diphenylacetamide (**181**) proceeds diastereoselectively to afford the *cis*-glycidic acid derivative (**182**) in the presence of tetrahexylammonium bromide (THAB) as phase-transfer reagent and KOH as a base (Scheme 49).[97] When LiOH is used as a milder base, complete stereocontrol is achieved into *trans*.

The Darzens condensation cyclohexanone (**183**) with chloroacetonitrile (**184**) to the coupling product (**185**) was performed using aqueous sodium hydroxide and a new phase-transfer catalysts (MTPC), 2-benzylidine-*N*,*N*,*N*,*N*′,*N*′,*N*′-hexaethoxylpropane-1,3-diammonium dichloride (Scheme 50).[98] The effect of various experimental parameters on the reaction rate has been studied, and based on the results, a suitable mechanism has been proposed.

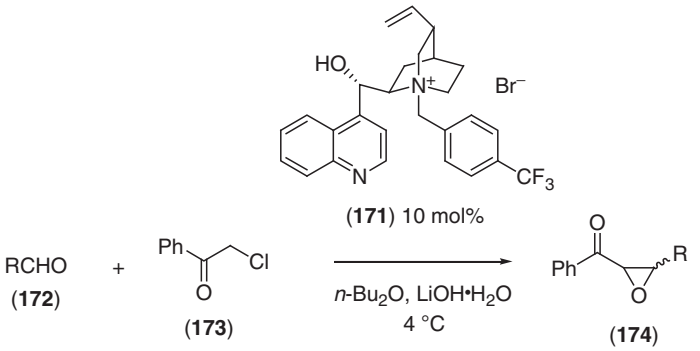
New phase-transfer catalyst, bis ammonium salt (**186**) derived from BINOL, has been developed for the asymmetric Darzens reaction of aromatic aldehydes with haloamide (**187**), affording the corresponding coupling products (**188**) (Table 10).[99] Their absolute stereochemistry was determined.

The Darzens condensation of aromatic aldehydes with α-chloroesters (**189**) is promoted by polystyrene-supported phase-transfer catalyst (polystyrene-supported triethylammonium chloride, PS-TEAC, **191**) to afford the *cis*- and *trans*-coupling products (**190**) (Scheme 51).[100,101] Other phase-transfer catalysts such as polystyrene-supported cinchonidium chloride (**192**) and tetrahexylammonium bromide (**193**) can be used in the Darzens condensation of aromatic aldehydes with ethyl chloroacetate (**194**) (Figure 4).

Bead-shaped insoluble polymer-supported six-site phase-transfer reagent (**195**) was synthesized and applied as catalyst for the Darzens condensation of benzophenone (**196**) with chloroacetonitrile (**197**) in the presence of NaOH (Scheme 52).[102]

The Darzens condensation of aromatic, α,β-unsaturated, and aliphatic aldehydes with *tert*-butyl-chloroacetate afforded *tert*-butyl-glycidates, with *trans*/*cis* ratios 2.4–7.7.[103] When tetrabutylammonium bromide (TBAB) was added as phase-transfer catalyst, the ratio reversed to *cis*/*trans* 1.7–5.2. Rate constants of halohydrin anion formation, their cyclization, hydrolysis of diastereomers of glycidates, as well as the structure of the corresponding conformers of halohydrin were considered.

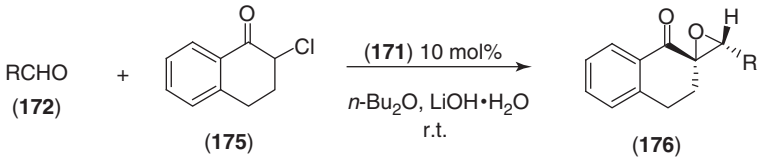
Table 7 Asymmetric Darzens condensation under phase-transfer conditions



No.	*R*	*Time (h)*	*Yield of **174** (%)*	*ee*[a]
1	*i*-Pr	60	80	53
2	Et	117	32	79
3	*n*-Pr	160	82	57
4	*i*-Bu	134	71	69
5	*i*-$BuCH_2$	91	50	62
6	Et_2CHCH_2	117	76	58
7	$Ph(CH_2)_2$	114	83	44
8	*c*-Hex	61	47	63
9	Ph	69	43	42

[a]Absolute configurations of **174a**, **174b**, **174c**, and **174i** were determined to be (α*S*, β*R*) by comparison of optical rotation.

Table 8 Asymmetric Darzens condensation under phase-transfer conditions using α-chloro cyclic ketone (**175**)



No.	*R*	*Time (h)*	*Yield of **176** (%)*	*ee*
1	*i*-Pr	61	96	69
2	*i*-Bu	63	86	74
3	*t*-$BuCH_2$	84	86	86
4	Et_2CH	252	67	84
5	*c*-Hex	62	80	69
6	Ph	43	67	59

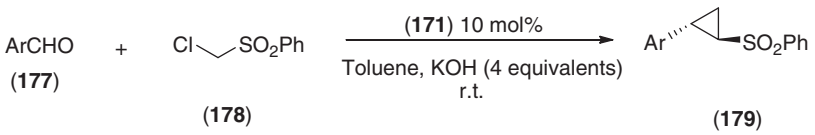
The phase-transfer catalyst is also effective for the Darzens condensation of benzaldehyde with α-chloroester, α-chloroacid, or α-chloroacetonitrile in the presence of base.[104]

Enantioselective Darzens condensation of benzaldehyde with phenacyl bromide (**199**) proceeds using C_2 symmetric chiral organoselenide-lithium hydroxide complexes as Lewis acid/Brønsted base bifunctional catalyst to afford the epoxide (**200**) (Scheme 53).[105]

2.14.4.2 Synthetic Applications

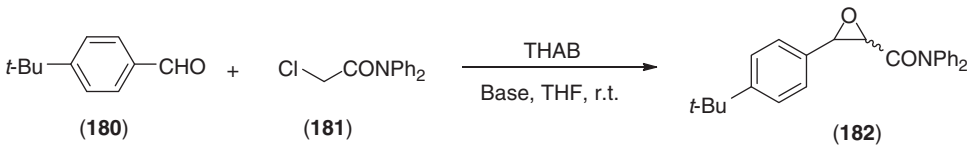
Enantiopure *cis*-α,β-epoxy carboxylic acid (**202**) were prepared via a modified Darzens condensation using the titanium-mediated bromination–aldolization of chiral acetate thioimide enolate and *N*-acetyloxazolidinethione (**201**), in the presence of diisopropylethylamine (DIPA) (Scheme 54).[106]

Table 9 Asymmetric Darzens condensation under phase-transfer conditions using chloromethyl phenylsulfone (**178**)



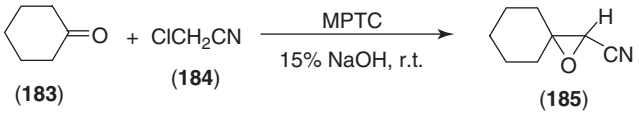
No.	*Ar*	*Time (h)*	*Yield of **179** (%)*	*ee*[a]
1	4-BrC_6H_4	1	80	64
2	3-BrC_6H_4	1.5	69	71
3	4-MeC_6H_4	2	84	78
4	4-*t*-Bu-C_6H_4	2	70	81
5	4-Ph-C_6H_4	1.5	71	72
6	3-PhO-C_6H_4	1.5	83	65
7	3-Me-C_6H_4	1	82	74
8	β-Naphthyl	1	94	68

[a]*ee* was determined by HPLC analysis.



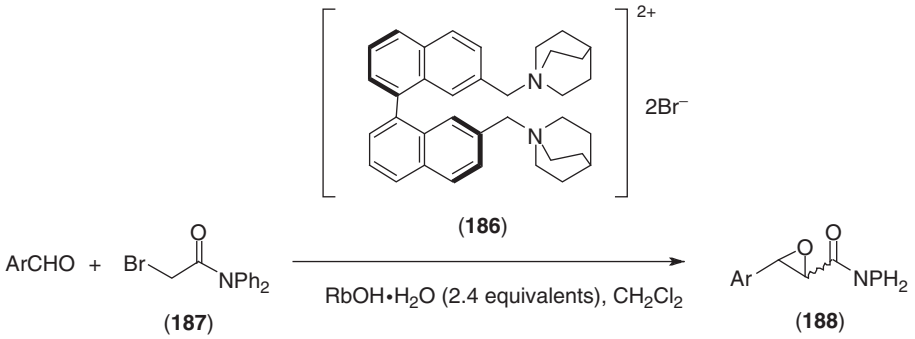
Yield: 61%, *cis* only

Scheme 49

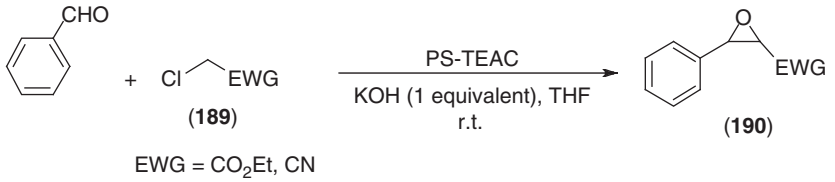


Scheme 50

Table 10 Asymmetric Darzens condensation under phase-transfer conditions using haloamide (**187**)



No.	*Ar*	*Conditions*	*Yield of **188** (%)*	*cis/trans*	*ee of cis*	*ee of trans*
1	3-BrC_6H_4	r.t., 14 h	93	2.4	51	60
2	4-$MeOC_6H_4$	r.t., 24 h	82	8.1	62	60
3	2-$MeOC_6H_4$	−10 °C, 132 h	>95	2.2	57	67
4	4-MeC_6H_4	−30 °C, 137 h	77	2.0	64	70
5	4-*t*-Bu-C_6H_4	r.t., 34 h	70	2.8	63	64



Scheme 51

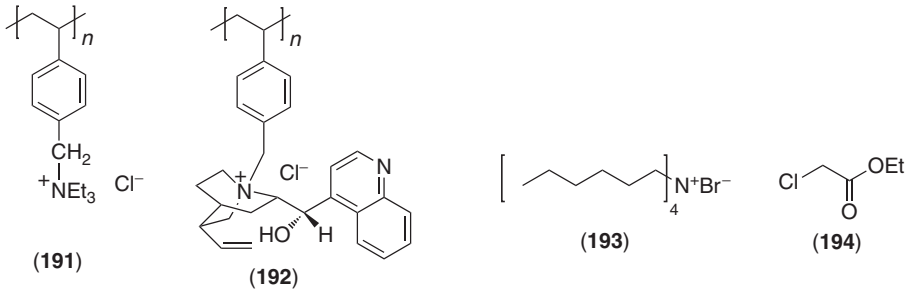
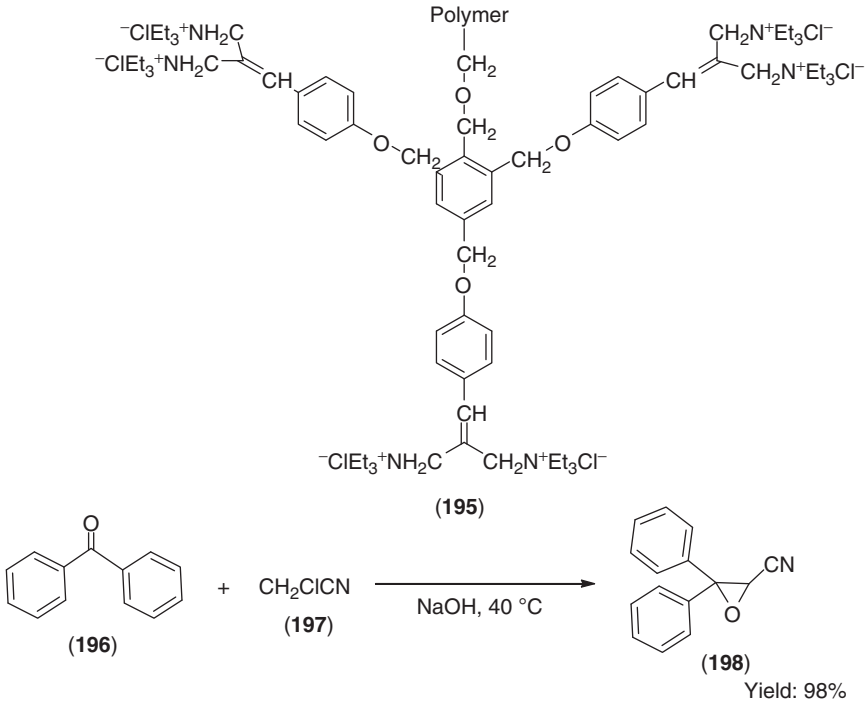


Figure 4 Polystyrene-supported triethylammonium chloride, PS-TEAC (**191**), polystyrene-supported cinchonidinium chloride (**192**), tetrahexylammonium bromide (**193**), and ethyl chloroacetate (**194**).



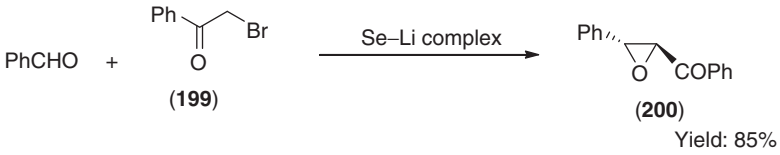
Scheme 52

In the presence of $Rh_2(OAC)_4$, the Darzens condensation of α,β-unsaturated carbonyl compounds with aryl-, heteroaryl-, and vinyldi-azoacetates gives diastereoselective synthesis of trisubstituted epoxides. For example, the reaction of cyclohexenone (**203**) with phenylazoacetate (**204**) affords epoxide (**205**) as a 6.8:1 mixture of diastereomers (Scheme 55).[107]

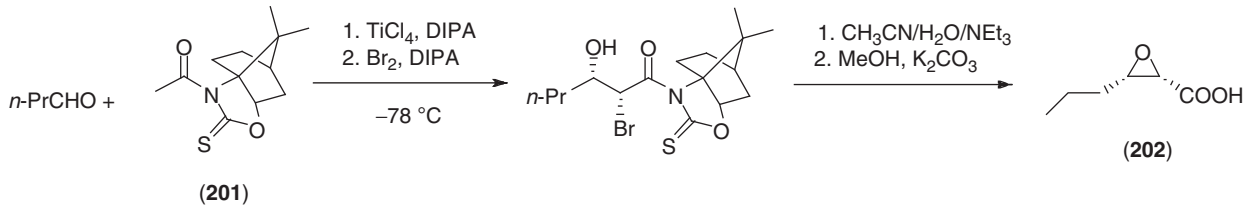
Highly enantioselective Darzens condensation into glycidic amides (**209**) is possible when using chiral camphor-derived sulfonium amides (**208**), which is prepared by alkylation of sulfide (**206**) with *N*,*N*-diethyl bromoacetamide (**207**) (Scheme 56).[108,109]

The Yb(OTf)3 catalyzes ring-opening of glycidic amides (**210**) with complete regioselectivity at the C_3 position for both S and N nucleophiles (Scheme 57).[109]

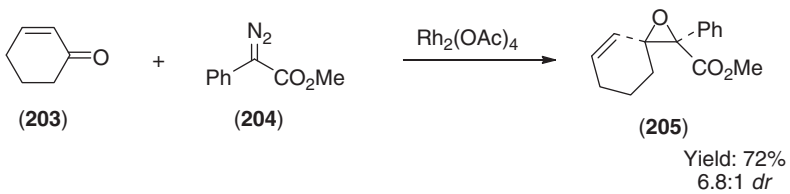
The Darzens condensation is utilized for the first step in the synthesis of alkylphenanthrene (**211**) (Scheme 58).[110]



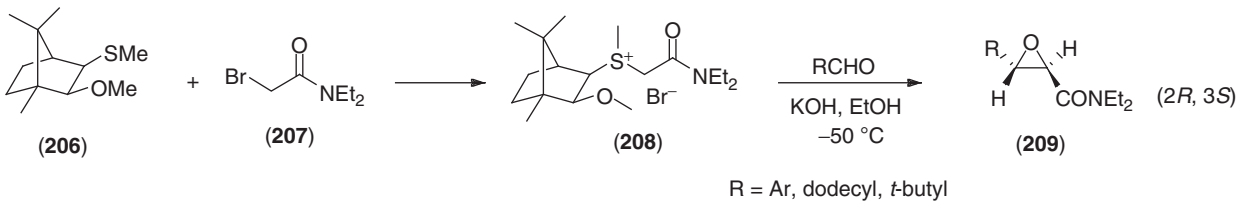
Scheme 53



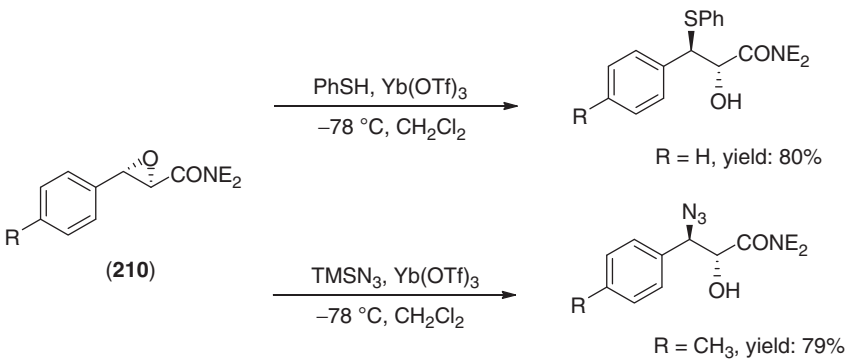
Scheme 54



Scheme 55

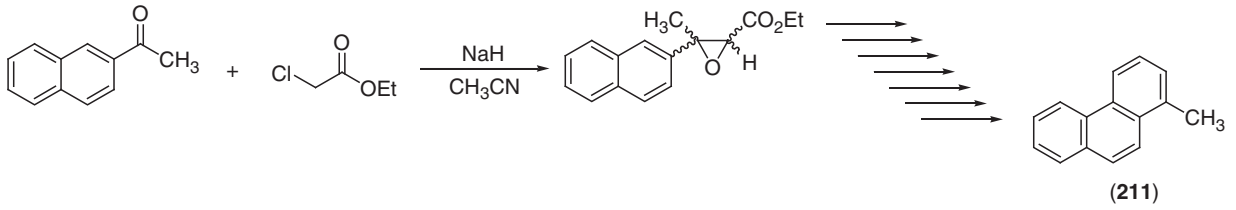


Scheme 56

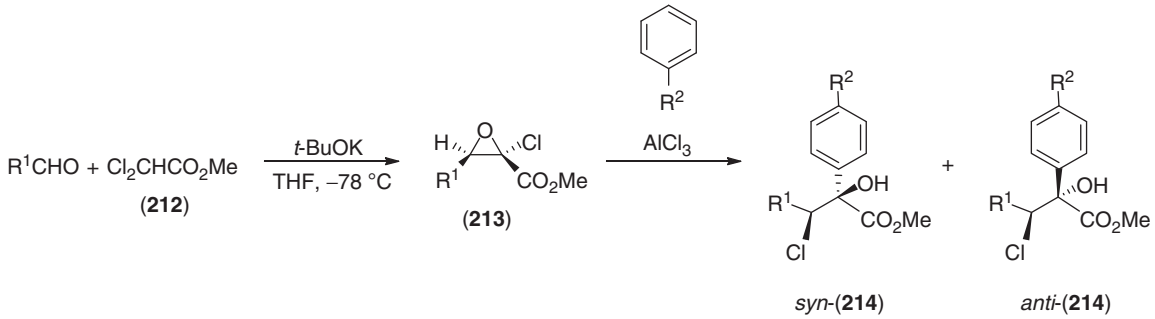


Scheme 57

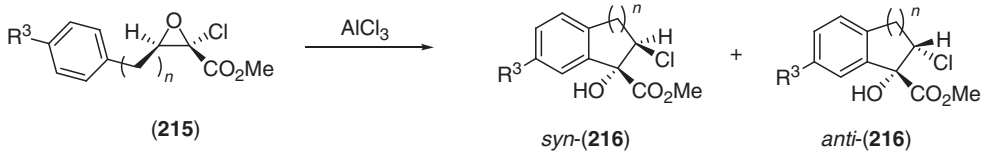
The epoxide (**213**) obtained by the Darzens condensation of aldehydes with methyl dichloroacetate (**212**) reacts with aromatic compounds in the presence of aluminum trichloride nucleophilically to afford α-aryl-β-chloro-α-hydroxyalkanoate (**214**) (Scheme 59).[111] The intramolecular nucleophilic addition of epoxide (**215**) results in cyclization of compound **216** (Scheme 60).[111]



Scheme 58



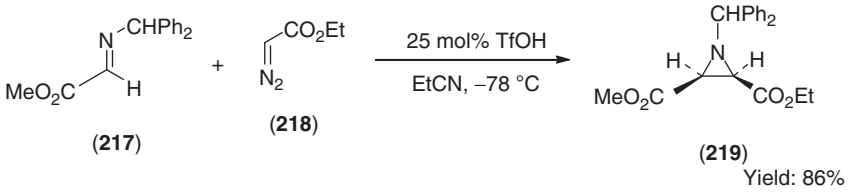
Scheme 59



Scheme 60

Pig's liver esterase was used efficiently in phosphate buffer for the separation of stereoisomeric mixture of *cis*/*trans*-ethyl arylglycidates produced by the Darzens condensation.[112]

The Brønsted acid catalyzes direct aza-Darzens condensation of Schiff base (**217**) with ethyl diazoacetate (**218**) to synthesize *N*-alkyl *cis*-aziridines (**219**) (Scheme 61).[113] Significantly, no products resulting from acid-promoted aziridin ring-opening were observed.

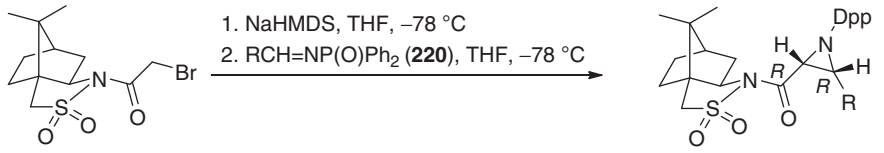


Scheme 61

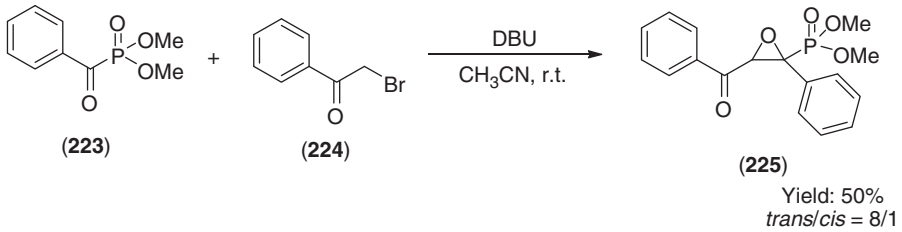
Cis-aziridines are selectively obtained by the aza-Darzens condensation of *N*-diphenylphosphinyl imine (*N*-Dpp, **220**) with chiral enolate derived from camphorsultam in the presence of NaHMDS as a base (Scheme 62).[114] Use of the chiral enolate derived from both antipodes of *N*-bromoacetyl 2,10-camphorsultam, (2*R*)-**221** and (2*S*)-**221**, with *N*-diphenylphosphinyl aryl and *tert*-butylimines proceeded in generally good yield to give (2′*R*,3′*R*)- or (2′*S*,2′*S*)-*cis*-*N*-diphenylphosphinyl aziridinoyl sultams (**222**) of high *de*.

However, the stereoselectivity of the reaction is dependent on the structure of the imine substituent: when the chiral enolate was reacted with arylimines substituted in the *ortho*-position, mixture of *cis*- and *trans*-2′*R*,3′*R*-aziridines were obtained, often with a complete selectivity in favor of the *trans*-isomer.[115]

The Darzens condensation of acyl phosphonates **223** with α-halo ketones **224** in the presence of base at room temperature affords *cis*- and *trans*-epoxyphosphonates **225** in good chemical yield (Scheme 63).[116] The diastereoselectivity of this



Scheme 62



Scheme 63

condensation reaction is easily controlled by changing the base. When DBU is used, the diastereomeric ratio (*trans*/*cis*) reaches up to 8/1.

Highly region- and stereocontrolled ring-opening reactions of aziridines have considerable value in organic synthesis. This is particularly true for aziridine 2-carboxylic acids and esters which not only lead to α- and β-amino acids but also can be transformed into vinyl aziridines and aziridino alcohol which themselves are useful building blocks and auxiliaries.[117] Enantiopure *N*-sulfinylaziridine 2-carboxylate esters **226** are utilized as building blocks in highly stereoselective asymmetric syntheses of amino acids (Figure 5). The *trans*-*N*-(*p*-toluenesulfinyl)-2-methyl-2-carbomethoxy-3-phenylaziridine (**229**) is synthesized by an asymmetric aza-Darzens condensation of *N*-sulfinyl imine **227** with methyl α-bromopropionate (**228**) in the presence of lithium bis(trimethylsilyl)amide (LiHMDS) as a base (Scheme 64).[118]

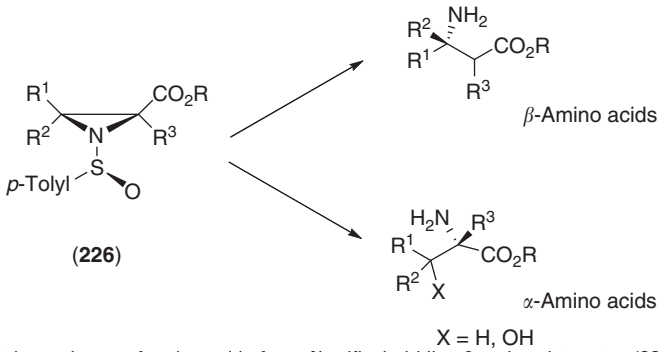
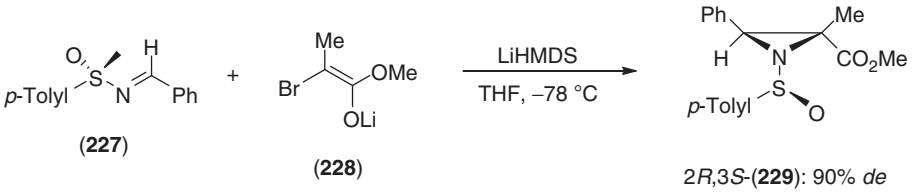
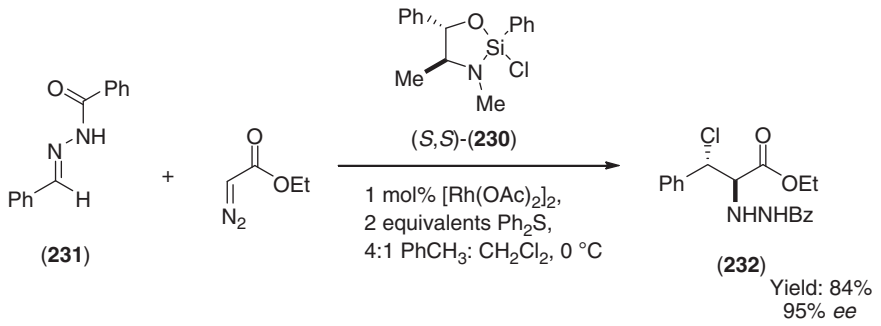


Figure 5 Stereoselective asymmetric syntheses of amino acids from *N*-sulfinylaziridine 2-carboxylate ester (**226**).



Scheme 64

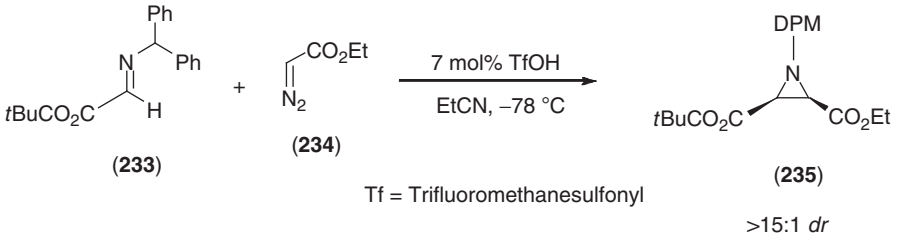
Dual functionality of chiral silane Lewis acid compound, (*S*,*S*)-**230**, enables tandem asymmetric aza-Darzens/ring-opening reactions to afford the compound (**232**) in 84% yield as a single regioisomer and diastereomer (>20:1 *rr* and *dr*) in 97% *ee* (Scheme 65).[119] The formation of complex between silane and hydrazon (**231**) plays an important role in these tandem reactions.



Scheme 65

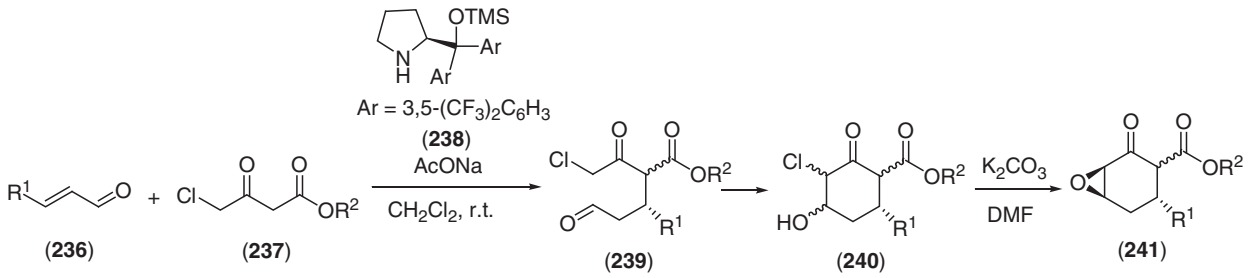
The aza-Darzens condensation of ethyl diazoacetate with Schiff bases using organic boronate catalysts as weak Lewis acids has also been reported.[120]

Strong Brønsted acid such as triflic acid acts as a catalyst for the diastereoselective aza-Darzens condensation of an imine (**233**) with ethyl diazoacetate (**234**) to aziridine (**235**), which is the product of a formal [2 + 1] cycloaddition reaction (Scheme 66).[121] *N*-Diphenylmethyl (DPM) imines **233** are derived from electron-deficient aldehydes.



Scheme 66

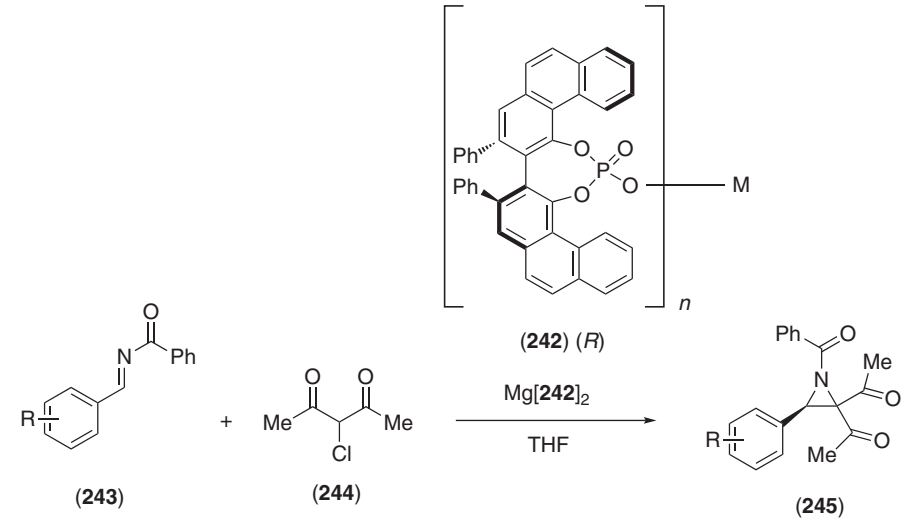
Asymmetric organocatalytic one-pot Michael–Darzens condensation gave highly functionalized complex epoxycyclohexanone derivatives (**241**).[122] The reaction of α,β-unsaturated aldehydes (**236**) with γ-chloro-β-ketoesters (**237**) in the presence of 2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxomethyl]pyrrolidine **238** and AcONa as additive in CH_2Cl_2 afforded an intermediate **239**, which is converted into aldol intermediate **240**. The product **240** is then transformed into optically active epoxycyclohexanones (**241**) in the presence of K_2CO_3 and DMF as cocatalyst via aldol-S_N2 reaction (Darzens condensation) (Scheme 67).



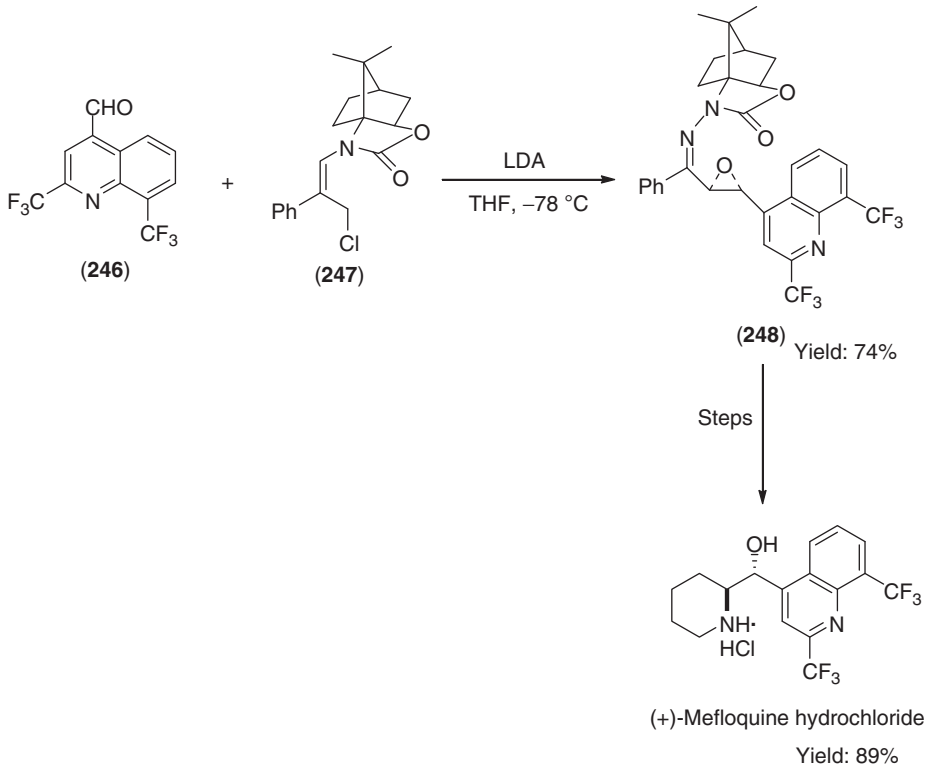
Scheme 67

Vaulted biphenanthrol magnesium phosphate salt (**242**) catalyzes asymmetric aza-Darzens condensation of *N*-benzoyl imine **243** with α-chloro-1,3-diketone (**244**), affording trisubstituted aziridine **245** (Scheme 68).[123]

The asymmetric Darzens condensation of aldehyde **246** with *N*-amino cyclic carbamate (ACC) chiral auxiliary (**247**) affording *trans*-diastereomer (**248**) is used for the total synthesis of (+)-mefloquine hydrochloride as an important antimalarial drug (Scheme 69).[124]



Scheme 68



Scheme 69

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2.15 Metal Homoenolates

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This chapter is a revision of the previous edition chapter by Isao Kuwajima, Eiichi Nakamura, Vol. 2, pp 441–454, © 1991, Elsevier Ltd.

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Glossary

Amphiphilic allylation A synthetic transformation responsible for the generation of both allyl cation and allyl anion species. Allyl acetates and carbonates, like allyl alcohols themselves, are reluctant to undergo heterolytic C–O bond cleavage. Pd(0) complexes activate these allylating agents to form π-allylpalladium intermediates through oxidative addition and serve as allyl cation equivalents to react with a wide range of nucleophiles (Tsuji–Trost reaction). However, transmetalation of the π-allylpalladium with organometalloids such as triethylborane, diethylzinc, and trialkylstannane enhances nucleophilicity to serve as allyl anion equivalents. Both electrophilic and nucleophilic allylations can be achieved under similar reaction system.

Barbier reaction An organic reaction responsible for the preparation of organometallic reagents from alkyl halides and metals (Mg, Al, Cr, Zn, In, Sn, Sm, etc.) or their salts in the presence of carbonyl compounds. As allyl halides are highly reactive toward Grignard reagents to afford the dimers as major by-products, it is quite hard to make allyl Grignard reagents separately. The way around this problem is to make allyl Grignard reagents in the presence of carbonyl compounds accompanying the formation of alcohols by nucleophilic attack of the allyl Grignard reagents on carbonyl compounds *in situ*.

Homoallylation An organic reaction responsible for the introduction of 1-butenyl-4-anion equivalent, '$^{-}CH_2CH_2CH{=}CH_2$,' toward electrophiles such as carbonyl compounds and alkyl halides. Homoallylation of aldehydes and ketones provides 4-penten-1-ol derivatives, 'bis-homoallyl alcohols.'

Homoenolate anion The synthetic equivalent for the propanal carbanion, '$^{-}CH_2CH_2CHO$.' The structure is the umpolung equivalent of an electrophilic reagent such as α,β-unsaturated aldehydes, for example, acrolein. Homoenolate anions react with some electrophiles, such as alkyl halides and carbonyl compounds, to form C–C bonds at the β-carbon atom.

Reductive coupling A synthetic transformation in which two or more π-systems (alkenes, alkynes, C$=$O and C$=$N bonds) are joined by C–C bond formation with the aid of a reducing agent in a single synthetic step. Reductive coupling reactions enable regio- and stereoselective double-bond construction and the enantio- and diastereoselective formation of alcohol and amine stereocenters by transition metal catalysts (Ni, Rh, Co, Ir, Ti, etc.) with stoichiometric reducing agents (H_2, $HSiR_3$, BR_3, ZnR_2, $AlHR_2$, etc.). These reactions include mechanisms initiated by oxidative cyclization of two π-components to form a metallacycle, by oxidative addition to metal alkyl groups or hydride species, and by oxidative addition to one of the π-components.

Umpolung The reversal of the normal polarity of a functional group. Acyl groups are generally electrophilic, whereas acyl anions are nucleophilic. The acyl anion synthon implies an umpolung of the acyl functional group. For example, cyclic thioacetals prepared from dithiols and aldehydes are transformed into the nucleophilic carbanions by treatment with strong bases. The carbanion is added to the carbonyl compounds following hydrolysis of the thioacetals to regenerate the functionalized electrophilic carbonyl groups. The sequential reactions are considered as the reversal of polarization of the carbonyl groups.

 doi:10.1016/B978-0-08-097742-3.00216-0

2.15.1 Introduction

The addition of carbon nucleophiles to carbonyl electrophiles is the most important strategy for C–C bond formation. Allylations of carbonyls with allylmetal species, aldol reactions, and ene reactions are incomparably powerful tools for modern organic synthesis. Although metal homoenolates are convenient and useful three-carbon chain synthon for nucleophilic functionalizations, there have been limitations due to difficulty in preparation and stability of metal homoenolate anion. In this chapter, some efficient C–C bond transformations involving transition metal-mediated reactions with siloxycyclopropane, α-heteroallylmetal, β-alkoxycarbonylallylmetal, and butenyl carbanion as homoenolate equivalents are particularly described.

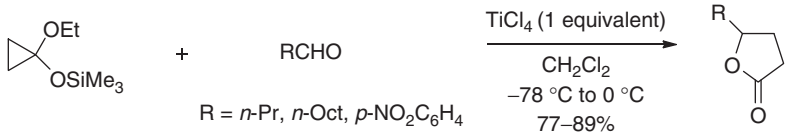
2.15.2 Preparation and Reactivity of Metal Homoenolates

2.15.2.1 Transition Metal-Mediated Reactions of Zinc Homoenolates

Homoenolate represents a three-carbon synthon containing β-anionic carbon atom to a carbonyl group and can serve as an important nucleophile for C–C bond formations. In contrast to enolate, the anionic site of homoenolate is too reactive; therefore, β-metal carbanion undergoes the irreversible cyclization to form the metal oxyanionic tautomer (Scheme 1).

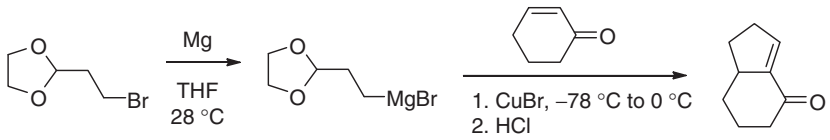
Scheme 1

Although any attempts to use homoenolate anion have not been achieved so far, the preparation of metal homoenolates often causes serious synthetic problems. The first example of the homoaldol reaction using homoenolate and carbonyls has been demonstrated by Nakamura and Kuwajima.[1] In the presence of $TiCl_4$, the addition of cyclopropane ketal as an ester homoenolate anion equivalent to a carbonyl compound delivers γ-butyrolactone in high yields (equation 1). Although the chlorination of hydroxyl group of homoaldol reaction products often emerges as a side reaction promoted by $TiCl_4$, the combination of $TiCl_4$ and $Ti(O\text{-}t\text{-}Bu)_4$ effectively improves the synthesis of various γ-butyrolactones from aldehydes and commercially available siloxycyclopropanes.[2]



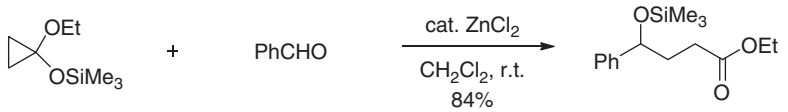
(1)

As an efficient method for homoaldol reaction, it has been reported that copper-catalyzed conjugate addition of the acetal-embedded Grignard reagent to cyclohexenone, deprotection, and intramolecular aldol condensation furnishes the bicyclic cyclopentene ring (Scheme 2).[3]



Scheme 2

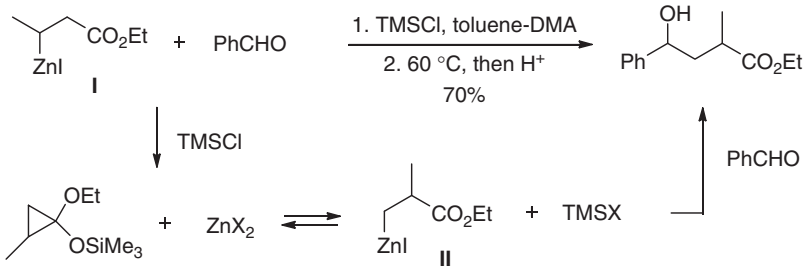
A remarkable innovative reaction with generation of zinc homoenolate has been developed. Zinc homoenolate is generated by the reaction of siloxycyclopropane with zinc chloride and reacts with PhCHO to give γ-siloxy esters *via* regioselective cleavage of the cyclopropane ring (equation 2).[4]



(2)

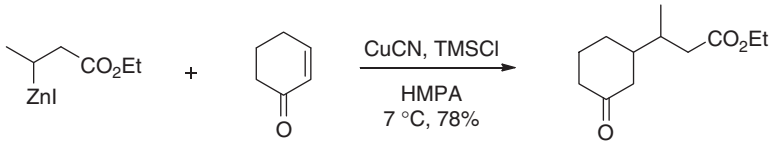
β-Zincioesters prepared from β-iodoesters and Zn-Cu in toluene/*N*,*N*-dimethylacetamide (DMA) undergo the remote Reformatsky reaction with aldehydes promoted by trimethylsilyl chloride to provide γ-hydroxy esters (Scheme 3).[5] The reaction of zinc

homoenolates with aldehydes proceeds via siloxycyclopropane intermediate involving an isomerization of zinc ester (**I**) to (**II**), in which α-methyl-γ-hydroxy ester is selectively produced in moderate yield.



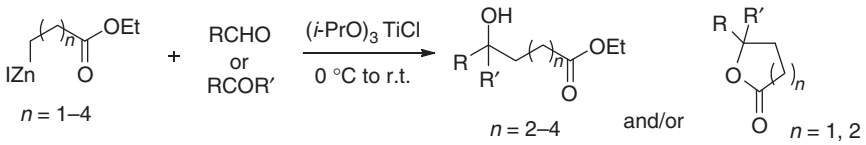
Scheme 3

Organozinc reagents bearing electrophilic functionalities such as ester and nitrile serve as Michael donors and add to α,β-unsaturated aldehydes, ketones, and esters in the presence of TMSCl and CuCN (equation 3).[6] The regiochemistry is in sharp contrast to the reactions with aldehyde shown in Scheme 3.

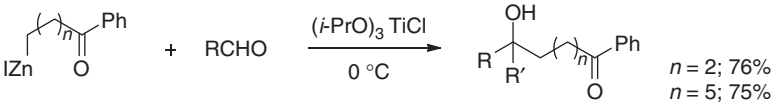


(3)

Chlorotriisopropoxytitanium-mediated condensation of β-, γ-, δ-, and ε-zinc esters with aldehydes and ketones provides the hydroxy esters and/or lactones (equation 4).[7] The most outstanding advantage of this method is exemplified by the selective reactions of zinc ketones with aldehdyes (equation 5). Ti(IV)-mediated condensation of γ- ($n=2$) and ζ-zinc ketones ($n=5$) with aldehydes proceeds smoothly to provide hydroxy ketones in reasonable yields.

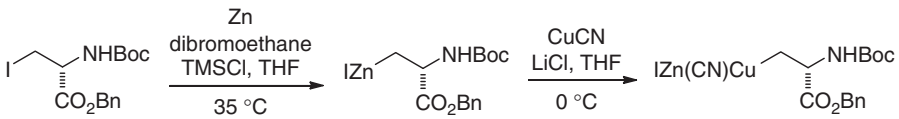


(4)

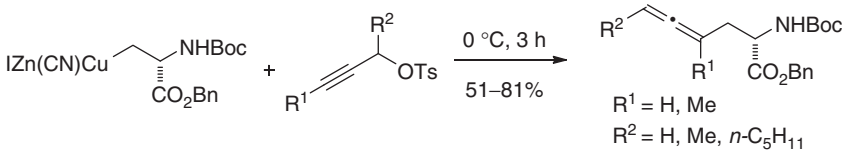


(5)

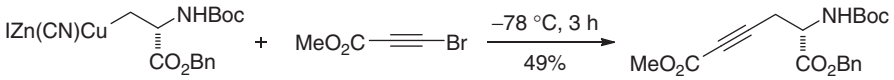
Serine-derived zinc homoenolates are readily prepared from the protected iodoalanine and zinc dust by treatment with TMSCl under ultrasonic activations (Scheme 4).[8] Amino acid homoenolates participate in the coupling reactions with substituted propargyl tosylates, acetylenic bromides, and alkenyl and aryl halides to furnish enantiomerically pure allenic, acetylenic, and heteroarylated amino acids in good to reasonable yields (equations 6–9).



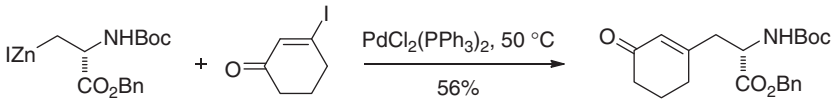
Scheme 4



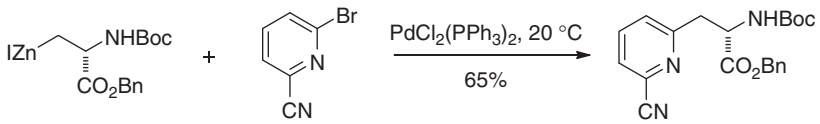
(6)



(7)

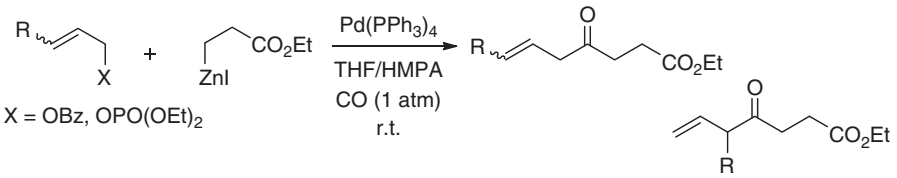


(8)



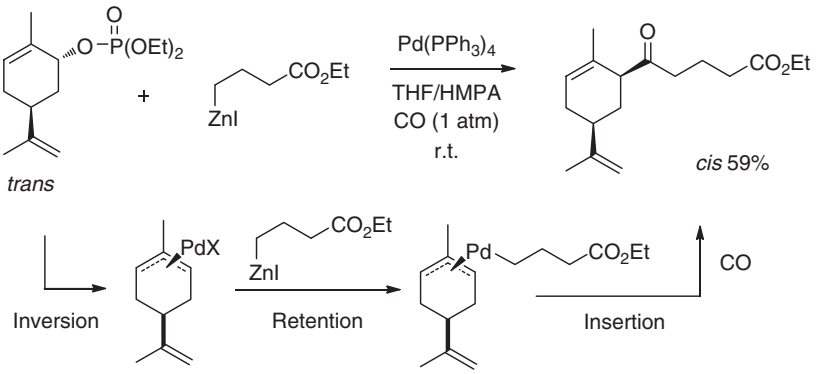
(9)

A wide variety of organozinc reagents such as β- and γ-zincio esters undergo a three-component reaction with allyl benzoates or allyl phosphates under carbon monoxide pressure to provide unsymmetrical ketones at ambient temperature promoted by Pd$(PPh_3)_4$ catalyst.[9] In this case, the use of hexamethylphosphoramide (HMPA) as a cosolvent is essential to success for carbonylation (equation 10).



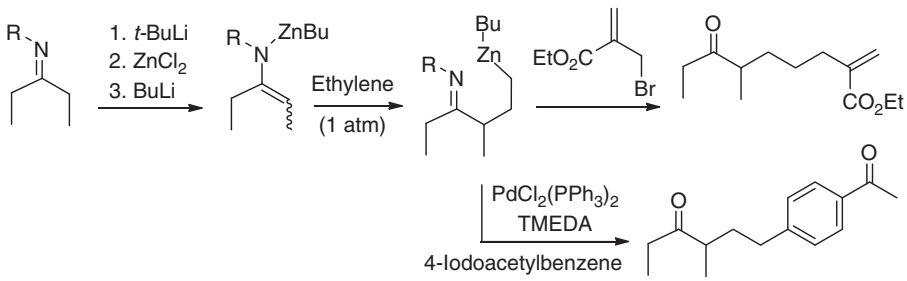
(10)

The stereochemical outcomes indicate that carbonylative coupling reaction proceeds stereospecifically with overall inversion at the allylic stereocenters and suggest that a sequence of steps outlined in Scheme 5 proceeds without losing stereochemical integrity.



Scheme 5

Zinc enamides prepared from *N*-aryl imines undergo addition to unactivated olefins, such as ethylene, 1-octene, and isobutylene, in order to generate α-alkylated γ-zincioimines, which can take part in the further C–C bond formations with carbon electrophiles to give α-alkylated ketones in a three-component-coupling manner (Scheme 6).[10] These transformations provide

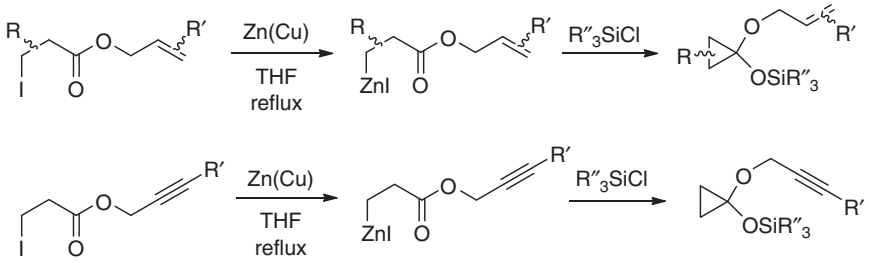


Scheme 6

new methods for the efficient synthesis of α-secondary and -tertiary alkylated ketones that have been difficult to obtain by the conventional method relying on the reaction of alkyl halides with metal enolates and enamides.

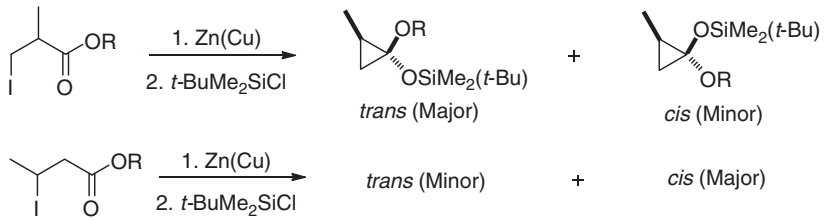
2.15.2.2 Preparation and Reaction of 1-Siloxycyclopropane

1-Allyloxy-1-siloxycyclopropanes and 1-propargyl-1-siloxycyclopropanes are synthesized from allyl β-iodopropionates and propargyl β-iodopropionates, respectively, by treatment with Zn–Cu and silylating agents (Scheme 7).[11]



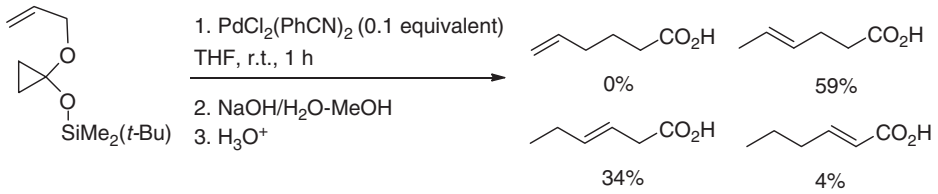
Scheme 7

In this case, the stereoselectivity with which β-iodo-α-methylpropionates provide the *trans* isomers is generally higher than the one with which the corresponding β-iodobutyrates furnish the *cis* isomers (Scheme 8).[12] There seems to be no apparent correlation between the stereoselctivity and the steric bulk of the alcoholic parts, R, of the iodoesters.

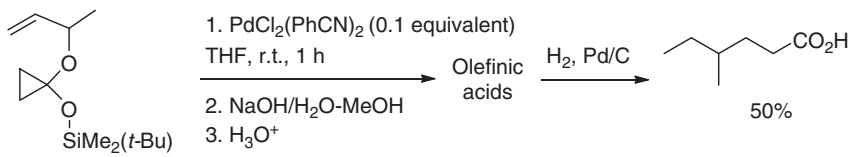


Scheme 8

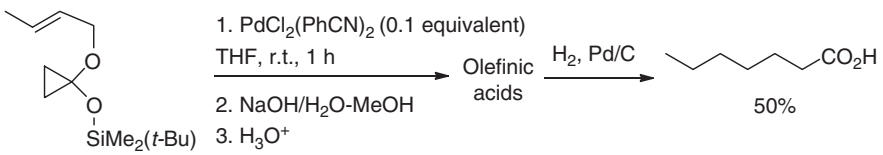
Pd(II) complex catalyzes the rearrangement of 1-allyloxy-1-siloxycyclopropanes to provide a mixture of Δ^2-, Δ^3-, Δ^4-hexenoic acids. The rearrangement proceeds via a double-bond isomerization followed by a ring opening of cyclopropane (equation 11).[13] *O*-α-methally and *O*-crotyl-1-siloxycyclopropanes are subjected to the rearrangement to give the carboxylic acids in reasonable yields (equations 12 and 13). The regiospecificities seem to support the reaction mechanism via Pd-catalyzed olefinic isomerization and cyclopropane ring opening shown in Scheme 9.



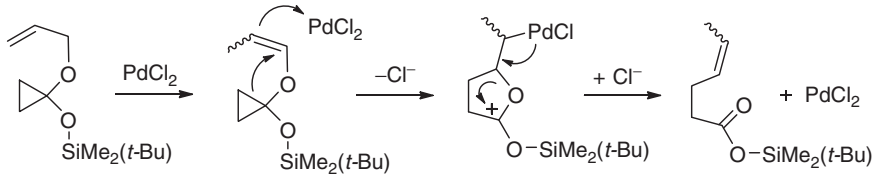
(11)



(12)

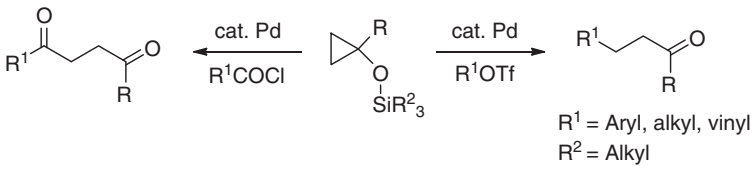


(13)

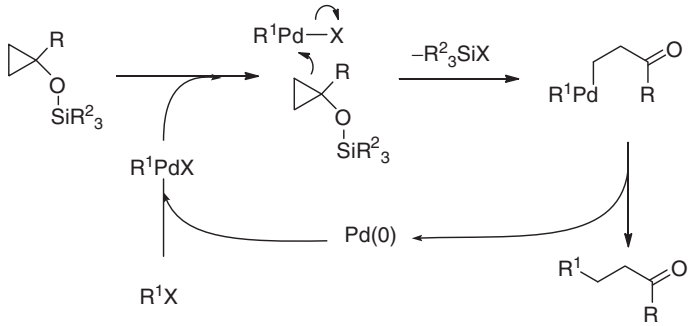


Scheme 9

The reaction of a wide variety of siloxycyclopropane with acid chlorides and aryl and vinyl triflates in the presence of Pd catalyst gives 1,4-diketones and β-substituted ketones, wherein both the cyclopropane ring cleavage and the C–C bond formation have been achieved in a single catalytic process (Scheme 10). An electrophilic organopalladium species cleaves the cyclopropane ring and the resulting β-palladium ketone intermediate undergoes reductive elimination to give the corresponding 1,4-diketons and β-substituted ketones (Scheme 11).[14]

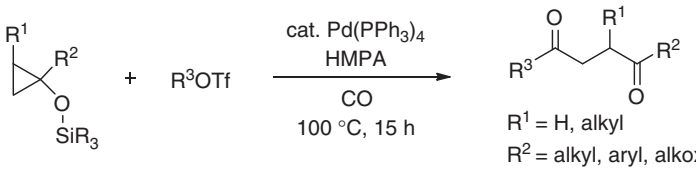


Scheme 10

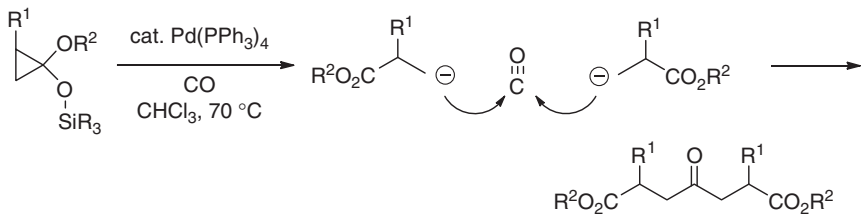


Scheme 11

Pd-catalyzed coupling reaction of siloxycyclopropane with an aryl triflate under carbon monoxide pressure (10–20 atm) in HMPA provides the alternate synthetic routes to 1,4-diketones (equation 14).[15] In chloroform, 4-keto pimelates are synthesized by three-component coupling of two molecules of a siloxycyclopropane and carbon monoxide (equation 15).



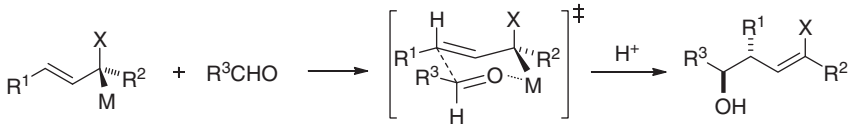
(14)



(15)

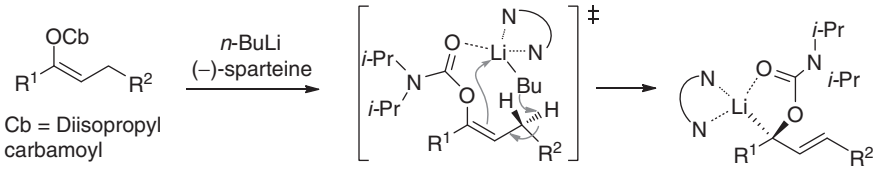
2.15.2.3 Lithium Homoenolates

Enantiomerically enriched, 1-heteroatom-substituted allyl lithium species serve as powerful homoenolate equivalents and are applicable to the synthesis of chiral γ-hydroxy ketones in a reasonable way.[16] The 1-nitrogen and -oxygen heteroatom-substituted allyl lithium species react with aldehydes and ketones with complete 1,3-transfer of chirality to form optically active homoaldol products through the six-membered ring transition state (Scheme 12). The substituent X is a complexing *N,N*-dialkylcarbamoyloxy group which enhances the kinetic acidity in the deprotection of the allylic precursor and is able to hold the counterion at the α-position.



Scheme 12

Efficient approach to 1-aryl ketone homoenolates by enatiotopos-differentiating γ-deprotonation of 1-aryl-1-alkenyl *N,N*-diisopropylcarbamates by *n*-BuLi/(–)-sparteine is demonstrated (Scheme 13, Table 1). Asymmetric carbolithiation of enol carbamate and treatment with ketones provide the homoaldol adducts in reasonable yields with excellent enantioselectivity. During removal of the *pro-R* proton at C3 position in the nine-membered cyclic transition state, the lithium cation migrates along the π-system to C1 position in order to form the chiral five-membered lithium species, and then reacts with carbonyl compounds at the γ-posotion (Scheme 14).



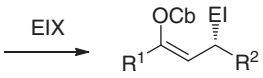
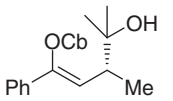
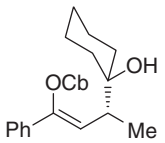


Table 1. Reaction of Allyl Lithium with Electrophile

EIX	product (R^1 = Ph, R^2 = Me)	yield (%), *ee* [%]
Acetone		(69%), [97% *ee*]
Cyclohexanone		(57%), [93% *ee*]

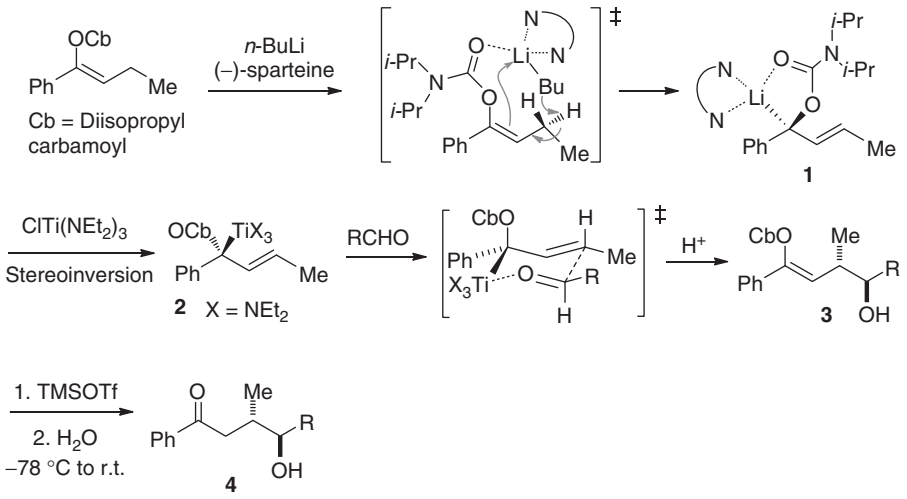
Scheme 13

The titanium compound **2**, which is formed from carbolithium **1** with stereoinversion, adds to aldehydes with 1,3-chirality transfer and provides optically active homoalodol adducts **3**. Hydrolysis of 1-aryl-1-alkenyl carbamates to γ-hydroxyketones is possible by treatment with TMSOTf and subsequent addition of water.

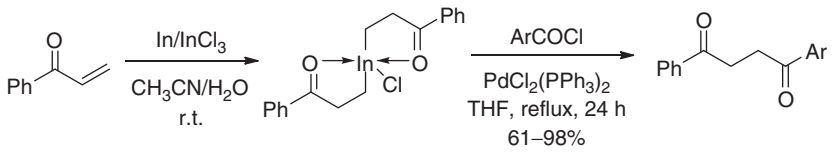
2.15.2.4 Indium and Lanthanide Homoenolates

Indium homoenolate is water tolerant and can serve as the carbon nucleophile for the C–C bond formation in aqueous media. Indium homoenolate is readily synthesized via the oxidative addition of In/$InCl_3$ to α,β-unsaturated aldehydes and ketones and is useful for the synthesis of 1,4-dicarbonyl compounds by subjecting it to acid chlorides in the presence of Pd catalyst (Scheme 15).[17]

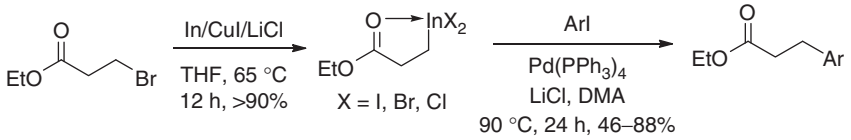
Esters-containing indium homoenolate via a direct insertion of indium into β-halo esters in the presence of CuI/LiCl is useful for C–C bond formations (Scheme 16).[18] The synthetic utility of the indium homoenolate is demonstrated by palladium-catalyzed cross-coupling reaction with various aryl halides in DMA. The cross-coupling reaction proceeds efficiently with a great tolerance to functional groups such as formyl and hydroxyl groups.



Scheme 14

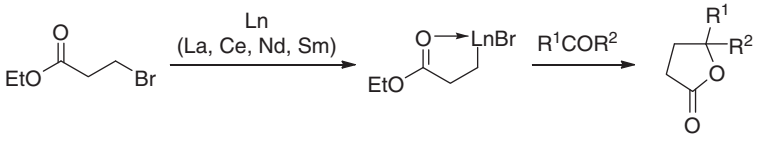


Scheme 15

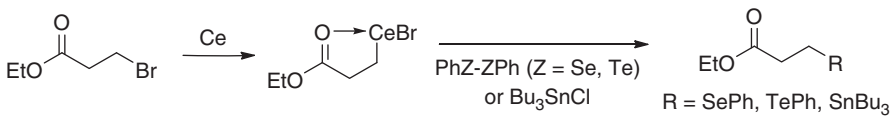


Scheme 16

The reaction of β-halopropionate esters with lanthanoid metals (La, Ce, Nd, Sm, etc.) in THF efficiently produces lanthanoid homoenolates, which then react with ketones to provide γ-butyrolactones under mild conditions (Scheme 17).[19] Furthermore, treatment of these lanthanoid homoenolates with diphenyl diselenide, ditelluride, and tri-*n*-butyltin halides forms β-phenylseleno, β-phenyltelluro, and β-tri-*n*-butylstannyl esters, respectively (Scheme 18).



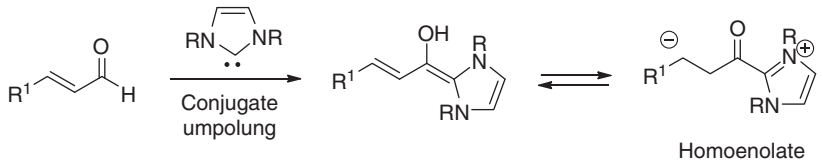
Scheme 17



Scheme 18

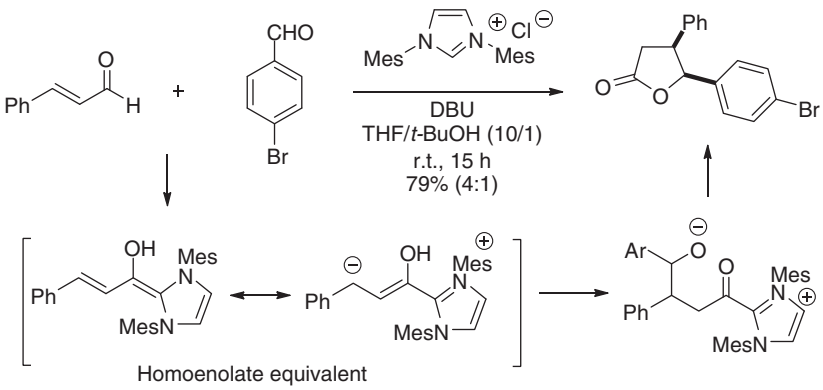
2.15.3 Homoenolates Generated by *N*-Heterocyclic Carbene (NHC)

Recent introduction of a protocol for the generation of homoenolate directly from enals by nucleophilic NHC catalysis has been reported for the modern organic synthesis.[20] Bode and Glorius using NHC catalyst independently developed a conceptually new approach for the generation of a homoenolate from an enal.[21,22] The addition of NHC to an α,β-unsaturated aldehyde can generate a conjugated enol following tautomerization to the homoenolate equivalent (Scheme 19).

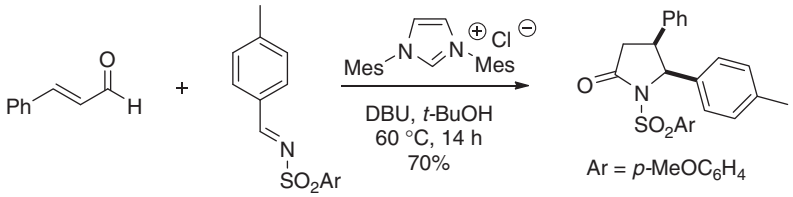


Scheme 19

The homoenolate derived from NHC undergoes enal–aldehyde annulation with aldehydes leading to the efficient synthesis of γ-butyrolactones. The reaction proceeds by addition of the homoenolate to an aldehyde to form an alkoxide intermediate, which is trapped intramolecularly by the activated carboxyl surrogate (Scheme 20). Using aldimines as electrophiles, synthesis of γ-lactams is also accomplished under similar way (equation 16).[23]

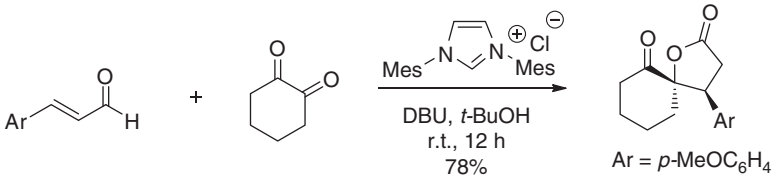


Scheme 20



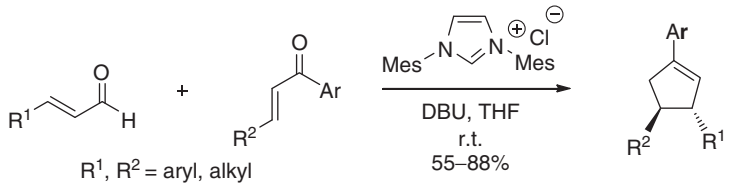
(16)

In the presence of a catalytic amount of 1,3-dimesitylimidazol-2-ylidene (IMes), the reaction of 1,2-cyclohexanedione with a wide array of cinnamaldehydes provides the spiro-γ-butyrolactones in high yields with excellent diastereoselectivity (equation 17).[24]



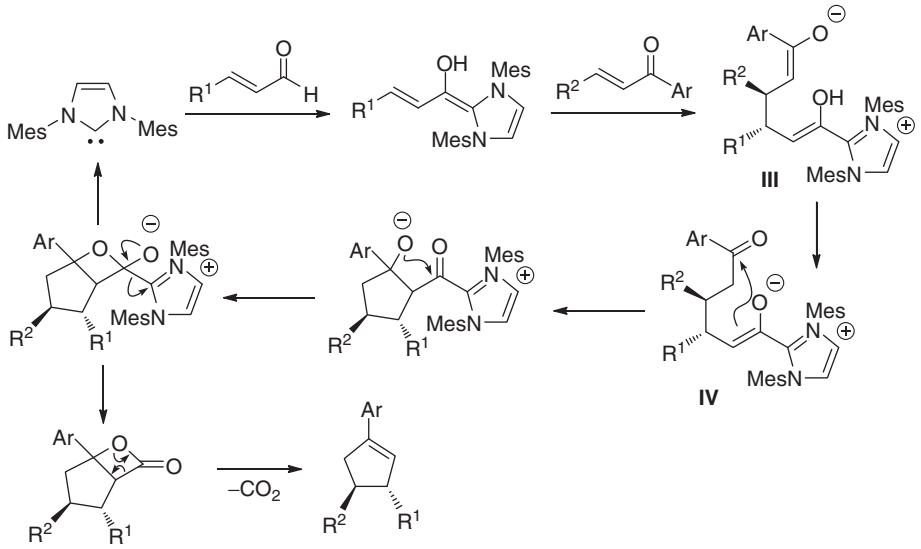
(17)

When enones are used as electrophiles, the reaction feature has changed dramatically. Efficient formation of 3,4-*trans*-disubstituted 1-arylcyclopentenes is observed via the homoenolate coupling reaction process (equation 18).[25]



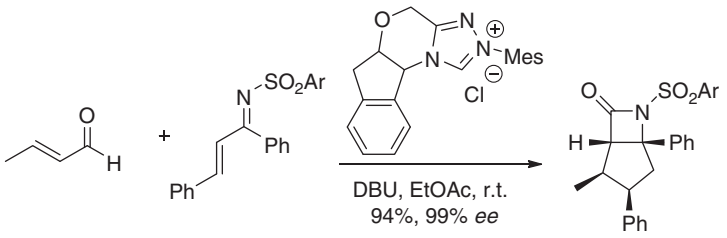
(18)

It is assumed that the conjugate addition of homoenolate to chalcone produces enolate **III**, which does not immediately engage in an intramolecular aldol reaction, instead, it undergoes proton transfer to generate more stable enolate intermediate **IV** (Scheme 21). Subsequent intramolecular aldol reaction of enolate **IV** proceeds to give the cyclopentene via β-lactonization and a retro [2+2] cycloaddition process of the β-lactone with liberation of carbon dioxide.



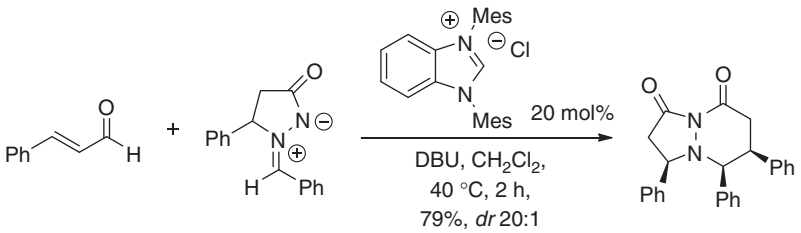
Scheme 21

In an extension of this reaction, bicyclic β-lactams are synthesized from α,β-unsaturated aldehyde and unsaturated *N*-sulfonyl ketimines. *cis*-Configuration of the cyclopentane is observed by crossed-benzoin-oxy-Cope reaction involving secondary orbital overlap between the Breslow intermediate and the unsaturated aldimine (equation 19).[26]

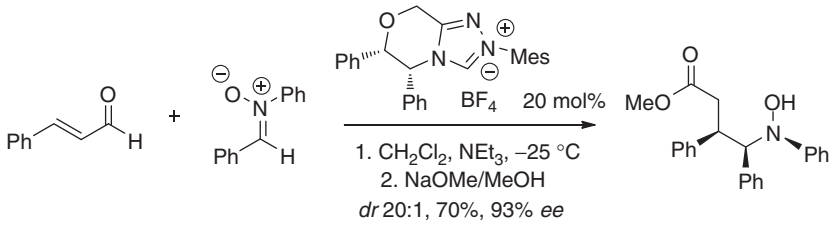


(19)

Homoenolate-mediated C–N bond formation has been demonsrtated by cycloaddition reactions with 1,3-dipoles. Azomethine imines and nitrones undergo the formal [3+3] cycloaddition reaction with enals promoted by NHC catalyst to form pyridazinones and γ-amino esters (equations 20 and 21).[27,28]

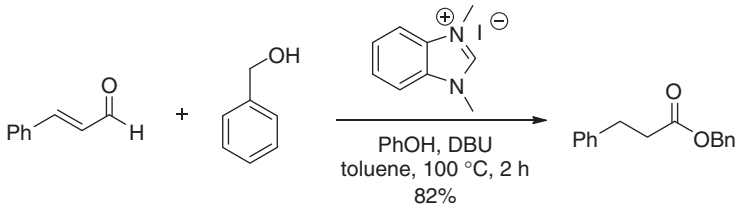


(20)



(21)

Scheidt and Chan have reported that enal can be converted to a saturated ester by NHC-catalyzed addition reaction of alcohols (equation 22).[29] Phenol acts as a proton source to convert NHC-bound enol from the homoenolate and readily accelerates nucleophilic displacement by the alcohols.

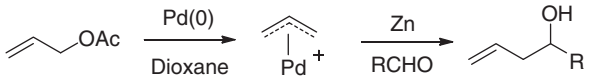


(22)

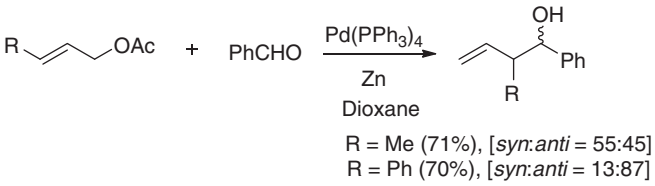
2.15.4 Transition Metal-Catalyzed Nucleophilic Allylation of Carbonyls

2.15.4.1 Umpolung of π-Allylpalladium by Zinc Dust

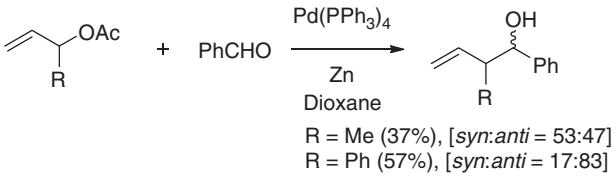
π-Allylpalladium is recognized as an allyl cation equivalent and is widely utilized for the allylation of a variety of soft nucleophiles. Umpolung of π-allylpalladium prepared from allylic alcohols and their derivatives can be accomplished by reduction with metals or organometallic compounds and can be applicable for efficient C–C bond formation serving as allyl anion equivalents toward carbonyl electrophiles.[30] Allylic acetates are reduced by zinc dust in the presence of a catalytic amount of $Pd(PPh_3)_4$ to serve as allylic anions reacting with various aldehydes to afford the homoallylic alcohols (Scheme 22).[31] When two equivalents of allylic acetates are used, the isolated yields of homoallyl alcohols decrease compared with the yields of five equivalents of the acetates. Aldehydes regioselectively attack at highly substituted allylic positions of the π-allylpalladium to give a single regioisomer as branched homoallyl alcohols (equations 23 and 24).



Scheme 22



(23)

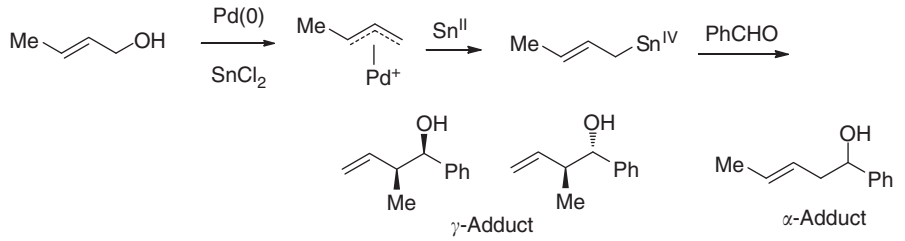


(24)

2.15.4.2 Reaction of π-Allylpalladium with Tin(II) Chloride and Allylstannane

Allylic alcohols can be applied to the carbonyl allylation as allyl anion equivalents promoted by $PdCl_2(PhCN)_2$ catalyst and $SnCl_2$ (Scheme 23).[32] The nucleophilic allylation of benzaldehyde with *trans*-crotyl alcohol takes place in any polar solvent, where $SnCl_2$

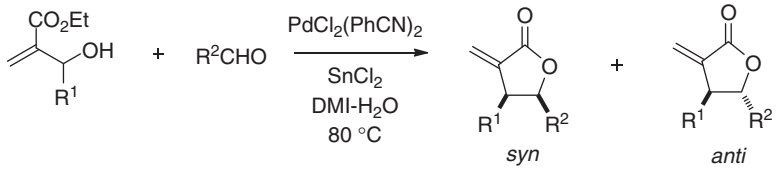
is dissolved to form allyltin(IV) intermediates effectively. The addition of large amount of water in solvent enhances the *anti* stereoselectivity.



solvent	yield %	*syn*:*anti*:α-adduct
DMI	63	29:71:0
THF	72	22:25:53
THF (10 equivalents H_2O)	74	16:84:0
DMSO (3 equivalents H_2O)	84	86:14:0
DMSO (170 equivalents H_2O)	70	16:84:0

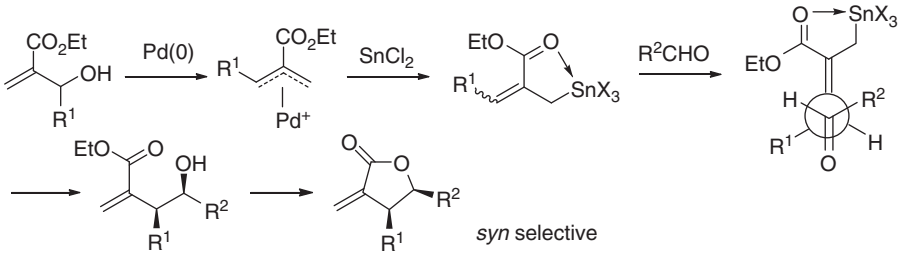
Scheme 23

Under similar conditions, ethyl 2-(hydroxymethyl)acrylates undergo 2-ethoxycarbonylallylations of various kinds of aldehydes to produce α-methylene-γ-butyrolactones with high *syn* stereoselectivity (equation 25).[33] In this case, the lactones can formally be considered as adducts of homoenolates and aldehydes. The *syn* addition proceeds via an acrylic antiperiplanar transition state, which suggests the existence of coordination of oxygen atom of the ester group to Sn(IV) atom in allyltin intermediate in order to disturb the formation of six-membered transition state (Scheme 24).



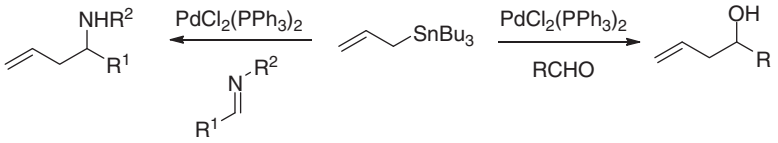
(25)

R^1 = Me, R^2 = Bu, 40% [*syn*:*anti* = 95:5]
R^1 = Me, R^2 = *c*-C_6H_{11}, 38% [*syn*:*anti* = 96:4]
R^1 = Me, R^2 = *p*-$MeO_2CC_6H_4$, 40% [*syn*:*anti* = 95:5]
R^1 = Ph, R^2 = *p*-$MeO_2CC_6H_4$, 18% [*syn*:*anti* = 100:0]

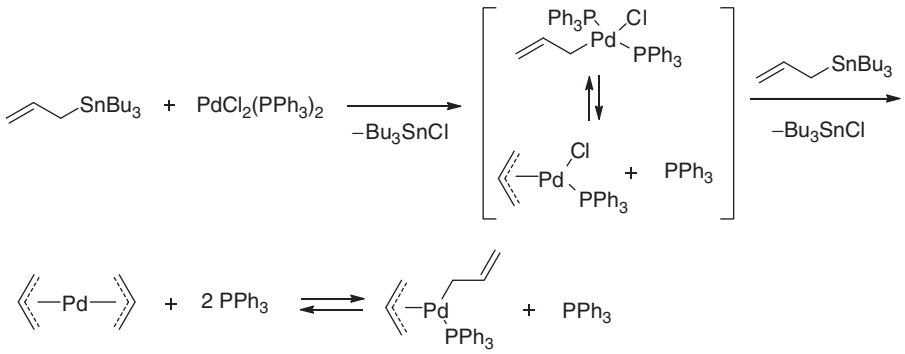


Scheme 24

Reactions of allylstannanes with aldehydes and aldimines are catalyzed by $PdCl_2(PPh_3)_2$ complex giving rise to the corresponding homoallyl alcohols and homoallylamines, respectively (Scheme 25).[34] Not only allyltributylstannane but also methallyl- and crotyltributylstannane can be utilized in the similar catalytic system. The reaction proceeds with the formation of bis-π-allylpalladium intermediate as an allyl anion equivalent, which is confirmed by NMR spectroscopy (Scheme 26). The nucleophilic reactivity of this intermediate is in marked contrast to the ordinary allylstannanes. It is widely known that the reactivity of allylstannanes to aldehydes is higher than that of aldimines in the presence of Lewis acid, whereas it is notable that the reactivity of bis-π-allylpalladium to aldimines are higher than that of aldehydes.

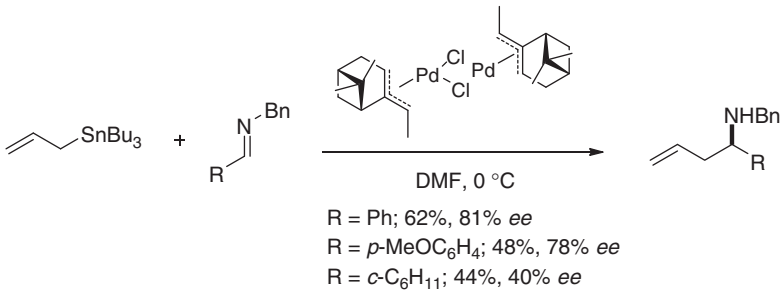


Scheme 25



Scheme 26

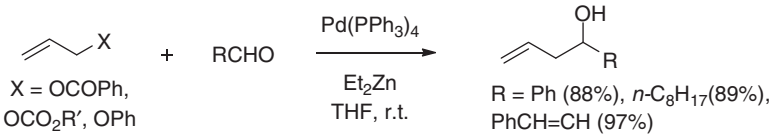
Asymmetric allylation of aldimines providing chiral homoallylamines is accomplished by treatment with allylstannanes and π-allylpalladium chloride dimer which is derived from (*1S*)-β-(−)-pinene (equation 26).[35] The asymmetric induction is successful for aldimines prepared from alkylamines; however, no asymmetric induction is observed for aniline-aldimines.



(26)

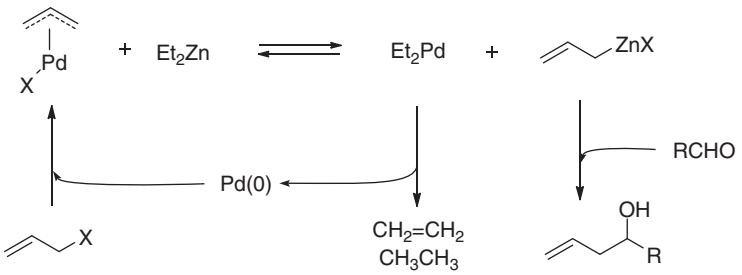
2.15.4.3 Umpolung of π-Allylpalladium Promoted by Diethylzinc and Triethylborane

Allyl esters, carbonates, halides, and phenyl ethers undergo the nucleophilic allylations of aldehydes, ketones, and esters to provide homoallyl alcohols at room temperature in the presence of diethylzinc and $Pd(PPh_3)_4$ catalyst (equation 27).[36] The reactions are undertaken under Barbier conditions involving allylzinc species generated by transmetallation of π-allylpalladium with diethylzinc (Scheme 27). The allylzinc species undergoes allylation of carbonyl compounds, and diethylpalladium decomposes via reductive elimination and/or β-hydrogen elimination to provide Pd(0) species and volatile organic compounds.

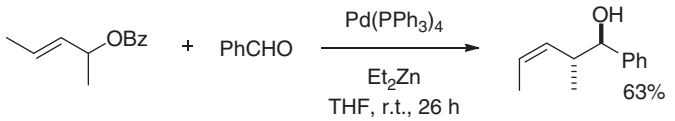


(27)

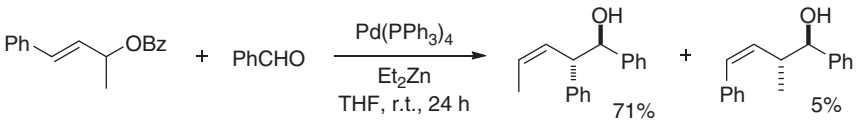
Although 1- and 3-monosubstituted allylic benzoates generally show a low diastereoselectivity, 1,3-disubstituted allyl benzoates display a remarkably high diastereoselectivity, providing (*Z*)-*anti*-isomers exclusively (equations 28 and 29).[37] Bicyclic lactone provides *trans,syn*-adduct as a single diastereomer in almost quantitative yields (equation 30). Stereochemical outcome is outlined in Scheme 28, which involves oxidative addition of the lactone to Pd(0), with inversion of configuration and transmetallation with diethylzinc, as well as retention of configuration. Allylation of PhCHO proceeds *via* six-membered chair-like transition state, placing the phenyl group in an equatorial position.



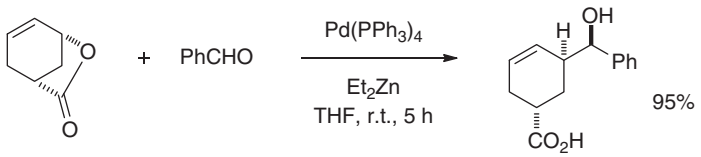
Scheme 27



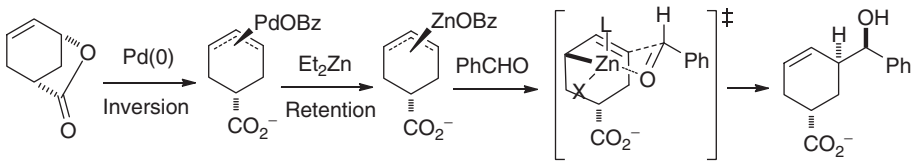
(28)



(29)

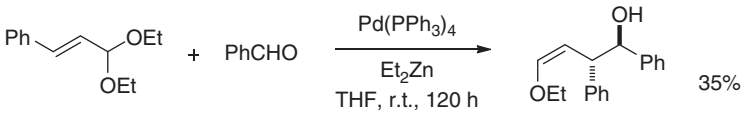


(30)

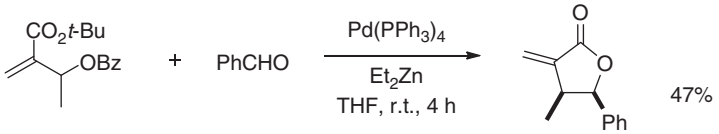


Scheme 28

Cinnamaldehyde diethyl acetal undergoes umpolung by diethylzinc to react with PhCHO to furnish (*Z*)-*anti* 4-ethoxy homoallyl alcohol with excellent regio- and stereoselectivity (equation 31). *β*-Alkoxycarbonyl allyl benzoate provides *syn*-adducts with PhCHO exclusively and spontaneously cyclizes to give *α*-methylene-*γ*-butyrolactone derivatives under similar conditions (equation 32).[38] These lactones are regarded as the reaction products of aldehydes and *β*-carbanion equivalents.



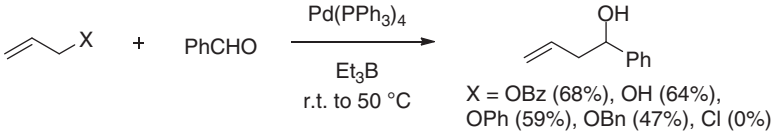
(31)



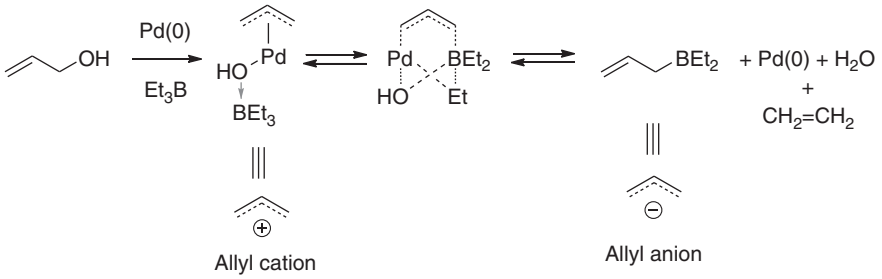
(32)

Triethylborane promotes the similar umpolung of *π*-allylpalladium generated *in situ* from allyl esters, ethers, and alcohols with Pd(0) catalyst and provides the nucleophilic allylation product of aldehydes (equation 33).[39] In this case, allyl halides fail to undergo the nucleophilic allylations. Triethylborane acts as Lewis acid to activate the allylic alcohols giving rise to the

π-allylpalladium by oxidative addition (Scheme 29). In the presence of electrophiles such as aldehydes and ketones, triethylborane promotes an exchange reaction of ethyl and allyl groups through umpolung of π-allylpalladium, and then serves as ally anion equivalent in a similar way to the reaction by diethylzinc.

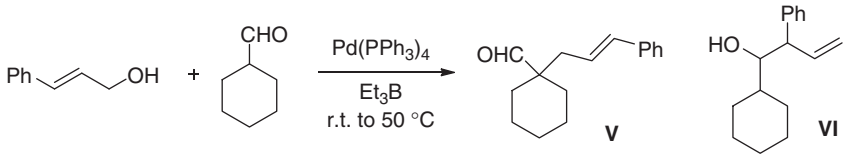


(33)



Scheme 29

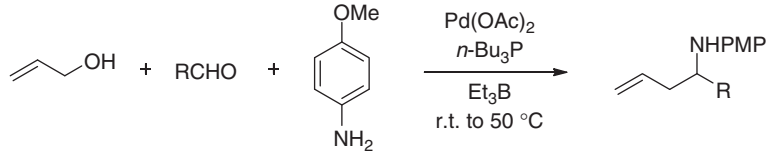
α-Allylic alkylation of aliphatic aldehydes can be readily achieved by direct use of aldehydes and allylic alcohols in the presence of Pd(0) catalyst, triethylborane, triethylamine, and lithium chloride at room temperature of 50 °C (equation 34).[40] The addition of lithium chloride and triethylamine retards the transmetallation of π-allylpalladium with triethylborane and provides α-allylated aldehyde **V** predominantly.



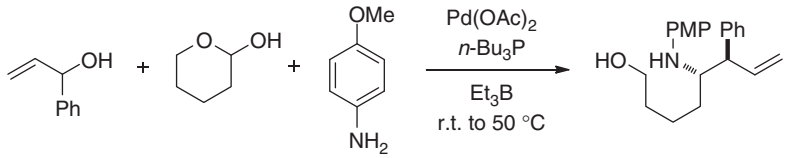
(34)

Run	Additive	yield (%) V	yield (%) VI
1	none	30	39
2	Et_3N (1.2 equivalents)	70	23
3	LiCl (1.0 equivalent)	0	0
4	Et_3N (1.2 equivalents) + LiCl (1.0 equivalent)	92	4

The Pd/triethylborane system has been successfully extended to the nucleophilic allylation of various aldimines derived from aromatic aldehydes and aliphatic aldehydes with primary amines (equation 35).[41] *N,O*-Acetals prepared from *p*-anisidine and lactols can participate in the similar nucleophilic allylation to give ω-hydroxyhomoallylamines with high regio- and stereoselectivity (equation 36).[42]

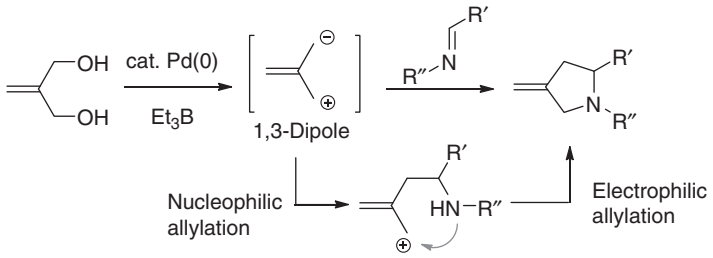


(35)



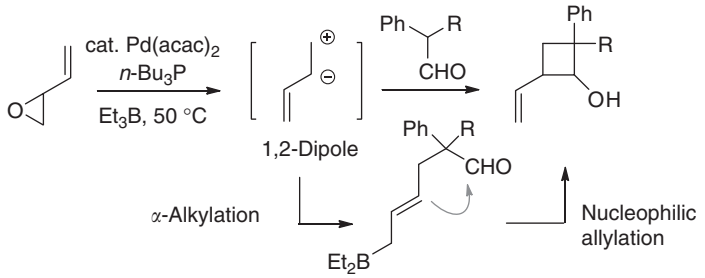
(36)

The similar catalytic system consisting of Pd(0) catalyst and triethylborane promotes the amphiphilic allylation of aldimines with 2-methylenepropane-1,3-diol to give pyrrolidines in one pot (Scheme 30).[43] Symmetric allylic alcohols can serve as 1,3-zwitter ionic species, and the sequential nucleophilic and electrophilic allylations proceed in this order.



Scheme 30

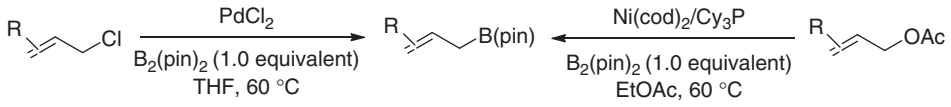
Vinyl epoxide works as a synthetic zwitter ion species, 3-butenyl-2-anion-1-cation equivalent, and is also capable of undergoing amphiphilic allylation of aldehydes under Pd(0)/triethylborane system to give 2-vinyl-cyclobutanol (Scheme 31).[44]



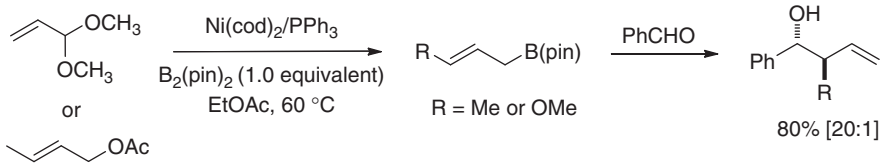
Scheme 31

2.15.4.4 Transition Metal-Catalyzed Allylation of Carbonyls with Allylmetal Species

Allylic boronates represent versatile building blocks for modern organic synthesis. Highly efficient and practical methods for the preparation of allylic boronates are demonstrated.[45] Pd-Catalysts such as $Pd_2(dba)_3$, $PdCl_2$, and Pd/C promote the borylation of allylic halides with $B_2(pin)_2$ to convert allyl boronates without the assistance of a drybox (Scheme 32). Alternatively, allyl acetates and -ethers react with $B_2(pin)_2$ in the presence of Ni catalyst to provide allyl boronates with a high level of functional group and substituent tolerance. Benzaldehyde is directly added to unquenched borylation product promoted by Ni-catalyst to furnish the allylation products in highly regio- and stereoselectivity (Scheme 33).

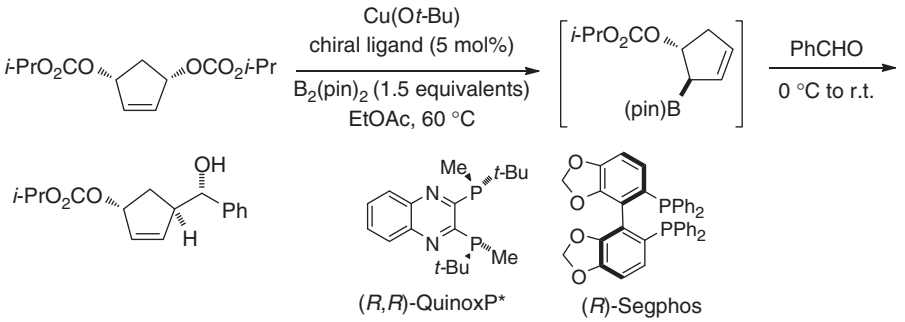


Scheme 32



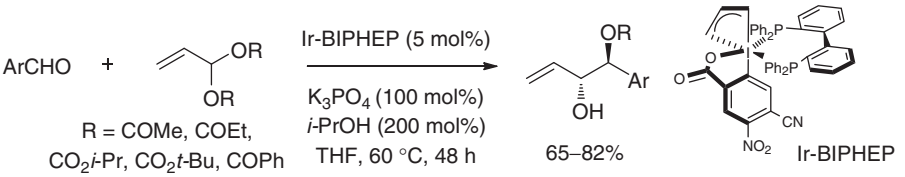
Scheme 33

Copper(I)-catalyzed asymmetric borylation and stereoselective allylation of aldehydes with *meso*-2-alkene-1,4-diol derivatives is reported (**Scheme 34**).[46] A reaction mixture of carbonate derivative of *meso*-2-alkene-1,4-diol and $B_2(pin)_2$ is treated with Cu(O*t*-Bu) catalyst and bidentate chiral ligands, followed by the addition of aldehyde at 0℃ to produce chiral homoallyl alcohols. Although the isolation of the allylcarbonate intermediate is not successful, the stereochemical outcome suggests the formation of the allylborane with high enantio- and diastereoselectivity.



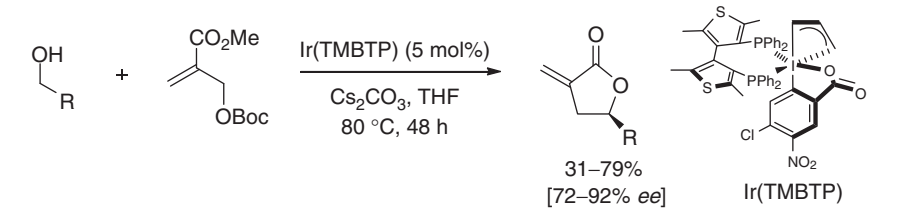
Scheme 34

Allylic *gem*-dibenzoate engages in reductive coupling reaction to diverse aldehydes to furnish products of *anti*-alkoxyallylation with high regio- and stereocontrol and exceptional levels of enantioenrichment by *ortho*-cyclometalated iridium catalyst generated from $[Ir(cod)Cl]_2$, 4-cyano-3-nitrobenzoic acid, allyl acetate, and the chiral phosphine ligands 2,2-bis(diphenylphosphino)biphenyl (BIPHEP) or SEGPHOS (equation 37).[47] Isopropyl alcohol serves as the terminal reductant to promote the Ir-catalyzed transfer hydrogenation with absolute stereocontrol.

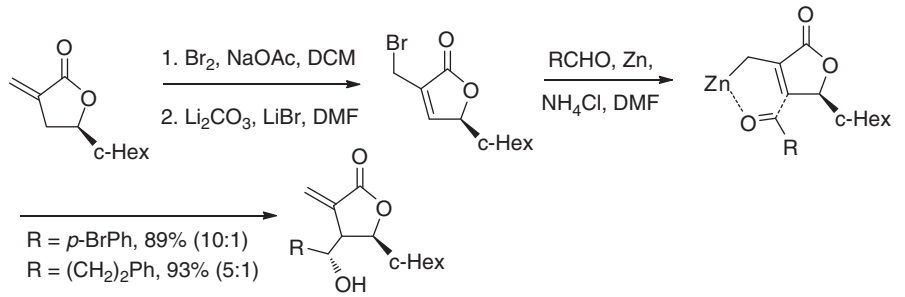


(37)

In the presence of a chiral cyclometalated iridium catalyst, Ir(2,2,5,5-tetramethyl-3,3-bis(diphenylphosphine)-4,4-bithiophene; TMBTP), C–C coupling reaction of acrylic ester and primary alcohols occurs in order to provide enantiomerically enriched 5-substituted α-exo-methylene γ-butyrolactone (equation 38).[48] Bromination of the 5-substituted α-exo-methylene γ-butyrolactones followed by zinc-mediated reductive aldehyde addition provides the β-hydroxymethyl-γ-butyrolactones through the zinc-chelated 6-membered transition state (**Scheme 35**).

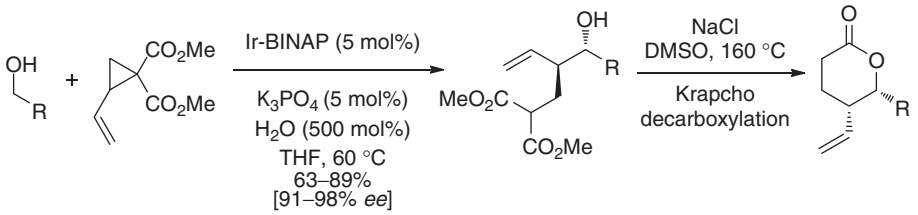


(38)



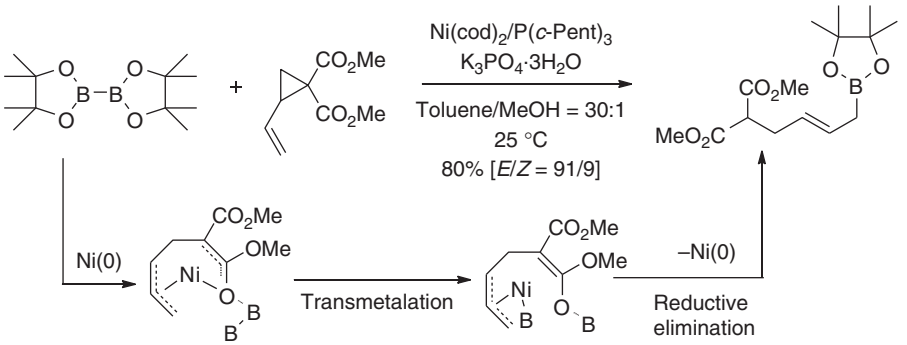
Scheme 35

Exposure of vinylcyclopropanes bearing two alkoxycarbonyl groups on the cyclopropane ring to the mixture of primary alcohols and chiral Ir-catalyst results in the formation of enantiomerically enriched homoallyl alcohols via umpolung of electrophilic allylmetal species to the nucleophilic allylmetal species (Scheme 36).[49] The allylation products are transformed to *cis*-4,5-disubstituted δ-lactones by Krapcho decarboxylation.

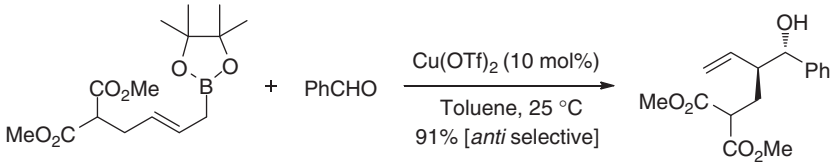


Scheme 36

Nickel-catalyzed borylative ring-opening reaction of vinylcyclopropane with $B_2(pin)_2$ provides allylic boronates in high *E*-stereoselectivity (Scheme 37).[50] Activated vinylcyclopropane undergoes oxidative addition to Ni(0) complex to afford π-allyl(oxa-π-allyl)nickel species. Allylic boronates are obtained via transmetalation with $B_2(pin)_2$ and π-allylnickel species. Thus, the formed allylic boronate reacts with benzaldehyde smoothly in the presence of $Cu(OTf)_2$ catalyst in toluene at room temperature to afford the corresponding homoallyl alcohols with high *anti* stereoselectivity (equation 39).



Scheme 37

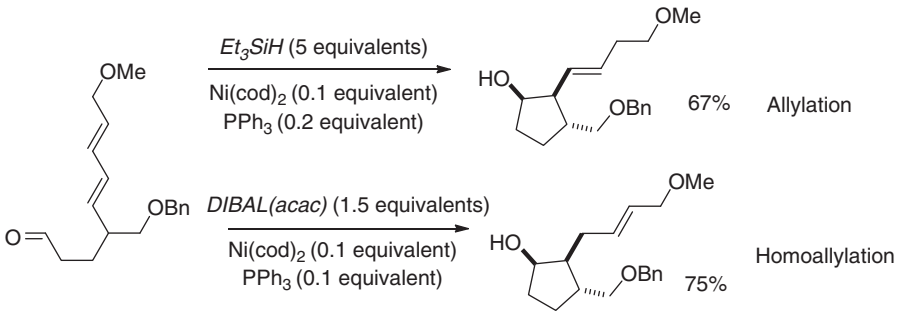


(39)

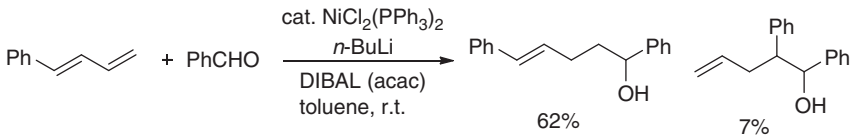
2.15.5 Homoallylation of Carbonyls with Butenyl Carbanion Equivalent

Homoallylation of carbonyls is an important strategy for C–C bond transformation and can formally play as a homoaldol reaction. However, this process has received little attention owing to the limited structural flexibility of the homoallylating agents ($CH_2{=}CHCH_2CH$-metal).[51] Nickel-catalyzed functionalizations of conjugated dienes as homoallyl anions involving reductive coupling reaction are useful methods for the efficient modern organic synthesis.[52] The kind of reducing agents determines the course of the reductive coupling reaction of carbonyls with conjugated dienes. For instance, in the presence of $Ni(cod)_2/PPh_3$ catalyst, triethylsilane promotes ω-dienyl aldehyde to undergo the intramolecular allylation to provide homoallylic alcohol, whereas diisobutylaluminum hydride (DIBAL) (acac) induces the same dienyl aldehyde to selectively undergo homoallylation to afford bis-homoallyl alcohol as a sole product (Scheme 38).[53]

Intermolecular reductive coupling reaction proceeds by exposure of 1-phenyl-1,3-butadiene to PhCHO in the presence of $NiCl_2(PPh_3)_2$ catalyst activated by *n*-BuLi and a stoichiometric amount of DIBAL(acac) to give a mixture of linear and branched bis-homoallyl alcohols (equation 40).[54]

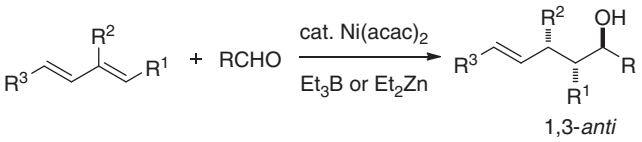


Scheme 38



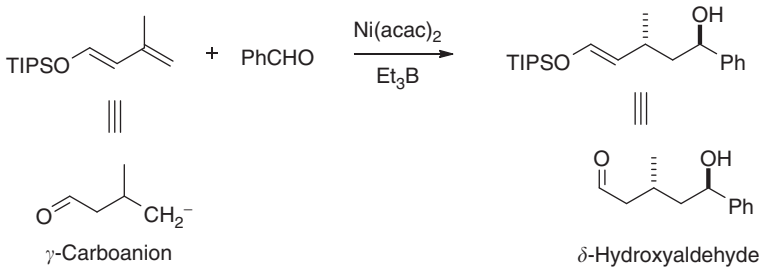
(40)

Ni-catalysts are able to promote the homoallylation of aldehydes with a wide variety of 1,3-dienes in the presence of triethylborane or diethylzinc as reducing agents to form bis-homoallyl alcohols with excellent regio- and stereoselectivity (equation 41).[55]



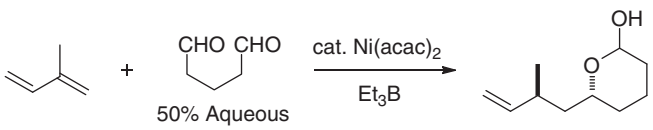
(41)

The homoallylation shows remarkably high regio- and stereoselectivity, yielding a 1:1 adduct of a diene and aldehyde. C2 alkylated dienes, such as isoprene, myrcene, and 2,3-dimethylbutadiene, especially effectively react with aldehydes at C1 position to provide bis-homoallyl alcohols with excellent 1,3-*anti* stereoselectivity. The reactions with siloxy- and alkoxy-substituted dienes are of great synthetic use. The representative result of the reaction of 1-siloxy-3-methylbutadiene and PhCHO is shown in Scheme 39. The product is easily converted to *anti*-5-phenyl-5-hydroxy-3-methylpentanal; hence, 1-siloxybutadiene is regarded as a synthetic equivalent of bis-homoenolate.

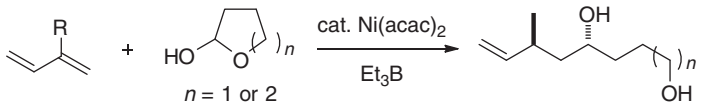


Scheme 39

Triethylborane is unique Lewis acid among organometallic reagents and withstands hydrolysis by water and alcohols. The reaction system of Ni/triethylborane is tolerated in the homoallylation of aldehydes that are only storable and stable in aqueous solution. Glutaraldehyde in 50% aqueous solution and cyclic hemiacetals provide the corresponding homoallylation products with high regio- and stereoselectivity as well as aromatic aldehydes (equations 42 and 43).[56]

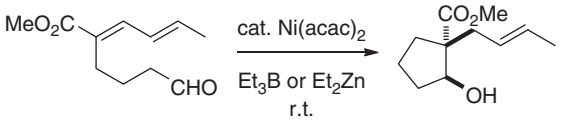


(42)



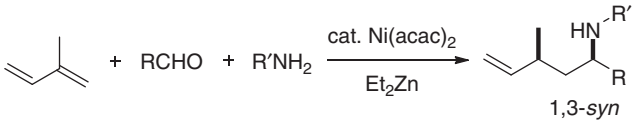
(43)

Under similar conditions, intramolecular homoallylation of *ω*-dienyl aldehydes proceeds at room temperature to afford five- and six-membered *cis*-2-allylcycloalkanols with high regio- and stereoselectivity (equation 44).[57] The reaction with triethylborane requires a longer period of time for completion of the reactions, whereas diethylzinc promotes the reaction smoothly being complete within half an hour.



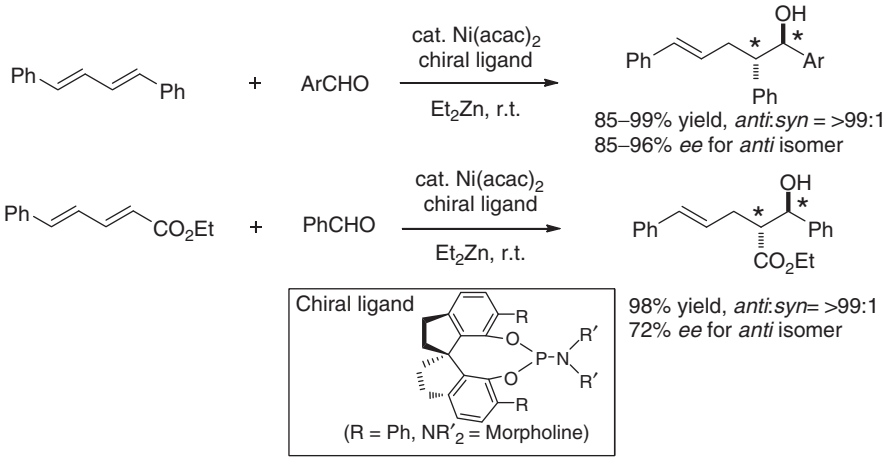
(44)

The diethylzinc/Ni-catalytic system is successfully extended to the homoallylation of aldimines, which are prepared *in situ* from aromatic aldehydes and primary amines (equation 45).[58] Although aldimines are generally less reactive than aldehydes toward carbon nucleophiles, good yields of bis-homoallylemines are obtained from aldimines under this diethylzinc/Ni-catalytic system. More interestingly, the reaction of aldimines with isoprene proceeds in an opposite sense of stereoselectivity to that of aldehydes and selectively provides 1,3-*syn*-bis-homoallylamines.



(45)

Asymmetric reductive coupling reactions of dienes and aldehydes are also developed.[59] Ni-catalyzed asymmetric homoallylation of aldehydes with 1,3-dienes proceeds by treatment of chiral spirobiindane phosphoramidite ligand with diethylzinc to furnish chiral bis-homoallyl alcohols with excellent regio- and stereoselectivity (**Scheme 40**).

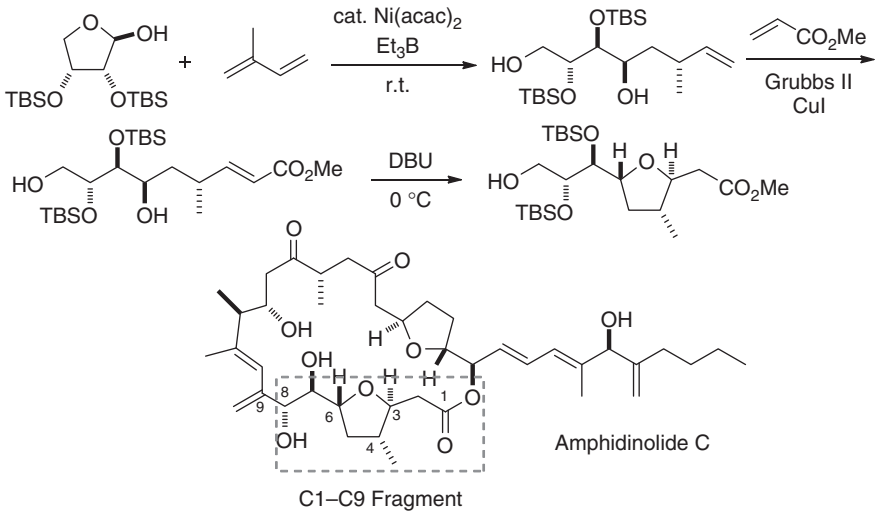


Scheme 40

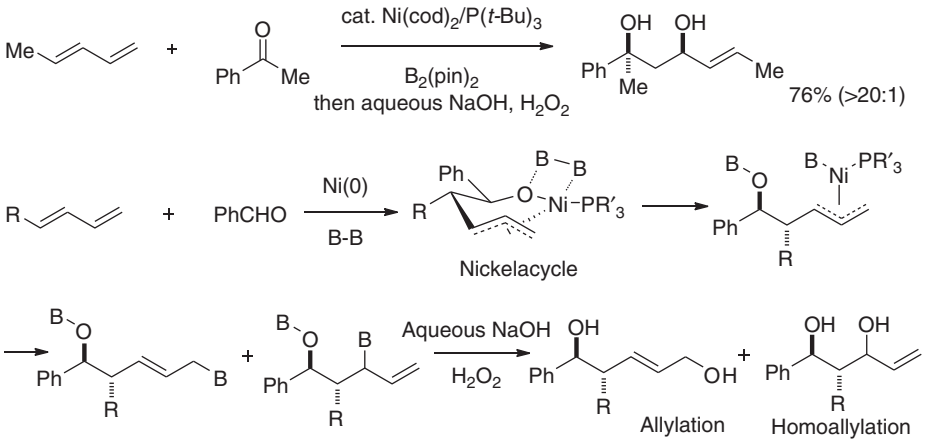
Homoallylation of aldehyde with isoprene is used as an important step for the construction of amphidinolide C (**Scheme 41**).[60] Homoallylation of erythrolactol proceeds smoothly under Ni/triethylborane system, followed by cross metathesis with methyl acrylate to afford *ω*-hydroxy *α,β*-unsaturated ester, which is the precursor of C1–C9 fragment of amphidinolide C.

Nickel-catalyzed borylative coupling reactions of diene and aldehyde are also reported. In the presence of $Ni(cod)_2$ catalyst and $B_2(pin)_2$, aldehydes react with 1,3-dienes to provide 4-pentene-1,3-diols and 2-pentene-1,5-diols by oxidative hydrolysis with hydrogen peroxide (**Scheme 42**).[61] Oxanickelacycles undergo the *σ*-bond metathesis with $B_2(pin)_2$, giving rise to the regioisomeric mixture of allyl boronic esters, and afford the allylation and homoallylation products. The reaction of ketone and piperylene provides the homoallylation product as a single isomer by $Ni(cod)_2/P(t\text{-}Bu)_3$ catalytic system.

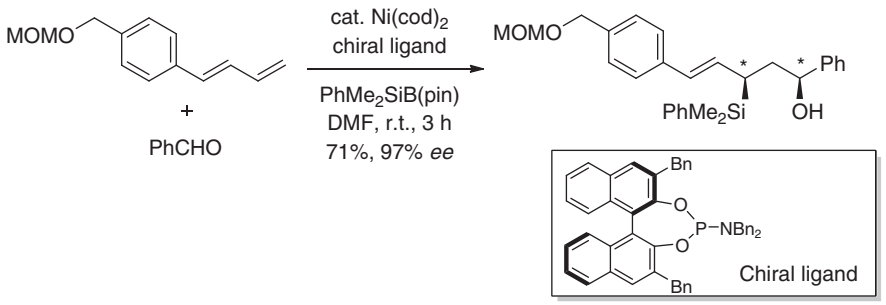
Ni-Catalyzed silylborative coupling reactions with aldehydes and 1,3-dienes give the bis-homoallyl alcohols having an allylsilane unit (equation 46).[62] This procedure is applied to the synthetic approach to optically active *α*-chiral allylsilanes.



Scheme 41



Scheme 42



(46)

2.15.6 Conclusion

In this chapter, some recent synthetic methodologies involving metal homoenolate equivalents such as siloxycyclopropane, β-zincio esters, α-heteroallylmetals, β-alkoxycarbonylallylmetals, NHC-catalyzed coupling reactions of enals, and Ni-catalyzed homoallylations were described. Because the preparation of metal homoenolate is intensively difficult, these methods are among

the most efficient and convenient C–C bond formations with carbonyl compounds via homoaldol reactions. These reactions tolerate a wide variety of functionalities and may find wide applications to the synthesis of complicated natural products.

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2.16 The Bimolecular and Intramolecular Mannich and Related Reactions

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This chapter is a revision of the previous edition chapter by Harry Heaney, Vol. 2, pp 733–752, © 1991, Elsevier Ltd.

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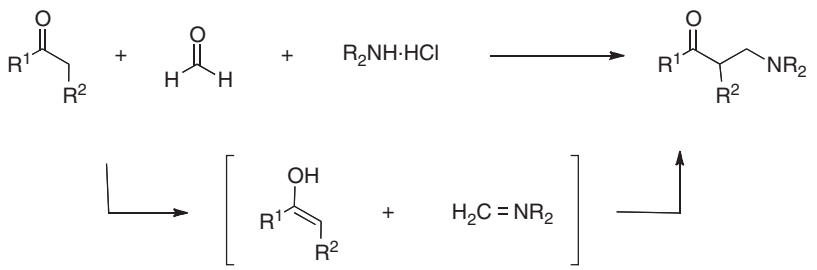
Glossary

Direct Mannich-type reaction The reaction in which parent carbonyl compound is employed as a nucleophile.
Enamine Nitrogen analogue of enol and synthesized from aldehyde or ketone with secondary amine.
Indirect Mannich-type reaction The reaction of the activated form of carbonyl compound, that is, generated stoichiometrically either *in situ* or by prior synthesis and isolation, and imines.
Organocatalysis Acceleration of organic reactions promoted by small organic molecule as a catalyst.
Vinylogous Mannich reaction The addition reaction of homoenolate analog with imines.

2.16.1 Introduction

The Mannich reaction is one of the most important class of reactions in organic chemistry, providing β-amino ketones and aldehydes (Mannich bases) starting from ketone, formaldehyde, and secondary amine (Scheme 1).[1] Because Mannich bases are prevalent in biologically active compounds and are also useful intermediates for the preparation of β-lactams and β-amino acids,



Scheme 1

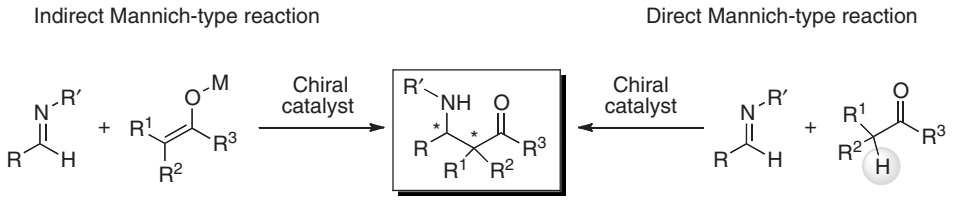
the Mannich reaction attracted much attention among synthetic organic chemists. A number of nitrogen-containing biologically active compounds were synthesized by use of the Mannich reaction.

Although the classical Mannich reaction is a useful method for the preparation of β-amino carbonyl compounds and played an important role in the medicinal chemistry, the application of the Mannich reaction was limited due to several problems in the classical Mannich reaction, which follows:

1. Lack of regioselectivity in the carbonyl compounds (ketone).
2. Only reactive aldehyde, such as formaldehyde or acetaldehyde, proved to be suitable substrates.
3. Control of stereoselectivity was difficult.
4. Side reactions.

In order to overcome the above-mentioned problems, preformed enolate and/or preformed imines were employed in the early stage by means of Lewis acid catalyst. The Mannich-type reaction is also called as an imino-aldol reaction or aza-aldol reaction. The Mannich-type reaction was extensively studied, resulting in the development of chiral Lewis acid catalysts, leading in turn to the enantioselective version of the Mannich-type reactions. In the late 1990s, direct Mannich-type reactions, which obviated the use of preformed enolates, flourished in both the metal-catalyzed reactions and organocatalyzed reactions. In the previous edition, published in 1992, several chapters focused on the Mannich and related reactions, including diastereoselective reactions.[2] Subsequently, general review articles of Mannich reactions appeared.[3] Because enantioselective and catalyzed versions of the Mannich and related reactions emerged and flourished dramatically[4] after publication of the first edition in 1992, this chapter deals with the reactions, classified as metal-catalyzed reaction, organocatalyzed reaction, and other categories, which include ion pair catalysis, and combined metal and organo-catalysis.

In this review article, 'indirect Mannich-type reaction' is used for the reaction of the activated form of carbonyl compound that is generated stoichiometrically either *in situ* or by prior synthesis and isolation, and imines. In contrast, 'direct Mannich-type reaction' refers to a process in which a parent carbonyl compound is employed as a nucleophile (Scheme 2).



Scheme 2

Although vinylogous Mannich-type reactions are included, the reactions of nitromethane with imines, namely aza-Henry reactions (nitro-Mannich reactions), are beyond the scope of this chapter.

2.16.2 Metal-Catalyzed Mannich-Type Reactions

2.16.2.1 Mannich Reaction with Preformed Enolate and Its Analogs (Indirect Mannich-Type Reactions)

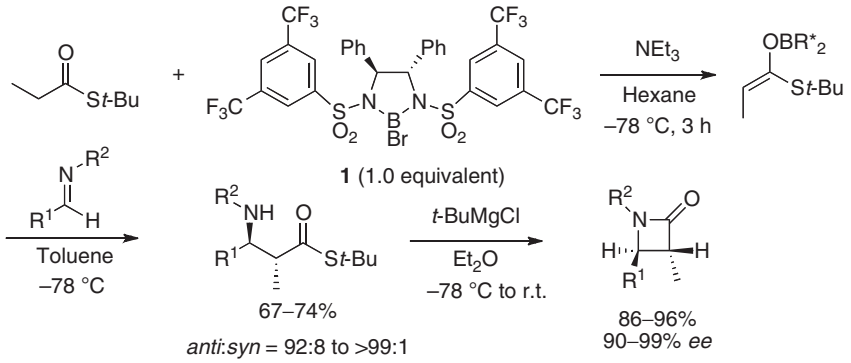
Corey reported the first enantioselective synthesis of β-amino esters starting from achiral imines and esters. Treatment of *S*-*tert*-butyl thiopropionate with 1.0 equivalent of chiral organoboron reagent **1** generated *trans*-boron enolate *in situ*, which underwent Mannich-type reaction with *N*-benzyl or *N*-allyl imines to furnish β-amino-α-methyl thioester in favor of the *anti*-isomer. Subsequent treatment with *tert*-BuMgCl furnished the corresponding β-lactam with an excellent enantioselectivities (Scheme 3).[5]

Yamamoto and coworkers developed[6] a Mannich-type reaction of *N*-benzyl aldimine with ketene silyl acetal by means of the stoichiometric amount of a Brønsted acid-assisted chiral Lewis acid **2** (Scheme 4).

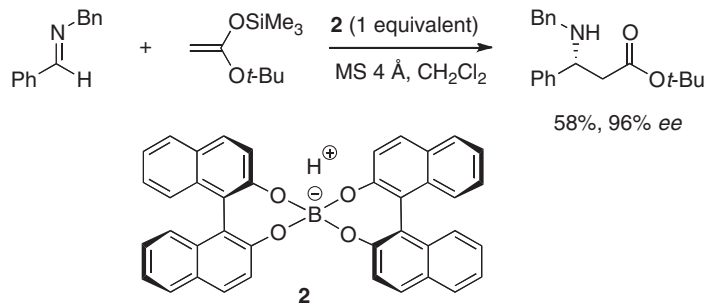
The Tomioka group developed enantioselective addition of lithium enolate, generated from 3-pentyl isobutyrate (2.0 equivalents) with lithium cyclohexylisopropylamide, with aldimine in the presence of chiral ether ligand **3** (2.6 equivalents) in toluene at −50 °C to furnish the corresponding β-lactam in 85% yield and with 88% *ee* (Scheme 5).[7]

Although there are several enantioselective Mannich-type reactions, a truly catalytic and enantioselective version of the Mannich-type reaction was not reported until 1997.[8]

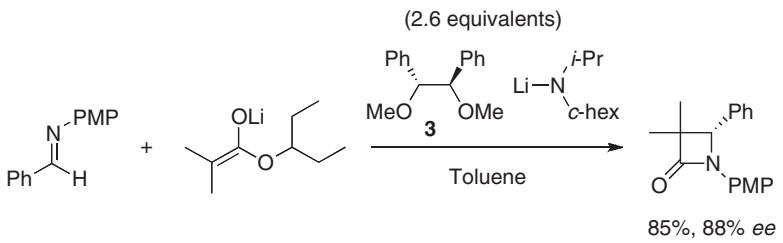
The Kobayashi group reported the indirect Mannich-type reaction of ketene silyl acetal with an aldimine bearing an *N*-2-hydroxyphenyl moiety by means of a catalyst **4** (Figure 1), which was derived from (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol and $Zr(Ot\text{-}Bu)_4$.[9] Use of aldimines bearing an *N*-hydroxyphenyl moiety and addition of *N*-methylimidazole (NMI) as an axial ligand are requisite to attain excellent enantioselectivities (Scheme 6). Based on NMR studies, they proposed the structure **5**, wherein two (*R*)-6,6′-dibromo-2,2′-binaphthols locate at equatorial positions around the Zr and *N*-methylimidazole coordinate at the axial positions. The catalytic reaction is assumed to proceed by isomerization of the zirconium catalyst **5** to **6** when aldimines coordinate the zirconium.[10]



Scheme 3



Scheme 4



Scheme 5

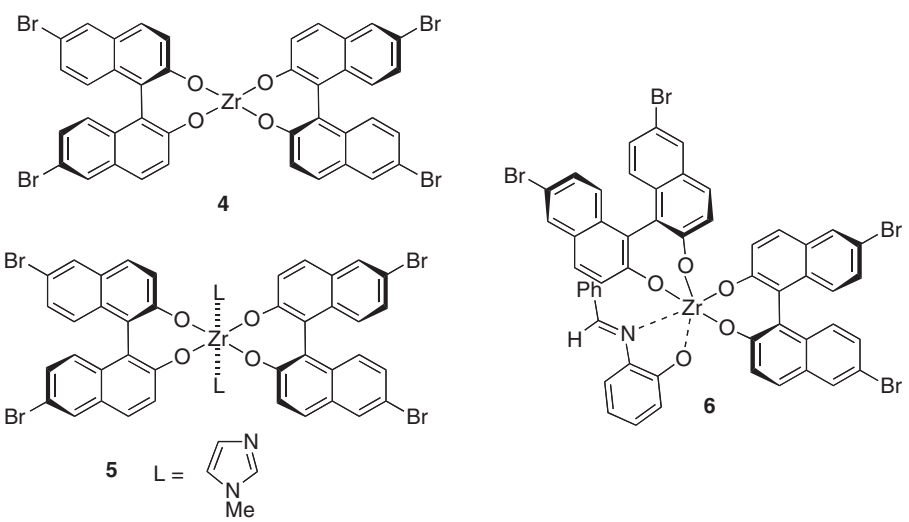
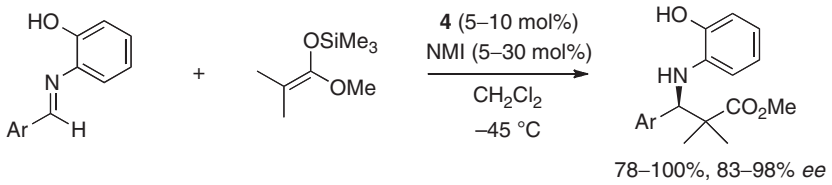


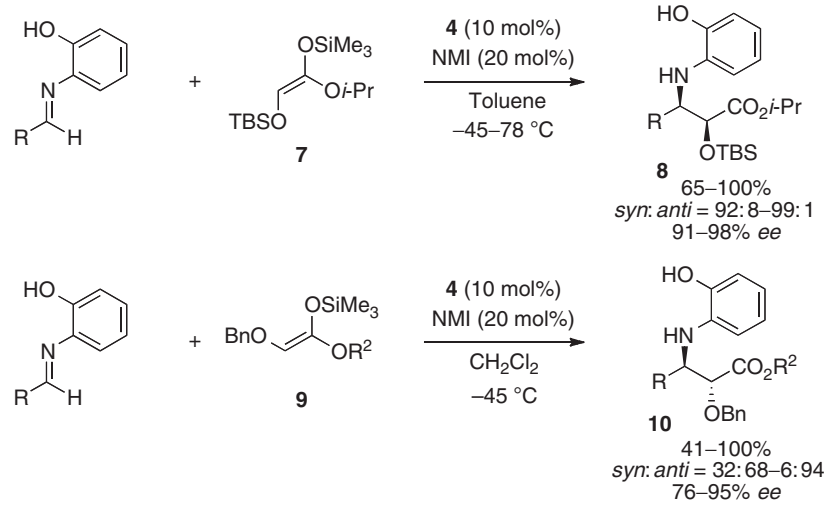
Figure 1 Chiral zirconium catalyst and active species.



Scheme 6

The authors also found in the same paper even more active catalyst bearing a CF_3 moiety at the 6-position and realized very low catalyst loading (0.5 mol%) in the indirect Mannich-type reaction.

In addition to the enantioselectivity, diastereoselectivity could be controlled by the Zr catalyst **4**. Use of ketene silyl acetal **7** selectively furnished *syn*-adducts **8** with excellent enantioselectivity, whereas ketene silyl acetal **9** preferentially afforded *anti*-adducts **10** (Scheme 7).[11] In addition to aldimines derived from aromatic aldehydes, an aldimine derived from cyclohexanecarboxaldehyde proved to be a suitable substrate.



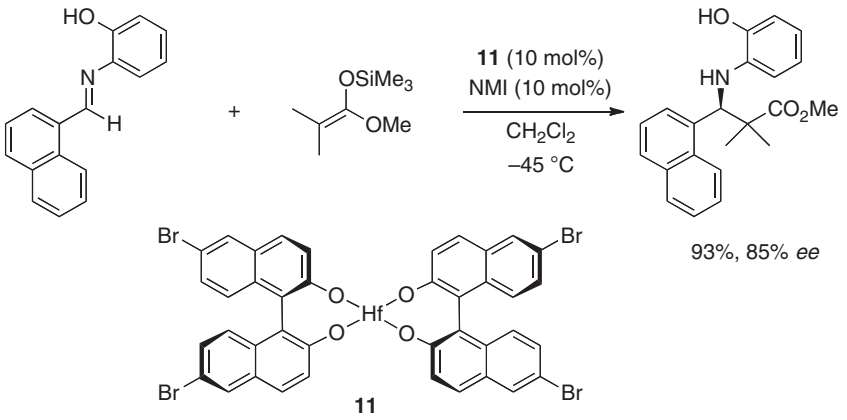
Scheme 7

Although Lewis acid catalysts, in general, are sensitive to moisture and oxygen, air-stable, storable, and highly selective chiral Lewis acid catalyst for the Mannich-type reaction was developed by treatment of (*R*)-6,6′-$(C_2F_5)_2$-2,2′-binaphthol with Zr(O*t*-Bu)$_4$, *N*-methylimidazole, in the presence of 5AMS in benzene at 80 °C followed by removal of solvent. The catalyst can be stored for more than three months in air at room temperature without loss of activity. Moreover, the catalyst can be recovered and reused.[12] X-ray analysis of the single crystals of the zirconium catalyst including *N*-benzylimidazole in place of *N*-methyimidazole elucidated that $Zr_4(\mu\text{-BINOLate})_6(\mu_3\text{-OH})_4$, in which four hexacoordinated zirconium atoms and six BINOL ligands existed. The single crystals exhibited excellent catalytic activity even in the absence of imidazole derivatives.[13] Analogous hafnium-based catalyst **11** exhibited comparative activity with the zirconium catalyst in the Mannich-type reaction, and the corresponding adduct was obtained with high enantioselectivity (Scheme 8).[14] The hafnium catalyst did not contain *N*-methylimidazole, which was confirmed by X-ray analysis.

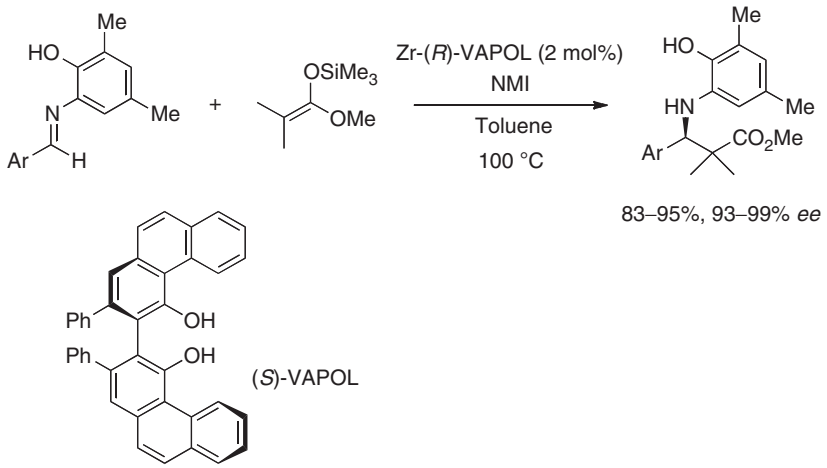
Wulff and coworkers reported highly enantioselective indirect Mannich-type reaction by means of a novel Zr catalyst bearing an (*S*)-VAPOL scaffold, giving rise to the products in high yields and with excellent enantioselectivities (Scheme 9).[15,16] Although 20 mol% of the catalyst is required at room temperature, the catalyst loading could be lowered to 2 mol% without compromising the enantioselectivity even at 100 °C. Interestingly, the chiral induction of the Mannich reaction did not show temperature dependence over the range of 25–100 °C.

The Kobayashi group designed a multidentate ligand and found that the complex derived from Zr(O-*t*-Bu)$_4$, NMI, and **12** or **13** was effective as a catalyst for the Mannich-type reaction (Scheme 10).[17] They investigated the structure of the chiral zirconium complex prepared from Zr(O-*t*-Bu)$_4$, a tridentate BINOL derivative, and NMI, and found that more than three kinds of complexes were observed by NMR analyses. Based on the density functional theory (DFT) calculation, they proposed a complex as the active catalyst.

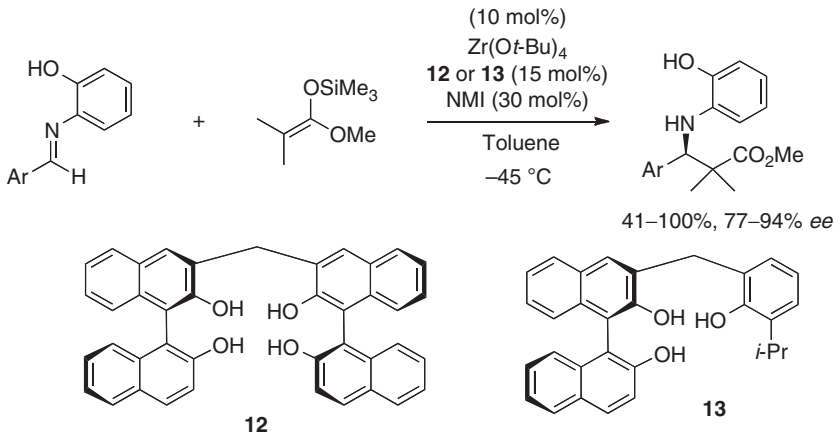
Iron complex also catalyzed the Mannich-type reaction efficiently.[18] An iron complex generated from $FeCl_2$, (*R*)-3,3′-diiodo-1,1′-binaphthalene-2,2′-diol (3,3′-I_2BINOL), in the coexistence of *i*-Pr_2NEt turned out to be the most effective, and addition of protic additives such as methanol enhanced the rate of the reaction dramatically. The corresponding β-amino esters were obtained in moderate to good enantioselectivities (Scheme 11).



Scheme 8

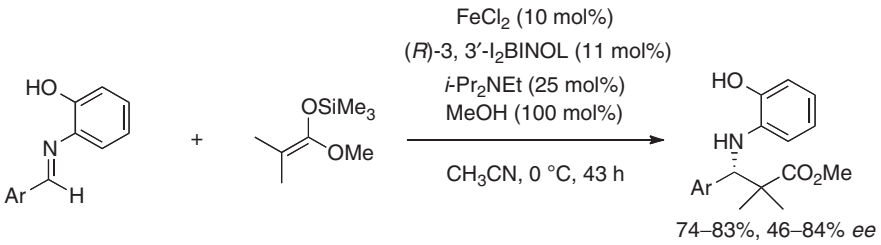


Scheme 9

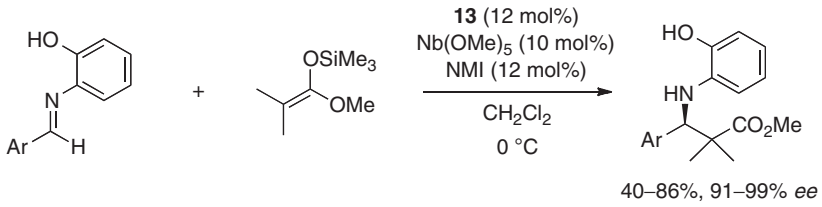


Scheme 10

Chiral niobium (V) catalyst also proved effective for the enantioselective Mannich-type reactions. Starting from a complex derived from $Nb(OEt)_5$, **13**, and NMI in CH_2Cl_2 at 0 °C, Mannich-type reaction of ketene silyl acetal with aldimine bearing an *N*-2-hydroxyphenyl moiety proceeded highly enantioselectively to furnish the corresponding *β*-amino esters with excellent enantioselectivity (Scheme 12).[19] Single crystals of a Nb complex were obtained from a solution of $Nb(OEt)_5$, **13**, and NMI. X-ray



Scheme 11



Scheme 12

analysis elucidated the structure of complex **14** (Figure 2). A bridged complex **15** was proposed as the active species for the Mannich-type reaction based on the NMR studies.

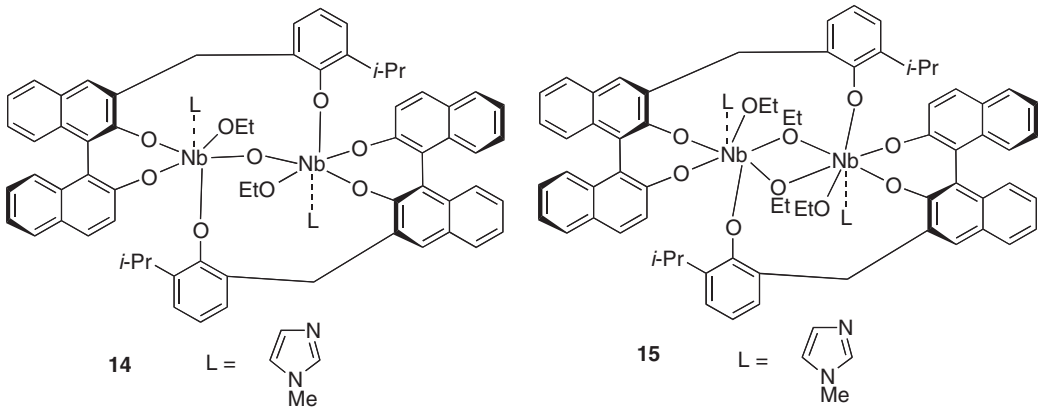
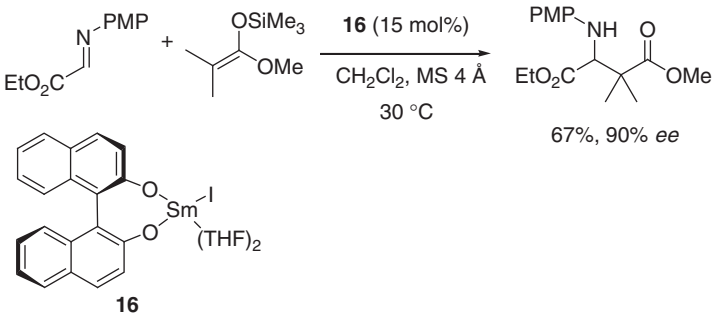


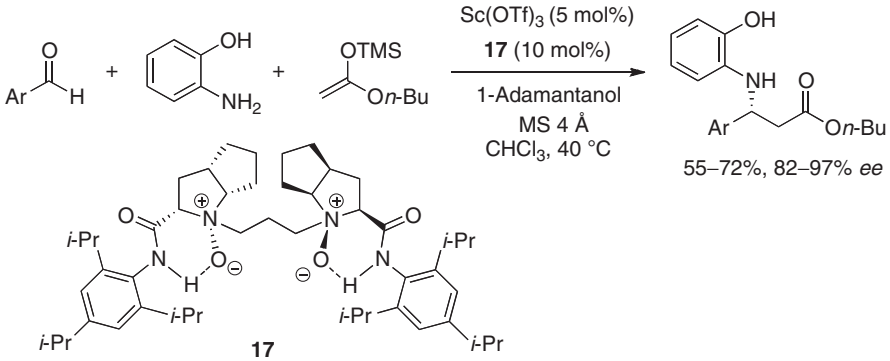
Figure 2 Structure of the chiral niobium catalyst.

In addition to aldimines derived from aromatic aldehydes and *p*-methoxyaniline, aldimine derived from glyoxylate participated in the Mannich-type reaction. The Collin group employed a complex **16**, which was generated from (*R*)-BINOL and $SmI_3(THF)_3$ as a catalyst for the Mannich-type reaction of ketene silyl acetal with α-imino ester, giving rise to the addition product in 67% and with 90% *ee* (Scheme 13).[20] They observed that enantioselectivity was improved by the maturation time.



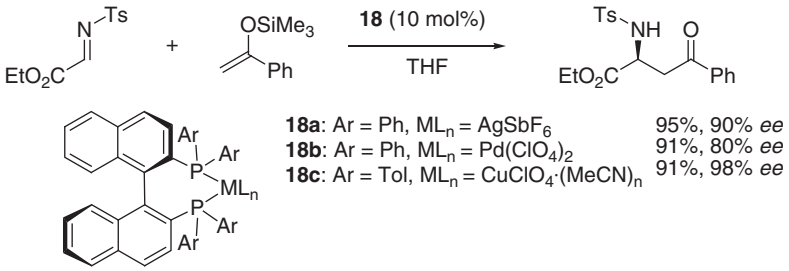
Scheme 13

Mannich-type reactions so far discussed employ aldimines synthesized in advance. Three-component Mannich-type reaction of aldehyde, *o*-aminophenol, and ketene silyl acetal was promoted by 5 mol% of C_2-symmetric *N*,*N*′-dioxide **17** and scandium triflate (2:1) complex to furnish *β*-amino esters with high to excellent enantioselectivities (Scheme 14).[21] Although the Mannich-type reaction is limited to aromatic aldehydes, preparation of aldimines was obviated.



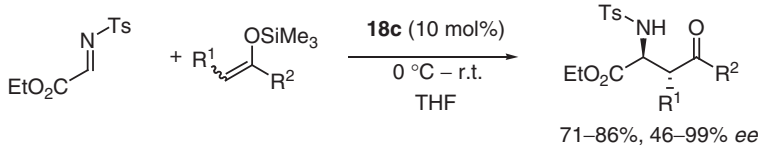
Scheme 14

In comparison to *N*-aryl imines, *N*-acyl and *N*-sulfonyl imines are more reactive, though stability is lower. The Lectka group studied the Mannich-type reaction of silyl enol ether with *N*-tosyl *α*-imino ester by means of (*R*)-BINAP-transition metal complex **18**, and found that 5 mol% of (*R*)-BINAP-$AgSbF_6$ complex provided the adduct in 90% *ee* at –80 °C.[22] Examination of the metal salts elucidated that although (*R*)-BINAP-$Pd(ClO_4)_2$ complex afforded lower *ee* (80% *ee*), use of (*R*)-Tol-BINAP-$CuClO_4 \cdot (CH_3CN)_n$ complex **18c** performed the best, giving high yield (91%) and selectivity at 0 °C (98% *ee*) (Scheme 15).



Scheme 15

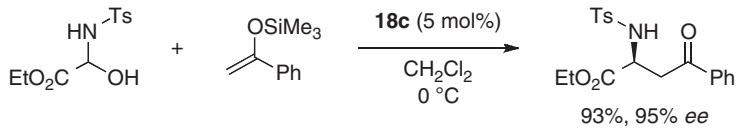
The complex **18c** is also effective for the diastereoselective and enantioselective Mannich-type reaction to furnish adducts with high diastereoselectivity and with excellent enantioselectivities.[23] Silyl enol ethers derived from both acyclic ketones and cyclic ketones proved to be suitable substrates (Scheme 16).



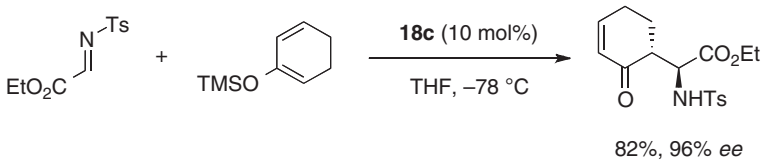
Scheme 16

In addition to unstable α-imino ester, its *N*,*O*-acetal also participated in the Cu(I)-catalyzed Mannich-type reaction successfully (Scheme 17). Because the *N*,*O*-acetals are easy to prepare and more stable than the parent α-imino ester itself, the protocol is of importance from a practical point of view.[24] Corresponding adducts were obtained in high yield and with excellent enantioselectivity.

Jørgensen studied the reaction of *N*-tosyl α-imino ester with Danishefsky's diene by means of (*R*)-Tol-BINAP-$CuClO_4$ complex **18c** to give aza Diels-Alder adduct with excellent enantioselectivities. In striking contrast, use of a cyclic diene led to the formation of the Mannich adduct with excellent enantioselectivities (Scheme 18).[25]

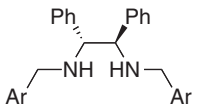


Scheme 17



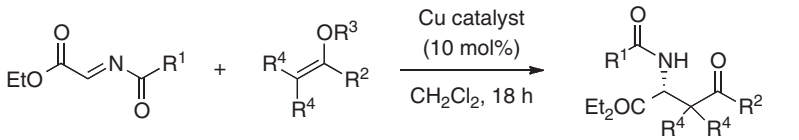
Scheme 18

The Kobayashi group also developed a Cu-catalyzed Mannich-type reaction of silyl enol ether with α-imino ester.[26] The optimum catalyst system depends on the *N*-acyl group: whereas aldimines bearing a long-chain alkyl group required $Cu(OTf)_2$-diamine **19a** (Figure 3), more reactive *N*-benzoyl imine was catalyzed by the $CuClO_4$-(*S*)-xylyl-BINAP complex at −78 °C (Scheme 19). Furthermore, methyl vinyl ether derivative also participated in the reaction successfully. It is noted that this is the first example using a vinyl ether in catalytic asymmetric Mannich-type reactions.



19a: Ar=1-naphthyl
19b: Ar=Ph
19c: Ar=2-$MeOC_6H_4$

Figure 3 Chiral diamine ligand.



R^1=$C_{11}H_{23}$: $Cu(OTf)_2$ + **19a**, 0 °C, 85–97%, 90–94% *ee*
R^1=Ph: $CuClO_4$ + (*S*)-xylyl-BINAP, −78 °C, 76–85%, 90–97% *ee*

Scheme 19

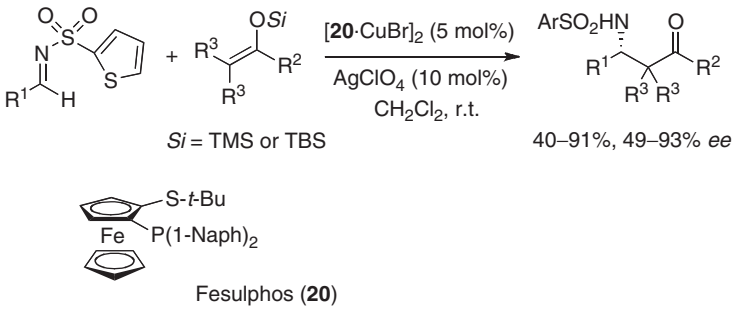
α-Imino ester bearing a readily removable protecting group such as Boc, Cbz, and Troc underwent enantioselective Mannich-type reaction with silyl enol ether by means of $Cu(OTf)_2$–**19** complex. *N*-Boc α-imino ester proved to be the suitable substrate.[27]

The Carretero group developed a Mannich-type reaction of ketene silyl acetal or ketene silyl thioacetal with aldimines bearing a 2-thienylsulfonyl group on nitrogen by means of Cu(I)-Fesulphos (**20**) (Scheme 20).[28] Aldimines derived from a range of aromatic aldehydes and cyclohexanecarboxaldehyde furnished the adducts with good to high enantioselectivities.

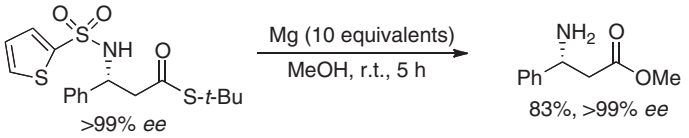
2-Thienylsulfonyl group can be readily removed by treatment with Mg in MeOH without affecting the optical purity (Scheme 21). Thioester was concurrently transformed to methyl ester.

Pd(II) complex **21** catalyzed a Mannich-type reaction of silyl enol ether with *N*-aryl-α-imino ester to furnish the corresponding adducts in high enantioselectivities (Scheme 22).[29] Binuclear μ-hydroxo complex, $[\{Pd((R)\text{-tol-binap})(\mu\text{-}OH)_2\}]^{2+}(BF_4^-)_2$, **22**, is supposed to be the active catalyst.

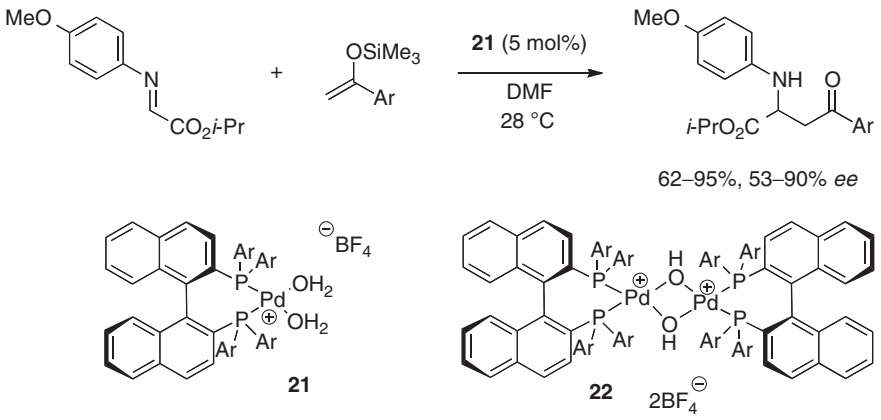
Sodeoka et al. subsequently synthesized a palladium complex **23** with the polymer-supported BINAP ligand, $[\{Pd((R)\text{-tol-binap})(\mu\text{-}OH)_2\}]^{2+}(BF_4^-)_2$. They found that the μ-hydroxo complex were found to be good catalysts for the Mannich-type reaction of silyl enol ether with α-imino ester (Scheme 23).[30] Although the catalyst was reusable, the *ee* dropped slightly after reuse.



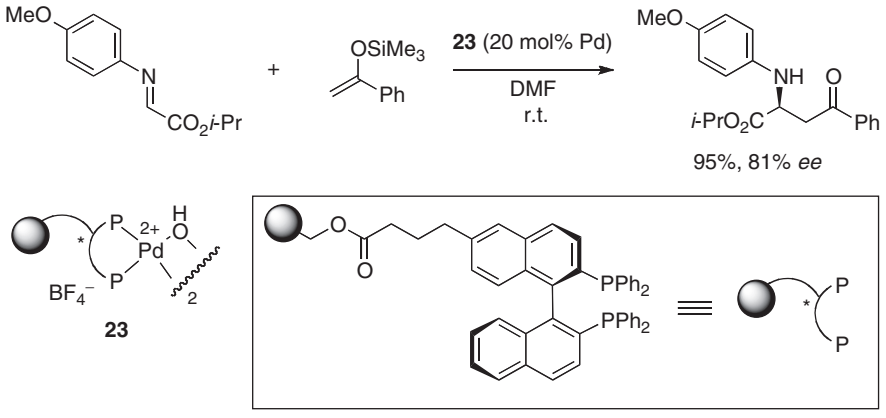
Scheme 20



Scheme 21

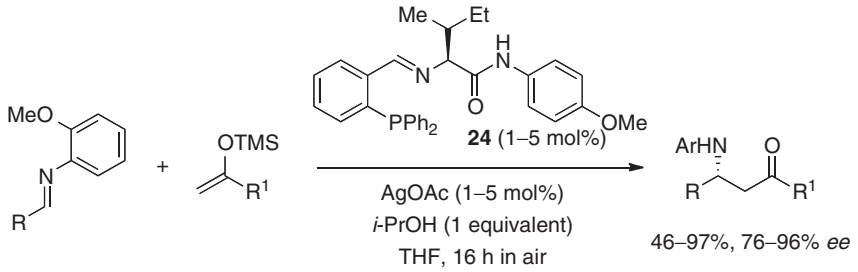


Scheme 22



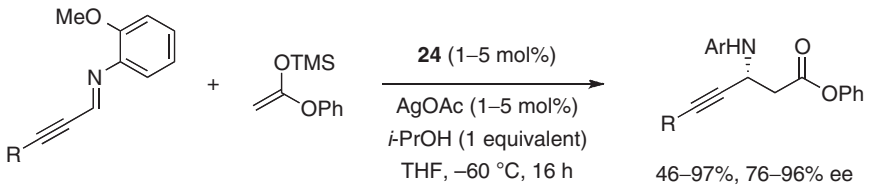
Scheme 23

Hoveyda and coworkers developed the Ag-catalyzed Mannich-type reaction of silyl enol ether with aryl, alkyl, alkenyl, and alkynyl aldimines by use of readily available *iso*-Leu-derived phosphine **24** as a chiral ligand (Scheme 24).[31] The Mannich reaction can be performed in undistilled solvent under an atmosphere of air in the presence of 1 equivalent of *i*-PrOH.



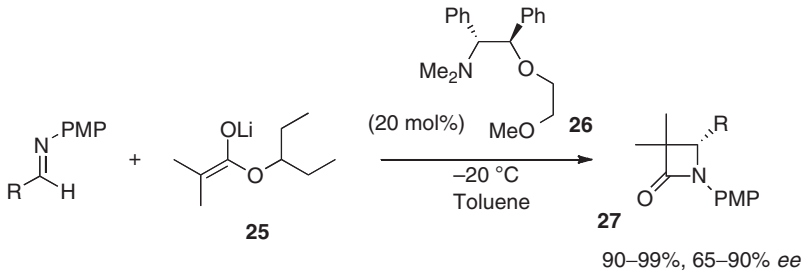
Scheme 24

The same group subsequently developed a Mannich-type reaction of ketene silyl acetal with alkynyl imines, giving rise to the highly enantioselective synthesis of *β*-alkynyl-*β*-amino acid derivatives by means of the same chiral Ag catalyst derived from **24** and AgOAc (Scheme 25).[32] Hydrogenation of the alkynyl group delivered difficult-to-access *β*-alkyl-*β*-amino esters.



Scheme 25

As an extension of the previous report using excess amounts of chiral ligand, the Tomioka group reported the addition of lithium enolate **25** to aldimines in the coexistence of sub-stoichiometric amount of amino diether **26** as a chiral ligand to give *β*-lactams **27** with high enantioselectivities (Scheme 26).[33]

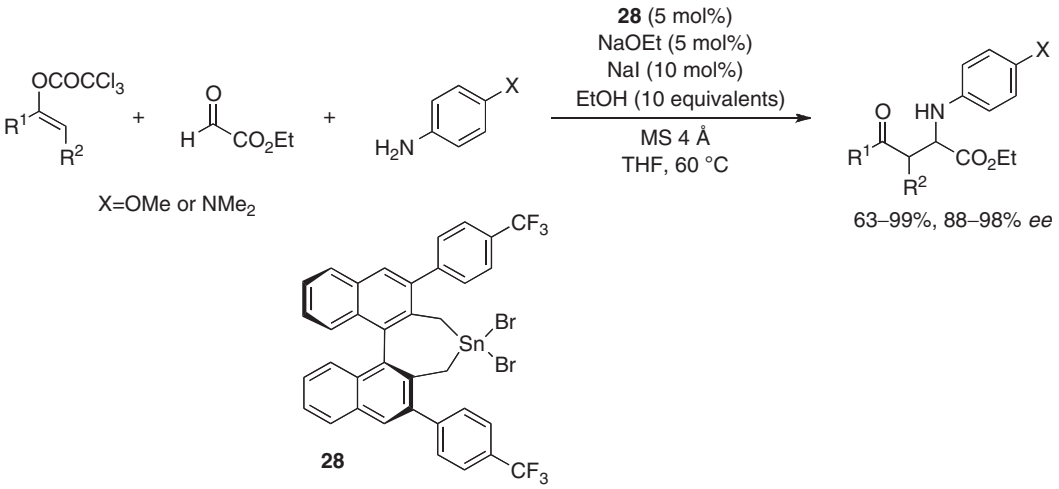


Scheme 26

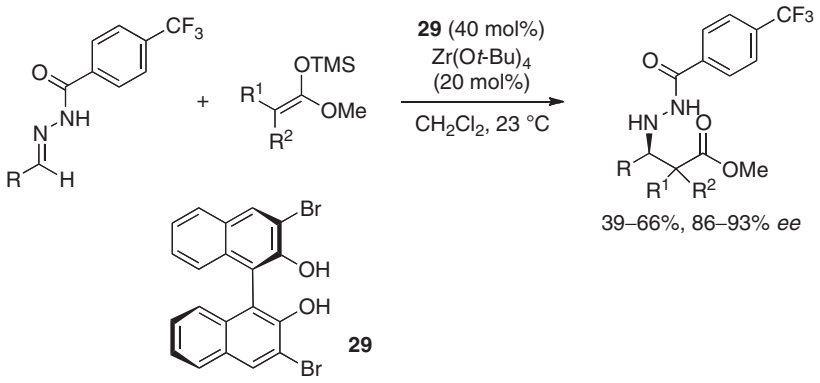
The Yanagisawa group developed a three-component Mannich-type reaction of alkenyl trichloroacetates by means of the tin BINOL catalyst **28** (Scheme 27).[34] Tin bromide ethoxide complex, $R^*_2SnBr(OEt)$, is proposed to be the active species in the catalytic cycle to furnish the Mannich-type adducts in up to 98% *ee*.

2.16.2.2 Reaction with Acyl Hydrazone[35]

Because *N*-acyl hydrazones cannot be readily prepared and stored, they will act as stable imine surrogates. Even aldimines derived from aliphatic aldehydes are stable. A new zirconium catalyst was prepared from zirconium(IV) *t*-butoxide and (*R*)-3,3′-dibromo-1,1′-bi-2-naphthol **29**. The complex catalyzed the Mannich-type reaction of ketene silyl acetal with *N*-acyl hydrazones. *N*-Acyl hydrazone derived from aliphatic as well as aromatic aldehydes participated successfully to give the adducts in good to high enantioselectivities (Scheme 28). Ketene thioacetals also proved to be suitable substrates.[36]

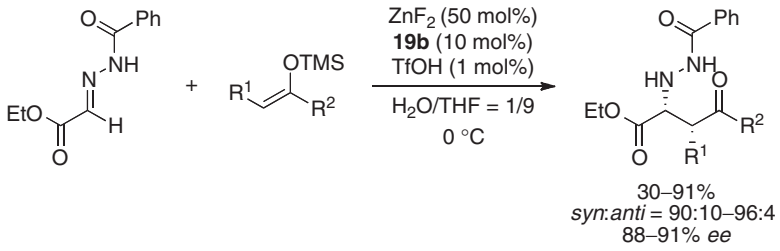


Scheme 27



Scheme 28

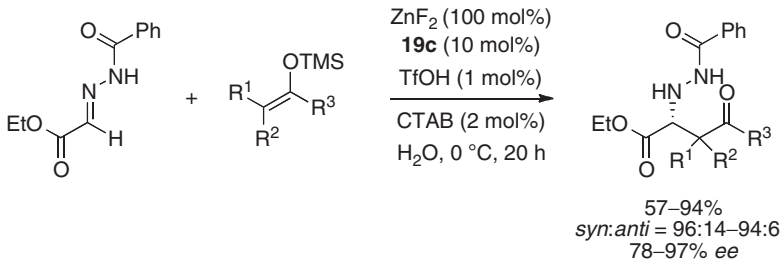
N-Acyl hydrazones, derived from glyoxylate, also participated in the reaction in aqueous media by use of diamine ligand **19b** and ZnF_2.[37] The use of water and a small amount of TfOH is essential for the reactions to proceed efficiently (Scheme 29).



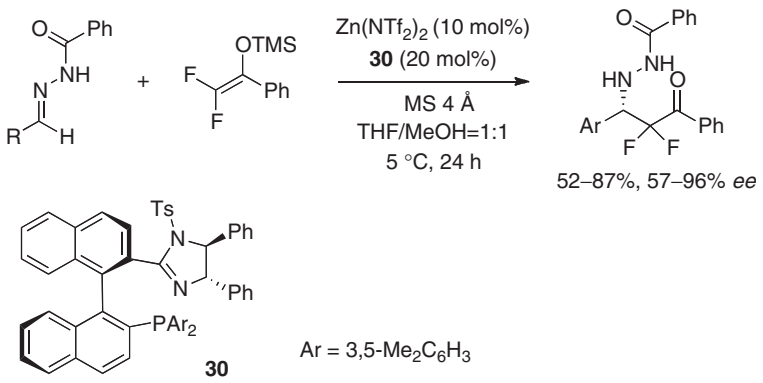
Scheme 29

The zinc-catalyzed enantioselective Mannich-type reaction proceeded smoothly in water in the absence of organic solvent by means of the chiral Zn catalyst, derived from ZnF_2 and **19c** (Scheme 31). Addition of cetyltrimethyammonium bromide (CTAB) as a surfactant accelerated the reaction to furnish the adducts with excellent enantioselectivities[38] (Scheme 30).

Difluoroenol silyl ether also participated successfully in the Mannich-type reaction of difluor with *N*-acyl hydrazone by use of a chiral Zn(II) complex, derived from $Zn(NTf_2)_2$ and **30**, as catalysts to furnish β-amino-α,α-difluoroketones with good to excellent enantioselectivities (Scheme 31). Acyl hydrazone derived from aliphatic aldehyde as well as aromatic aldehyde were suitable substrates.[39]

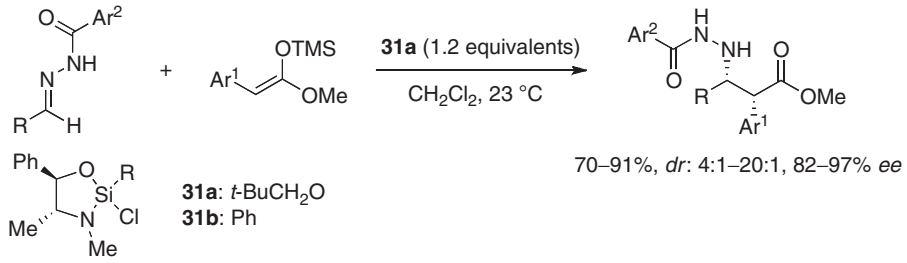


Scheme 30

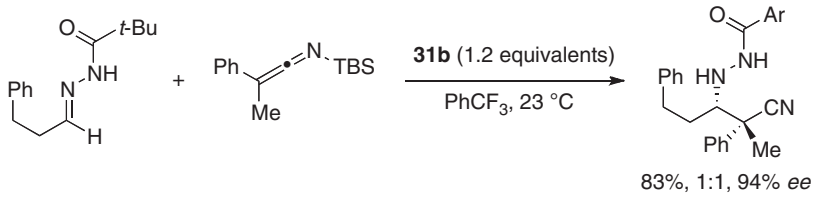


Scheme 31

The Leighton group reported a Mannich reaction of acyl hydrazones and α-aryl silyl ketene acetals and α-aryl-α-alkyl silyl ketene imines by means of chiral silicon Lewis acid **31**.[40] The reactions provide access to α-aryl-β-hydrazido esters and α-aryl-α-alkyl,β-hydrazido nitriles with high to excellent enantioselectivities (Schemes 32 and 33).



Scheme 32

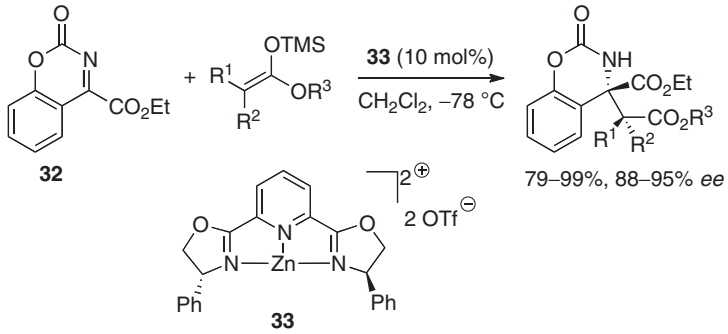


Scheme 33

2.16.2.3 Mannich-Type Reactions with Ketimines

Enantioselective construction of quaternary carbon centers constitutes a challenging task. Although a range of aldimines proved to be suitable substrates for the enantioselective Mannich-type reaction, ketimines had not been extensively studied as substrates due

to intrinsic lower reactivity. The Jørgensen group developed the first catalytic enantioselective Mannich-type reaction of ketimines, which provide access to optically active α- and β-amino acid derivatives. In order to challenge the issue, Jørgensen's group designed rigid α-imino ester **32** as a substrate based on the concept of 'intrinsic protecting group anchoring.' Upon employment of 10 mol% of the (*R*,*R*)-Ph-pybox-Zn(OTf)$_2$ catalyst **33** in the presence of H_2O in CH_2Cl_2, corresponding adducts were obtained in high yields and with excellent enantioselectivities (Scheme 34).[41]



Scheme 34

Shibasaki's group developed a highly enantioselective Mannich-type reaction of ketene silyl acetal with a ketimine bearing an *N*-bisarylphosphinoyl moiety by means of chiral Cu(I) catalyst.[42] Combined use of CuOAc and (*R*)-DTRM-SEGPHOS (Figure 4) and an equimolar amount of (EtO)$_2$Si(OAc)$_2$ in THF furnished the corresponding β,β-disubstituted amino acid derivatives. A catalyst system of CuOAc/DUPHOS (R = *i*-Pr or 4-(*t*-Bu)Cy) in combination with (EtO)$_3$SiF proved to be useful for ketimines derived from alkenyl alkyl ketones (Scheme 35).

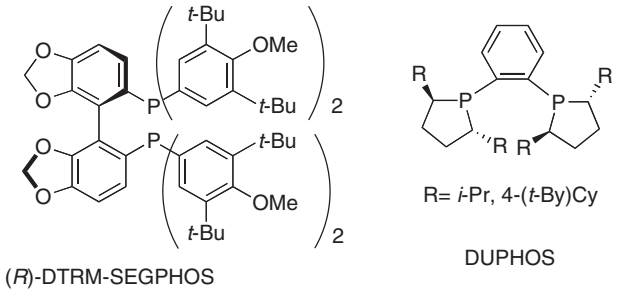
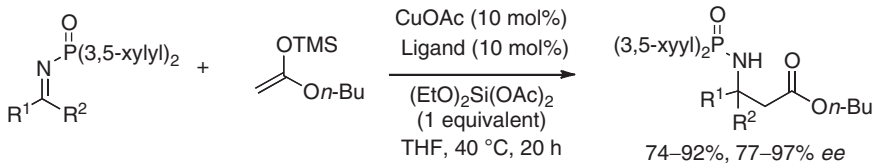


Figure 4 Chiral diphosphine ligand.



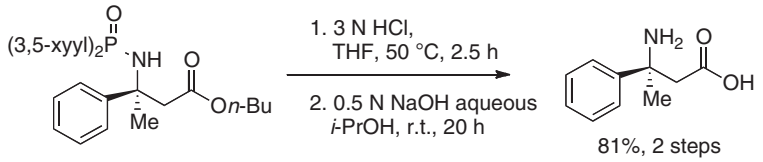
Scheme 35

The Mannich adduct was successfully converted to a β,β-disubstituted amino acid in high yield by removal of the phosphinoyl group under acidic conditions followed by hydrolysis of the ester with aqueous NaOH (Scheme 36).

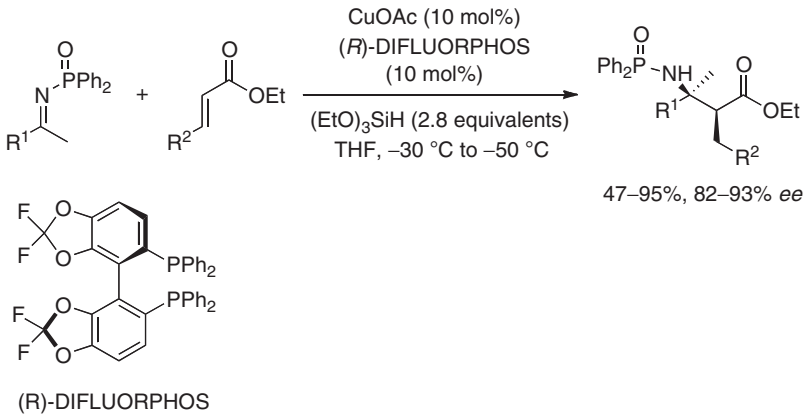
The same group developed an enantioselective reductive Mannich reaction by means of CuOAc-DIFLUORPHOS complex as a catalyst and (EtO)$_3$SiH as a reducing agent to furnish α,β,β-trisubstituted amino acid derivatives in high yields and with high enantioselectivities (Scheme 37).[43]

2.16.2.3.1 Direct Mannich-type reaction

Because prefunctionalization of carbonyl compounds to enolate equivalent is obviated, a direct Mannich-type reaction is an efficient method for the formation of β-amino carbonyl compounds. Shibasaki and coworkers described the first enantioselective direct Mannich reaction of unmodified ketone in 1999 by means of the heterobimetallic complex, (*R*)-LaLi$_3$tris(bisnaphthoxide)



Scheme 36



Scheme 37

complex (LLB) (Figure 5), which was employed for the enantioselective direct aldol reaction in 1997.[44] The complex catalyzed the three-component reaction between propiophenone, formaldehyde, and pyrrolidine in the presence of MS3Å as a dehydrating agent to provide the corresponding β-amino ketone in 16% yield and with 64% *ee* (Scheme 38).[45] Because iminium salt would be the reaction intermediate, the same group employed isolable *N,O*-acetal as a precursor of the iminium salt. Although LLB and another heterobimetallic chiral complex, (*R*)-AlLibis(binaphthoxide) (ALB), was not effective, a cooperative catalyst derived from ALB and $La(OTf)_3 \cdot nH_2O$ in the presence of MS3A furnished the corresponding β-amino ketones in modest enantioselectivities (Scheme 39). They observed the association of ALB and $La(OTf)_3 \cdot nH_2O$ by the laser desorption/ionization time-of-flight mass (LDI-TOF MS) spectrum.

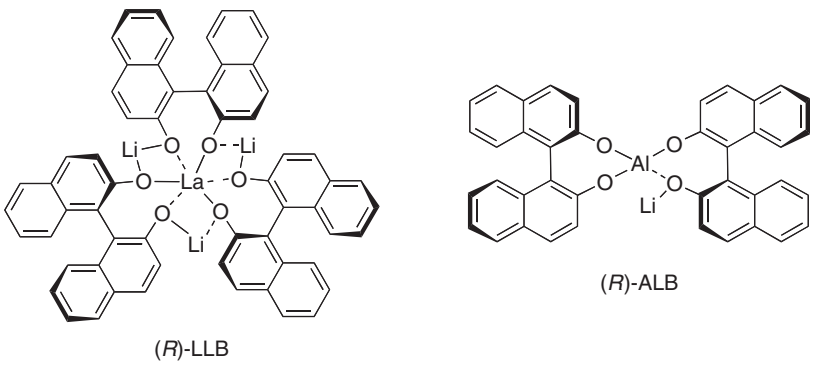
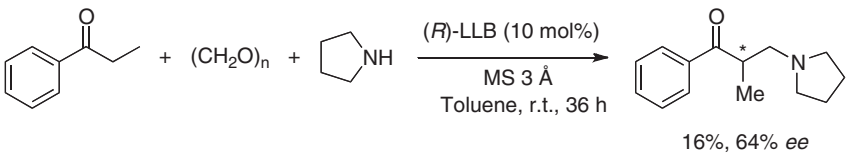
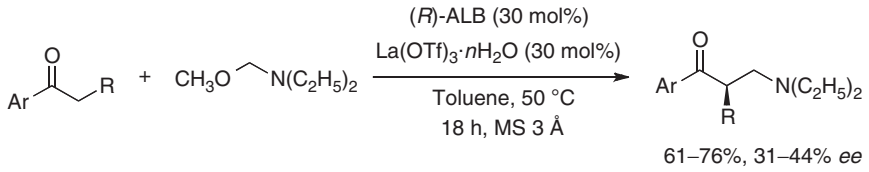


Figure 5 Chiral La and Al complexes.



Scheme 38



Scheme 39

The same group reported pioneering work on the Et_2Zn/(*S*,*S*)-linked BINOL (**34**) (**Figure 6**)[46] catalysis using readily removable *N*-protective diphenylphosphinoyl (Dpp) imine and Boc-imine, which selectively provided either *anti*- or *syn*-*β*-amino alcohols, respectively (**Schemes 40** and **41**).[47] The presence of the methoxy group at the ortho-position of the phenyl ring is essential for achieving the excellent enantioselectivities. It is noteworthy that the high catalyst TON was achieved in both *anti*- and *syn*-selective Mannich-type reactions (TON), up to 4920 for *anti*-isomer and up to 1760 for *syn*-isomer.

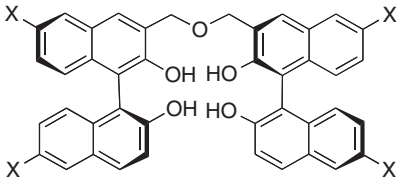
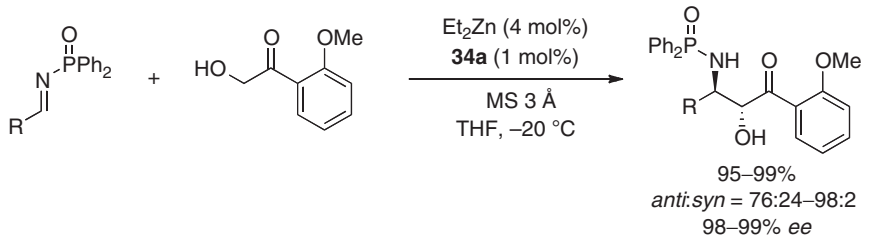
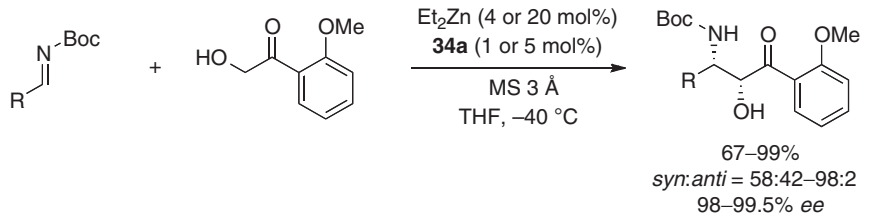


Figure 6 Chiral linked BINOL.



Scheme 40



Scheme 41

They proposed the transition state models (**Figure 7**) to rationalize the stereochemical outcome. In order to avoid the steric repulsion between the Dpp-group and zinc-enolate, the Mannich-type reaction proceeded by transition state **35**, leading to the *anti*-isomer. In contrast, sterically less demanding *N*-Boc imine gave rise to *syn*-isomer preferentially by way of transition state **36**, wherein steric repulsion between a substituent (R) of imine and zinc-enolate was avoided.

Trost and coworkers reported the direct Mannich reaction of α-hydroxyacetophenone derivatives with α-imino glyoxylate by means of a dinuclear Zn catalyst **37**,[48] which was originally developed for the catalytic asymmetric aldol reaction,[49] furnishing the α-hydroxy-*β*-amino carbonyl compounds in preference of the *syn*-isomer and with excellent enantioselectivities (**Scheme 42**).

The same group employed a similar direct Mannich reaction with aldimine bearing a readily removable *N*-protecting group by means of the dinuclear Zn catalyst **43** to give *syn*-α-hydroxy-*β*-amino carbonyl compounds with high enantioselectivities

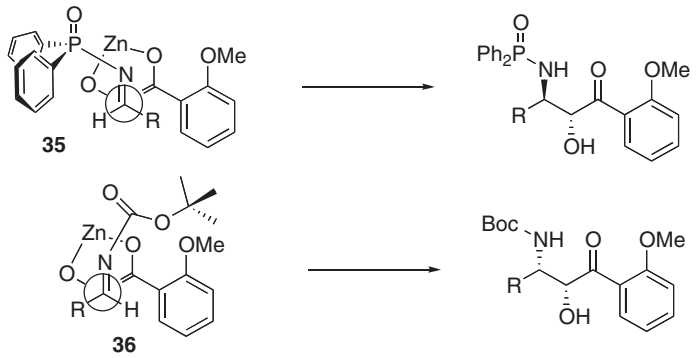
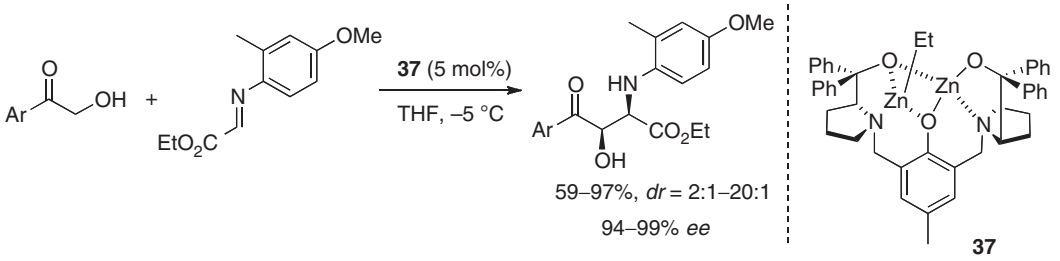
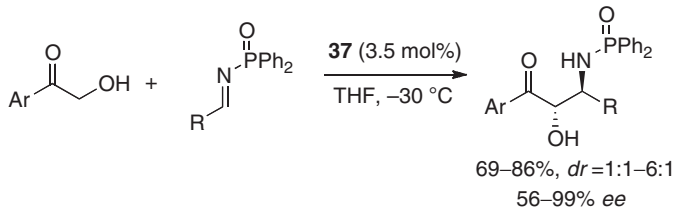


Figure 7 Transition state model of the zinc-catalyzed Mannich-type reaction.

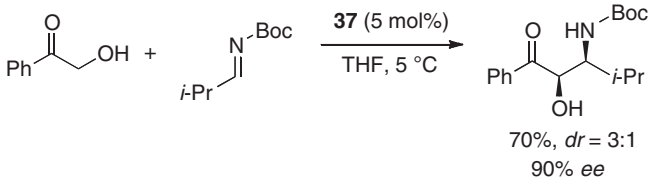


Scheme 42

(Scheme 43).[50] Interestingly, use of *N*-Boc aldimine resulted in the preferential formation of *anti*- α-hydroxy-β-amino ketones (Scheme 44).



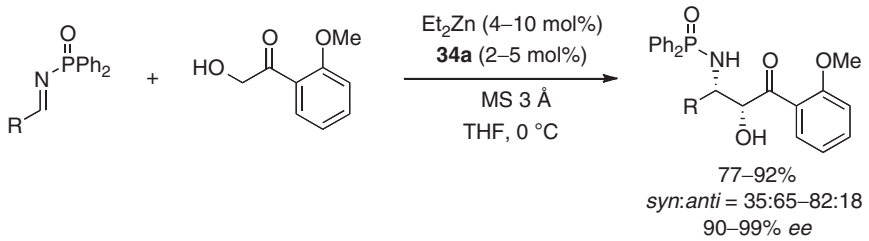
Scheme 43



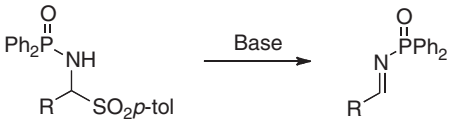
Scheme 44

The Shibasaki group reported a Mannich-type reaction of α-hydroxymethyl aryl ketone with aliphatic aldimines by means of the linked BINOL ligand **46**[51] in combination with Et_2Zn.[52] Excellent enantioselectivities were achieved, though the diastereoselectivities were modest (Scheme 45). It is critical to use aldimines prepared from α-amido sulfone by treatment with the $NaHCO_3/CH_2Cl_2$ biphasic system (Scheme 46).[53]

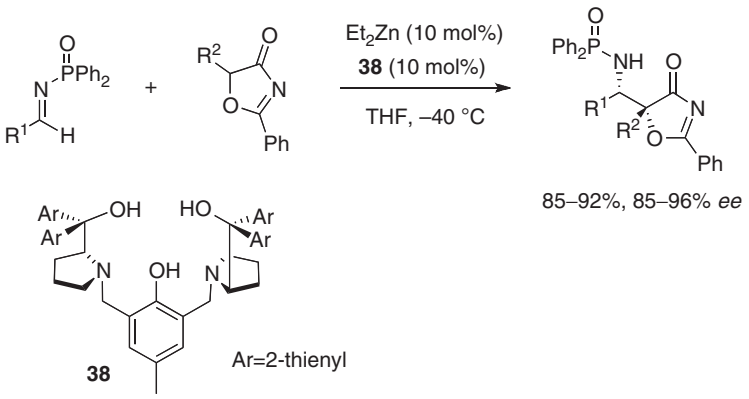
Wang and coworkers reported a Mannich reaction of 5*H*-oxazol-4-ones with *N*-Dpp aldimines by use of Et_2Zn (10 mol%), ligand **38** (10 mol%) in combination with diphenylphosphinamide in THF at 0 °C to furnish the adducts with excellent diastereoselectivity and with high enantioselectivities (Scheme 47).[54]



Scheme 45

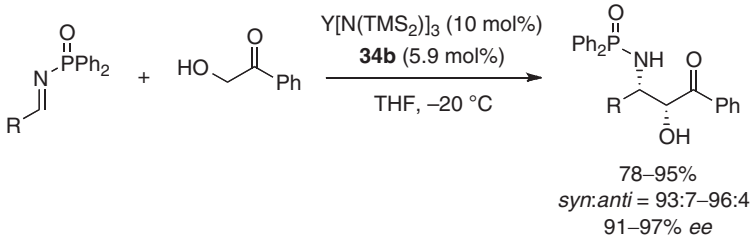


Scheme 46



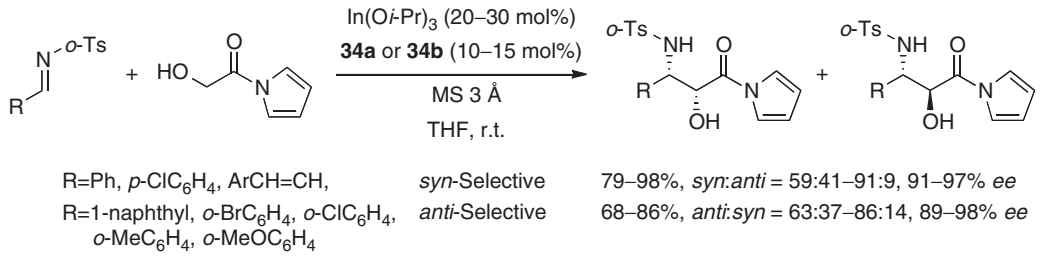
Scheme 47

Y[N(SiMe$_3$)$_2$]$_3$/TMS-linked BINOL complex **34** catalyzed the direct Mannich-type reaction of α-hydroxy phenyl ketone with *N*-phosphinoyl imine. The Mannich-type reaction afforded the corresponding *β*-amino-α-hydroxy ketones with a high level of *syn*-selectivity as well as excellent enantioselectivity (Scheme 48).[55] The high oxophilicity of the rare earth metal facilitated the coordination of the oxygen atom of a Dpp group to ytterbium to render the imine *s-cis* conformation, thereby avoiding steric repulsion. Acyclic *anti*-periplanar transition state leading to *syn*-product is proposed.



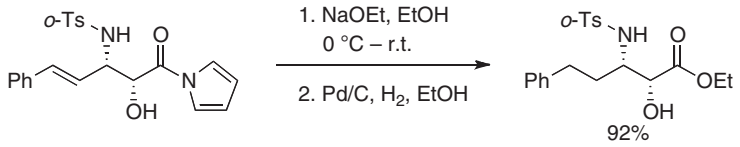
Scheme 48

The same group subsequently employed *N*-(hydroxyacetyl)pyrroles as ester equivalent of donor for the direct Mannich reaction by means of In(*i*-OPr)$_3$-linked BINOL complex **34**.[56] The diastereoselectivity depended on the R-group of the aldimines: aldimines bearing Ph, *p*-ClC$_6$H$_4$, and ArCH=CH moieties on carbon-exhibited *syn*-selectivity with excellent enantioselectivities while aldimines bearing 1-naphthyl, *o*-BrC$_6$H$_4$, *o*-ClC$_6$H$_4$, *o*-MeC$_6$H$_4$, and *o*-MeOC$_6$H$_4$ moieties on carbon-exhibited *anti*-selectivity with excellent enantioselectivities (Scheme 49). Because the enantiofacial selectivities toward aldimines are the same, the diastereoselectivity is ascribed to the steric interaction between the pyrrole ring and the imine R-group.



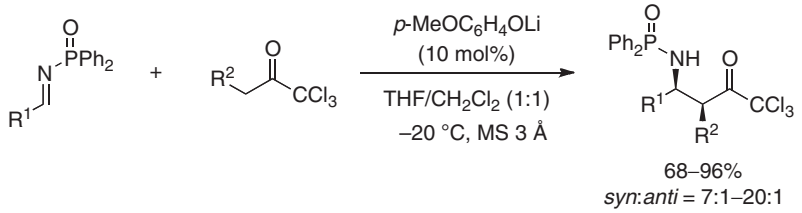
Scheme 49

Because the *N*-acyl pyrrole unit was readily transformed into an ethyl ester unit, the *N*-acyl pyrrole unit was utilized as an ester surrogate (Scheme 50).



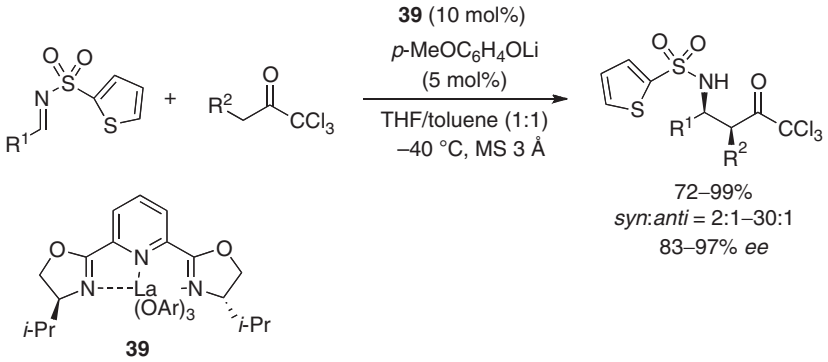
Scheme 50

Shibasaki's group reported that 1,1,1-trichloromethyl alkyl ketone underwent a Mannich reaction with *N*-diphenylphosphinoyl aldimine under the influence of phenoxide to furnish *β*-amino-*α*-alkyl esters in preference to the *syn*-isomer (Scheme 51).[57]



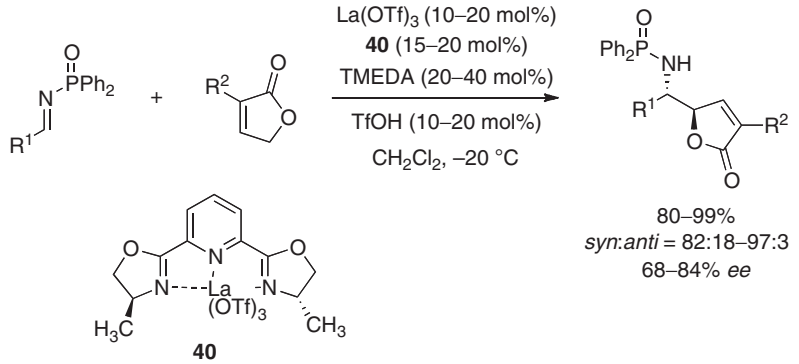
Scheme 51

They subsequently developed an enantioselective version of the Mannich reaction of *N*-(2-thienyl)sulfonyl aldimine with trichloromethyl ketone under the influence of La(III)-pybox catalyst **39**, furnishing the corresponding trichloroketones in excellent enantioselectivity in favor of the *syn*-isomer (Scheme 52).[58] A range of aldimines derived from aliphatic as well as aromatic aldehydes participated in the reaction successfully. Because the trichloro unit could be easily transformed to the ester unit, the present method is useful for the preparation of *β*-amino-*α*-alkyl substituted esters in high optical purity.



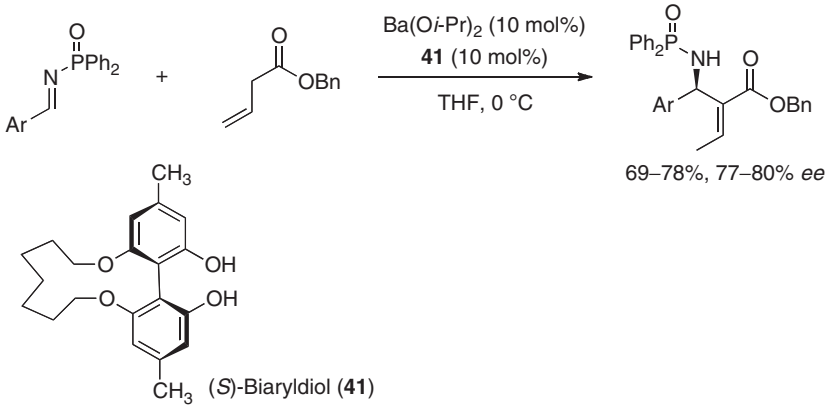
Scheme 52

Direct catalytic Mannich-type reaction of γ-butenolides with *N*-Dpp aldimines, derived from both aromatic and aliphatic aldehyde, was catalyzed by La(OTf)$_3$-MePybox-TMEDA in combination with TfOH to furnish the corresponding adducts in excellent enantioselectivities (Scheme 53).[59]



Scheme 53

A barium-catalyzed direct Mannich-type reaction of β,γ-unsaturated ester with *N*-phosphinoyl imine was developed.[60] An enantioselective version using (*S*)-biaryldiol **41** as a ligand was subsequently reported, giving rise to β-methyl aza Morita–Baylis–Hillman (MBH) type products in high enantioselectivities (Scheme 54).



Scheme 54

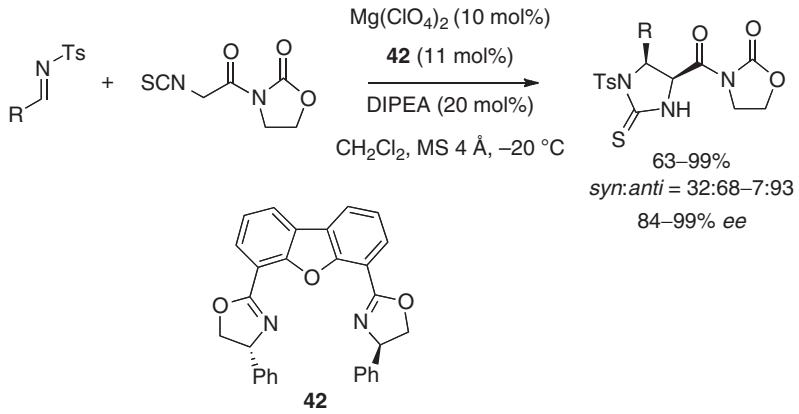
The Willis group employed Mg(ClO$_4$)$_2$ in combination with a DBFox ligand for the direct Mannich-type reaction of isothiocyanate-substituted oxazolidinone with *N*-Ts aldimines, derived from both aromatic and aliphatic aldehydes, furnishing the adduct in favor of the *anti*-isomer with excellent enantioselectivities (Scheme 55).[61]

Shibasaki developed an *anti*-selective direct Mannich-type reaction of α-ketoamide donors as synthetic equivalents of homoenolates. A homodinuclear Ni complex (Ni$_2$–**43**) prepared from the biphenyldiamine-based dinucleating Schiff base **43** (Figure 8) promoted the reaction of α-ketoanilides with *o*-Ns imine to give the products in up to 99% yields, with an *anti*/*syn* ratio greater than 50:1, and with up to 95% *ee* (Scheme 56).[62]

Spirooxindoles are a privileged structural motif found in many alkaloids and unnatural biologically active compounds. Kanai et al. developed an efficient method for the enantioselective synthesis of spirooxindoles bearing a nitrogen atom at the C3′ position of the oxindole unit. They employed the catalyst derived from Sr(O*i*-Pr)$_2$ and Schiff base **44** for the two-step conversion by Mannich reaction and subsequent cyclization reaction (Scheme 57).[63] Corresponding spirooxindoles were obtained with high diastereoselectivity as well as excellent enantioselectivities. Aldimines derived from aromatic aldehydes and heteroaromatic aldehydes were found to be suitable substrates.

The Jørgensen group developed a Cu(II)-catalyzed direct Mannich-type reaction of α-keto ester with *N*-tosyl α-imino ester by means of PhBOX-Cu(OTf)$_2$ complex to furnish highly functionalized 4-oxo-glutamic acid ester derivatives in high yield and diastereoselectivity, and with excellent enantioselectivity. The adducts were converted into highly functionalized, optically active α-amino-γ-lactones (Figure 9, Scheme 58).[64]

Similarly, Cu(II) complex is also effective for the direct Mannich reaction with malonates. A Cu(OTf)$_2$/(*R*)-*t*-Bu-BOX complex proved to the catalyst of choice (Scheme 59).[65]



Scheme 55

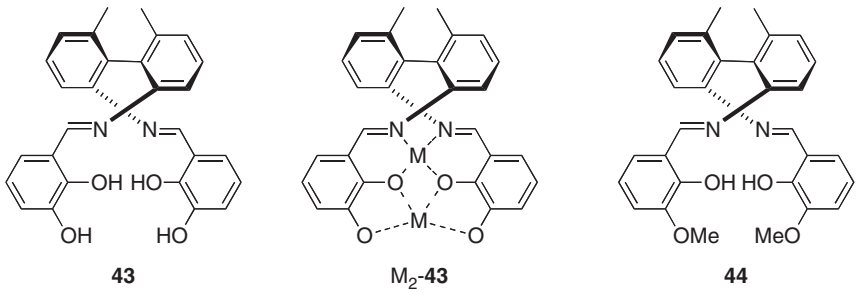
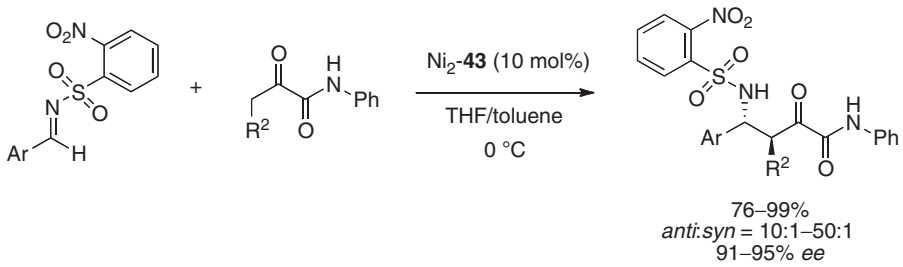
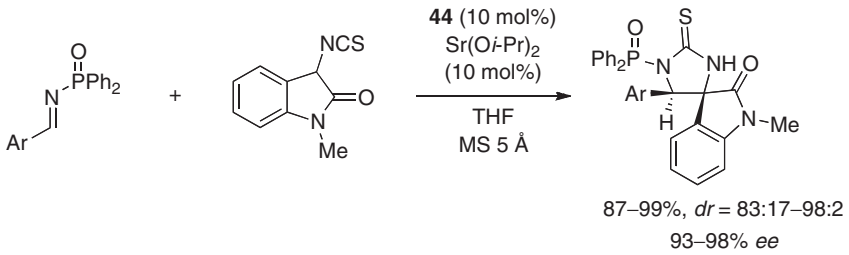


Figure 8 Structure of the dinucleating Schiff bases and dinuclear complex.

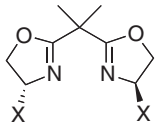


Scheme 56



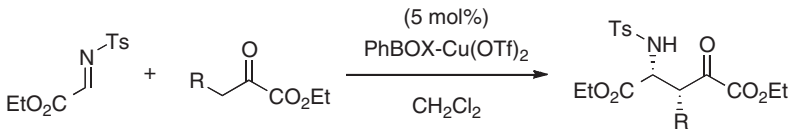
Scheme 57

The same group reported a diastereoselective and highly enantioselective Mannich reaction of α-imino ester with glycine alkyl esters by use of P,N-ligand **45**-$CuClO_4$ complex to give the addition products in good yields and excellent enantioselectivities (Scheme 60).[66]

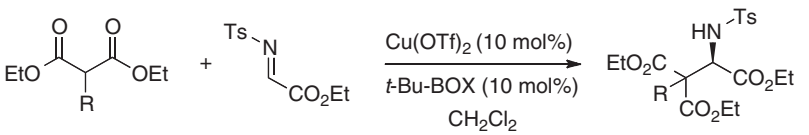


Ph-BOX: X = Ph
t-Bu-BOX: X = *t*-Bu

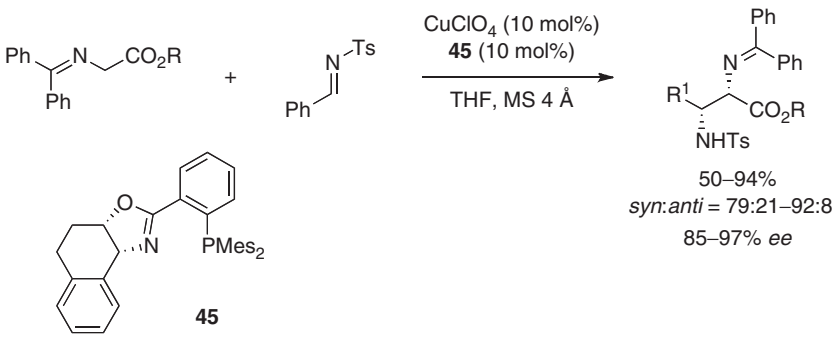
Figure 9 Bisoxazoline ligands.



Scheme 58



Scheme 59



Scheme 60

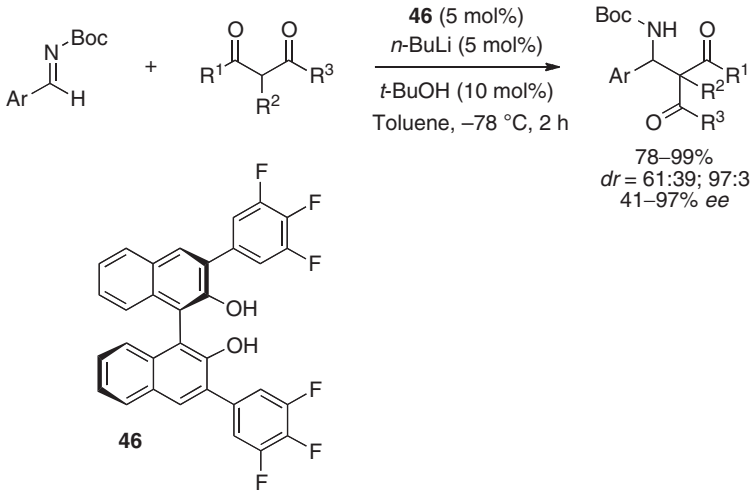
Ishihara's group developed a direct Mannich reaction of 1,3-dicarbonyl compounds with *N*-Boc aldimines by means of the chiral Li(I) salt of 3,3′-(3,4,5-$F_3C_6H_2)_2$-binaphthol **46**.[67] A range of 1,3-dicarbonyl compounds such as 1,2-diketone, 1,3-keto ester, 1,3-keto lactone, 1,3-keto thioester, and 1,3-keto amides were found to be suitable substrates (Scheme 61).

Less reactive malonates, however, could not be used in the chiral Li catalysis. The same group subsequently found that the Mg salt of BINOL is effective for the direct Mannich reaction of malonate (Scheme 62).[68]

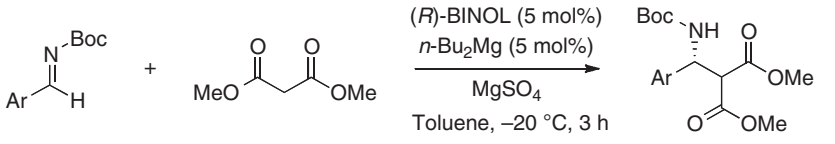
The Sodeoka group developed a highly enantioselective Mannich-type reaction of *β*-keto ester with aldimines by means of Pd(II) dihydrate-based catalyst **47a**, derived from (*R*)-TolBINAP (Scheme 63).[69] The reaction was applicable to a range of imines derived from glyoxylate as well as simple aromatic and *α*,*β*-unsaturated aldehydes, furnishing stereochemically elaborated *β*-amino carbonyl compounds in up to 99% *ee* (Scheme 64).[70] The Brønsted acid, generated during the formation of the Pd enolate, played an important role in activating the imines.

The related catalyst system **47b**, derived from (*R*)-DM-SEGPHOS, is highly effective for the addition of malonates to dihydroisoquinolines, giving rise to the formation of tetrahydroisoquinoline derivatives in high enantioselectivities (Scheme 65).[71]

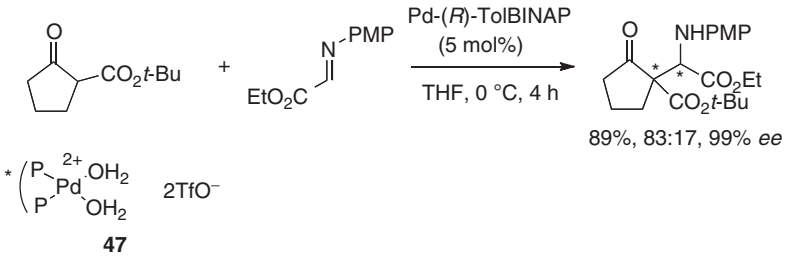
Kobayashi's group reported the Lewis acid-catalyzed three-component direct Mannich-type reaction of simple aromatic and enolizable aliphatic aldehydes, secondary amines, and glycine derivatives (Scheme 66).[72] The reaction exhibited perfect diastereoselectivity.



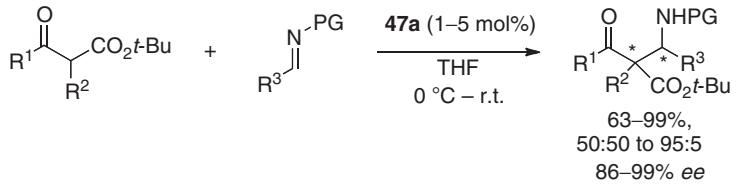
Scheme 61



Scheme 62



Scheme 63

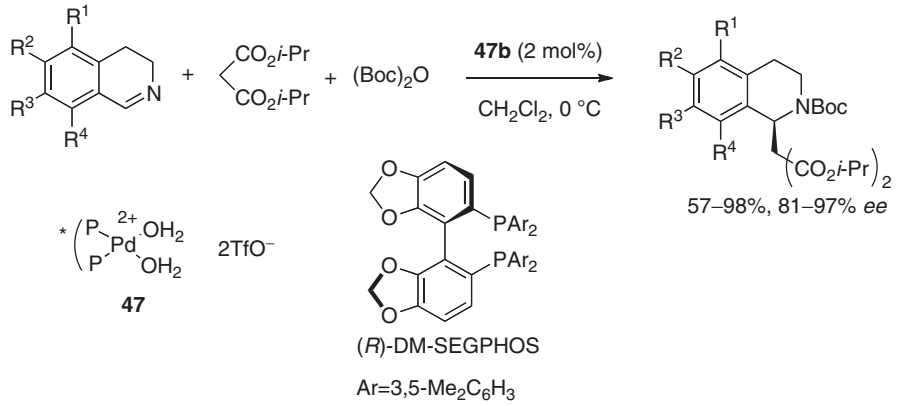


Scheme 64

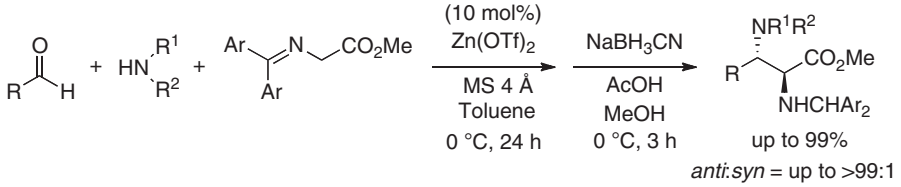
They subsequently investigated the catalytic enantioselective version of the three-component Mannich-type reaction and found that CuOTf in combination with (*R*,*R*)-DUPHOS is effective in furnishing the corresponding adduct with good enantioselectivity, although the diastereoselectivity was low (Scheme 67).

The Feng group reported a Cu(II)-catalyzed version of the Mannich-type reaction of glycine Schiff base using an *N*,*N*′-dioxide ligand to give the adducts with excellent enantioselectivities (Scheme 68).[73]

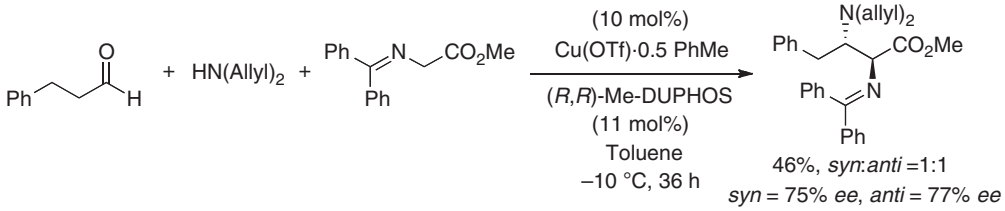
Carretero and coworkers reported a Mannich reaction of glycinate Schiff bases with aliphatic imines generated *in situ* from α-amido sulfones.[74] Imines with linear and branched alkyl chains, including substrates bearing a functional group, can be efficiently applied to give β-alkyl-α,β-diamino acid derivatives in favor of the *syn*-isomer with excellent enantioselectivities (Scheme 69).



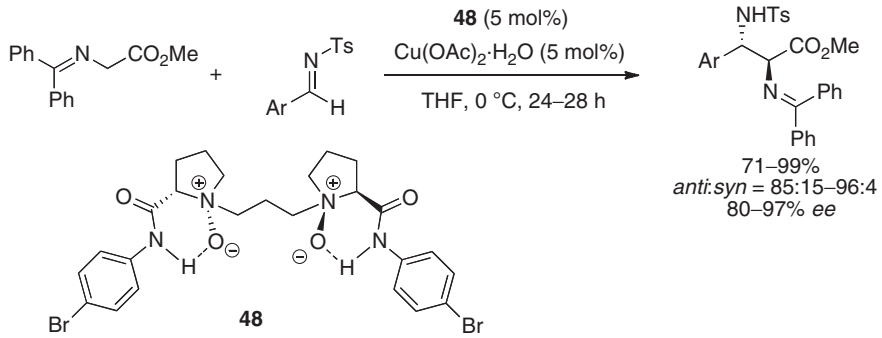
Scheme 65



Scheme 66



Scheme 67

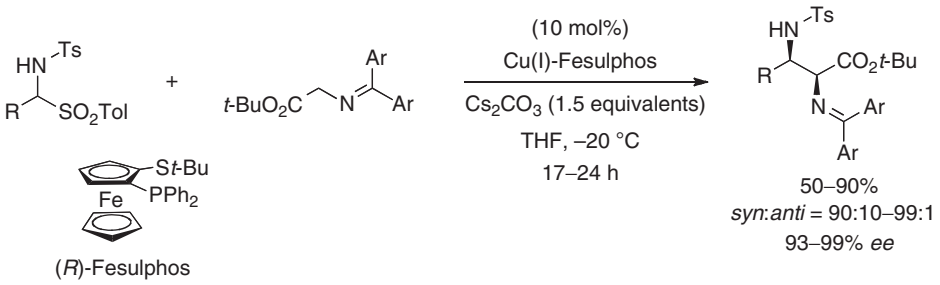


Scheme 68

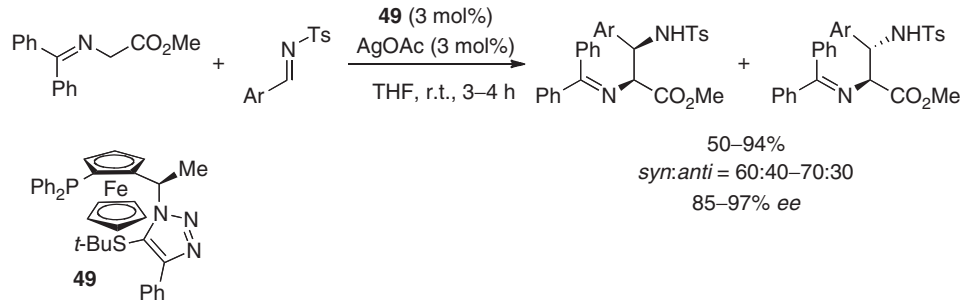
The Fukuzawa group employed the AcOAc/ThioClickFerrophos (**49**) complex for the Mannich reaction of glycine Schiff base with *N*-Ts aldimines to generate adducts with high enantioselectivities (Scheme 70).[75]

2.16.2.3.2 Vinylogous Mannich-type reaction

The vinylogous Mannich reaction is an addition reaction of homoenolate analog with imines and is a useful method for the preparation of γ-butenolide derivatives.[76]



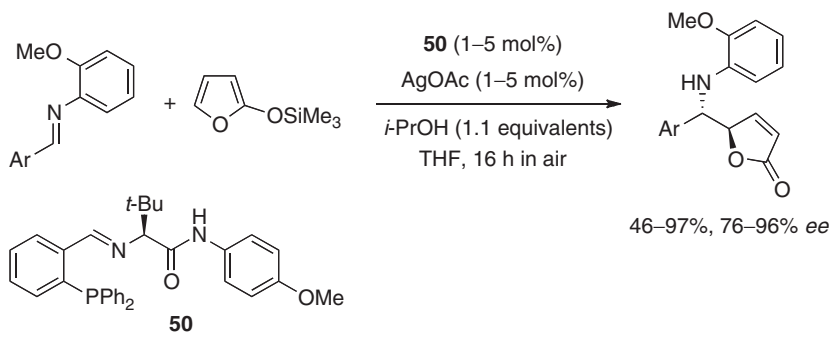
Scheme 69



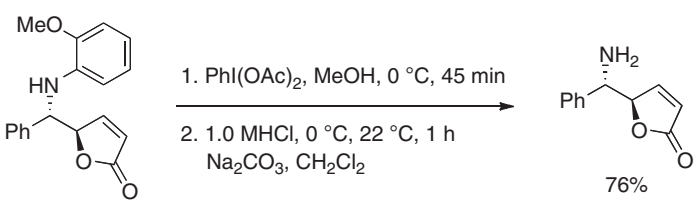
Scheme 70

Martin and Lopez reported the first enantioselective vinylogous Mannich reaction in 1999. The addition reaction of siloxyfuran to aldimines bearing a *N*-(2-hydroxyphenyl) moiety proceeded by means of Ti(O*i*-Pr)$_4$-(*S*)-BINOL complex to furnish the adduct in up to 54% *ee*.[77]

Hoveyda and Snapper developed a highly diastereoselective and enantioselective protocol for the asymmetric vinylogous Mannich reaction by use of the chiral silver-chiral phosphine complex **50**.[78] A range of aldimines derived from aromatic aldehydes proved to be suitable substrates to give γ-butenolides with excellent enantioselectivities (Scheme 71). Because the 2-methoxyphenyl moiety on nitrogen could be oxidatively removed (Scheme 72), the present method provides a practical method for the preparation of γ-butenolide on a multigram scale with only 1 mol% catalyst loading.

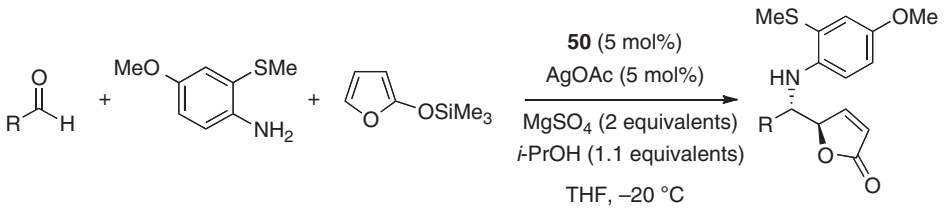


Scheme 71



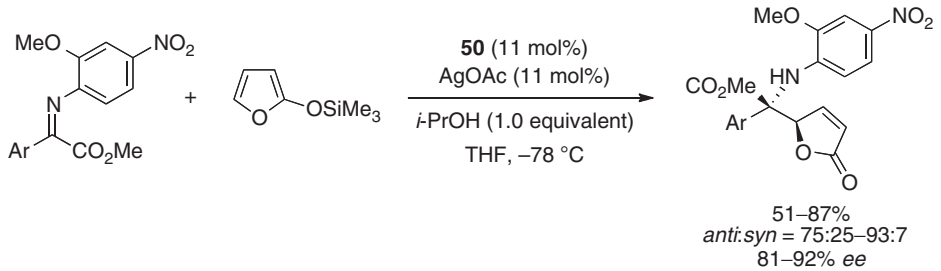
Scheme 72

Although the method was not successfully applied to aliphatic imines, the same group investigated the amine moiety and reported an efficient method for the three-component vinylogous Mannich reaction starting from aliphatic aldehyde, 4-methoxy-2-methylthioaniline, and siloxyfuran. The vinylogous Mannich reaction exhibited broad substrate scope, and a range of aliphatic aldehydes proved to be suitable substrates to give the corresponding γ-butenolides in high yields and with excellent enantioselectivities (>99:1) (Scheme 73).[79] The same group also succeeded in the vinylogous Mannich reaction with ketimines, derived from α-keto esters, wherein use of a 2-methoxy-4-nitrophenyl moiety on nitrogen is critical (Scheme 74).[80]



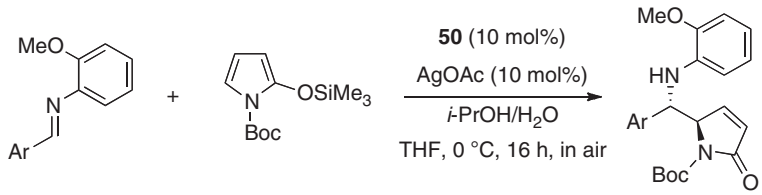
R = cyclohexyl, *i*-Pr, cyclopropyl, *i*-Bu, *t*-Bu, $PhCH_2CH_2$, $CH_3(CH_2)_5$

Scheme 73

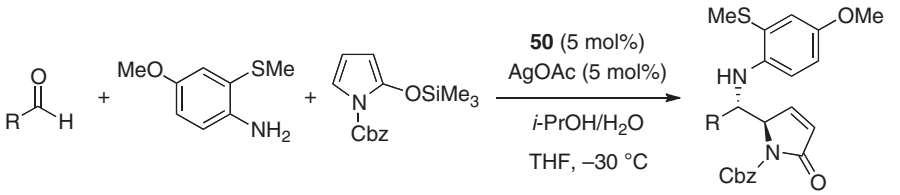


Scheme 74

In addition to siloxyfuran, *N*-Boc-2-(trimethylsilyloxy)pyrrole also underwent vinylogous Mannich reaction with *N*-(2-methoxyphenyl)aldimines derived from aromatic aldehyde to give α,β-unsaturated δ-amino-γ-butyrolactams in good enantioselectivities by means of **50** (Scheme 75).[81] Although aldimines derived from aliphatic aldehydes gave inferior results under the reaction conditions, the same group reported a method for the three-component vinylogous Mannich reaction by use of 4-methoxy-2-methylthioaniline, achieving excellent enantioselectivity even with aliphatic aldehydes (Scheme 76).[82]



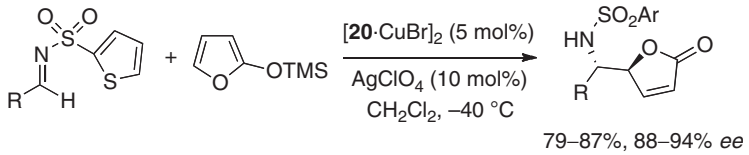
Scheme 75



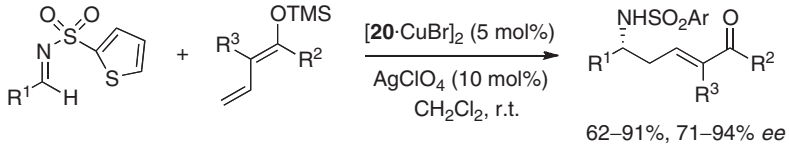
R = Me_2CHCH_2, C_6H_{13}, Me_2CH, Me, $PhCH_2CH_2$, $CH_3(CH_2)_6$, $TBSOCH_2$,

Scheme 76

The Carretero group subsequently reported a vinylogous Mannich reaction by means of Cu(I)-Fesulphos (**22**) as a catalyst.[83] *N*-(2-Thienylsulfonyl)imine exclusively furnished the γ-adduct in high yields and with high to excellent enantioselectivities (Scheme 77). Both silyl dienol ethers and 2-trimethylsilyloxyfuran proved to be suitable substrates (Scheme 78).

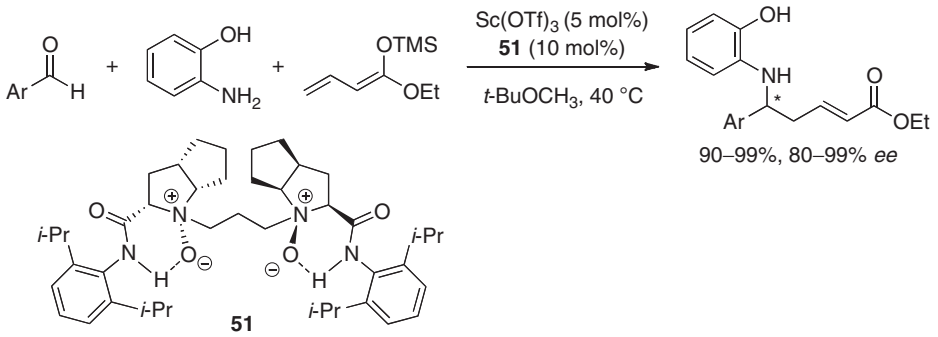


Scheme 77



Scheme 78

Feng's group developed an efficient method for the three-component vinylogous Mannich-type reaction of an acyclic silyl dienol ether, an aldehyde, and 2-aminophenol by use of the chiral *N*,*N*′-dioxide **51**-scandium(III) complex as the catalyst (Scheme 79).[84] A variety of aromatic aldehydes proved to be suitable substrates, and the corresponding δ-amino-α,β-unsaturated esters were obtained in 90–99% yields and with good to excellent enantioselectivities.



Scheme 79

Similarly, the *N*,*N*′-dioxide **52**-Sc(OTf)$_3$ complex also catalyzed the direct highly diastereo- and enantioselective asymmetric vinylogous Mannich-type reaction of aldimines with α-algelica lactone (Scheme 80).[85]

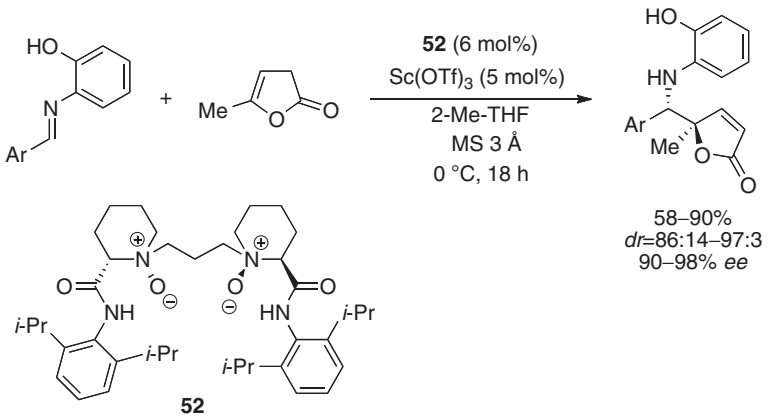
2.16.3 Organocatalyzed Mannich-Type Relations

Although a number of metal-based catalysts and biocatalysts were developed, relatively few asymmetric transformations had been reported employing organic molecules as catalysts before 2000. Organocatalysts have emerged as novel enantioselective catalysts since 2000.[86] Thereafter, organocatalyzed versions of the Mannich and related reactions have been extensively studied.[87]

In this section, organocatalyzed Mannich reactions are classified based on the catalysts employed. For historical reasons, this section commences with proline catalysis, followed by cinchona alkaloid, thiourea, and chiral Brønsted acid catalysis.

2.16.3.1 Mannich Reactions Promoted by Proline and Proline Derivatives

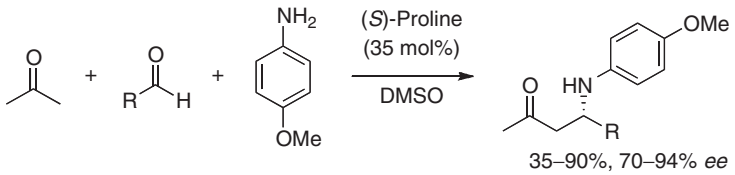
The first organocatalyzed Mannich reactions reviewed in this chapter are focused on proline catalysis.[88] (*S*)-Proline derivatives activate carbonyl compounds by forming enamine, and at the same time acidic protons such as carboxyl groups activate the carbonyl group by hydrogen bond.[89]



Scheme 80

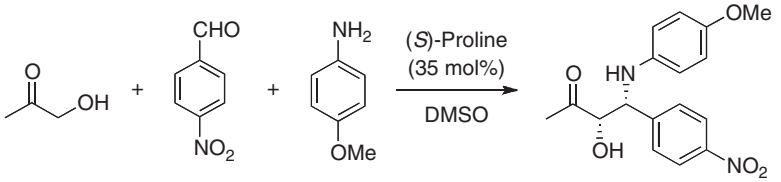
2.16.3.1.1 Syn-selective reactions

The first intermolecular proline-catalyzed Mannich reaction was reported in 2000 by List.[90] On treatment of acetone, aldehyde, *p*-anisidine with 35 mol% of (*S*)-proline in dimethyl sulfoxide (DMSO) at r.t., intermolecular Mannich reaction proceeded smoothly to furnish the corresponding *β*-amino ketone in good yields and with high to excellent enantioselectivities (Scheme 81). Aliphatic unbranched aldehydes as well as aromatic aldehydes proved to be suitable substrates. DFT calculation supported rationalization of the stereoselectivity of the Mannich reaction.[91]



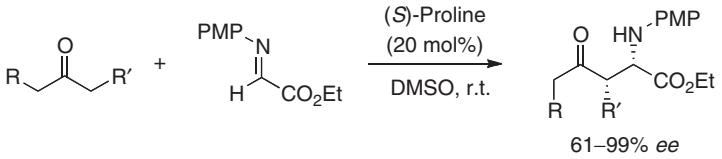
Scheme 81

The research group investigated the catalytic activity of a range of amino acids as well as the substrate scope, and found that ethyl methyl ketone, α-methoxy acetone, and α-hydroxy acetone also proved to be suitable substrates (Scheme 82).[92] Interestingly, although ethyl methyl ketone exhibited moderate regioselectivity in preference to the ethyl carbon (2.5:1), methoxyacetone and hydroxyacetone exclusively reacted at the carbon-bearing oxygen substituent. Furthermore, the present Mannich reaction exhibited excellent diastereoselectivity, giving rise to *syn*-1-hydroxy-2-amino ketones in high chemo-, regio-, diastereo-, and enantioselectivities in good yields.



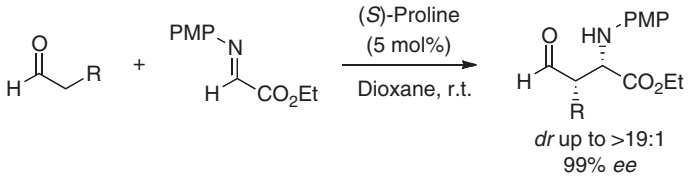
Scheme 82

α-Imino glyoxylate was successfully employed as an acceptor in the (*S*)-proline-catalyzed direct Mannich reaction,[93] and furnished functionalized α-amino acids with excellent enantioselectivities together with high *syn*-selectivity (Scheme 83).[94]



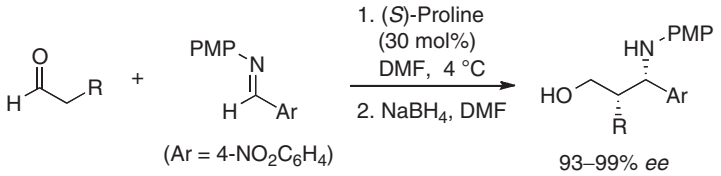
Scheme 83

The Barbas group studied the Mannich reaction utilizing aldehyde as a donor for the first time.[95] Heptanal was treated with α-imino glyoxylate in the presence of 5 mol% of (*S*)-proline in dioxane to afford the corresponding Mannich adduct in preference to the *syn*-isomer and with excellent enantioselectivity (Scheme 84).



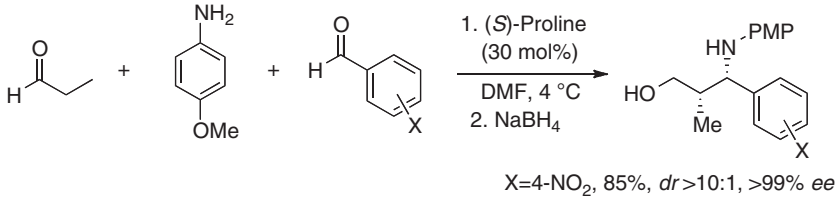
Scheme 84

At that time, only preformed α-imino ethyl glyoxylate had been used as an acceptor in direct Mannich reactions employing unmodified aliphatic aldehydes as donors, and the authors further studied the Mannich reaction of aliphatic aldehyde and preformed aldimine from aromatic aldehyde and *p*-anisidine. The Mannich reaction was highly sensitive to the temperature and reaction conditions. The best results were obtained when performing the reaction in DMF at 4 °C and adding the propanal (2 equivalents) as a cold (4 °C) 1 M solution in DMF over 14 h by syringe pump. These conditions afforded the highest conversion and, upon *in situ* $NaBH_4$ reduction of the Mannich adduct, provided the β-amino alcohol predominantly as one diastereomer in 81% yield and 99% *ee* (Scheme 85).



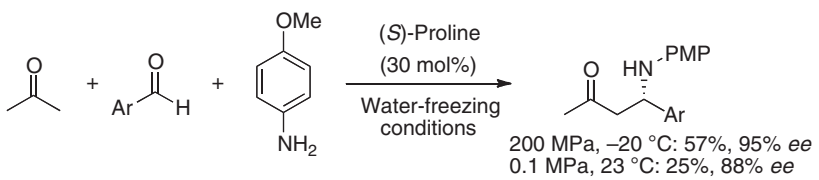
Scheme 85

Barbas et al.[93] and Hayashi et al.[96] independently developed a one-pot, three-component direct Mannich reaction of aldehyde at almost the same time by means of 30 mol% of (*S*)-proline. Although it is critical to control the reaction temperature, the cross Mannich adduct was obtained in high yield in preference to the *syn*-isomer, and with excellent enantioselectivity, with cross-aldol reaction and self-Mannich reaction being completely suppressed (Scheme 86).



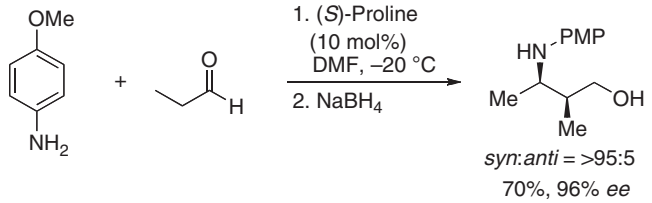
Scheme 86

Hayashi's group reported that the water-freezing induced-pressure method widens the scope and generality of the three-component Mannich reaction, attaining both better yield and enantioselectivity. The high pressure (approximately 200 MPa) was readily realized by freezing water (−20 °C) in a sealed autoclave. The increases in the yield and the optical purity are ascribed to the high pressure and low temperature, respectively (Scheme 87).[97]



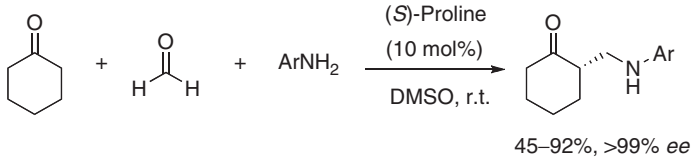
Scheme 87

The self-Mannich reaction of propanal also proceeded effectively to give *syn*-3-amino-2-methylbutan-1-ol derivative in 70% yield and 96% *ee* (Scheme 88).



Scheme 88

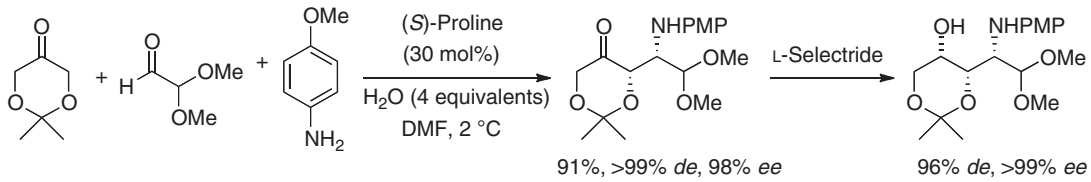
The Córdova group also developed a one-pot, three-component direct Mannich reaction.[98] Although a range of aldehydes had been employed for the three-component direct Mannich reaction, formaldehyde had not been utilized. They developed a direct catalyzed method that provides α-aminomethylated ketones in high yields with up to 99% *ee* by use of an aqueous solution of formaldehyde under the simple operational procedure (Scheme 89).[99]



Scheme 89

Bolm et al. reported the proline-catalyzed three-component direct Mannich reaction of cyclohexanone, formaldehyde, and various anilines. The three-component Mannich reaction proceeded by means of as low as 0.5 mol% of (*S*)-proline to give amino alcohol after *in situ* reduction of the resulting ketone in up to 86% yield and with up to 98% *ee*.[100] The Mannich-type reaction was accelerated thermally under microwave irradiation.

(*S*)-Proline-catalyzed direct Mannich reaction could be applied for the synthesis of amino sugars. The Enders group studied the direct three-component Mannich reaction with α-oxygenated aldehyde to give the corresponding *β*-amino ketone with excellent enantioselectivity. The addition of 1–10 equivalents of water led to an increase in the stereoselectivity. Subsequent reduction of the ketone with L-selectride furnished protected 2-amino-2-deoxy-L-xylose derivative with excellent stereoselectivity (Scheme 90).[101,102]



Scheme 90

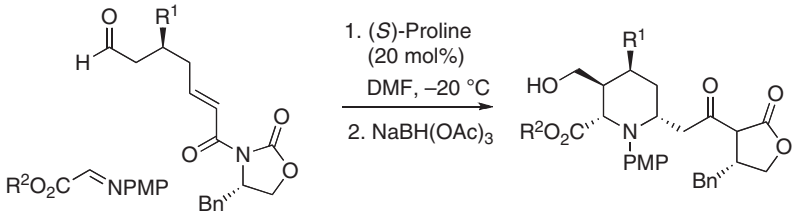
The direct three-component Mannich reaction of α-oxygenated aldehydes resulted in the formation of protected amino-tetroses.[103] Application of the methodology furnished polyoxamic acid derivative after *in situ* reduction of the resultant ketone.

A domino Mannich-aza-Michael reaction was achieved by means of 20 mol% of (*S*)-proline toward the stereoselective synthesis of highly substituted pipecolic esters.[104] The functionalized aldehyde, obtained in enantiomerically pure form through Cope rearrangements of silylated *syn*-aldol products, was treated with α-imino glyoxylate and 20 mol% of (*S*)-proline to give pipecolic esters in one step in moderate yields (Scheme 91).

Sequential Mannich-aza-Michael reactions of α-imino glyoxylate with aldehyde led to the formation of either 2,5-*trans*- or 2,5-*cis* pyrrolidines with high diastereoselectivity as well as excellent enantioselectivity.[105] Mioskowski applied the (*S*)-proline catalyzed Mannich reaction for the practical and efficient total synthesis of potent insulinotropic (2*S*,3*R*,4*S*)-4-hydroxyisoleucine.[106]

2.16.3.1.2 Mannich reaction with N-Boc aldimine

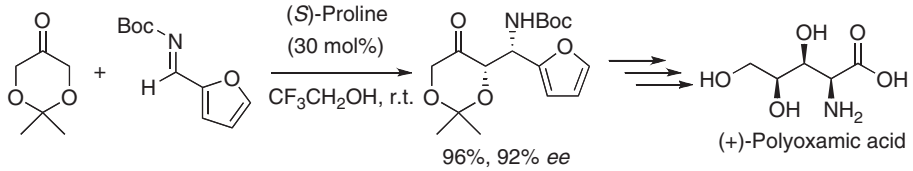
Aldimines bearing an *N*-*p*-methoxyphenyl (PMP) group were extensively employed as acceptors in the proline-catalyzed direct Mannich reaction. One of the problems associated with the *N*-PMP group is the difficulty in the cleavage of the protecting group.



Scheme 91

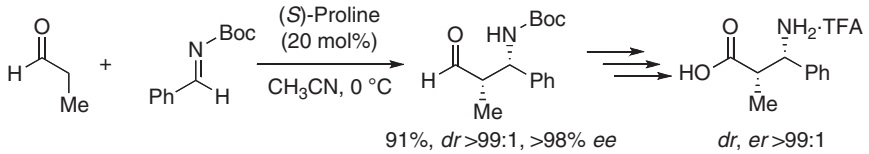
Ceric ammonium nitrate has been extensively employed for the cleavage of the *N*-PMP group.[107] Efficient methods for the deprotection of *N*-PMP group are reported, including anodic oxidation,[108] $PhI(OAc)_2$,[109] trichloroisocyanuric acid,[110] and laccase.[111] In contrast to the *N*-PMP group, one can cleave the *N*-Boc group readily under acidic conditions. Weak points of the *N*-Boc group are that (1) aldimine must be formed in advance, (2) only aromatic aldimine can be employed.

The Enders group employed *N*-Boc (*t*-butoxycarbonyl) imine for the proline-catalyzed Mannich reaction for the first time.[112] They obtained the corresponding adduct with excellent enantioselectivity and achieved the total synthesis of (+)-polyoxamic acid (Scheme 92).



Scheme 92

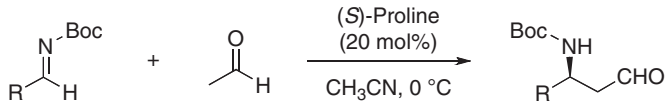
List et al. also reported the direct Mannich reaction of unmodified aldehyde with *N*-Boc aldimine to generate *β*-amino aldehyde with excellent diastereo- and enantioselectivity, which was readily transformed into *β*-amino acid (Scheme 93).[113]



Scheme 93

2.16.3.1.3 Mannich reaction with acetaldehyde

Acetaldehyde is one of the most reactive and versatile aldehydes. There are several problems associated with potential use of acetaldehyde in proline-catalyzed Mannich reactions, including: (1) acetaldehyde rapidly reacts itself via aldol condensation to form oligomers; and (2) Mannich products derived from aldehyde itself may undergo further reaction. The List group succeeded in suppressing the side reactions by use of a higher excess of acetaldehyde (5–10 equivalents). Treatment of a range of *N*-Boc aldimines with acetaldehyde in the presence of (*S*)-proline (20 mol%) in acetonitrile at 0 °C furnished the desired *β*-amino aldehydes with excellent enantioselectivities and in good yields (Scheme 94).[114,115]



Scheme 94

The resulting *β*-amino aldehyde is an important chiral building block for the preparation of a range of nitrogen-containing compounds, which include 2,3-diaminie, *β*-amino acid, and piperidines.

Hayashi's group also reported the Mannich reaction of acetaldehyde with *N*-Bz aldimines by means of prolinol silyl ether **53a**[116] (Figure 10) and *p*-nitrobenzoic acid.[117] Subsequent reduction with $LiAlH_4$ furnished the corresponding *N*-Bz-alcohols with

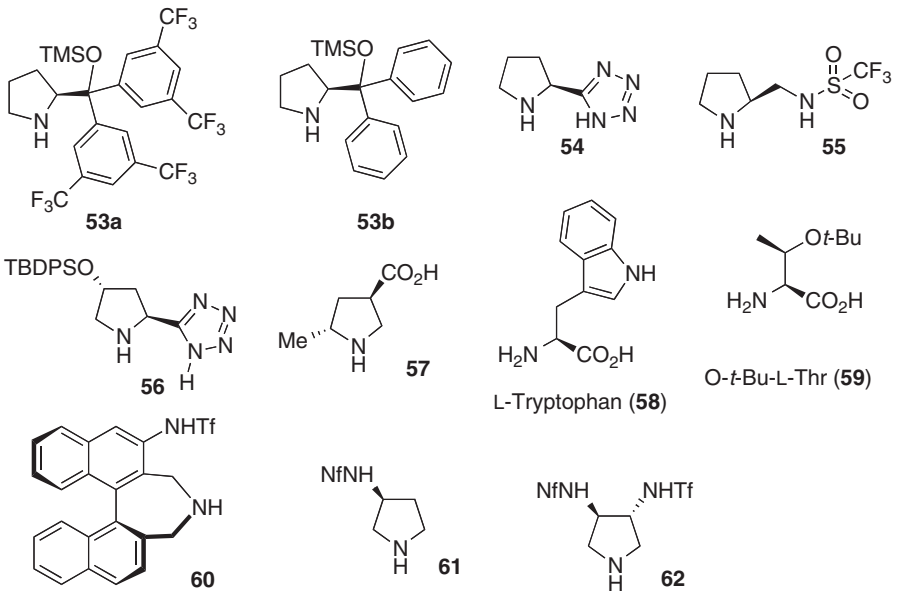
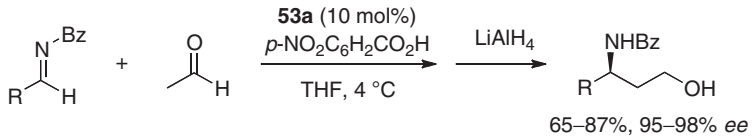


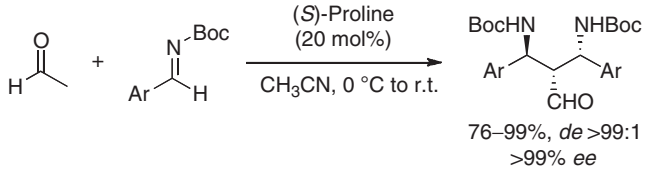
Figure 10 Modified proline ligands.

excellent enantioselectivities (Scheme 95). Theoretical studies elucidated that the formation of the enamine intermediate is the rate-determining step and that once the enamine is formed, it reacts with the protonated imine with no activation barrier.



Scheme 95

The List group subsequently developed a Mannich reaction of acetaldehyde with *N*-Boc aldimine. Initially formed α-unbranched aldehydes underwent a second Mannich reaction to furnish double-Mannich addition products with extremely high enantiomeric excesses (Scheme 96).[118] Aldimines derived from heteroaromatic aldehyde as well as aromatic aldehyde participated successfully in the reaction. An aldimine derived from aliphatic aldehyde also gave the adducts with excellent diastereo- and enantioselectivity in modest yield.

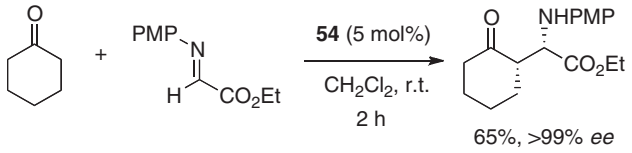


Scheme 96

2.16.3.1.4 Modified proline catalysis

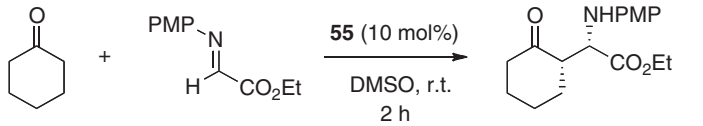
A notable drawback of the catalyst is that polar solvents such as DMSO must be employed due to the insoluble nature of proline itself toward less polar solvents. Furthermore, high catalyst loading (10–30 mol%) was required for completion of the reaction. In order to obviate the problems, a number of proline analogs, which possess high solubility in conventional solvents, were developed. The Ley group synthesized a proline derivative bearing a tetrazole moiety **54** and demonstrated its catalytic activity for the Mannich reaction of ketone with *N*-PMP-protected α-imino ester. Corresponding Mannich adducts were obtained with excellent enantioselectivities.[119] The tetrazole catalyst **54** exhibits remarkable advantages over (*S*)-proline in that it is soluble in nonpolar solvents and that the catalyst loading could be reduced to 5 mol% without loss of enantioselectivity. It is noted that the catalyst loading could be reduced to as low as 1 mol% by slightly extending the reaction time from 2 h to 16 h without sacrificing the enantioselectivity.

Seeberger's group applied the Mannich reaction catalyzed by **54** to a continuous-flow reactor system, and observed significant acceleration of the reaction rate[120] (Scheme 97).



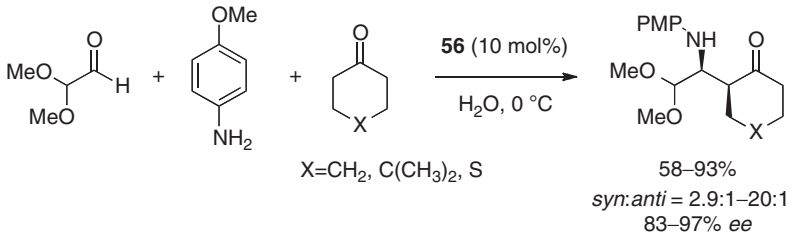
Scheme 97

Wang et al. developed pyrrolidine-sulfonamide **55** and applied it for the Mannich reaction of ketone with α-imino glyoxylate. The corresponding adducts were obtained with excellent enantioselectivities (Scheme 98).[121] Conventional solvents such as $CHCl_3$, THF, and EtOAc could be employed successfully. It is noted that catalyst loading was reduced to as low as 2 mol% by slightly extending the reaction time.



Scheme 98

Hayashi and coworkers developed a silyloxytetrazole hybrid catalyst **56** and achieved the three-component Mannich reaction of α,α-dimethxyacetaldehyde in water in the absence of organic solvent. Excellent enantioselectivities were realized, and the usage of organic solvents could be reduced (Scheme 99).[122]



Scheme 99

2.16.3.1.5 Anti-selective Mannich reaction

In contrast to metal-catalyzed reactions that provide both *syn*- and *anti*-1,2-amino alcohols, highly enantioselective organocatalyzed approaches had been limited to *syn*-1,2-amino alcohols.

Barbas developed a novel pyrrolidine-based organocatalyst, (3*R*,5*R*)-5-methyl-3-pyrrolidinecarboxylic acid (**57**), based on the consideration that enamine geometry will be altered so that *s*-trans conformation of the (*E*)-enamine reacts in the C–C bond forming transition state and C–C bond formation occurs at the *re*-face of the enamine intermediate and *si*-face of the (*E*)-aldimine, thereby leading to *anti*-Mannich adduct (Figure 11). Their group reported highly *anti*-selective Mannich reaction of aldehyde and α-imino glyoxylate (Scheme 100).[123] *Anti*-selective Mannich reaction of ketone with α-imino glyoxylate was also reported by means of **57**.[124]

The same research group developed a novel method for the *anti*-selective Mannich reaction by means of primary amine catalyst.[125] Screening of amino acids elucidated that L-tryptophan (**58**) is the catalyst of choice for the three-component Mannich reaction of α-hydroxyacetone derivatives to give the corresponding Mannich adducts with high *anti*-selectivity and with excellent enantioselectivities (Scheme 101).

They also developed *anti*-Mannich reactions of dihydroxyacetone and acyclic dihydroxyacetone derivatives with a variety of imines by means of *O*-*t*-Bu-L-threonine (**59**) (Scheme 102).[126] This approach complements the proline-based strategies in the preparation of amino sugars. Hydrogen bond-stabilized (*Z*)-enamine is assumed to be involved in the reaction intermediate to furnish *anti*-isomer selectively.

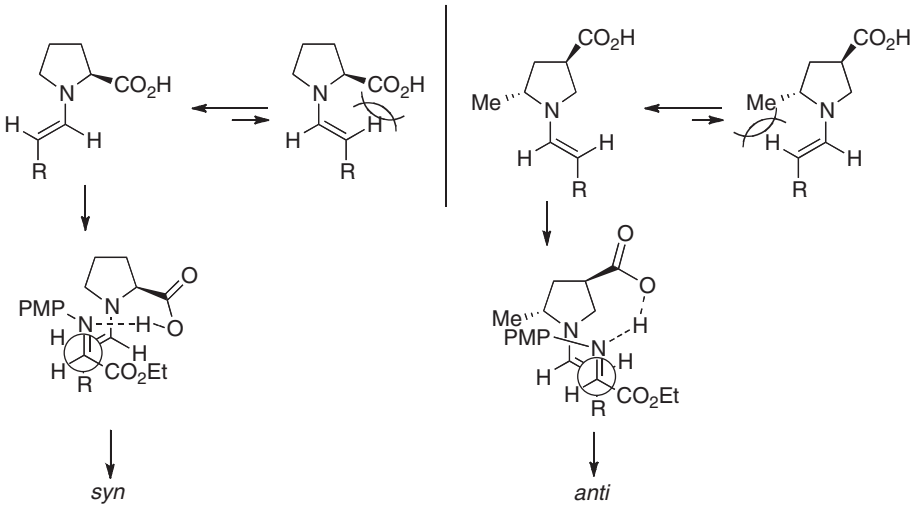
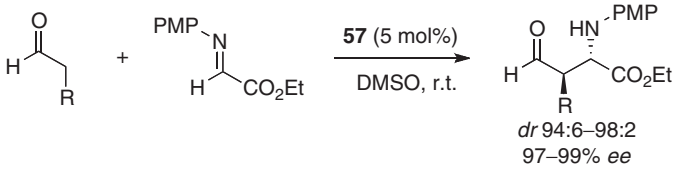
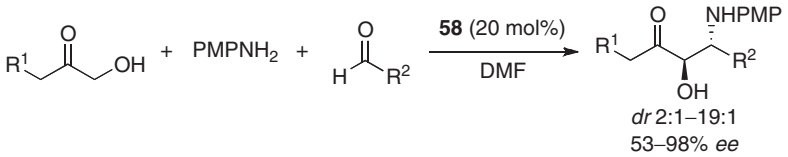


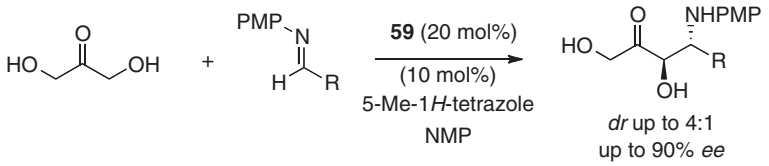
Figure 11 Rationalization of the stereochemical outcome.



Scheme 100



Scheme 101



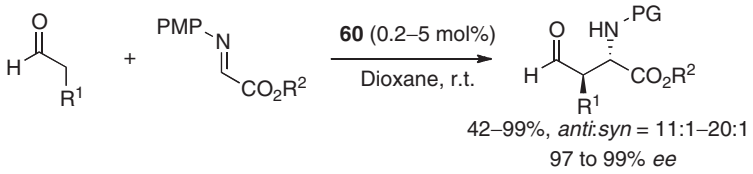
Scheme 102

Maruoka et al. developed a novel proline analog **60**, bearing a longer spatial distance between the amino group and the sulfonamide moiety than amine and the carboxyl group in (*S*)-proline.[127] Direct Mannich reaction of aldehyde with α-imino glyoxylate proceeded with high *anti*-selectivity and with excellent enantioselectivities (Scheme 103).

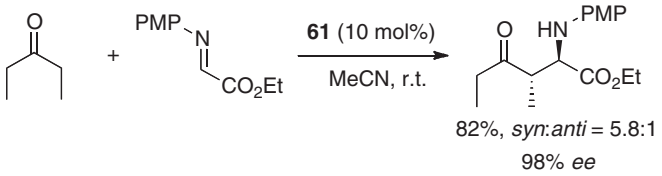
The same group developed a new pyrrolidine-based sulfonamide **61**, which effectively catalyzed the Mannich reaction of sterically demanding 3,3-dimethylbutanal and a less reactive acyclic ketone to give *anti*-adducts predominantly (Scheme 104).[128]

C_2-symmetric chiral pyrrolidine-based amino sulfonamide **62** was employed for the *anti*-selective direct Mannich reaction (Scheme 105).[129]

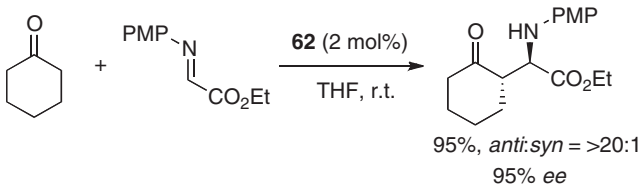
The same group developed an *anti*-selective Mannich reaction of aldehyde with *N*-Boc aldimine by means of **60**. The corresponding adducts were obtained with excellent enantioselectivities (Scheme 106).[130] It is noted that acetaldehyde also participated in the Mannich reaction successfully.



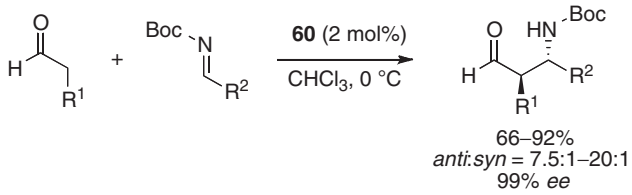
Scheme 103



Scheme 104

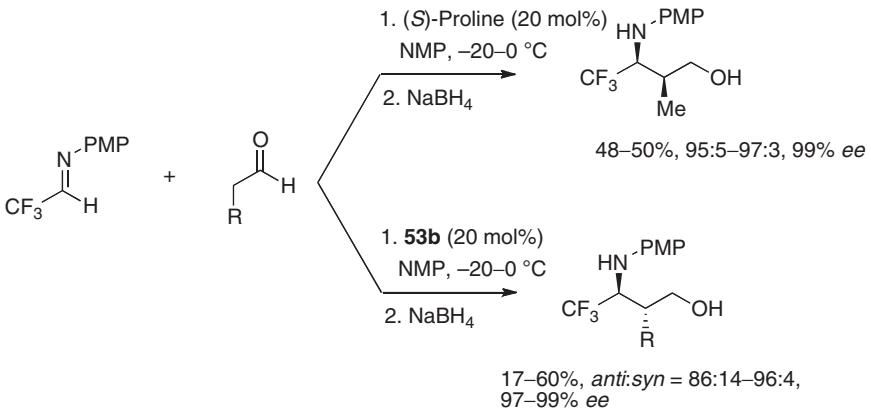


Scheme 105



Scheme 106

Fustero and coworkers reported the Mannich reaction of fluorinated aldimines with aldehyde. The corresponding fluorinated amino alcohol derivatives were obtained with excellent enantioselectivities upon treatment with $NaBH_4$. Whereas use of (*S*)-proline gave *syn*-isomer highly selectively,[131] use of diphenylprolinol silyl ether **53b** furnished *anti*-isomers preferentially (Scheme 107).[132]

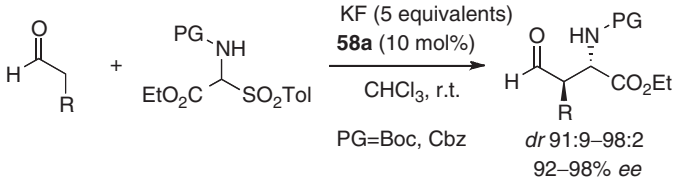


Scheme 107

The enantioselective Mannich reaction of acetone with *N*-aryl-aldimine, derived from ferrocenecarbaldehyde, was realized by means of (*S*)-proline.[133]

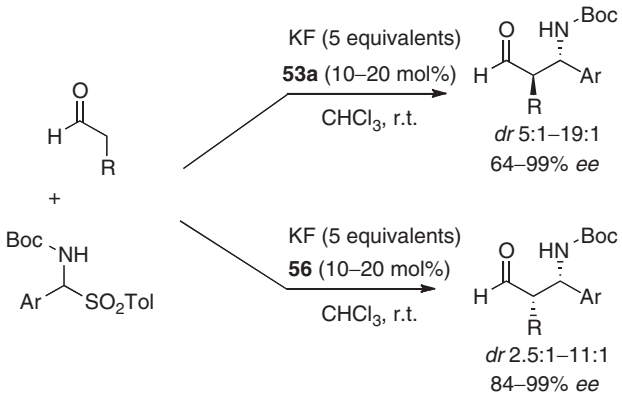
2.16.3.1.6 Proline-catalyzed Mannich reaction with amido sulfone

The instability of *N*-carbamoyl imines is one of its intrinsic disadvantages as acceptor in the Mannich reaction. In order to overcome this drawback, *N*-carbamoyl imines were generated *in situ* from stable α-amido sulfones by treatment with inorganic base and were subjected to nucleophilic reaction.[134] Melchiorre and coworkers developed a simple and convenient method for the direct *anti*-selective Mannich reactions of aliphatic aldehydes with *in situ*-generated *N*-carbamoyl imines. Diaryl prolinol silyl ether **53a** turned out to be the catalyst of choice, and the corresponding Mannich adducts were obtained with high *anti*-selectivity as well as excellent enantioselectivities (Scheme 108).[135]



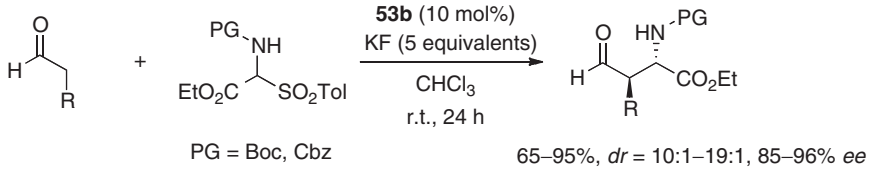
Scheme 108

The same group obtained both *anti*- and *syn*-isomers highly diastereoselectively as well as excellent enantioselectively in the organocatalyzed Mannich reaction with α-amido sulfone by proper choice of the commercially available organocatalyst (Scheme 109).[136] This method features the operational simplicity of the method: the highly reactive *N*-carbamoyl-protected aldimines were generated *in situ* from stable and easily handled α-amido sulfones.



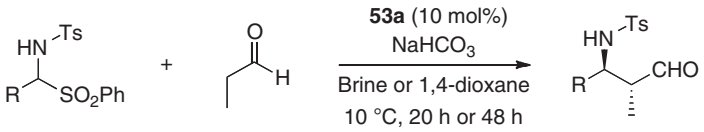
Scheme 109

α-Amido sulfone derived from glyoxylate also successfully participated in the direct and highly enantioselective Mannich reactions of aldehydes (Scheme 110).



Scheme 110

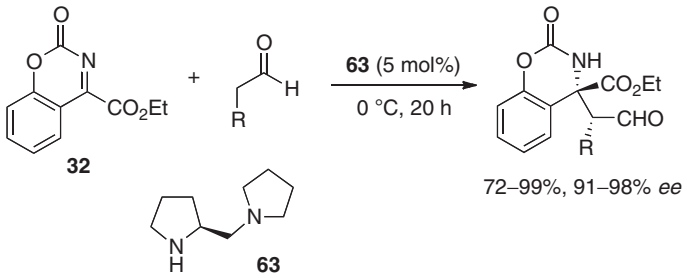
The Hayashi group also reported a highly *anti*-selective Mannich reaction of propanal with α-amido sulfones, derived from aliphatic aldehydes by means of **53a** (Scheme 111).[137] It is noted that amido sulfones derived from a range of aliphatic aldehydes proved to be suitable substrates. Either brine or 1,4-dioxane is a suitable solvent for attaining high *anti*-selectivity and excellent enantioselectivity.



Scheme 111

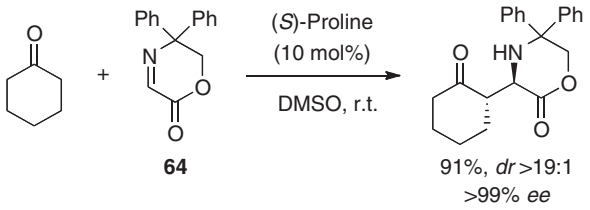
2.16.3.1.7 Proline-catalyzed Mannich reaction with ketimines

Ketimines are, in general, less reactive than aldimines because of their low electrophilicity and the increased steric hindrance to nucleophilic attack on the C=N bond. Jørgensen's group took advantage of the reactivity of the cyclic ketimine **32** for the direct enantioselective Mannich reactions of ketimines with aldehydes by means of 5 mol% of chiral diamine **63**, leading to chiral quaternary α-amino acid derivatives with excellent enantioselectivities (Scheme 112).[138]



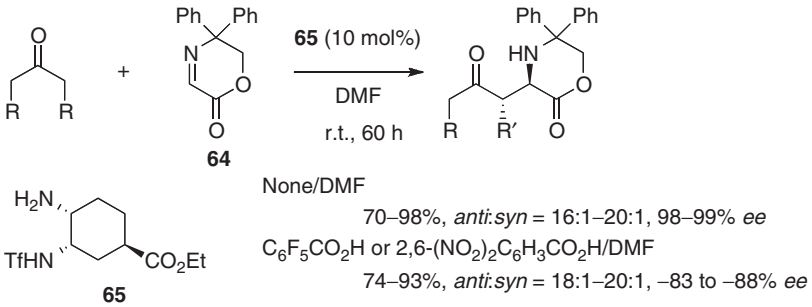
Scheme 112

Glorius and coworkers hypothesized that cyclic α-imino glyoxylate **64** would be a useful alternative to imine substrate locked in *Z* configuration, and the change in the configuration of the imine double bond should result in the formation of *anti*-configured amino acid derivatives. As expected, the Mannich reaction of the cyclic imine with cyclohexanone proceeded in an excellent diastereo- and enantioselective manner to give the corresponding *anti*-Mannich adduct (Scheme 113).[139]



Scheme 113

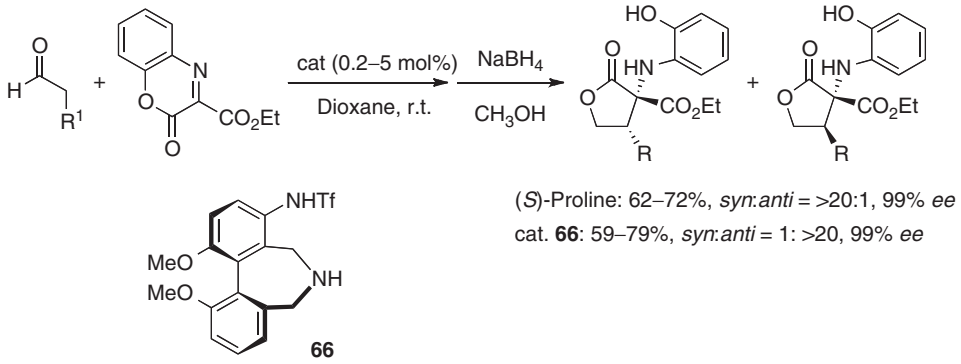
The Maruoka group succeeded in obtaining both enantiomers of the *anti*-Mannich adducts derived from cyclic α-imino glyoxylate **64** by using a single organocatalyst **65** either in the presence or absence of chiral acid as additives (Scheme 114).[140]



Scheme 114

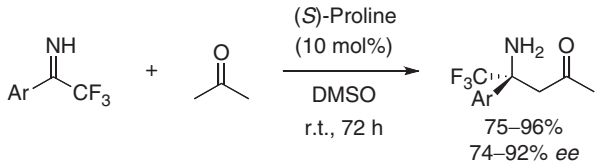
Maruoka developed a direct Mannich reaction of aliphatic aldehydes with cyclic ketimines to give γ-lactones bearing a quaternary carbon center at the α-position with complete enantioselectivity.[141] Interestingly, whereas use of (*S*)-proline as a

catalyst resulted in the preferential formation of *syn*-isomer, use of **66** led to the exclusive formation of the *anti*-isomer (Scheme 115).



Scheme 115

Vovk and coworkers developed an organocatalyzed Mannich reaction of ketimine for the first time by use of aryl trifluoromethyl ketimines as substrate (Scheme 116).[142] Corresponding β-amino-β-trifluoromethyl ketones were obtained with high enantioselectivities. Interestingly, protection of the imine nitrogen is not required.



Scheme 116

2.16.3.2 Cinchona Alkaloid Catalysts

Schaus and coworkers reported a diastereo- and enantioselective direct Mannich reaction of β-ketoesters with *N*-carbamoyl aldimines by means of cinchona alkaloid catalysts.[143,144] Both cinchonine (**67**) and cinchonidine (**68**) (Figure 12) furnished the corresponding adducts, and with excellent enantioselectivities. Although cinchonine and cinchonidine are not enantiomers, changeover of the enantiofacial selectivity was observed (Scheme 117).[145] Aldimines derived from a variety of aromatic aldehydes participated in the reaction.

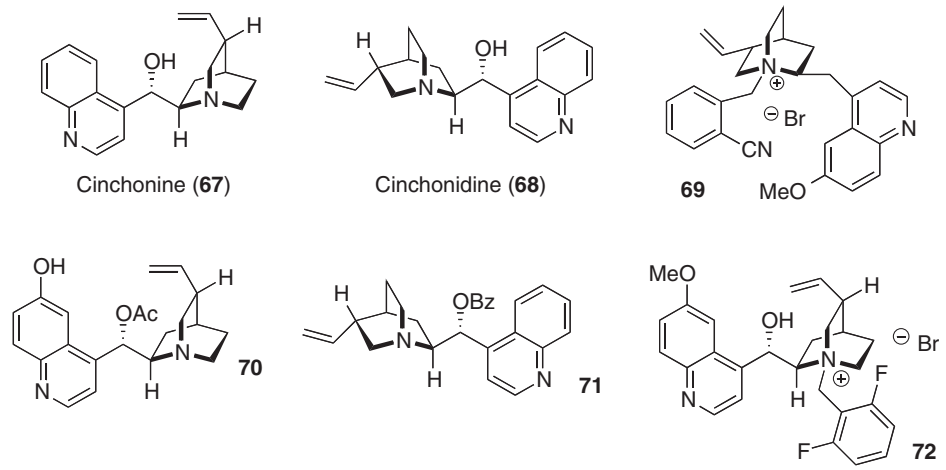
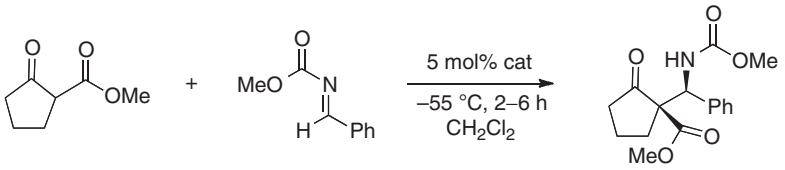
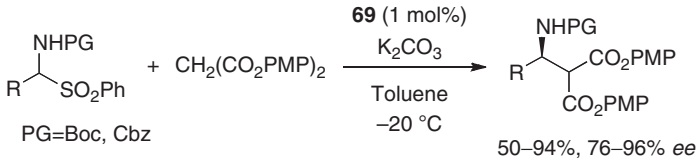


Figure 12 Cinchona alkaloids and derivatives.



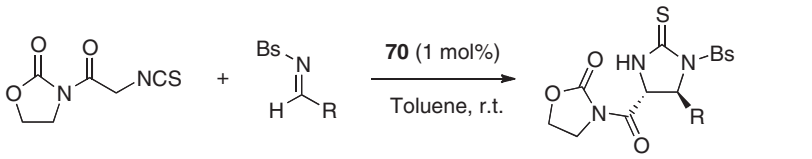
Scheme 117

Ricci and coworkers reported that phase-transfer catalyst **69** promoted the Mannich reaction of *N*-carbamoyl imines from α-amido sulfone.[146] The corresponding Mannich adducts were obtained in high yields with excellent enantioselectivities (Scheme 118). It is noted that aldimines derived from enolizable aliphatic aldehydes proved to be suitable substrates.



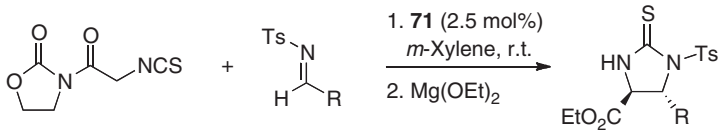
Scheme 118

Seidel and coworkers reported a novel method for the preparation of α,β-diamino acid derivatives by the Mannich reaction of α-isothiocyanato imides with *N*-sulfonyl imines.[147] *syn*-α,β-Diamino acid derivatives were obtained in a highly diastereo- and enantioselective fashion using 1 mol % of **70**, readily available from quinidine (Scheme 119). Aldimines derived from aliphatic aldehydes as well as aromatic aldehydes gave the corresponding adducts with excellent enantioselectivity. Interestingly, the catalyst loading could be reduced to as low as 0.25 mol% without sacrificing stereoselectivity.



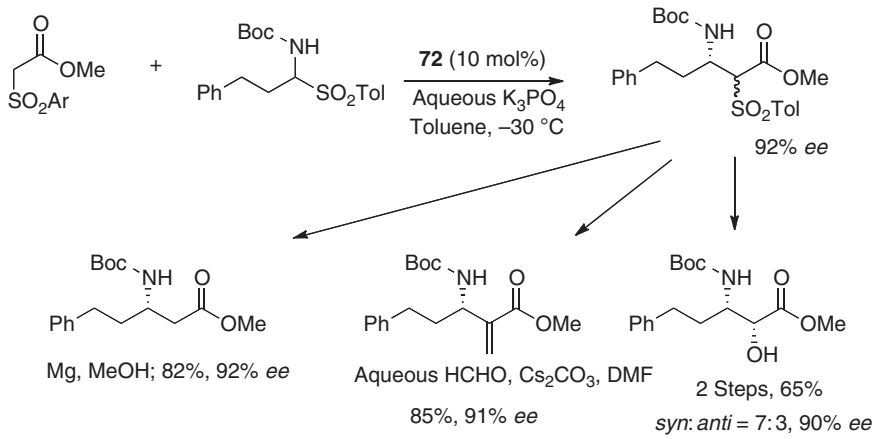
Scheme 119

Zhong and coworkers independently reported similar Mannich reactions of α-isocyanated imides with *N*-Ts aldimine by means of **71**, readily available from quinine.[148] α,β-Diamino acid derivatives were obtained with excellent enantioselectivities (Scheme 120).



Scheme 120

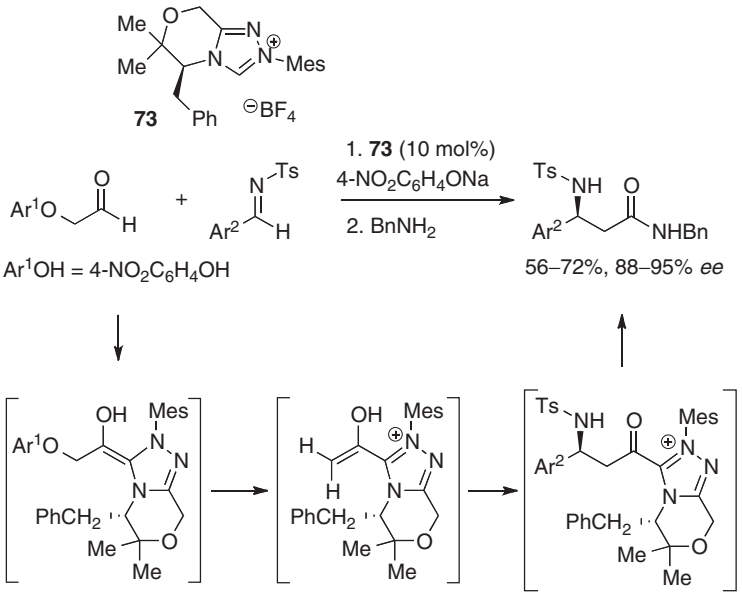
Ricci and coworkers reported Mannich reactions of α-sulfonylacetate with amido sulfone by means of 10 mol% of **72**.[149] The corresponding Mannich adducts were obtained with excellent enantioselectivities, which is a versatile intermediate for the preparation of β-amino ester, aza-MBH adduct, and α-hydroxy-β-amino ester (Scheme 121).



Scheme 121

2.16.3.3 *N*-Hetererocyclic Carbene Catalyst

Scheidt and coworkers reported the Mannich reaction of α-aryloxyacetaldehyde with *N*-tosyl aldimine by means of *N*-heterocyclic carbene catalyst **73** (Scheme 122).[150] *N*-Heterocyclic carbene intermediate, generated from **73** and base, added to aldehyde and with subsequent elimination of Ar^1O^- to furnish enol intermediate, which reacted with *N*-tosyl aldimine to give the Mannich adduct.



Scheme 122

2.16.3.4 Thiourea-Catalyzed Mannich Reactions

Thiourea catalysts have emerged as an efficient hydrogen bond catalyst, pioneered by Jacobsen and Takemoto.[151]

Jacobsen developed thiourea catalyst **74** (Figure 13) in 1988[152] and applied it as a catalyst for the Strecker reaction. Together, they subsequently reported Mannich-type reaction of ketene silyl acetal with *N*-Boc aldimines. β-Amino esters were obtained with excellent enantioselectivities (Scheme 123).[153]

The same group employed a bifunctional thiourea catalyst for the acyl-Mannich reaction of isoquinolines. Treatment of isoquinoline with acyl chloride furnished *N*-acylisoquinolium salt, which underwent a Mannich reaction with ketene silyl acetal by means of bifunctional thiourea catalyst **75** to give 1-substituted dihydroisoquinoline derivatives with high to excellent enantioselectivities (Scheme 124). This methodology is complementary to the Pictet–Spengler reaction.[154]

Chen and coworkers developed direct vinylogous Mannich reaction of α,α-dicyanoalkene with *N*-Boc aldimines by means of bifunctional thiourea catalyst **76** to give the adducts with excellent enantioselectivities (Scheme 125).[155] It is noted that the catalyst loading could be reduced to as low as 0.1 mol% without sacrificing enantioselectivity.

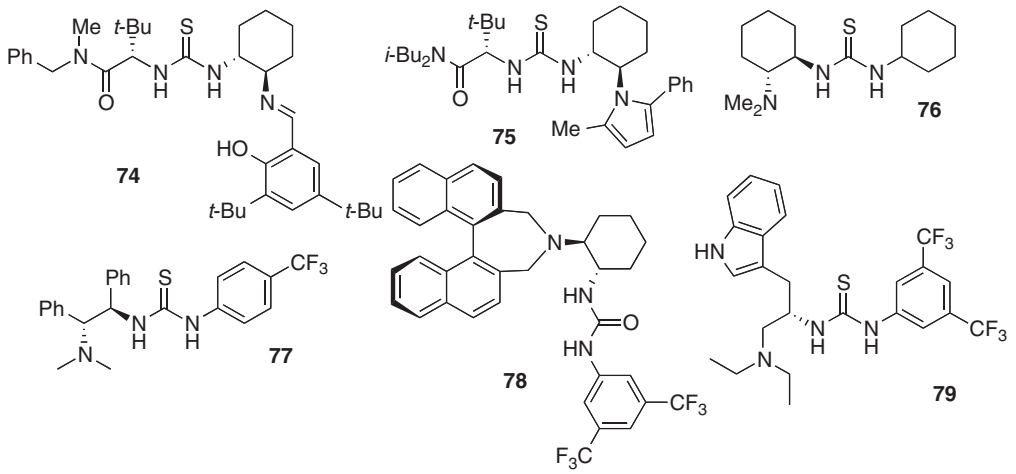
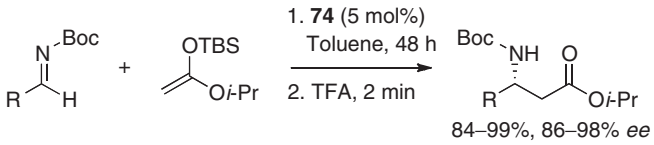
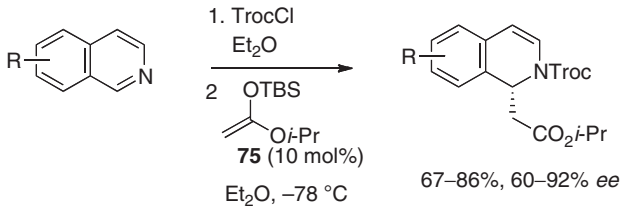


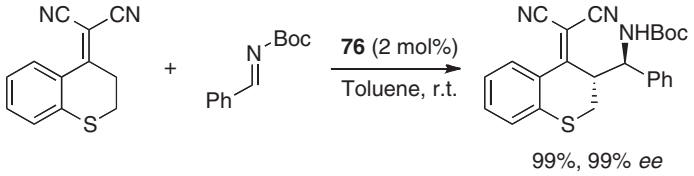
Figure 13 Thiourea and urea catalysts.



Scheme 123



Scheme 124

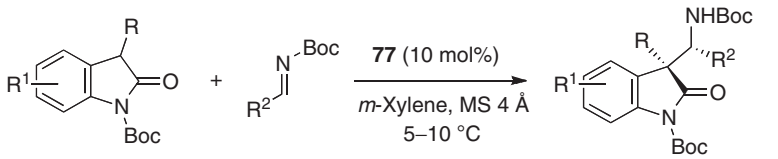


Scheme 125

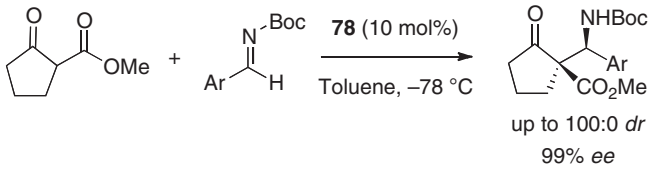
The same group reported the Mannich reaction of 3-substituted oxindoles. The Mannich adducts, bearing adjacent quaternary and tertiary carbon centers, were generally obtained in good to excellent enantioselectivities by means of **77** (Scheme 126).[156]

The urea catalyst bearing a binaphthyl backbone **78** also catalyzed the Mannich reaction of *β*-ketoester with *N*-Boc aldimines.[157] Quaternary and tertiary carbon centers were constructed with excellent selectivities (Scheme 127).

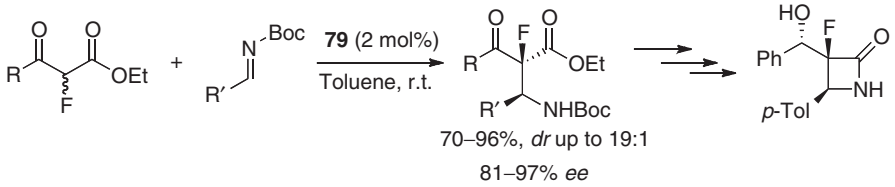
Lu and coworkers developed a novel tryptophan-derived bifunctional thiourea catalyst **79** and applied it for the asymmetric Mannich reaction of fluorinated ketoesters with *N*-Boc aldimines.[158] Fluorinated quaternary and tertiary stereocenters could be constructed with good diastereoselectivity and with excellent enantioselectivities. The Mannich adduct was readily transformed into *α*-fluoro-*β*-amino acids and *α*-fluoro-*β*-lactams (Scheme 128). DFT calculations elucidated that the indole moiety of the catalyst played a crucial role in substrate binding.



Scheme 126



Scheme 127



Scheme 128

2.16.3.5 Mannich-Type Reactions Catalyzed by Cinchona Alkaloid-Thiourea Hybrid Catalyst

The Schaus group prepared hydroquinine-derived thiourea **80** (Figure 14), and reported a Mannich reaction of *N*-acyl aldimine with dimethyl malonate, furnishing the Mannich adducts with excellent enantioselectivities (Scheme 129).[159] They also studied the MMFF conformation search to identify the lowest energy conformer and proposed that the malonate anion formed a hydrogen bond with the thiourea moiety and the quinoline ring blocked one face of the nucleophile (Figure 15).

In contrast, the thiourea catalyst **81**, derived from cinchonine, catalyzed the Mannich reaction of malonate with *N*-Boc and *N*-Cbz aldimines to furnish the opposite enantiomers with high enantioselectivities (Scheme 130).[160]

Deng reported the Mannich reaction of malonates with *N*-Boc aldimines by means of 9-thiourea cinchona alkaloids such as **82** and **83**.[161] *N*-Boc aldimines derived from aromatic aldehyde furnished the adducts in high yields and with excellent enantioselectivities (Scheme 131). Interestingly, aldimines derived from aliphatic aldehyde also gave the corresponding adducts with excellent enantioselectivities, although the yields were moderate.

Pihko identified bifunctional tertiary amine-thiourea catalysts, which contain a rigid *trans*-1,2-aminoindanol scaffold and a urea group that activates the thiourea group through intramolecular hydrogen bonds in a cooperative fashion.[162] They reported the direct Mannich reaction of malonate with *N*-Boc aldimine to furnish the corresponding adducts with excellent enantioselectivities. A thiourea catalyst **84** was found to be the catalyst of choice for aldimines derived from aromatic aldehyde, and **85** was suitable for aldimines derived from aliphatic aldehydes.

Deng reported the asymmetric Mannich reaction of *in situ*-generated carbamate-protected imines by means of **86**.[163] The Mannich reaction starting from *N*-Boc α-amido sulfones, prepared from a broad range of aromatic and heteroaromatic aldehydes, furnished the corresponding Mannich adducts in high chemical yields and with excellent enantioselectivities. It is noted that *N*-Boc α-amido sulfones derived from aliphatic aldehyde participated successfully in the reaction by use of 10 mol% of **86** and Na_2CO_3 (Scheme 132).

Coltart and coworkers developed a direct Mannich reaction of phenylacetate thioester with *N*-sulfonyl aldimine by means of 5 mol% of **80** to give *β*-amino thioester with high *syn*-selectivity and with moderate enantioselectivities (Scheme 133).[164]

Zhao's group reported a three-component direct Mannich reaction between aromatic aldehydes, *p*-toluenesulfonamide, and unfunctionalized ketones by means of bifunctional quinidine thiourea catalyst **87** (Scheme 134).[165] The corresponding *N*-tosylated *β*-aminoketones were obtained in high yields and with excellent diastereo and enantioselectivities.

An efficient organo- and gold-catalyzed one-pot synthesis of dihydropyridines was achieved.[166] On treatment of *N*-Boc aldimine and propargylated malonitrile with **86** followed by with PPh_3AuNTf_2, a Mannich reaction and subsequent

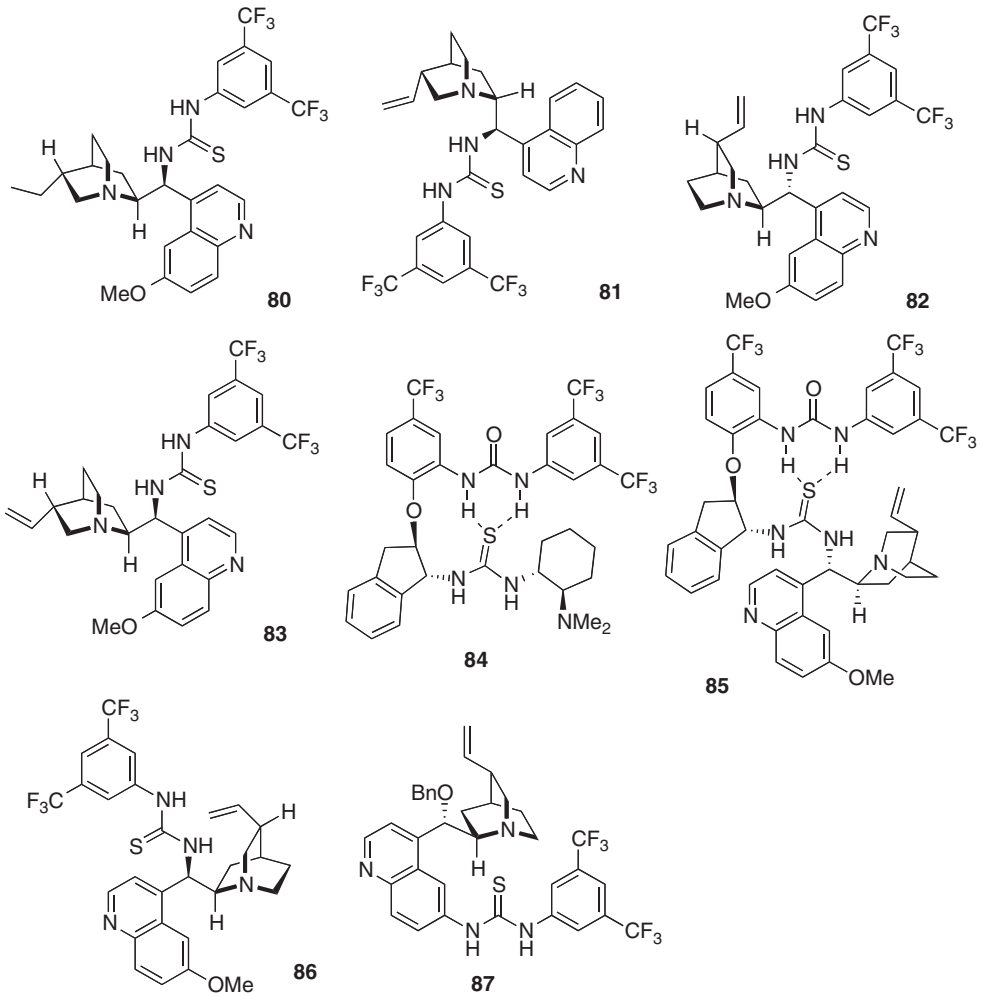
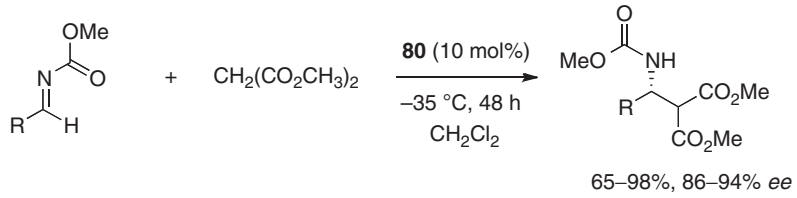


Figure 14 Cinchona alkaloid-thiourea hybrid catalysts.



Scheme 129

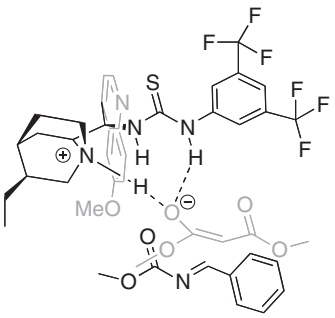
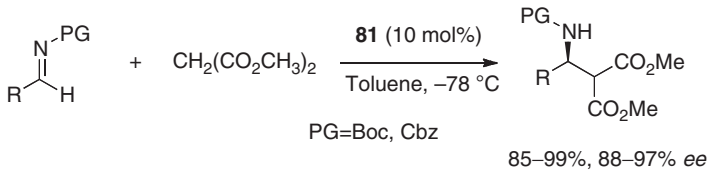
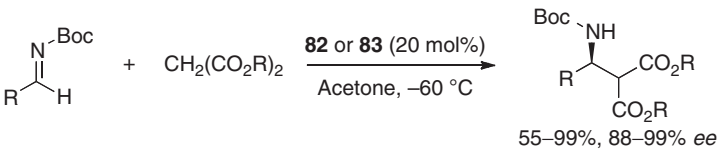


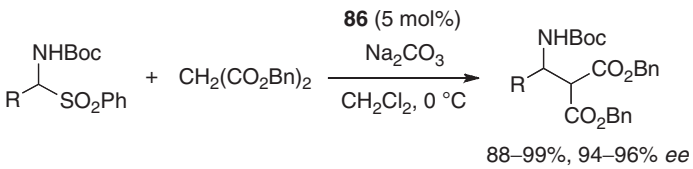
Figure 15 Proposed transition state of the Mannich-type reaction.



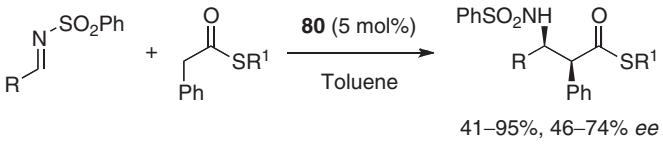
Scheme 130



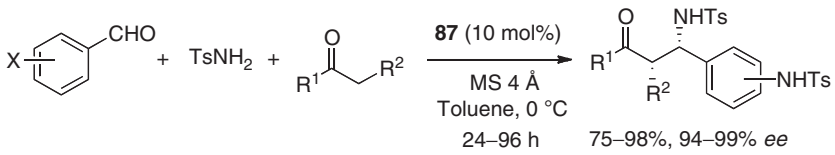
Scheme 131



Scheme 132

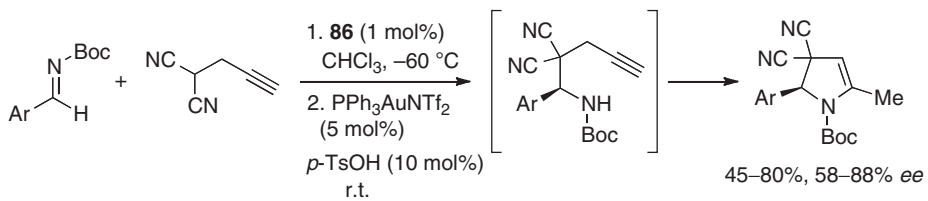


Scheme 133



Scheme 134

gold-catalyzed alkyne hydroamination and isomerization took place to give dihydropyridines with high enantioselectivities (Scheme 135).



Scheme 135

2.16.3.6 Brønsted Acid-Catalyzed Mannich and Related Reactions

2.16.3.6.1 Brønsted acid-catalyzed Mannich-type reactions

Phosphoric acid has emerged as a novel chiral Brønsted acid catalyst since 2004.[167] Chiral Brønsted acid protonates imines, thereby forming iminium salt bearing a chiral counter anion, and directs the attack of the nucleophile to the iminium salt. Akiyama et al. developed chiral phosphoric acid bearing 3,3′-(4-nitrophenyl)-substituted BINOL derivative **88a** (Figure 16), which worked efficiently as a catalyst for the Mannich-type reaction of ketene silyl acetal with aldimines, derived from aromatic aldehyde and *o*-hydroxyaniline.[168] *β*-Amino-*α*-alkyl or *α*-siloxy carboxylates were obtained in preference to the *syn*-isomer, and the *ee* of the *syn*-isomer reached 96% *ee* (Scheme 136). Theoretical study elucidated that the phosphoric acid played two roles: (1) phosphoric acid hydrogen-activated aldimine by acting as a Brønsted acid; and (2) phosphoryl oxygen formed a hydrogen bond with the *o*-hydroxy group by acting as a Lewis base, thereby fixing the nine-membered transition state[169] (Figure 17). Hence, the phosphoric acid worked as a bifunctional catalyst bearing both Brønsted acidic and Lewis basic sites.

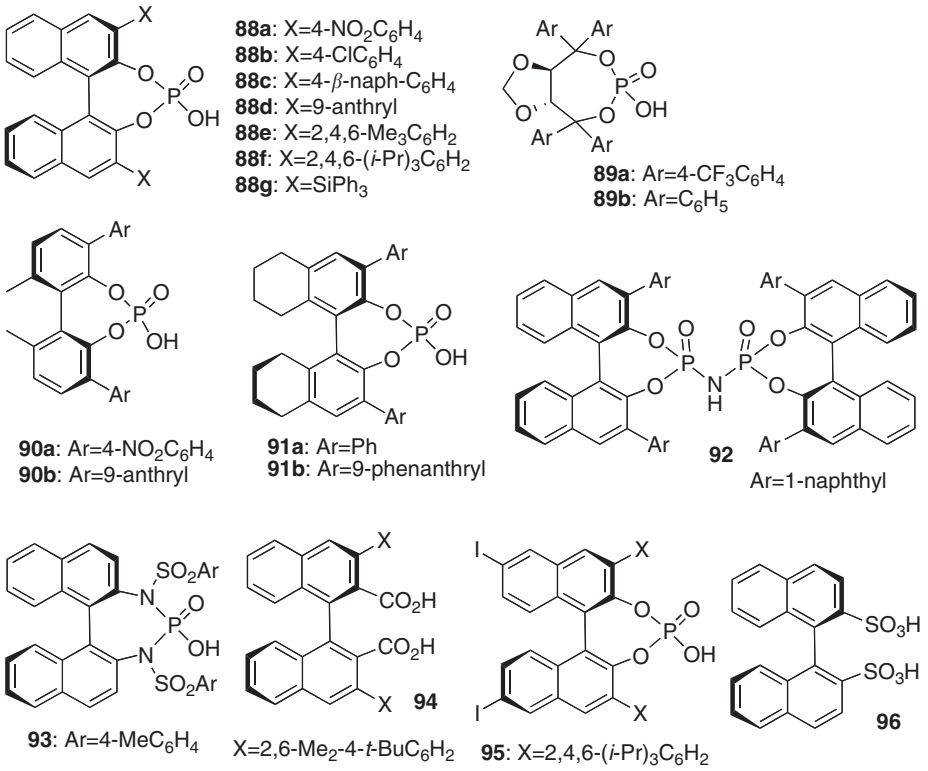
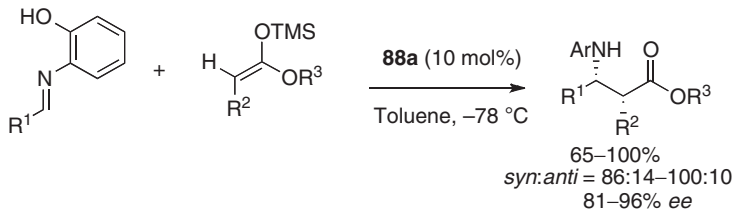


Figure 16 Phosphoric acids.



Scheme 136

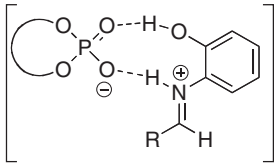
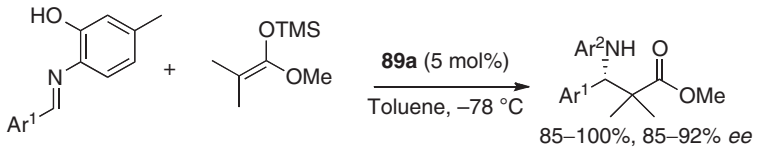


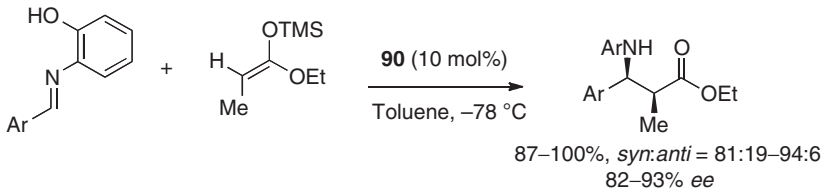
Figure 17 Hydrogen bond complex between phosphoric acid and aldimine.

Chiral phosphoric acid derived from TADDOL also catalyzed the Mannich-type reaction of ketene silyl acetal with *N*-aryl aldimine derived from 2-aminophenol derivative.[170] A phosphoric acid bearing the 4-trifluoromethylphenyl group **89a** exhibited the highest catalytic activity and the corresponding *β*-amino esters were obtained with high enantiomeric excesses (Scheme 137). Introduction of a phenyl group bearing an electron-withdrawing group is essential for the present Mannich reaction. Interestingly, a phosphoric acid with tetra-phenyl substituted phosphoric acid **89b** did not show any catalytic activity.



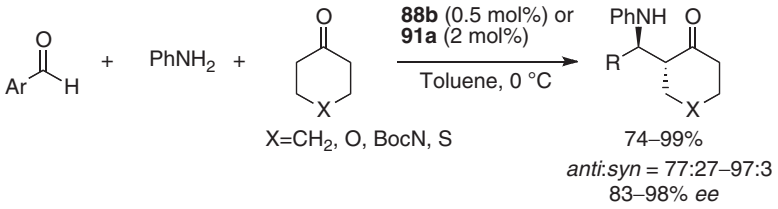
Scheme 137

They also reported a phosphoric acid bearing a biphenol backbone and examined its catalytic activity in the Mannich-type reaction of ketene silyl acetal with aldimines derived from aromatic aldehyde and 2-aminophenol (Scheme 157).[171] A phosphoric acid bearing 4-nitrophenyl groups at the 3,3′-position, **90**, exhibited catalytic activity comparable to that with the binaphthyl moiety (Scheme 138).



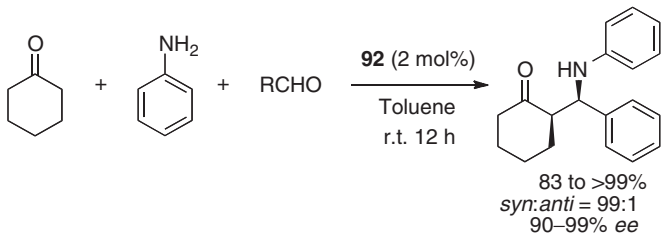
Scheme 138

Gong and coworkers developed a three-component direct Mannich reaction of cyclic ketones with *N*-aryl aldimines, generated *in situ* from aromatic aldehydes and aniline, by means of phosphoric acids, either **88b** a bearing 4-ClC_6H_4 moiety or **91a** with a H_8-BINOL backbone.[172] The phosphoric acid **88b** exhibited high catalytic activity, and as low as 0.5 mol% of the catalyst promoted the direct Mannich reaction of cyclic ketone with imines, derived from aromatic aldehydes bearing an electron withdrawing group, to give the corresponding adduct in preference of the *anti*-isomer with excellent enantioselectivity (Scheme 139).



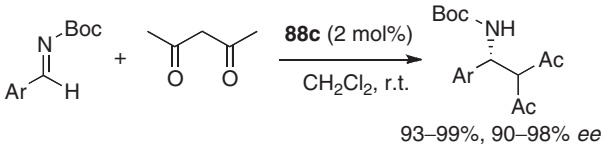
Scheme 139

Double axially chiral bisphosphoryliminde **92** was designed and developed as a novel Brønsted acid[173] and was applied to the three-component Mannich reaction. *Syn*-*β*-amino ketones were obtained exclusively in high yields and with excellent enantioselectivities.[174] Both aliphatic and aromatic aldehydes proved to be suitable substrates (Scheme 140).



Scheme 140

The Terada group reported the direct Mannich reaction of acetylacetone with *N*-Boc aldimine under the influence of 2 mol% of phosphoric acid **88c**, bearing a *β*-naphthylphenyl group at the 3,3′-position. The corresponding adducts were obtained with excellent enantioselectivities (Scheme 141).[175] A dual role of the phosphoric acid is proposed as a transition state model (Figure 18).



Scheme 141

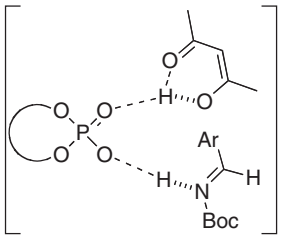
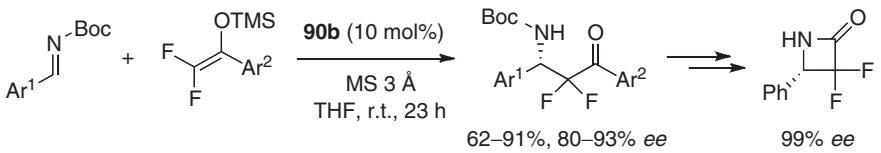


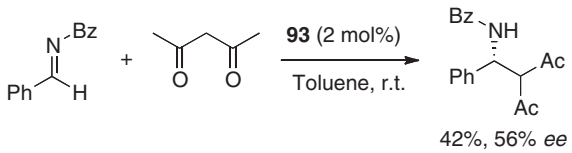
Figure 18 Hydrogen bond network between phosphoric acid, acetylacetone, and *N*-Boc imine.

Chiral biphenol-derived phosphoric acid **90b** is effective as a catalyst for the Mannich-type reaction of difluoroenol silyl ether with *N*-Boc aldimine to give *β*-amino-*α*,*α*-difluoroketones with good to high enantioselectivities (Scheme 142).[176] The adduct was transformed into *α*,*α*-difluorinated *β*-lactam by Baeyer–Villiger oxidation and a subsequent ring closure sequence.



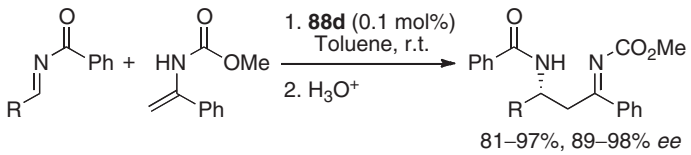
Scheme 142

Chiral phosphorodiamidic acid **93** catalyzed the direct Mannich reaction of *N*-acyl aldimine with acetylacetone to furnish the Mannich adduct with moderate enantioselectivity (Scheme 143).[177]



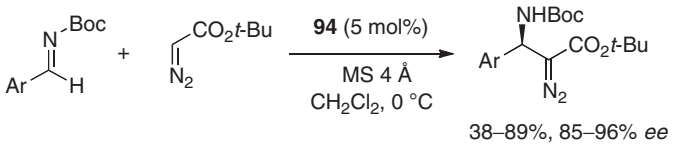
Scheme 143

The Terada group employed enecarbamate[178] as a nucleophile and reported the aza-ene type reaction by means of **88d**.[179] Corresponding *β*-amino ketones were obtained in high yields and with excellent enantioselectivities (Scheme 144). The catalysis with a high substrate/catalyst (S/C) ratio provides a practical route to 1,3-diamine derivatives of synthetic and biological importance.



Scheme 144

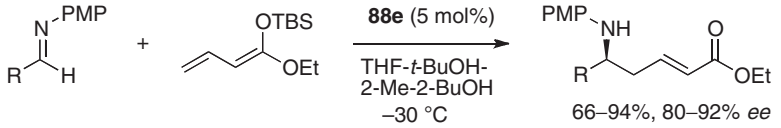
Maruoka developed a Mannich reaction of diazoacetate with *N*-Boc imine derived from aromatic aldehydes by means of (*R*)-1,1′-binaphthyl-2,2′-dicarboxylic acid **94**. A dicarboxylic acid bearing a 2,6-Me_2–4-*t*-Bu-C_6H_2 moiety at the 3,3′-position was the catalyst of choice (Scheme 145).[180]



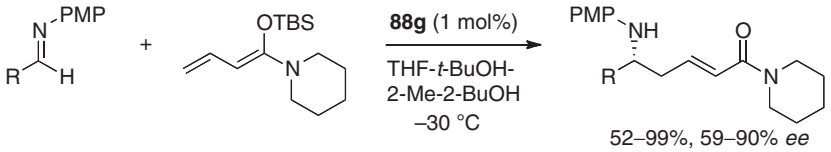
Scheme 145

2.16.3.6.2 Vinylogous Mannich reaction

Schneider and coworkers reported the first catalytic vinylogous Mukaiyama–Mannich reactions of acyclic silyl dienolates and aromatic imines to furnish highly valuable δ-amino-α,β-unsaturated carboxylic acid ester in high yields, complete regioselectivity, and good to very good enantioselectivities by means of chiral phosphoric acid **88e**.[181] They found that a solvent system containing equal amounts of THF/*t*-BuOH/2-Me-2-BuOH (v:v = 1:1:1) in the presence of 1.0 equivalent of water and 5 mol% of a phosphoric acid **88e** bearing a mesityl group gave the best results (Scheme 146). Although aldimines derived from aliphatic aldehydes were problematic under the reaction conditions, aldimines derived from a range of aliphatic aldehydes underwent the vinylogous Mannich reaction smoothly by means of chiral phosphoric acid **88f** (TRIP) in THF to furnish the adducts in good yields and with high enantioselectivities.[182] Subsequently, they extended the process to the vinylogous Mukaiyama–Mannich reaction of vinylketene silyl *N*,*O*-acetals and imines by means of **88g** (Scheme 146).[183] Because introduction of an amine moiety significantly increased the nucleophilicity, the catalyst loading could be reduced as low as 1 mol% (Scheme 147).

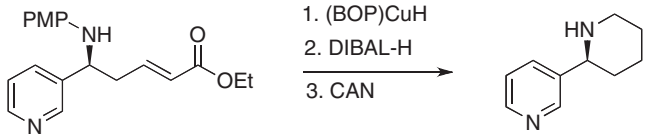


Scheme 146



Scheme 147

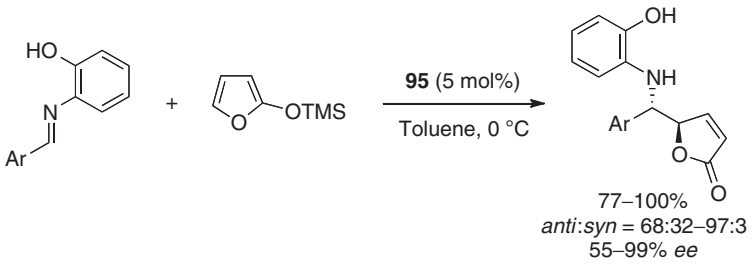
The same group prepared the vinylogous Mannich adduct with a 2-pyridyl moiety with 92% *ee* and achieved the synthesis of the tobacco alkaloid (*S*)-anabasine in three steps (Scheme 148).[184]



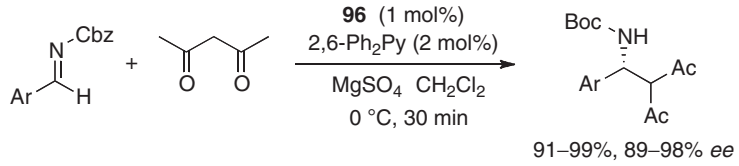
Scheme 148

Akiyama et al. developed a vinylogous Mannich reaction of siloxyfuran.[185] Introduction of iodine onto the 6,6′-position of phosphoric acid improved the enantioselectivity (Scheme 149). Aldimines derived from aliphatic aldehydes as well as aromatic aldehydes furnished the corresponding adducts in high yields and with high to excellent enantioselectivities by means of **95**.

Ishihara and coworkers developed a chiral Brønsted acid-base combined salt catalyst consisting of 1,1′-binaphthyl-2,2′-disulfonic acid and 2,6-diphenylpyridine.[186] The Mannich reaction of acetylacetone with *N*-Cbz aldimine was catalyzed by the smooth combination of 1 mol% of sulfonic acid **96** and 2 mol% of 2,6-diphenylpyridine to furnish the corresponding Mannich adducts with excellent enantioselectivities (Scheme 150). One of the advantages of the acid-base combined catalysts is that both



Scheme 149



Scheme 150

Brønsted acidity and bulkiness can be easily controlled by complexation with amine, thereby obviating the introduction of bulky substituents at the 3,3′-position of the binaphthyl skeleton.

2.16.3.7 Phase-Transfer Reactions and Ion Pair Catalyst and Related Systems

Ion pair catalyst has emerged as a novel catalyst system.[187]

Maruoka reported Mannich reaction of glycine Schiff base with α-imino ester under phase-transfer conditions **97** (Figure 19, Scheme 151).[188]

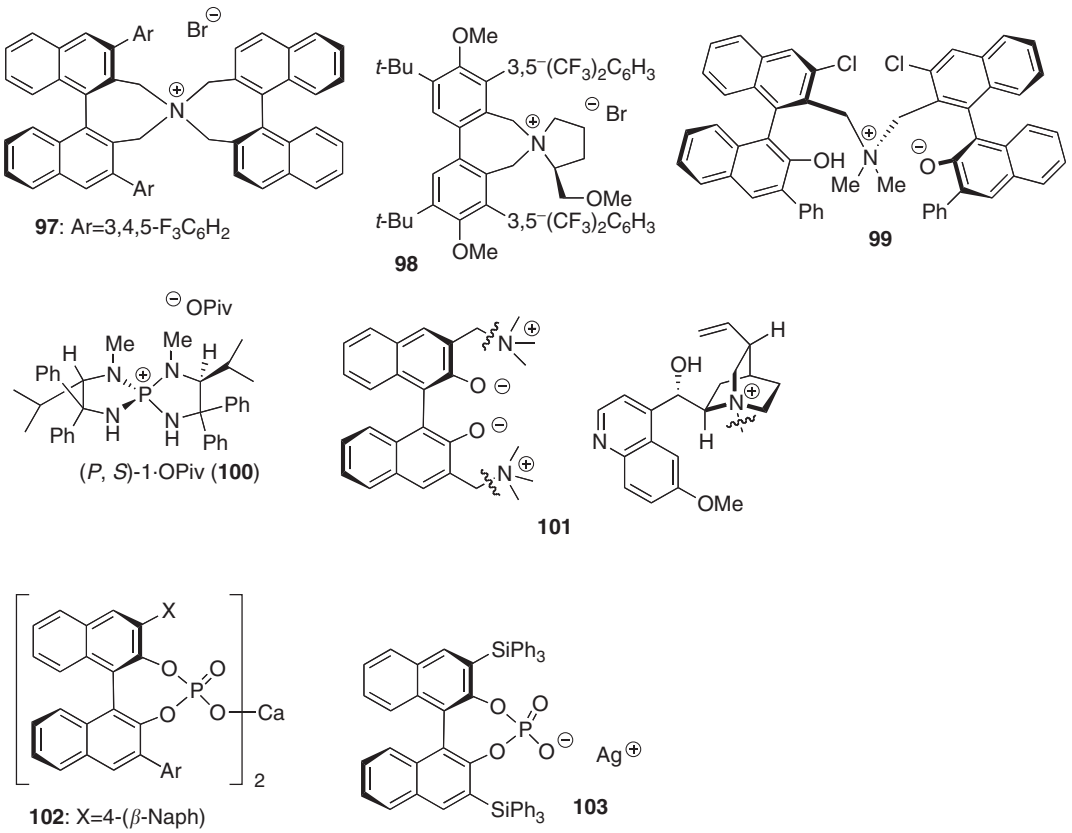
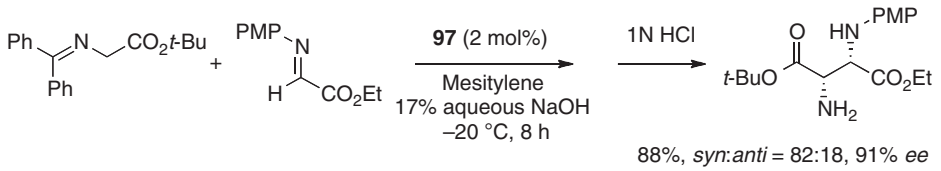
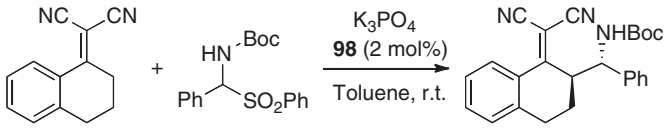


Figure 19 Phase transfer catalysts and ion pair catalysts.



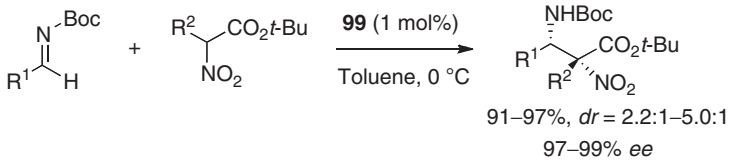
Scheme 151

Jørgensen's group reported the vinylogous Mannich reaction of dicyanoalkylidenes with α-amino sulfones under phase-transfer conditions.[189] The corresponding adducts were obtained with excellent diastereoselectivities and with high enantioselectivities by means of **98** (Scheme 152).



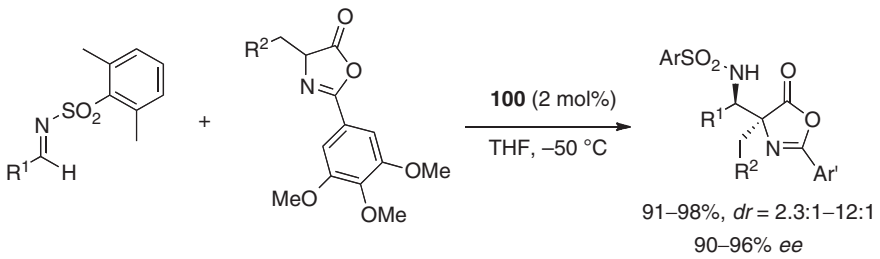
Scheme 152

Ooi and coworkers developed a chiral ammonium betaine as a highly enantioselective organic base catalyst in the direct Mannich-type reaction of α-substituted α-nitrocarboxylate with various *N*-Boc imines.[190] Generally, 1 mol% of **99** smoothly catalyzed the reaction in toluene at 0 °C, giving the corresponding adducts in excellent chemical yields in preference to *syn*-isomers with excellent enantioselectivities (Scheme 153).



Scheme 153

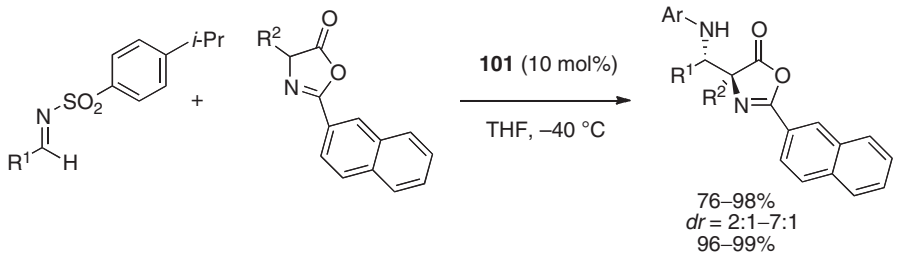
The same group developed [5,5]-*P*-spirocyclic tetraaminophosphonium salt **100** and applied it as a catalyst for the Mannich reaction of azlactone with *N*-sulfonyl aldimines (Scheme 154).[191] Use of pivalate anion is critical for attaining high reactivity. A range of aliphatic aldimines proved to be suitable substrates. It is noted that the reaction with sulfonyl imine, derived from acetaldehyde, proceeded smoothly in a highly enantioselective manner. The Mannich adduct could be readily hydrolyzed under acidic conditions to furnish α,β-diamino acid with excellent enantioselectivity.



Scheme 154

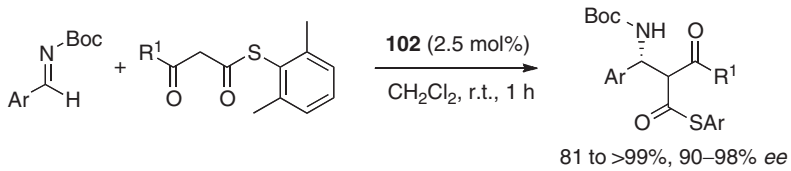
The Gong group reported a new type of chiral bis(betaine)base for the Mannich reaction of azlactone with aliphatic aldimines.[192] The organocatalyst is composed of a binaphthol moiety and cinchona alkaloid **101**. A range of *N*-sulfonyl aldimines derived from aliphatic aldehyde proved to be suitable substrates, and the adducts were obtained with excellent enantioselectivities (Scheme 155).

Ishihara and coworkers reinvestigated the direct Mannich reaction of acetylacetone with *N*-Boc aldimine by means of chiral phosphoric acid. It was found that phosphoric acid, purified by SiO_2, also exhibited excellent catalytic activity and identified that



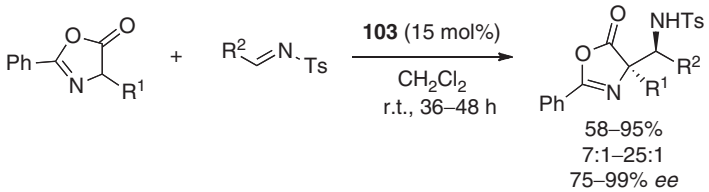
Scheme 155

chiral calcium phosphate **102** exerted catalytic activity in the Mannich reaction of acetylacetone with *N*-Boc aldimines[193] (Scheme 156).



Scheme 156

The Hui group employed phosphoric acid in combination with silver ion to promote the Mannich reaction of azlactone with *N*-tosyl aldimines (Scheme 157).[194]



Scheme 157

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2.17 Addition to *N*-Acyliminium Ions of Heteroatoms such as Oxygen, Nitrogen, Sulfur, and Selenium as Internal Nucleophiles

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This chapter is complementary of the previous edition chapter by Henk Hiemstra, W. Nico Speckamp, Vol. 2, pp 1047–1082, © 1991, Elsevier Ltd.

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 doi:10.1016/B978-0-08-097742-3.00221-4

Glossary

α-Amidoalkylation Incorporation of alkyl (aryl, heteroaryl, or heteroatom containing alkyl (aryl or heteroatyl group) fragment into the α-position of the lactam function in an intermolecular or intramolecular manner.
Dealkylation Loss of the alkyl group by departure of the alkyl group as a cation.
Electrochemical oxidation Anodic oxidation at α-position of the nitrogen amide, lactam, and carbamate.
Endocyclic cation Herein an *N*-acyliminium species in the inside of the nitrogen cycle.
Exocyclic cation Herein an *N*-acyliminium species in the outside of the nitrogen cycle.
Heteroatom Herein oxygen, nitrogen, sulfur, and selenium.
Heterocyclization Intramolecular trapping of *N*-acyliminium species with a heteroatom.
α-Hydroxy lactam Herein means also carbinol lactam.
***N*-acyliminium species** All these cationic species are generated *in situ* chemically under acidic conditions or electrochemically via anodic oxidation.

2.17.1 Introduction

The most common heterocyclic systems contain nitrogen or oxygen atoms, or both. For example, more than half of all known natural compounds are heterocycles and a very large proportion of drugs contain one or more heterocyclic rings. The presence of heteroatoms confers specific reactivity leading some heterocyclic compounds to behave chemically and biologically differently than their carbocyclic analogs. However, these heterocyclic systems containing, in addition to nitrogen and/or oxygen, a sulfur or a selenium atom are less common or even rare.

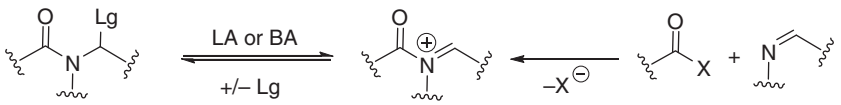
In particular, a number of heterocyclic compounds possessing or lacking an amide or lactam moiety, fused or not, appear to have interesting biological profiles and applications in all areas of materials chemistry, in various fields such as medicine and agriculture. Furthermore, these fused amides or lactams are used as starting substrates and reaction intermediates of choice in the synthesis of many types of alkaloids with, among others, marked pharmacological and catalytic properties in many areas of contemporaneous chemistry. A large number of these compounds can be obtained from Mannich reactions or the equivalent involving *N*-acyliminium ions as intermediate species.

2.17.2 Formation of the C–C Bond: General Aspects

2.17.2.1 *N*-Acyliminium Ions: Various Methods of Obtaining

The importance of the coupling reaction of the *N*-acyliminium ion is recognized as one of the most effective methods for the construction of the carbon–carbon bond in modern organic synthesis and is emphasized by the many optimizations carried out regularly in this area.[1] This addition reaction provides access to a wide range of natural and unnatural polycycles including structural units of alkaloids.[2]

The viability of this technique crucially depends on the ability to opportunely release both the *N*-acyliminium ion and the nucleophilic species, constituting the final step of the reaction sequence under appropriate conditions. Generally, *N*-acyliminium ions are generated *in situ* in solution by acid treatment of α-halo-, α-hydroxy-, α-acetoxy-, α-alkyloxy-, α-aryloxy-, α-alkylthio-, α-arylthio, α-arylsulfonyl-, and α-benzotriazolyl amides or carbamates (equation 1).[3]

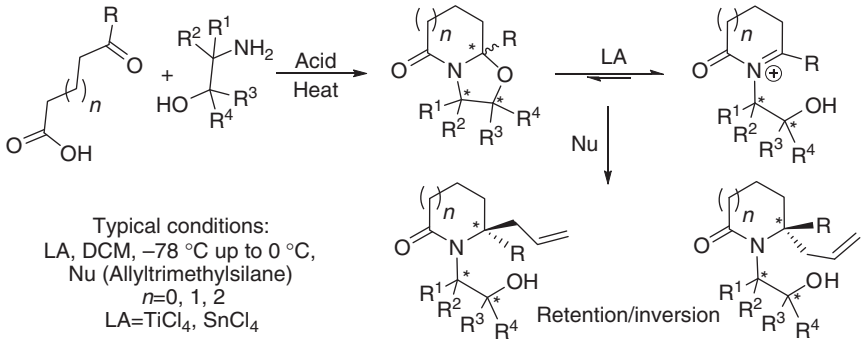


(1)

Lg (Leaving group) = Halogen, OR, OAr, OCOR, Bt (Benzotriazole), SAr, SO_2Ar, NHCOR, etc.

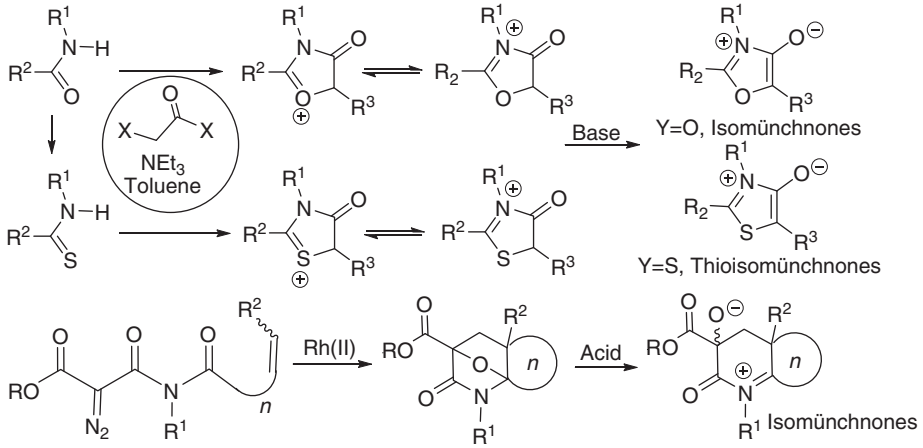
Defragmentation of amides into *N*-acyliminium ions

Approaches have been specifically developed to generate these highly reactive species. In this context, the more cited methods are the cleavage of *N*,*O*-bicyclic lactams in acid media (equation 2),[4] the dipolar cyclization to obtain isomünchnones[5] and isothiomünchnone cycloadducts (equation 3),[6] the radical decarboxylation of α-amino acids by electrochemistry, initiated in the 1980s by T. Shono (equation 4),[7,8] the decarboxylation of pyroglutamic acids and derivatives under acidic conditions (equation 4),[8] or by 'cuprous Cu^{+}' decomposition of *ortho*-diazobenzamides.[9]



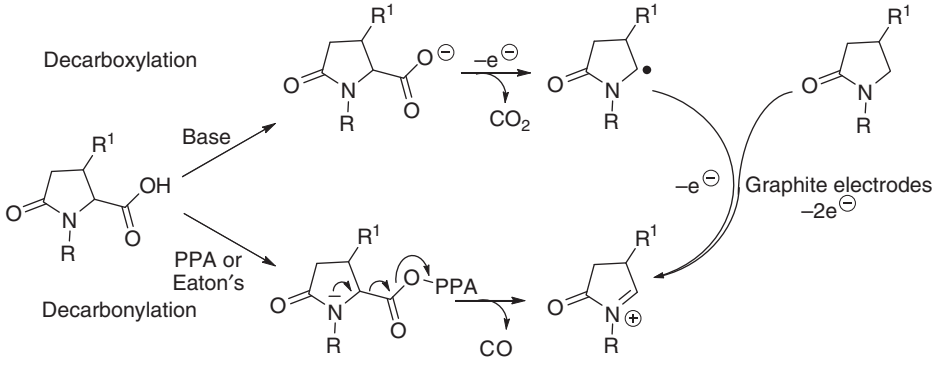
(2)

Use of *N,O*-bicyclic lactams for the generation of *N*-acyliminium ions



(3)

Generation of isomünchnones and isothiomünchnones as *N*-acyliminium ions

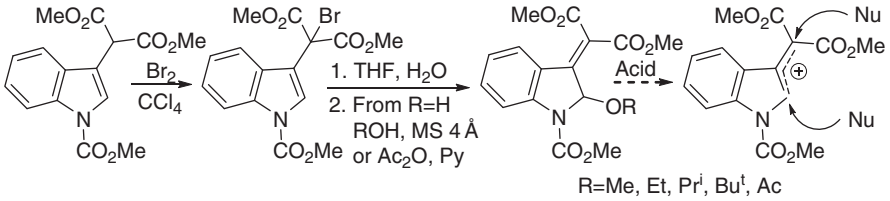


(4)

N-acyliminium ions via decarboxylation and decarbonylation

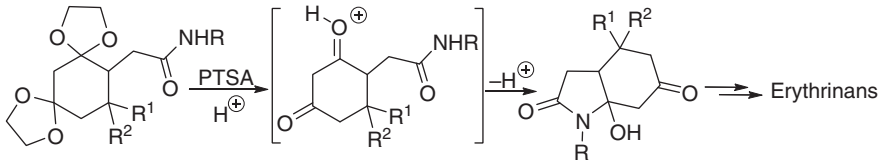
The high stability of these cationic species is the result of the carbonyl function being present in the α position of the nitrogen atom, which gives unequalled and perhaps unlimited reactivity to these species. Hence, the fertile search for new simple approaches, shorter, more flexible, and easily exploitable in the development of new molecular scaffolds providing a molecular diversification throughout the scientific community.

In this context, four interesting approaches, including, for example, the Diels–Alder[12] and Domino[13] processes, have retained our attention for the preparation of *N*-acyliminium precursors as well as for their application areas and for their possible perspectives (equations 5–8).[10–13]



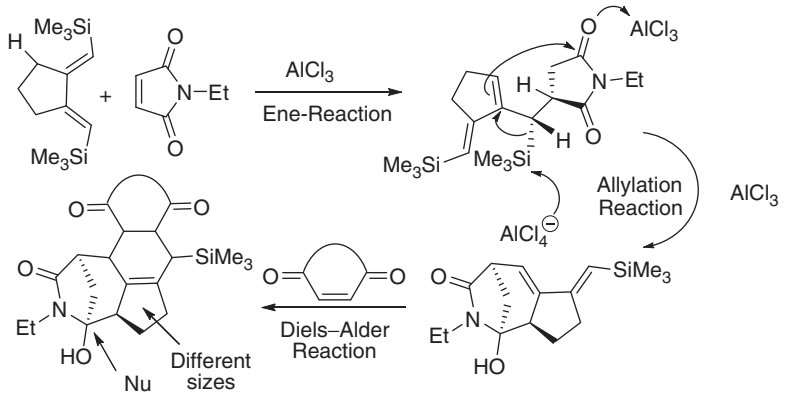
(5)

Bi-electrophile *N*-acyliminium cation[10]



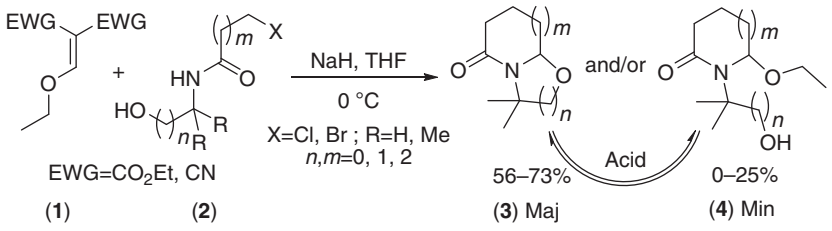
(6)

Tertiary *N*-acyliminium cation in total synthesis[11]



(7)

Diels–Alder generation of *N*-acyliminium cations[12]



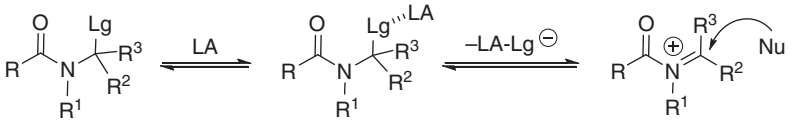
(8)

Domino process into *N,O*-bicyclic lactams[13]

2.17.2.2 Different Types of *N*-Acyliminium Ions and Used Acids

As mentioned above (equation 1), the generation of cationic species is mainly realized by acid activation in an at least stoichiometric amount (1–4 equivalents) in a reversible process (equation 9).

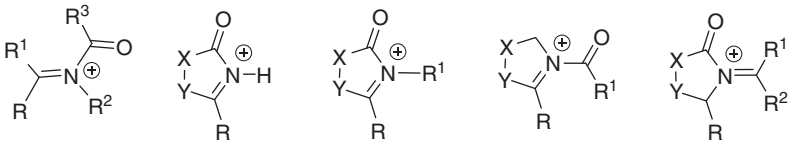
In most cases, protic acids (BA: HCO_2H, AcOH, H_2SO_4, trifluoroacetic acid (TFA), *p*-toluenesulfonic acid (PTSA), $MeSO_3H$, etc.) and Lewis acids (LA: BF_3OEt_2, $SnCl_4$, $TiCl_4$, etc.) are used. In a few cases, metal halides, such as $FeCl_3$, $ZnBr_2$, $MgBr_2$, or $LiClO_4$, are also employed.[14] Moreover, the current importance and potential of these Mannich-type reactions of *N*-acyliminium ions has led several research groups to develop catalytic processes employing conventional Lewis acids or nonconventional rare earth acids,[15] respecting the principles of green chemistry (solvent-free microwave activation, nontoxic solvents, reactions in water, etc.),[16] and also in racemic and asymmetric (1,1′-bi-2-naphtol (BINOL)-derivated phosphoric acids, chiral thioureas, etc.) procedures.[17]



(9)

Activation with Lewis acid (LA) and generation of *N*-acyliminium ions

N-acyliminium ions exhibit high structural and reactive variability depending on the nature of the R, R^1, R^2, and R^3 groups and, consequently, are of particular interest in organic synthesis. Acyclic *N*-acyliminium ion (type 1), endocyclic (type 2), and exocyclic (type 3) are distinguished (**Scheme 1**). Some examples of *N*-acyliminium ions illustrating this are published; and five-membered cyclic structures constitute the most commonly studied and documented ones in the literature.



Scheme 1 Different types of *N*-acyliminium ions.

The majority of *N*-acyliminium ions described in the literature contain at least one hydrogen atom in the α-position of the amidic nitrogen atom. Tertiary *N*-acyliminium ions may exist but have received little attention, probably due to the difficulties encountered during their generation as well as the instability of hydroxy lactam precursors.[18,19]

2.17.3 Formation of the C–X Bond (X = O, N, S, and Se)

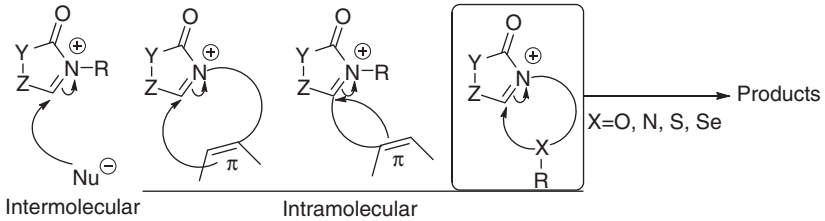
2.17.3.1 Generalities

In addition to the carbon–carbon bonds,[1,2] the formation of carbon–heteroatom (C–X) bonds generally contributes significantly to the quest for molecular diversity. In fact, the C_{sp3}–C_{sp3} bonds are widespread and protocols to access them abound in the literature, due to the thermal stability of the C_{sp3}–C_{sp3}, unlike C_{sp3}–X bonds (especially with X = O, N, S, and Se), which are less stable. In terms of binding energies (E in kJ mol^{-1}), it seems that these C_{sp3}–X bonds are less stable (and their formation is though reversible) compared with C_{sp3}–C_{sp3} bonds whose high binding energy (E = 346–348 kJ mol^{-1}) is the driving force of the reaction.[20] If there are, in general, coherences for all selected characteristics in both the column and in the row of the periodic table, there is however an irregularity concerning the energy of the C–N bond (305–308 kJ mol^{-1}) compared with both the C–O and C–C bonds.

2.17.3.2 Formation of the C–X Bond via the *N*-Acyliminium Ion Chemistry

2.17.3.2.1 Nature of the involved nucleophiles

Within the literature, the use of these cationic entities in intermolecular processes is common for introducing carbonated, oxygenated, nitrogenated, or sulfurated substituents onto the carbon adjacent to the nitrogen atom of the lactam.[1,2] In contrast, examples concerning the external nucleophile bearing a selenium, curiously, have yet to be described. Moreover, the majority of carbonated nucleophiles used correspond to a π system either aromatic, ethylenic, acetylenic, allylic, homoallylic, allenic, allylsilane, enoxysilane, or enolic, etc. (equation 10).



(10)

Inter- and intramolecular attack of *N*-acyliminium species

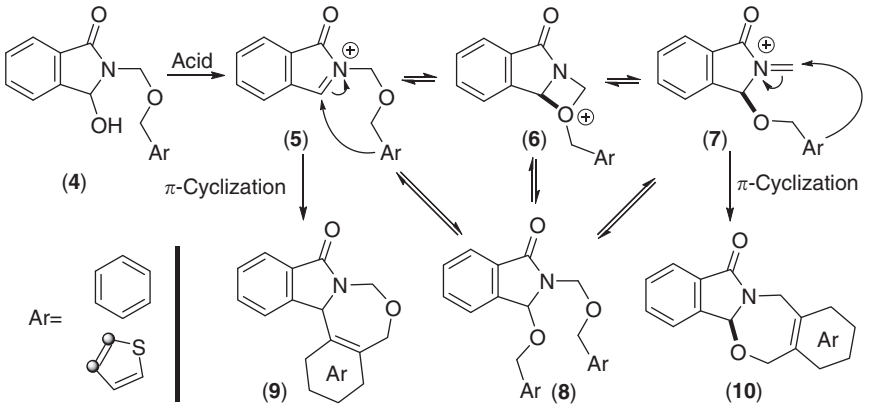
Moreover, the C–C bond formed by intramolecular α-amidoalkylation is widely explored by the scientific community (equation 10), to access the cyclic and/or spirocyclic systems, whereas the formation of a C–X bond (with X = O, N, S, Se) is rarely reported. This highlights the nucleophilicity of the heteroatom in an intramolecular version and thus offers an emerging new field of application.

Given these observations, this review provides a relatively exhaustive vision on this topic by addressing the cases of oxygen, nitrogen, sulfur, and selenium. Phosphorus, because of its special properties, is not included in the present review as a specific chapter or review would be necessary. Again surprisingly, although the chemistry is widely described, in particular, in an intramolecular version, very few cases using the heteroatom as an internal nucleophile have been reported.[1,2]

2.17.3.2.2 Rearrangement induced by a heteroatom

2.17.3.2.2.1 Rearrangement induced by oxygen or by selenium

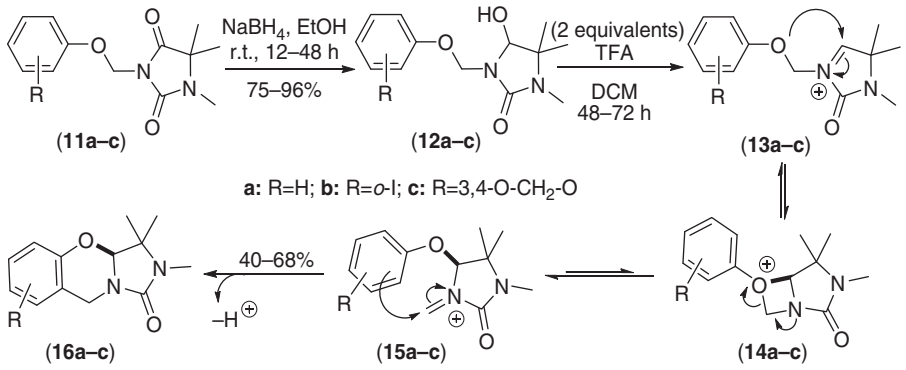
The first example of this rearrangement induced by the oxygen heteroatom was reported in 2003 by our group, during the synthesis of tricyclic 1,3-oxazepines.[21] From a mechanistic point of view (equation 11), the [1,3]benzoxazepines (**9**) are conventionally obtained through arylation of an endocyclic *N*-acyliminium ion (**5**) generated from the corresponding precursor alcohol (**4**) in the presence of catalytic amounts of Brönsted acid (PTSA, TFA).



(11)

Endocyclic/Exocyclic isomerization induced by *O*-cyclization process

The formation of the tricyclic lactam (**10**), is explained by the isomerization of the endocyclic ion (**5**) into the corresponding exocyclic ion (**7**) via the azaoxonium ion (**6**) all in equilibrium, ultimately followed by intramolecular π-cationic cyclization of the exocyclic *N*-acyliminium ion (**7**). Azaoxonium ion (**6**), the key intermediate in this sequence, results not only from an atypical intramolecular α-oxaamidoalkylation but also from bis-*N*,*O*-acetal (**8**), which is easily accessible from precursor (**4**) and benzyl alcohol in the presence of an acid catalyst. Under these conditions, the cyclic products (**9**) or (**10**) are also obtained. Product (**8**) can also be synthesized as the unique reaction product from alcohol (**4**) under alkaline conditions in good yields (75–81%). This hitherto unknown rearrangement has also been observed by the research group in the hydantoin series (equation 12).[22]



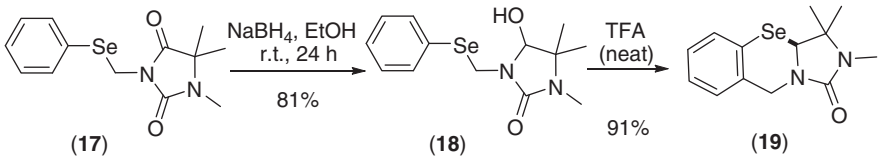
(12)

Endocyclic/Exocyclic isomerization via aza-oxonium species in hydantoin series

The α-hydroxy lactams (**12a–c**), conventionally obtained from **11a–c**, are treated with TFA in dichloromethane (DCM) under the conditions outlined above, and only the trimethylimidazo[5,1-*b*][1,3]benzoxazin-1-ones (**16a**) and (**16c**) are isolated. Their formation requires prior generation of the exocyclic ion (**15a–c**) obtained from the rearrangement of the azaoxonium ion (**13a–c**). In the case of **16b**, the classical regioisomer issued from the intramolecular π-cyclization of (**13b**) was also isolated in a 1:1 ratio, but the overall yield of the transformation is relatively modest (26%).

Given these results, it appears that the nature of the *N*-acyliminium ion generated *in situ* under acidic conditions and the nature and the position of the substituent on the aromatic ring are the important parameters of this transformation. Even more

interestingly, the replacement of the cationic species precursor by an oxygen atom with selenium does not change reaction pathways (equation 13). This again demonstrates that the nucleophilicity of the heteroatom plays a fundamental role in the domino process of α-heteroamidoalkylation/transposition/π-cyclization. The intramolecular arylation of the exocyclic *N*-acyliminium ion is the only product isolated in very good yield (91%).



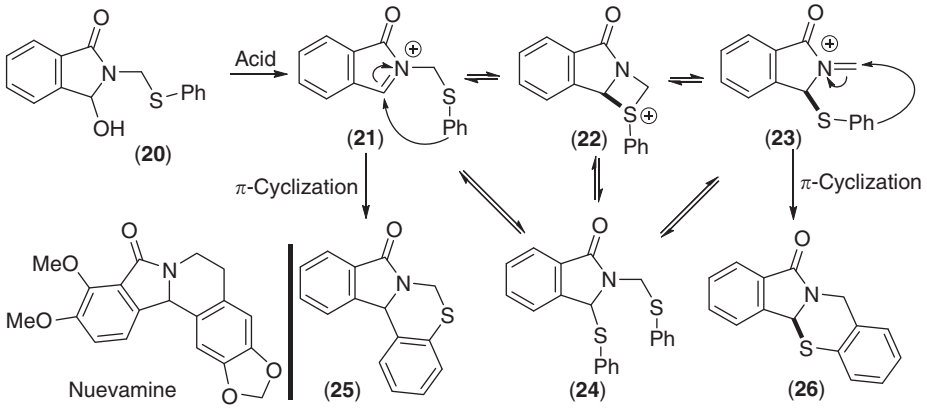
(13)

Endocyclic/Exocyclic isomerization via aza-selenium species in hydantoin series

On the basis of the results obtained in the oxygen and selenium series, it seems that, in addition to the parameters mentioned above, the size of the ring formed is one of the basic parameters for smooth running of this domino process.

2.17.3.2.2.2 Rearrangement induced by the sulfur atom

The domino process mentioned above was discovered by the research group in 2001, studying the behavior of carbinol lactams bearing a thioether oxide S–CH_2 bond, in acid media.[23] The goal of this study was to access sulfurated analogs of neuvamine alkaloid (equation 14) belonging to the family of Chilean protoberberines, which include also the so popular lennoxamine, chilenine, and (±)-cephalotaxine.



(14)

Endocyclic/Exocyclic isomerization via aza-sulfonium species in isoindolone series

Treatment of the *N*-acyliminium ion precursor (**20**) under acidic conditions (e.g., neat TFA, r.t., 12 h) led to an inseparable mixture of two isoindolo[1,3]benzothiazines isomers (**25**) and (**26**) in a 5.5:4.5 ratio (equation 14). The use of other acids such as AcOH or TFA at room temperature, after only 3 h of reaction, shows that these isoindolo[1,3]benzothiazines are the thermodynamic products of transformation. The disulfide (**24**) resulting from the latter reaction leads to the same mixture of two rings **25** and **26** in the same ratio when treated with TFA at reflux (92%).

These cyclization reactions proceed through an intramolecular α-amidoalkylation and conventional aromatic π-cationic cyclization of **21** and **23,** preceded by or not, by an atypical intramolecular α-thioamidoalkylation, in which the sulfur atom acts as the internal nucleophile (**22**).

The importance of these domino processes, which allow easy access to original structures in the oxygen, sulfur, and selenium series, is presented in greater depth and discussed in the following sections.

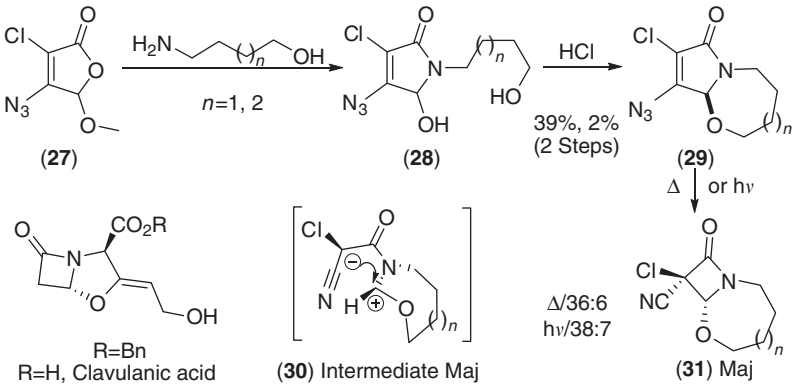
2.17.4 *N*-Acyliminium Cation Oxacyclization

In *N*-acyliminium ion chemistry, the formation of the C–X bond may involve oxygen, nitrogen, sulfur, or selenium. Those reactions using oxygen as the internal nucleophile are certainly the most described. Several families of chemicals are concerned by these modifications, and various strategies are employed to generate cationic species and also the oxygenated nucleophiles.

2.17.4.1 Syntheses of Azetidine Series

Clavulanic acid (equation 15) is a natural substance produced by *Streptomyces clavuligerus*. It is administered in combination with penicillin antibiotics such as amoxicillin and ticarcillin, to obtain a broad spectrum of therapeutic antibiotic activities. The discovery of clavulanic acid inhibitory properties of β-lactamase has led to an interest in the design of other derivatives of this family. As such, new synthetic approaches have been developed to obtain biologically active products.

The new approaches include the contraction of 4-azidopyrrolidin-2-ones onto corresponding 3-cyanoazetidin-2-ones, by thermolysis (90 °C, toluene) or photolysis (450 W, Hanovia lamp, 10 °C, CCl_4) (equation 15).[24] The 4-azidopyrrolidin-2-one precursors **(29)** were synthesized by intramolecular oxacyclization in acidic medium (HCl) of diols **(28)**, obtained from the 5-disubstituted methoxyfuranones (**27**).

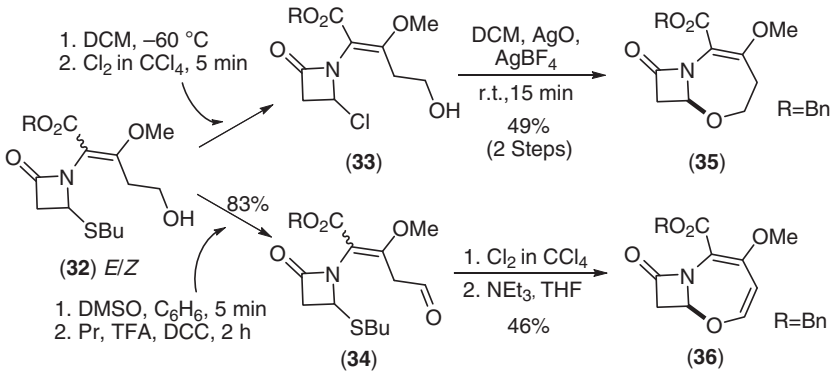


(15)

Intramolecular oxa-cyclization

The target, fused 3-cyanoazetidin-2-ones (**31**), was then obtained via the reaction intermediate (**30**). It is probable that this rearrangement is somewhat concerted as it passes through the *N*-acyliminium ion (**30**), in which an oxygen atom is also involved in the stabilization of the cation. The stereoisomer (**31**) was mainly obtained in the case of 1,3-oxazocines ($n=2$) and exclusively obtained in the case of 1,3-oxazepines ($n=1$).

Fused unsubstituted azetidines, (**35**) and (**36**), close to the structure of the clavulanic acid, have also been obtained by intramolecular interception of the *N*-acyliminium ion generated *in situ* (equation 16).

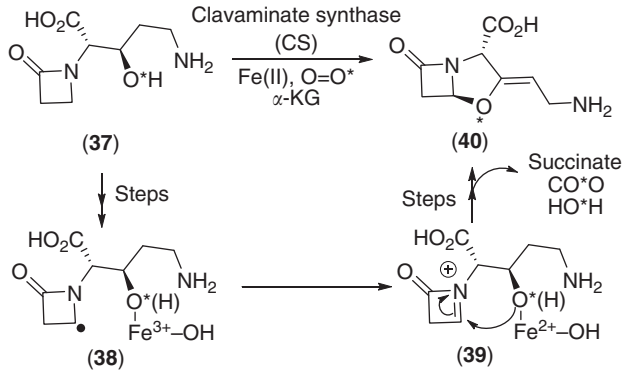


(16)

Intramolecular oxa-cyclization

Although within the cyclization precursor (**33**), the alcohol function displaces the chlorine atom activated by the $AgO/AgBF_4$ couple, cyclization of substrate (**34**) is managed by the intermediate of the enolate of the aldehyde, which is generated *in situ*. Under these conditions, the 1,3-azetidines fused to oxazepines (**35**) and (**36**) are obtained in two steps, with overall yields of 49% and 55%, respectively.[25]

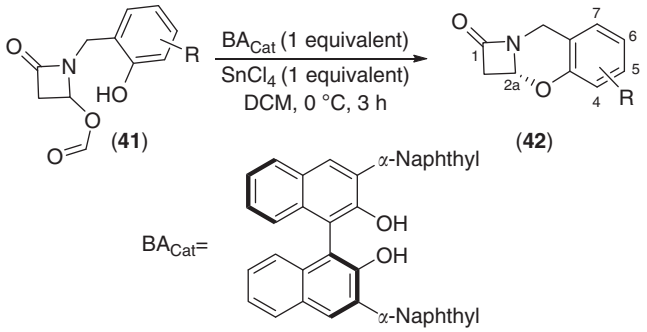
It is well known that oxygenase-Fe(II)-dependent deacetoxycephalosporin-C synthase (DAOCS) causes ring expansion of penicillins, resulting in deacetoxycephalosporin-C. The reaction occurs in the presence of α-ketoglutaric acid (α-KG) and molecular oxygen, to provide carbon dioxide and succinic acid. Oxygen provides one atom to the dioxygen, and the other for the formation of water.



Oxidative cyclization via C–O bond formation (17)

The conversion of proclavaminic acid (**37**) into clavaminic acid (**40**), a key intermediate in the biosynthesis of clavulanic acid, an inhibitor of β-lactamase,[26] involves participation of iron-bound oxygen. A speculative extension of this concept, to other classes of natural products bearing oxacycles, has been published. Such processes correspond to oxidation (mediated by the oxydoreduction of Fe(III)→Fe(II)) of radical (**38**) leading to an endocyclic *N*-acyliminium ion (**39**), followed by oxacyclization.

Recently, an asymmetric version of intramolecular oxacyclization has been obtained in an enantioselective manner of 3,4-benzo-5-oxacephames (**42**), by exploiting the catalytic properties of chiral BINOL derivatives.[27] During this reaction, (*S*)-3,3′-bis-α-naphthyl-BINOL proved to be the best catalyst even in the presence of stoichiometric amounts of $SnCl_4$ (equation 18).



Asymmetric C–O bond formation using BINOL derivative (18)

This cyclization process can be generalized to other substituents as shown in Table 1, although the mechanism for total enantioselectivity remains uncertain.

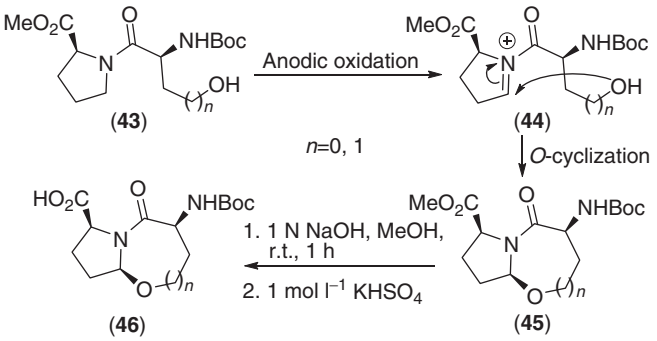
Table 1 Asymmetric cyclization of (**41**) with a combined BA/LA catalysis (equation 18)

Entry	*Substrate (**41**)*	*Substituent R*	*Product (**42**)*	*Yield (%)*[a]	ee *(%)*[b]
1	**41a**	H	**42a**	39	99
2	**41a**	H	**ent-42a**	42	99[c]
3	**41b**	5-MeO	**42b**	49	82
4	**41c**	6-Ph	**42c**	45	92
5	**41d**	4-Br,7-MeO	**42d**	50	95
6	**41e**	4-Br,7-OH	**42e**	52	0
7	**41f**	6-Br	**42f**	0	–

[a]Isolated yield, determined after flash chromatography on SiO_2 column.
[b]Enantiomeric excess was determined by chiral high-pressure liquid chromatography (HPLC).
[c]In this case, (*R*)-3,3′-bis-α-naphthyl-BINOL was used as chiral ligand.

2.17.4.2 Peptidomimetic Synthesis

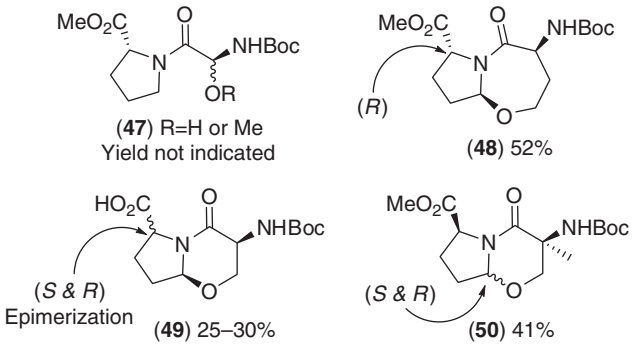
A general, efficient approach to the obtention of new rigid peptidomimetics starting from dipeptides, consists in the heterocyclization of an *N*-acyliminium ion, with the oxygen atom. The precursor is generated either electrochemically, by anodic oxidation of an amide, or chemically, by regioselective reduction of one carbonyl group of an imide.



(19)

Electrochemical C–O bond forming reaction in peptidomimetics

Among electrochemical oxidations, those of amides and lactams are common. Specific conditions of anodic oxidation (e.g., Pt anode, constant current 138 mA, 6.9 mA cm^{-2}, 5% Pr^iOH/MeCN, 1 mol l^{-1} $Bu_4^nBF_4$, 3.8 F mol^{-1}) of amides (**43**) can lead directly to bicyclic *N*,*O*-acetals (**45**) via the intermediate *N*-acyliminium ions (**44**), in 48% ($n=1$)[28] and 15% ($n=0$) yields,[29] respectively. When $n=0$, significant amounts of the oxidized open product (**47**) were isolated (**Scheme 2**).[29] The target bicyclic lactams (**46**) are obtained in very good yields, when $n=1$, after hydrolysis of ester (**45**). In contrast, when n=0, a mixture of two diastereoisomers (**49**)[29] and (**45**) in a ratio of 2.5:3.0 is obtained. The latter compound is derived from epimerization during hydrolysis at the C_{10} position bearing the acid group.

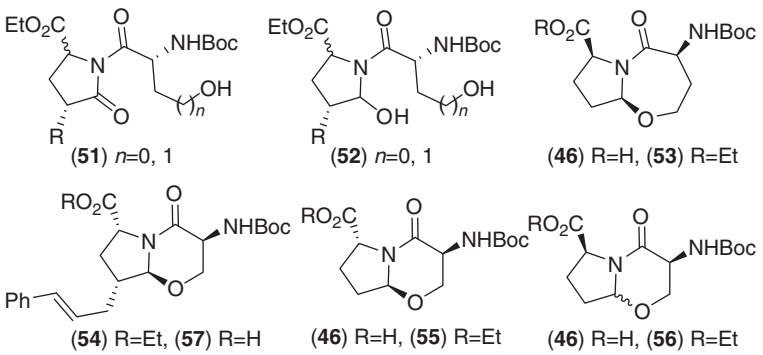


Scheme 2 Series of peptidomimetics.

The same sequence applied to the *trans* diastereoisomer of **43** with $n=1$ results in ester (**48**) in 52% yield.[28] However, when $n=0$, the introduction of a methyl group at the α-position of the carbamate leads to the cyclization product (**50**) in 41% yield,[29] as a mixture of two diastereoisomers, and the corresponding open-oxidized product, similar to **48**.

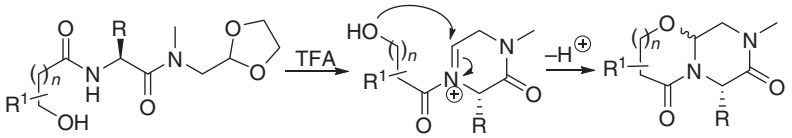
This approach, however, presents limitations: (1) yields are generally modest for bicyclic 5,7-lactams and very low for bicyclic 5,6-lactams and (2) formation of open oxidation by-products. As such, another approach has been explored.[30]

The chemoselective reduction of the endocyclic carbonyl function of **51** by a serine or a homoserine readily leads to hemiaminals (**52**) (e.g., $LiBEt_3H$, THF, −78 °C; **Scheme 3**). Treatment by a catalytic amount of TFA (30 mol%) solely generates oxacyclization products in modest 35% yields for bicyclic 5,7-lactams (**53**) and 5,6-lactams (**54**), but higher than 50% for 5,6-bicyclic lactams (**55**) and (**56**). These yields are generally better than those obtained by the electrochemical pathway. The same tendency is observed in stereoselectivity, with the exception of (**56**). During the hydrolysis of esters to the corresponding acids, yields are quantitative in all cases; epimerization was observed in the case of acid (**46**).



Scheme 3 Series of peptidomimetics.

Some polysubstituted bicyclic 6,5- and 6,6-lactams (**60**) have been obtained using similar protocols (equation 20). Indeed, treatment of dipeptides (**58**) with a protic acid leads stereoselectively to the oxacyclization products (**60**) via the intermediate *N*-acyliminium ions (**59**).[31] These rigid *β*-turn mimetics, obtained in good yields, constitute excellent scaffolds for further combinatorial chemistry.



(20)

C–O forming reaction in peptidomimetics

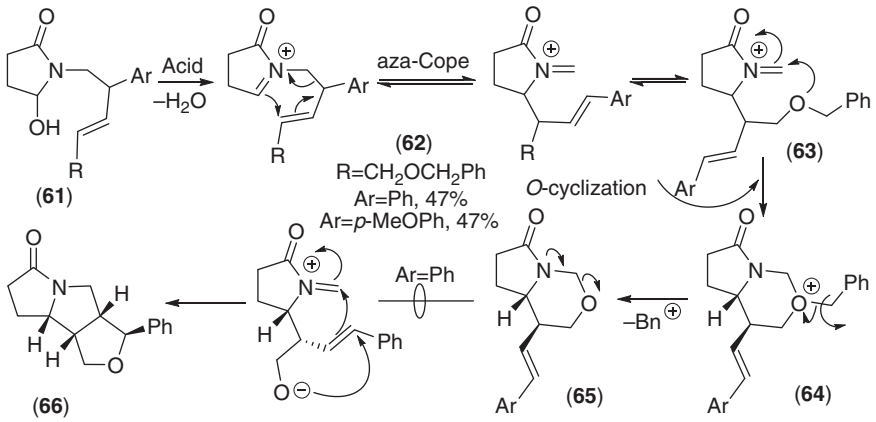
2.17.4.3 Synthesis of Pyrrolidines and Piperidines

2.17.4.3.1 Pyrrolidin-2-ones fused and unfused

The first example was described in the furo[3,4-*a*]pyrrolizines series, by Speckamp and coworkers.[22] In this study, the aza-Cope rearrangement of *α*-hydroxy lactams bearing an exocyclic double bond was obtained in acidic medium.

In this context, the treatment of precursor (**61**) with a Brönsted acid (HCO_2H or TFA) at room temperature leads to a mixture of two products (**65**) and (**66**) in a 1:1 ratio and 91% yield. In TFA at high temperatures, only the tricyclic system (**66**) is isolated (64%).[32]

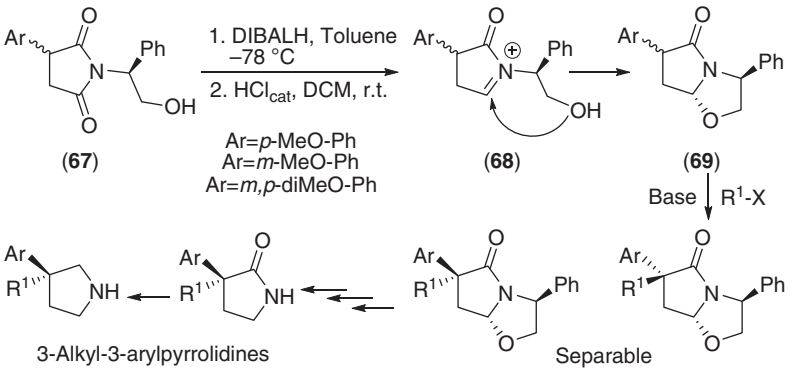
The formation of compound (**65**) is depicted (equation 21). Compound (**61**), under acidic conditions, undergoes an aza-Cope rearrangement into the exocyclic *N*-acyliminium ion (**62**) which, when $R=CH_2OBn$, instantly undergoes, via (**63**) intramolecular *O*-cyclization. Ultimately, the cationic bicyclic species (**64**) releases the stable benzyl cation to provide the bicyclic compound (**65**). The tricyclic product (**66**) is ultimately obtained by generating an exocyclic *N*-acyliminium ion, similar to **62**, followed by an olefin-mediated cascade oxacyclization.



(21)

Intramolecular oxygen attack of *N*-acyliminium species

Meyers and coworkers[4c,33] have shown that, during the synthesis of chiral nonracemic 3-alkyl-3-arylpyrrolidines by alkylation of bicyclic lactams, the necessary substrates for the ultimate reaction of C-alkylation (**69**) are readily available in two steps (equation 22).

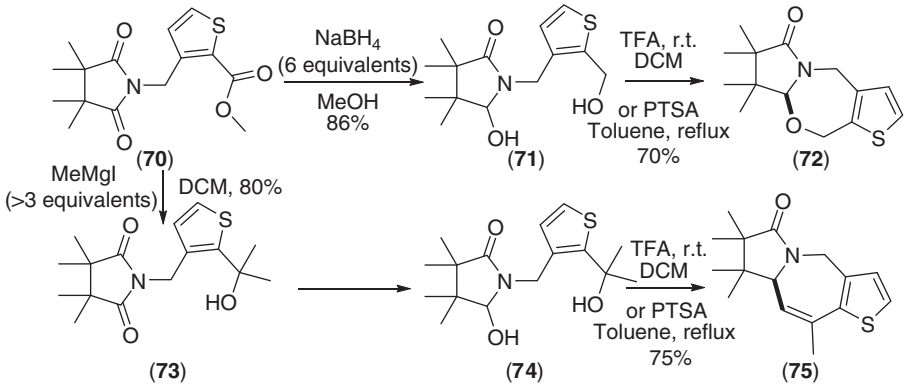


(22)

Access to chiral non-racemic 3-alkyl-3-arylpyrrolidines

Imides (**67**) are obtained from the (S)-phenylglycinol and 2-arylsuccinic acids in one step under thermal cyclodehydration, reduced regioselectively and then treated with a catalytic amount of acid. Bicyclic lactams (**69**) are obtained via an O-cyclization of **68** in yields ranging from 38% to 62%. The stereocontrol of this reaction, especially at the carbon–oxygen bond, is total and appears to proceed according to the Felkin–Ahn model.

On the same topics,[34] the reduction of the tetramethylsuccinimide-ester (**70**) provides the desired diol (**71**), accompanied by the imide-alcohol in a 3:7 ratio. This result underlines the low reactivity of the carbonyl group of the imide, compared with the ester function, in the reduction reaction by $NaBH_4$ in ethanol (80%), probably due to steric hindrance (equation 23). This was confirmed during treatment by a less hindered organomagnesium, of the imide ester (**70**). Indeed, when **70** was involved in a reaction with MeMgI, more than 3 equivalents of organomagnesium were necessary to transform the ester into the alcohol without addition onto the carbonyl function of the imide. Imide alcohol (**73**) thus obtained was reduced by using the same protocol as presented above and led to the expected product (**74**).

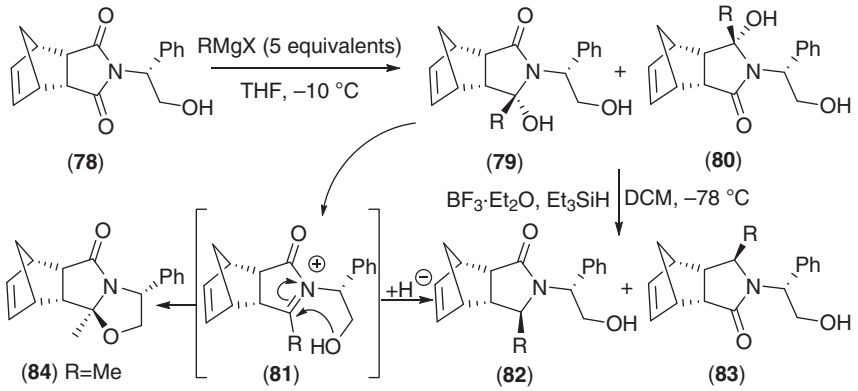


(23)

O-cyclization versus π-cyclization in heterocyclic systems

Diols (**71**) and (**74**) were treated with a protic acid under heated conditions (PTSA, toluene, reflux) or at room temperature (TFA, DCM). The results show that the *O*-cyclization reaction is effective in the case of the primary alcohol (**71**), whereas, with the tertiary alcohol (**74**), only a concurrent π-cyclization reaction is observed. Products (**72**) and (**75**) issued from these transformations were obtained in comparable yields of 70–75%, even under different acidic conditions.

Similar studies conducted on reductive alkylation of chiral *endo*-imides have also been undertaken by Huang's research team.[35] In fact, the addition of methyl magnesium iodide in a first stage is best accomplished on the least hindered convex face of the *endo*-imide (**78**). The resulting mixture of (**79**) and (**80**) was then treated under ionic hydrogenation conditions (equation 24), yielding a mixture of two lactams (**82**) and (**83**) in a 58:42 ratio via the *N*-acyliminium ion intermediate (**81**). No products derived from a completive cyclization reaction or a deprotonation of this cation could be observed. In contrast, when the hydroxy lactam (**79**) was isolated from the reaction medium and treated separately by PTSA, only the *O*-cyclization product (**84**) was isolated in a good yield, highlighting that ionic hydrogenation is a faster process than *O*-cyclization (Table 2).



(24)

O-cyclization versus reductive alkylation in *endo*-imide systems

A similar reaction pattern was observed when imide (**78**) was reacted with other organomagnesium derivatives such as EtMgBr, Bu^nMgBr, and $C_7H_{15}{}^nMgBr$ (Table 2).[35]

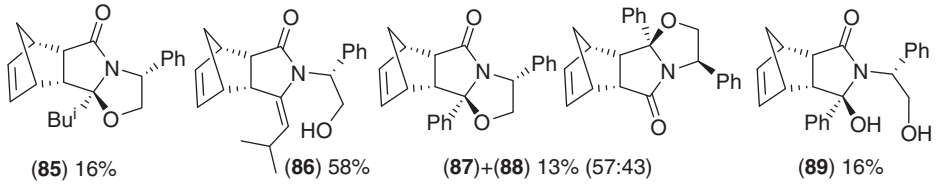
In contrast, the addition reaction with Bu^iMgBr gave a complex mixture (71%) and the subsequent reduction reaction led to the *O*-cyclization products of **85** and enamide (**86**), derived from the deprotonation of the *N*-acyliminium ion (**81**; Scheme 4). In the presence of PhMgBr, the mixture of addition products (**89**:**80**) (68:32) was subjected to reduction, as described above. The reaction

Table 2 Reductive-alkylation of *endo*-imide (**78**) (equation 24)

Entry	*R of RMgBr*	*Yield (%) (**79**+**80**)*	*Ratio (**82**)/(**83**)*	*Yield (%) (**82**+**83**)*	*Additional products*[c]
1	a: Me	97	58:42	93	–
2	b: Et	93	70:30	90	–
3	c: Bu^n	67	65:35	82	–
4	d: $C_7H_{15}^n$	72	71:29	89	–
5	e: Bu^i	71	nd[a]	Not formed	(**85**)+(**86**)
6	f: Ph	67	0:100[b]	44	(**87**)+(**88**)+(**89**)

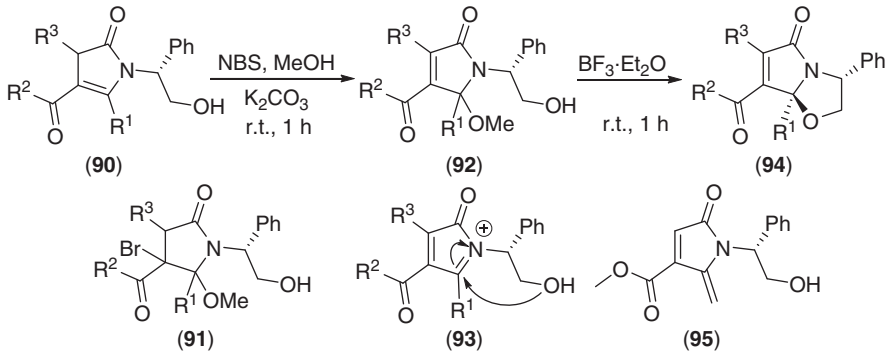
[a]Only a complex mixture was obtained.
[b]Only one isomer (**83f**) was obtained.
[c]See **Scheme 2** for the additional isolated products. The mixture of (**87**) and (**88**) is inseparable.

led to the lactamic diastereoisomer (**83**) as a major product, and two inseparable *O*-cyclization products (**87**) and (**88**) and an alcohol (**89**), resulting from the epimerization of diol (**79**).



Scheme 4

Enantiomerically pure α,β-unsaturated bicyclic lactams, hindered at the cationic center, have also been described.[36] Thus, treatment of enamidones (**90**) by NBS in MeOH provides ethers (**92**), through brominated derivatives in the α-position of the lactam carbonyl group (**91**). The action of a Lewis acid such as BF_3OEt_2 (equation 25) gave *N*-acyliminium salts (**93**), and then the unsaturated bicyclic lactams (**94**). The overall results are presented in Table 3.



(25)

O-cyclization versus reductive alkylation in *endo*-imide systems

Table 3 Bromomethoxylation and cyclization of chiral enamidones (**90**) (equation 25)

Entry	*Substrate*	R^1	R^2	R^3	*Product*	*Yield (%)*[a]
1	**90a**	Me	OMe	H	**94a**[b]	64
2	**90b**	Me	Me	H	**94b**	84
3	**90c**	$(CH_2)_4OBn$	OMe	H	**94c**	96
4	**90d**	Me	OMe	Ph	**94d**	50
5	**90e**	Me	OEt[c]	H	**94e**	22

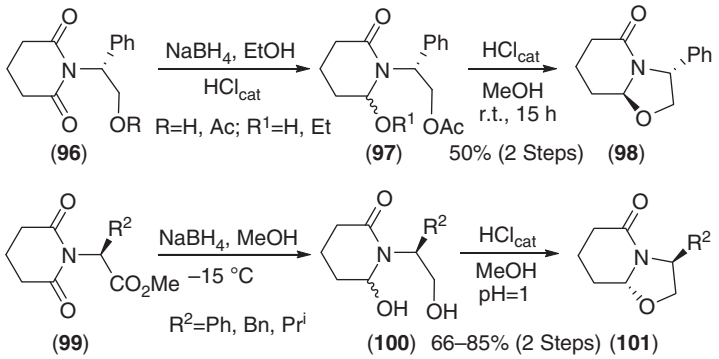
[a]The *de* was always >95%, as determined by proton nuclear magnetic resonance (^{1}H NMR) analysis of the crude mixture.
[b]No other characteristics of the by-product (**93**) were given by the researchers.
[c]The first step of the sequence was carried out in EtOH.

In almost all cases, the bicyclic lactams (**94**) were obtained in good yields as single diastereoisomers (*cis* diastereoisomers). The best result was obtained with **90c** in which $R^1=(CH_2)_4OBn$ but only in the case of **90a**, the cyclic product (**94a**) accompanied the deprotonation product (**95**) of the presumed *N*-acyliminium ion (**93**).

2.17.4.3.2 Synthesis of piperidin-2-ones fused or unfused

Bicyclic lactams in the piperidine series also represent choice intermediates for efficient access to many interesting compounds, synthetic or naturally occurring,[37] and are widely used by several research groups, in particular that of Meyers.[4c]

An alternative to the Meyers's method (equation 2), for the preparation of enantiopure bicyclic lactams in the piperidine series, was that of Speckamp and his group.[38] The enantiomeric isomer of the bicyclic systems (**98**) and (**101**) was described starting from glutarimides (**96**) and (**99**), respectively, in yields ranging from 50% to 85%. In the latter case, the diol intermediate (**100**) was not necessary, making the approach attractive, also diastereospecific, and consequently more generally applicable (equation 26).[39]

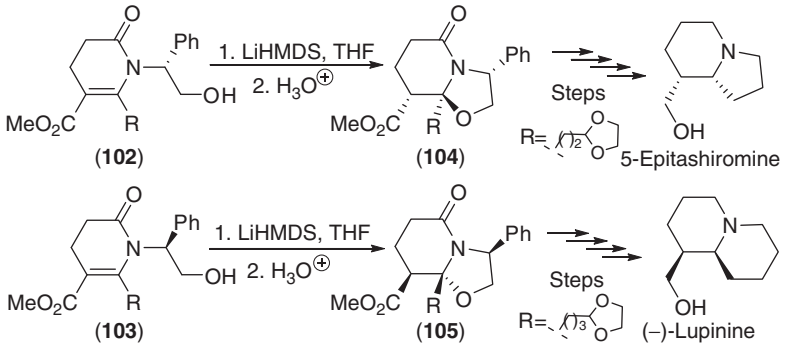


(26)

Reductive *O*-cyclization in piperidine systems

An even shorter access to these Meyers's systems, both in the pyrrolidine and in the piperidine series, was published by the research group (equation 8).[13] This domino approach, under new milder reaction conditions that do not employ acid, uses commercially available and inexpensive ethoxyacrylate derivatives as starting substrates for easy access to highly functionalized bicyclic γ- and δ-lactams. The reaction mechanism elucidated through theoretical calculations further shows that the α-ethoxy lactams analogs to compound (**97**) or (**100**) are the key intermediates. Nonetheless, their acid treatment led to the same bicyclic γ- and δ-lactam via a diastereoselective intramolecular *O*-cyclization.

Another nonacidic approach to *O*-cyclization has also been explored and cleverly exploited in the enantioselective synthesis of indolizidine and quinolizidine alkaloid derivatives, such as 5-epitashiromine and (–)-lupinine, respectively (equation 27).[40]



(27)

O-cyclization under basic conditions

In an exploratory study,[40] bicyclic lactams (**104**) and (**105**) were formed directly, but with low diastereoselectivity (*de*, 20%), under conditions of silyl ether deprotection, promoted by tetrabutylammonium fluoride (TBAF) of silyl protected precursors. After a large screening, the intramolecular Michael addition (*O*-ring closure) was carried out on enamidones (**102**) and (**103**) in a basic lithium medium (LiHMDS) at a low temperature. Under these conditions, the expected bicyclic lactams (**104**) and (**105**) were obtained after hydrolysis, in quantitative yields and with high diastereoselectivity (>95%).

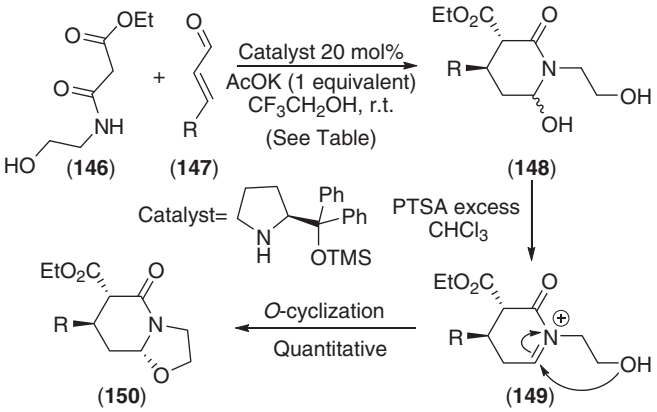
Another elegant and recent approach based on a Michael addition of amidomalonates to enals, followed by a cascade intramolecular formation of a hemiaminal, provides access to piperidine derivatives with good yields and excellent enantioselectivities.[41]

The cascade reaction starts with the addition of the active methylene (**106**) to (**107**) as a Michael acceptor in a nonconventional solvent (CF_3CH_2OH). Chiral piperidine (**108**) was isolated in yields varying between 44% and 73%, proving the effectiveness of the catalyst. The following addition of an acid (e.g., excess PTSA, $CHCl_3$) produced α-hydroxy lactams (**108**), which provided ultimately piperido-oxazolidines (**110**) in quantitative yields (Table 4).

Table 4 Cascade cyclization process of α-hydroxy lactams (**108**) (equation 28)

Entry	*Substrate*	*R*	*Product*[a]	*Yield (%)*[b]	dr[c]	ee *(%)*[d]	*Product*	ee *(%)*[d]
1	**107a**	Ph	**108a**	73	9:1	98	**110a**	93
2	**107b**	*p*-BrPh	**108b**	44	9:1	90	**110b**	<90
3	**107c**	*p*-NO_2Ph	**108c**	56	9:1	95	**110c**	<90

[a]The experimental conditions: A mixture of 0.30 mmol of (**106**), catalyst (20 mol%, 0.05 mmol), 0.25 mmol of (**107**), and AcOK (0.30 mmol) in CF_3CH_2OH (1 ml) was stirred at room temperature overnight. Crude product (**108**) was then purified by column chromatography on SiO_2.
[b]Isolated yield after column chromatography on SiO_2.
[c]Determined by ^1H NMR analysis of the crude reaction mixture.
[d]Determined by chiral HPLC analysis.



(28)

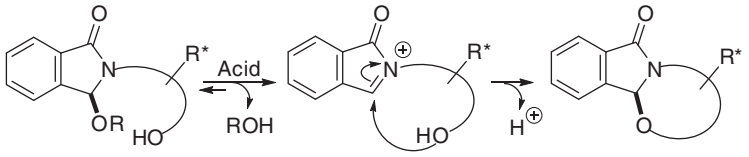
O-cyclization in the organocatalytic cascade process

In parallel, the cascade reaction was performed in a 'one-pot' procedure starting from Michael acceptors and leading to the final products (**110**) in good yields although with slightly lower enantioselectivity (*ee* = 93% for (**110a**) and *ee* < 90% for (**110b**) and (**110c**)).[58]

2.17.4.4 Reactivity of the *N*-Acyliminium Ions in the Isoindolone Series

2.17.4.4.1 Direct O-cyclization

Given the high stability of the *N*-acyliminium ions generated in the isoindolone series, several optimization studies have been initiated to best determine experimental protocols.



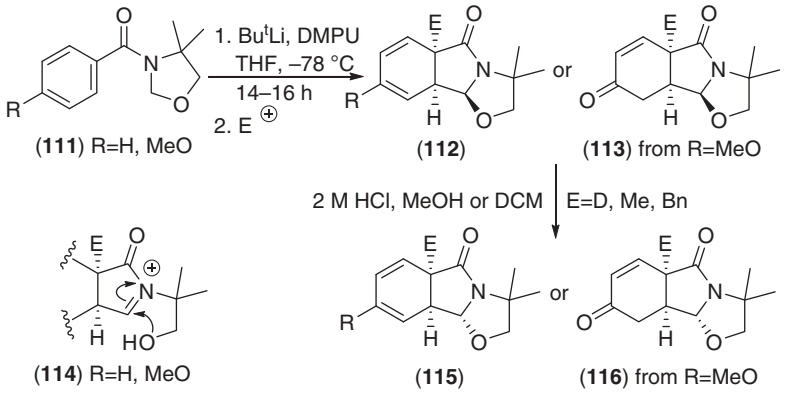
(29)

Direct *O*-cyclization process

The overall result of this transformation corresponds to the cleavage of an exocyclic C–O bond and formation of another endocyclic C–O bond, theoretically more favorable. This is confirmed by the work of Meyers, and others, on the use of bicyclic lactams in asymmetric synthesis. In particular, the cleavage of the C–O bond, generating the *N*-acyliminium ion, requires harsher conditions than those used when the same C–O bond is endocyclic.[4c]

Clayden and collaborators[42] have shown, in an electrocyclic cyclizing dearomatization reaction of lithiated *N*-benzoyloxazolidines (**111**), that the stereochemistry of the carbon of this endocyclic C–O bond has a thermodynamic control, exclusively during epimerization of tetrahydrooxazolo[2,3-*a*]isoindol-5(5*aH*)-ones (**112**) and (**113**), in an acidic medium. In the latter case, in addition to electrocyclic cyclizing dearomatization, deprotection of the MeO group by Bu^tLi was observed and was found to be

stable at the end of the reaction in ketone form. The formation of stable products (**115**) and (**116**) was achieved via an *N*-acyliminium ion (**114**) (equation 30).



(**111**) R=H, MeO (**112**) (**113**) from R=MeO

(**114**) R=H, MeO (**115**) (**116**) from R=MeO

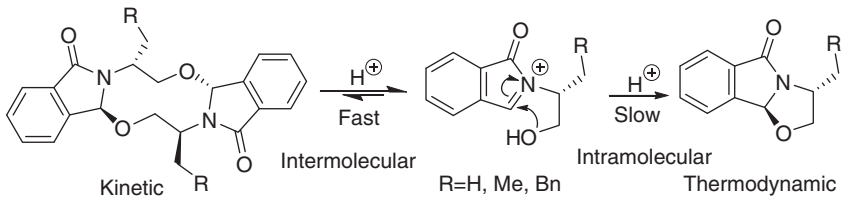
(30)

Epimerization of dearomatizing oxazolo[2,3-*a*]isoindolones

Details of works carried out on *O*-cyclization reactions, both in racemic and chiral series, are grouped into the following table (Table 5).

As shown in Table 5, several facts and generalities are worth noting: (1) the formation of the endocyclic C–O bond is stable independent of the ring size from 5 to 7; (2) in chiral series, *O*-cyclizations are stereoselective and, most often stereospecific; (3) in racemic series, *O*-cyclizations are diastereoselective when allowed by the substituent; and (4) reactions yields are good to very good, reproducible, and products can be synthesized in large quantities.

Another important fact is emphasized in entries 5, 6, 7, and 8 (Table 5). Indeed, under mild acidic conditions, only the dimers (entries 5 and 7) via an intermolecular *O*-cyclization reaction were obtained. Under harsher conditions, the chiral oxazolinoisoindolones (entries 6 and 8) were the only intramolecular *O*-cyclization products obtained. However, the prolongation of contact of the dimers with the acid ultimately led to the formation of monomers. Given these observations, it appears that these transformations are controlled by a kinetic rather than thermodynamic mechanism emphasizing the relative stability of the C–O bond in a five-membered ring in comparison with a 10-membered ring system.



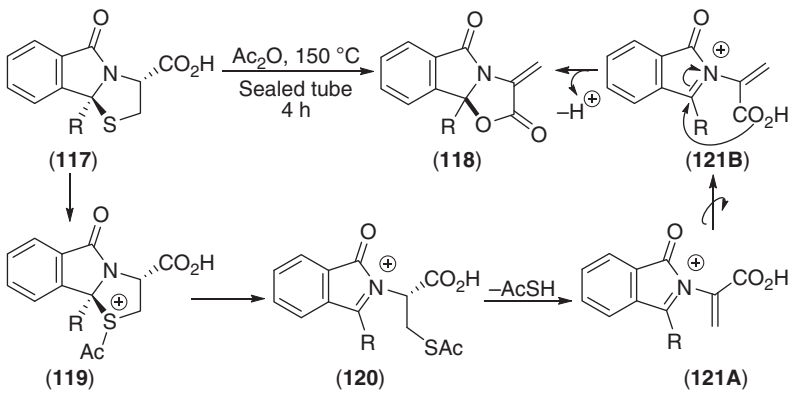
(31)

Kinetic versus thermodynamic control of the *O*-cyclization reaction

2.17.4.4.2 *O*-cyclization in a tandem process

Heterocyclization using the oxygen atom as internal nucleophile is described in Section 2.17.3.2.2, dedicated to rearrangement induced by a heteroatom (equations 11 and 12). Such an approach is an effective way of inducing rearrangement of an endocyclic *N*-acyliminium ion into the corresponding exocyclic ion one in the isoindolone,[20] the imidazolidinone,[21] and pyrrolidinone series.[32]

Another cascade process leading to *O*-cyclization was described by Pinho e Melo.[50] Thus, thermolysis of chiral thiazoloisoindolone carboxylic acids (**117**) in acetic anhydride leads to the corresponding oxazoloisoindolones (**118**) (equation 32).



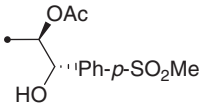
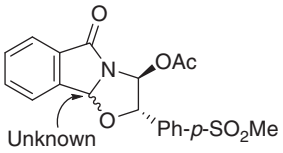
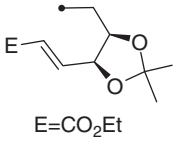
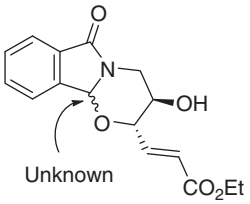
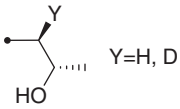
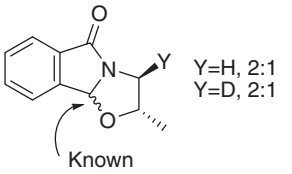
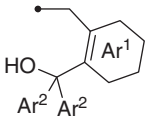
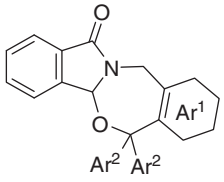
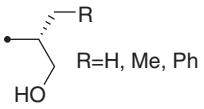
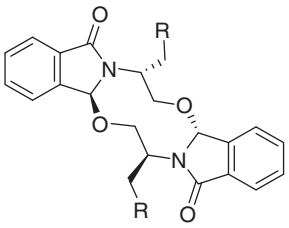
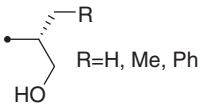
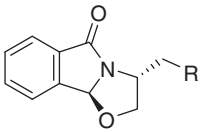
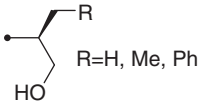
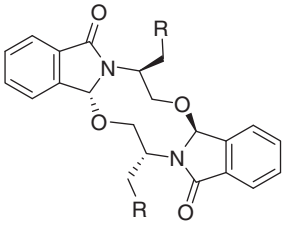
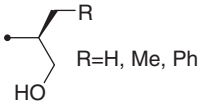
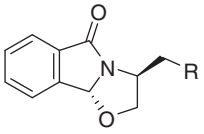
(**117**) (**118**) (**121B**)

(**119**) (**120**) (**121A**)

(32)

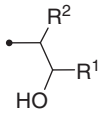
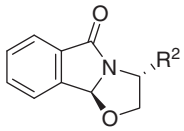
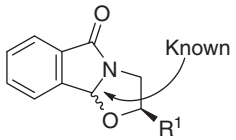
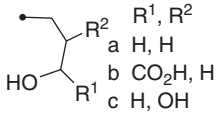
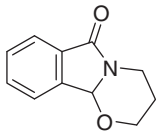
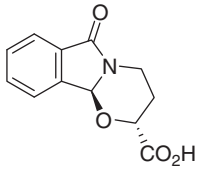
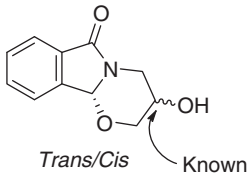
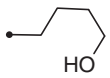
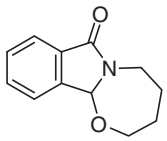
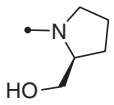
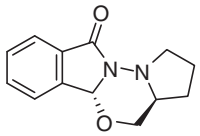
O-cyclization reaction induced by thionium ion in cascade process

Table 5 Direct *O*-cyclization of *N*-acyliminium species in isoindolone ring (equation 29)

Entry	*N-tethered group of isoindolone*	*Conditions*	*Product*	*Yield (%)*	*References*
1		$PTSA_{cat}$, benzene, reflux		68[a]	43
2		Concentrated H_2SO_4, H_2O, EtOH, reflux, 12 h		66	44
3		$PTSA_{cat}$, MS 4 Å, reflux, 12 h		30 in 3 steps[b]	45
4		$PTSA_{cat}$, DCM, reflux, 12 h		88 93 >99	46
5		AcOH excess, DCM, r.t., 36 h		70 42 NR	47
6		HCl_{cat}, $CHCl_3$, r.t., 24 h or TFA excess, DCM, r.t., 2 h		89 58–71 79–82	47
7		AcOH excess, DCM, r.t., 36 h		84 75 NR	47
8		HCl_{cat}, $CHCl_3$, r.t., 24 h or TFA excess, DCM, r.t., 2 h		94 84–88 69–74	47

(*Continued*)

Table 5 Continued

Entry	*N-tethered group of isoindolone*	*Conditions*	*Product*	*Yield (%)*	*References*
9	 R^1, R^2 a H, Me b H, Et c Me, H d Et, H	HCl_{cat}, $CHCl_3$, r.t., 24 h or TFA excess, DCM, r.t., 2 h	 *Trans* (a,b)	80 80	
			 *Cis/Trans* (c,d)	89 (2:1) 62 (2:1)	48
10	 R^1, R^2 a H, H b CO_2H, H c H, OH	HCl_{cat}, $CHCl_3$, r.t., 24 h or TFA excess, DCM, r.t., 2 h		85	48
				89	48
			 *Trans/Cis* Known	95(2:1)	48
11		HCl_{cat}, $CHCl_3$, r.t., 24 h or TFA excess, DCM, r.t., 2 h		65	48
12		$PTSA_{cat}$, benzene, DS, reflux, 12 h		82	49

[a]The reaction time is not given in reference.[43]
[b]Only the yield from three steps is given.
Abbreviations: Benz, benzene; NR, not realized; Thioph, thiophene.

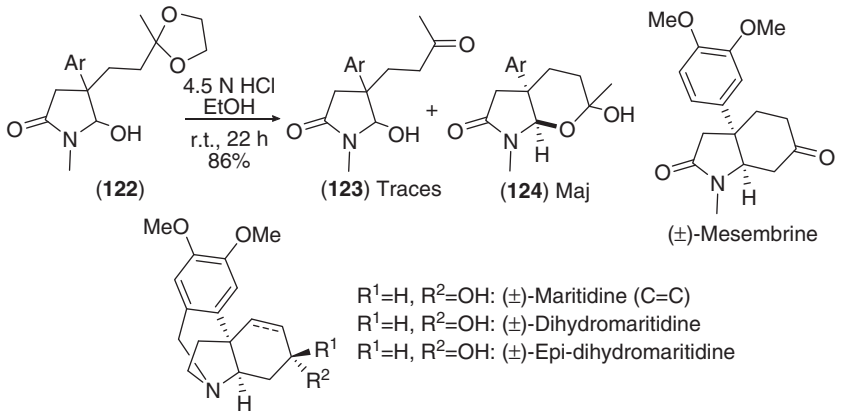
The reaction mechanism proposed for the formation of **118** is initiated by the formation of the thionium ion (**119**), which, under the impulsion of the lone pair of lactamic nitrogen, forms the *N*-acyliminium ion (**120**). Subsequently, removal of the thioacetic acid (AcSH) generates the cation (**121A**) in equilibrium with **121B**. The expected product (**118**) is obtained in a final *O*-cyclization with the oxygen atom of the acid function. It may also be possible that *O*-cyclization is performed via **120** by the same acid function and that the generated intermediate eliminates the thioacetic acid.

2.17.4.5 The *O*-Cyclization of *N*-Acyliminium Ions in Total Synthesis

The use of *N*-acyliminium ions for the C–C bond formation in the total synthesis of simple and complex nitrogenated compounds is one of the most widely used synthetic techniques in organic chemistry. The reaction is easy, compatible with the presence of

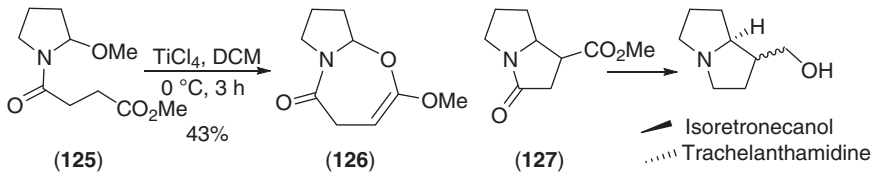
almost all chemical functions, can be performed on a large scale, and is achievable in racemic and asymmetric versions.[1] In *O*-cyclization, although formation of the C–O bond is much less common than that of the C–C bond, this reaction is nonetheless a key step in the syntheses of natural products.[4c]

The α-hydroxy lactam (**123**) has been identified as being the key substrate to access the alkaloids (±)-mesembrine and many (±)-maritidines (equation 33).[51] Attempts to hydrolyze the synthetic intermediate (**122**) lead to an *O*-cyclization product (**124**) in 86% yield. Treatment of ether (**124**) with 65% H_2SO_4 in water for a short time subsequently provides alcohol (**123**) in quantitative yield.



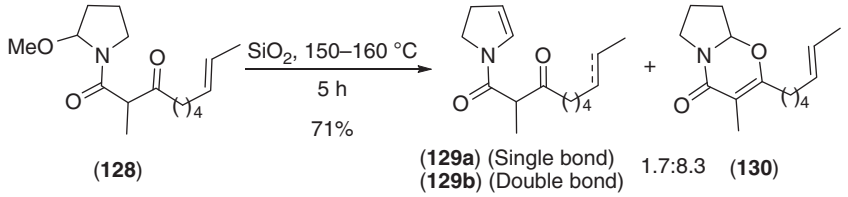
O-cyclization reaction via *O*,*O*-acetal function (33)

Wistrand and his team[52] when synthesizing (±)-isoretronecanol and (±)-trachelanthamidine demonstrated the particular reactivity of ester in the presence of an *N*-acyliminium ion (equation 34). Treatment of ester (**125**) with a Lewis acid ($TiCl_4$) did not however lead to the desired product (**127**), a direct precursor of target alkaloids. In this case, the intermediate enol caused an *O*-cyclization rather than intramolecular *C*-alkylation.



O-cyclization in pyrrolizidine alkaloid synthesis (34)

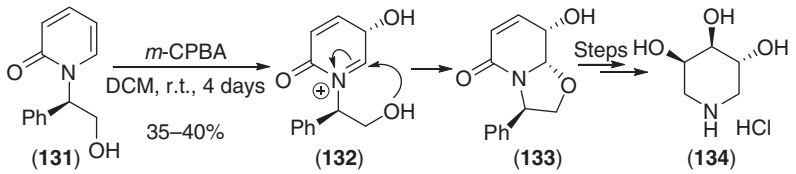
This unique and specific reactivity is attributed to the size of the formed ring 5,7 at the expense of 5,5 and probably the complexing properties of $TiCl_4$. Nonetheless, the created C–O bond is reversible and the product (**126**) shows an obvious instability in solution (equation 34). Similar behavior of a ketone function was later used in the total synthesis of pyrrolidinic metabolites isolated from *Penicillium brevicompactum*.[53] Pyrrolines (**129**) are known to have activities against insect juvenile hormone (JH) *in vivo*, and pyrrolidine (**170**) shows insecticidal properties (equation 35). These compounds and certain analogs have been obtained from the methoxy lactam (**128**) under very harsh conditions in a 1.7:8.3 ratio. Product (**129a**) is obtained by hydrogenation of olefin (**129b**).



Application of *O*-cyclization reaction via a ketone function (35)

Some polyhydroxypiperidines, as glycosidase inhibitors, have been synthesized by enantioselective oxidation of a pyridine nucleus, followed by *O*-cyclization (equation 36).[54] Specifically, the oxidation of (**131**) by *m*-CPBA (4 equivalents) led to the

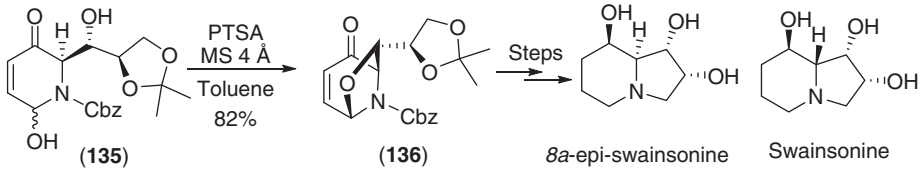
formation of an epoxy derivative, which was instantly cleaved to give the intermediate *N*-acyliminium ion (**132**). The intramolecular *O*-cyclization of the latter provided ether (**133**) and caused the formation of (3*R*,5*R*)-(**134**) and epiisofagomine azasugar.



(36)

m-CPBA oxidation inducing *O*-cyclization reaction in pyridone series

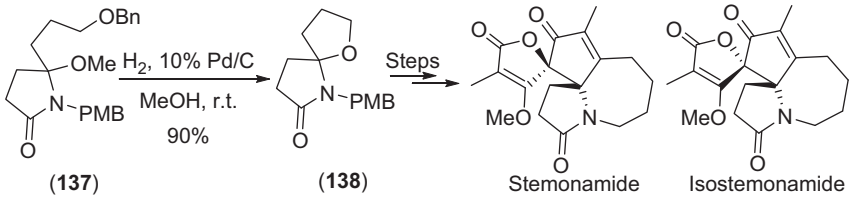
The best known reference in this field remains the swainsonine alkaloid. Total synthesis of swainsonine and epimers, and the structure–activity relationships studies accomplished form an impressive contribution to one's knowledge. Among these efforts, those of Aggarwal allow the synthesis of the 8a-epi-swainsonine starting from an enantiopure furanic aminoalcohol, using a stabilized sulfur ylide as chiral copula.[55] The α-hydroxy lactam (**135**) issued from this substrate, treated by PTSA in toluene, leads to the bicyclic *N*,*O*-acetal (**136**) according to a stereospecific *O*-cyclization reaction (equation 37). Ultimately, simple transformations derived from this derivative lead to the target 8a-*epi*-swainsonine.



(37)

Bridgehead *N*,*O*-aminal via *O*-cyclization reaction in pyridone series

Alkaloids from the pyrrolo[1,2-*a*]azepine family such as (±)-stemonamide and (±)-isostemonamide, used in traditional Chinese and Japanese medicine, were also synthesized through an intramolecular *O*-cyclization process (equation 38).[56] A key step in this sequence is the debenzylation of an ether group of **137**, followed by intramolecular *O*-cyclization. This tandem process led to azaspiro acetal (**138**), protected at its lactam nitrogen atom. This first step allowed the construction of the first spirocenter of the target alkaloids.

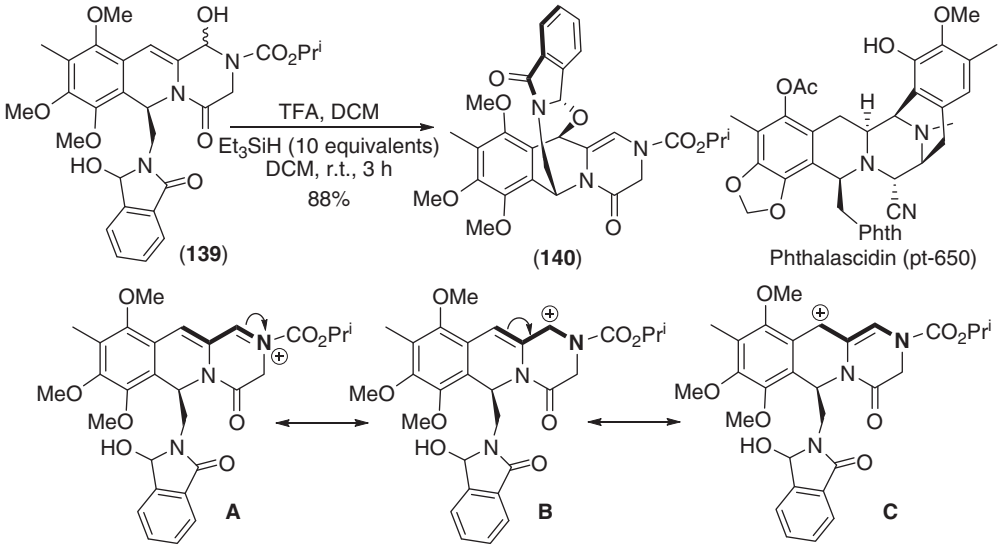


(38)

Spiro-*N*,*O*-aminal via *O*-cyclization reaction in pyrroloazepine series

The family of alkaloids containing the pyrazino[1,2-*b*]isoquinoline pattern is widespread in the plant world and is particularly rich in products of complex structure. Remarkable biological activities make them a prime target for a number of chemists. As a result, several approaches have been developed.

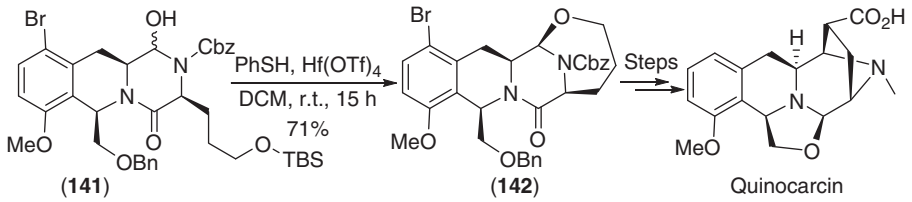
Avendaño and coworkers,[57] in their research on cytotoxicity of phthalascidin (Pt-650) derivatives, showed that intramolecular *O*-cyclization is also applicable to complex systems. For this purpose, the treatment under reductive alkylation conditions of **139** did not lead to the expected product derived from the *O*-cyclization of the *N*-acyliminium ion **A** (equation 39). The bridged product formed (**140**) appears not to be the result of *O*-cyclization of the *N*-acyliminium ion, but rather that of an allylic cation, vinylogous to an *N*-acyliminium ion **C**, in equilibrium with the cation **A** via **B**. In addition, the formation of this salt is faster than that of an ion generated from the isoindolic α-hydroxy lactam.



(39)

Bridgehead *N*,*O*-aminal via *O*-cyclization in pyrazino[1,2-*b*]isoquinoline series

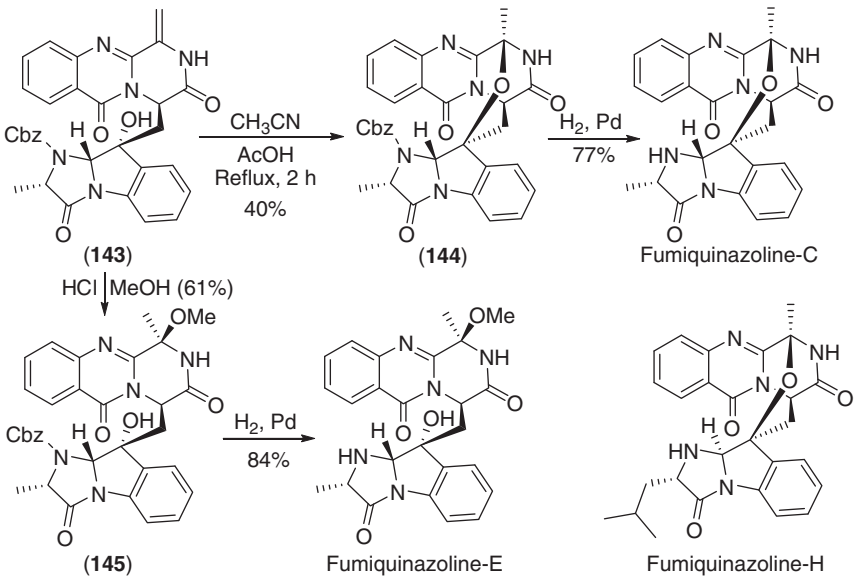
An important application of this *O*-cyclization reaction in total synthesis of the antitumor (–)-quinocarcin was achieved from 3-hydroxybenzaldehyde, in a linear sequence of 22 steps, with an overall yield of 16%, which is among the best compared with those previously obtained (equation 40).[58] The reaction sequence included the formation of the bridged *N*,*O*-acetal (**142**), starting from **141**, by a diastereospecific intramolecular *O*-cyclization reaction in an acid medium.



(40)

Bridgehead *N*,*O*-aminal via *O*-cyclization in pyrazino[1,2-*b*]isoquinoline series

Fungi belonging to the genera *Aspergillus* and *Penicillium* are a rich source of alkaloids such as (–)-fumiquinazolines C, E, and H. Although their cytotoxic properties are moderate, their complex structure has constituted the main research subject of several groups.

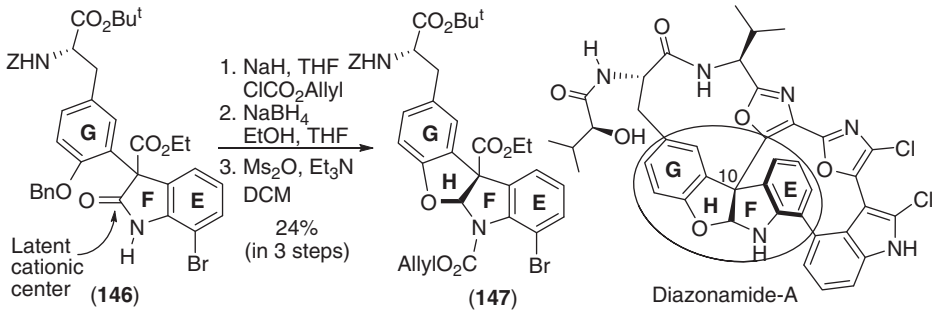


(41)

O-cyclization in the synthesis of cytotoxic fumiquinazolines

The formation of *N*-acyliminium salts and subsequent *O*-cyclization are crucial with this family of products. Indeed, the treatment of **143** with methanol in hydrochloric acid leads to the intermolecular *O*-addition product (**145**), the direct precursor of fumiquinazoline-E, after deprotection of the lactam nitrogen.[59] In contrast, acid treatment of **143**, in the absence of any traces of alcohol, leads to the protected fumiquinazoline-C (**144**). The first step in this sequence unfortunately gives poor yields because 60% of the initial product (**143**) is still recovered.

In a similar project, the main tetracyclic fragment E-F-H-G of the marine sea squirt secondary metabolite diazonamide-A was targeted. The approach uses a reduction–deprotection process of appropriated functionalized 3-arylindole-2-carboxylates associated with an intramolecular cyclization reaction with the oxygen atom as the internal nucleophile (equation 42).

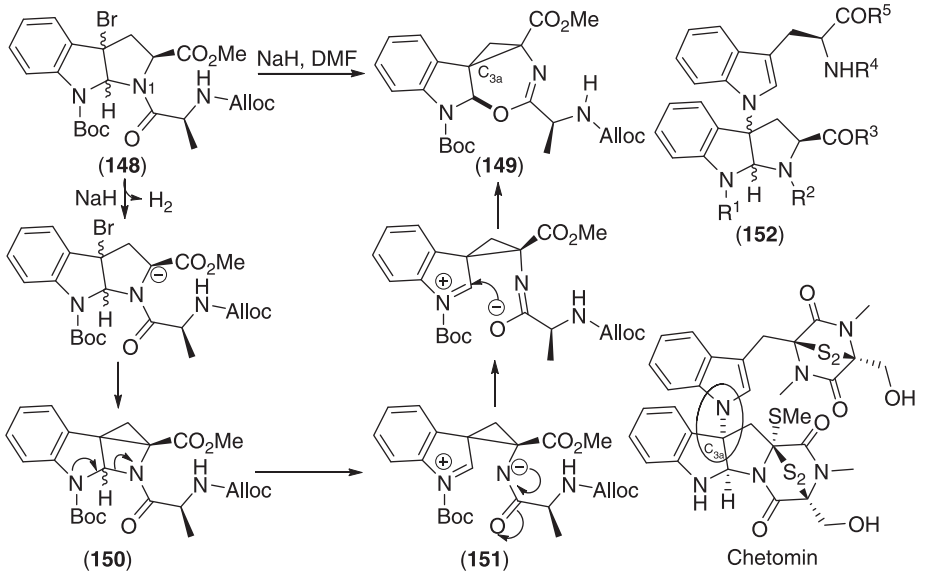


(42)

O-cyclization in total synthesis of sea squirt secondary metabolite diazonamide-A

The application of Vedejs' protocol to **146** (conditions 2 and 3; equation 42) results in the formation of the H ring of this set and ultimately leads to the desired skeleton E-F-H-G in **187**.[60] Stereochemically, **147** such as the starting substrate (**146**) constitutes a mixture of two inseparable diastereoisomers. However, the *cis* junction between the H and F rings of the two isomers is induced by configuration of the tyrosine stereocenter.

One of the characteristics of these scaffolds present in many natural products is to bear an unusual bond between position C_{3a} of the hexahydropyrroloindole and the indole nitrogen of a tryptamine or a tryptophan (e.g., **152**, equation 43). In this perspective, the treatment of brominated *N*,*N*-diprotected derivatives, like **148**, with NaH/DMF and *N*-protected derivatives of tryptophan, yielded products of expected *N*-alkylation (**152**). Only in the case of **148**, where the nitrogen N_1 is protected by an amide, did the reaction lead to the product (**149**) in good yield.[61]



(43)

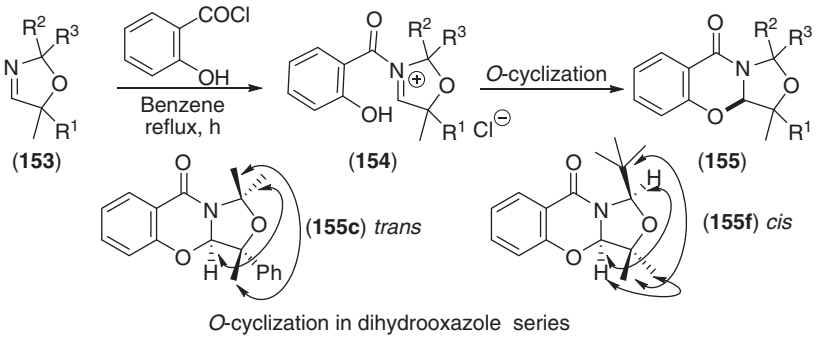
O-cyclization in orthogonal protecting groups in THPI basic evaluation

The postulated mechanism begins with the formation of the stabilized carbanion, which provides intermediate (**150**). Its cleavage into **151** followed by internal *O*-cyclization generates target (**149**) containing a less strained 1,3-oxazepine ring.

2.17.4.6 Particular *O*-Cyclizations

Some particular cases of *O*-cyclization deserve a separate treatment, because the protocols used to generate the *N*-acyliminium ions or their applications are sufficiently different from those mentioned previously.

As such, for example, 2,5-dihydrooxazoles (**153**) in the presence of salicylic acid chloride, under thermal conditions, provide γ-oxavalerolactams (**155**) in yields inferior to 60% (equation 44).[62] These products have the particularity of bearing two *N*,*O*-acetal functions and have many different applications.



O-cyclization in dihydrooxazole series (44)

Hindrance at the position C_2 or C_5 of the starting imine (**153**) appears to decrease the *O*-cyclization reaction yield of **154**, while controlling the stereochemistry of the final products (Table 6).

Table 6 *O*-cyclization in the formation of γ-oxavalerolactams (equation 44)

Entry	*Imine*	*Product*	R^1	R^2	R^3	*Yield (%)*	dr[a] (*trans*:*cis*)
1	**153a**	**155a**	CH_3	CH_3	CH_3	60	–
2	**153b**	**155b**	CH_3	$-(CH_2)_5-$		42	–
3	**153c**	**155c**	C_6H_5	CH_3	CH_3	44	83:17
4	**153d**	**155d**	C_6H_5	$-(CH_2)_5-$		48	85:15
5	**153e**	**155e**	CH_3	$CH(CH_3)_2$	H	29	33:67
6	**153f**	**155f**	CH_3	$C(CH_3)_3$	H	25	39:61

[a]Diastereomeric ratio determined from ^{1}H-NMR spectra of the crude product.

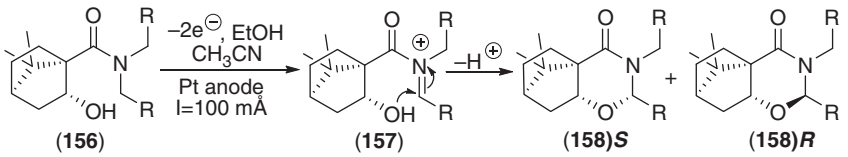
The *O*-cyclization processes of hindered amidoalcohols have previously been described. In this type of reaction, a highly diastereoselective anodic oxidation is seen (Table 7).[63]

Table 7 *O*-cyclization via intramolecular anodic oxidation (equations 45 and 46)

Entry	*Substrate*	*Electric charge (F)*	*R (or n)*	*R (or n)*	*Product*	*Yield (%)*	dr[a] (*S*:*R*)
1	**156a**	3.50	$-(CH_2)_3-$		**158a**	67	100:0
2	**156b**	3.50	H	H	**158b**	86	74:26
3	**156c**	3.50	CH_3	CH_3	**158c**	74 (14)[b]	58:42
4	**156d**	3.50	$-(CH_2)_2-$		**158d**	62	100:0
5	**159a**	5.00	0	0	**162a**	50 (32)[b]	25:75
6	**159a**	6.00	0	0	**162a**	49 (11)[b]	25:75
7	**159a**	6.50	0	0	**162a**	56 (09)[b]	25:75
8	**159a**	7.00	0	0	**162a**	74	25:75
9	**159a**	7.00	0	0	**162a**	32 (21)[b]	25:75
10	**159a**	7.00	0	0	**162a**	58	25:75
11	**159a**	7.00	0	0	**162a**	60	30:70
12	**159b**	3.50	1	1	**161b**	00 (93)[b]	–
13	**159b**	7.00	1	1	**161b**	40 (50)[b]	40:60

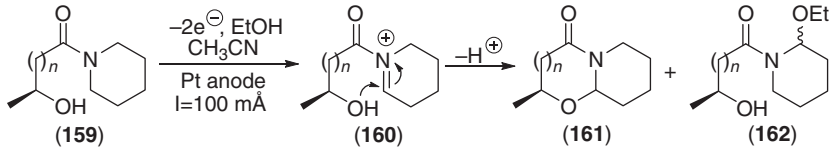
[a]The ratio was analyzed by 400 MHz NMR spectrum.
[b]In some cases the recovery starting material was observed.

In another example, tertiary amidoalcohols (**156**) containing isoborneol as bulky chiral entity were subjected to electrochemical oxidation under controlled conditions leading to cyclization products (**158**) via the *N*-acyliminium ion intermediates (**157**) with good diastereoselectivity (equation 45). For amides derived from piperidine (**156a**) and pyrrolidine (**156c**), the *O*-cyclization reaction became diastereospecific. In addition, the results of treatment of substrates (**159**), with different chain lengths, under identical electrochemical cyclization conditions, depend on the size of the side chain bearing the alcohol function (equation 46).



(45)

Electrochemical *O*-cyclization in chiral tertiary amido alcohols



(46)

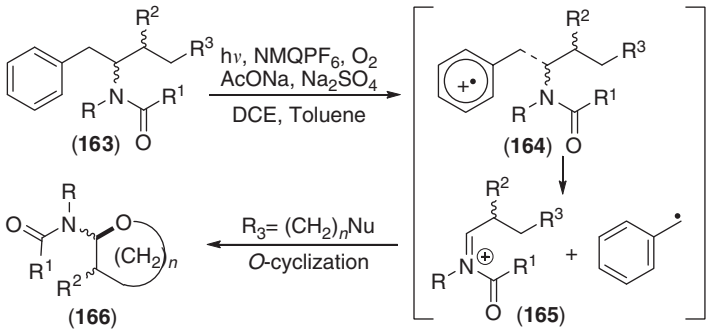
Electrochemical *O*-cyclization in chiral tertiary amido alcohols

Secondary or tertiary homobenzylic amides and carbamates of type (**163**), after the monoelectronic photochemical oxidation of the aromatic ring, and not of the carbon in the α-position of nitrogen (**164**), undergo a radical cleavage reaction to form *N*-acyliminium ions (**165**) while releasing a stable benzyl radical (Table 8).

Table 8 Homobenzylic amide electron-transfer induced *O*-cyclization (ETIOC) (equation 47)

Entry	*Substrate*	*R*	R^1	R^2	R^3	*Product*	*Yield (%)*	dr[a] (trans:cis)
1	**163a**	H	C_6H_{13}	H	$(CH_2)_2OH$	**166a**	75	–
2	**163b**	CH_3	C_6H_{13}	H	$(CH_2)_2OH$	**166b**	71	–
3	**163c**	H	C_6H_{13}	(*R*) CH_3	$(CH_2)_2OH$	**166c**	75	2.3:1
4	**163d**	CH_3	C_6H_{13}	(*R*) CH_3	$(CH_2)_2OH$	**166d**	67	>19:1
5	**163e**	H	C_6H_{13}	H	$(OCH_2)_2CH_2TMS$	**166e**	69[b]	No cyclisation
6	**163f**	H	C_6H_{13}	H	OCH_2O–THF	**166f**	69	–
7	**163g**	H	C_6H_{13}	H	$(CH_2)_2NHSO_2Ar$	**166g**	64	–
8	**163h**	H	Boc	(*R*) OCH_3	OCH_2O–THP	**166h**	63	2:1
9	**163i**	CH_3	Boc	(*R*) OCH_3	OCH_2O–THP	**166i**	–[c]	–

[a]The ratio was analyzed by 300 MHz NMR spectrum.
[b]No cyclization occured but only α-hydroxy lactam was isolated.
[c]The product decomposed on oxidation.



(47)

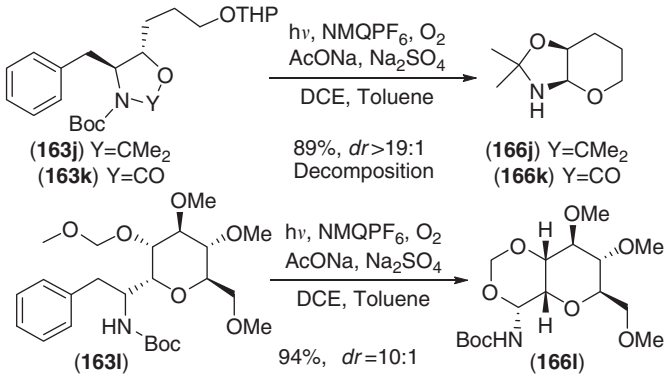
Mechanism of homobenzylic amide electron-transfer induced *O*-cyclization

Furthermore, the presence of a nucleophile, especially oxygenated, close to the cationic center, as in the case of $R^3=(CH_2)_nOR$, generates an intramolecular *O*-cyclization reaction that leads to acyl aminal (**166**), either racemic or chiral.[64]

These results emphasize the usefulness of a photooxidation agent (*N*-methylquinolinium hexafluoroborate ($NMQPF_6$)) that can act as a catalyst when oxygen is introduced into the reaction medium, or in an original fashion under aerobic conditions.

By incorporating an oxygen atom into the homobenzylic position of the starting substrate (**163j,k**, $Y=CMe_2$, CO), a photooxidation reaction and an electronic transfer (ETIOC) leads to the *O*-cyclization of an *N*-acyliminium salt intermediate into **166** (equation 48). However, in the case of a cyclic carbamate as part of the starting substrate (**166j**, Y=CO), the reaction product is not stable and decomposes. This is also effective with a polyoxygenated and highly acid-sensitive substrate (**163l**). The

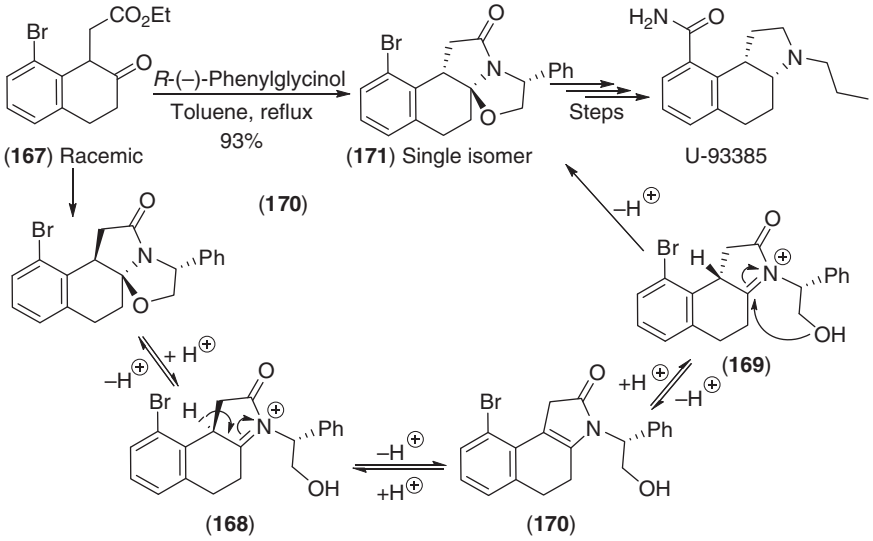
amidotrioxadecaline product (**166l**) isolated in excellent yield and good diastereoselectivity is present in the structure of some complex natural products with broad interests.



(48)

Incorporation of oxygen at the bis-homobenzylic position during electron-transfer induced *O*-cyclization

To complete this section of intramolecular *O*-cyclization reactions, it is worth noting their importance in the industrial context, especially for the pharmaceutical industry.[4c]



(49)

Application of *O*-cyclization in industrial large-scale production of U-93385

For example, Ennis and colleagues from the pharmaceutical company Pharmacia & Upjohn Inc.[65] have shown that condensation of the racemic ketoester (**167**) with the (R)-(–)-phenylglycinol produces the tetracyclic system (**171**) in 93% yield. The product is obtained as a single isomer, the absolute configuration of which has been determined and is illustrated by structure (**171**).

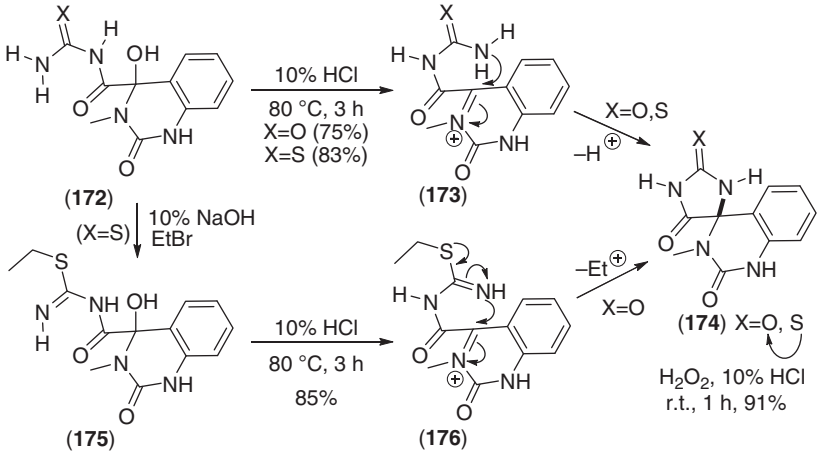
The researchers explain that this stereochemistry requires the formation of two *N*-acyliminium ions (**168**) and (**169**), in equilibrium in an acid medium via enamidone (**170**). Thermodynamic control leads to *O*-cyclization of (**169**) and then to the stereoisomer product (**171**). Subsequent functional modifications have permitted access to the target U-93385, which is a potent serotonin receptor-1A agonist. This chemistry has been validated and used to produce compound U-93385 and other similar products, on a large scale (multikilogram).

2.17.5 Azacyclization of *N*-Acyliminium Cations

The C_{sp3}–N bond has the least energy compared with the three C–C, C–N, and C–O bonds even if its length is between those of C–O and C–C bonds. It is highly polarized and localized on the side of the nitrogen atom. This helps the formation of hydrogen bonds in consequence of which many compounds containing such C–N bonds are soluble in water. Within *N*-acyliminium ion chemistry, the use of the nitrogen atom as an internal nucleophile to form ultimately a C–N bond requires in some cases its protection unlike the C and O atoms. This constitutes a possible constraint encountered in this chemistry.

2.17.5.1 Syntheses of Quinazoline Series

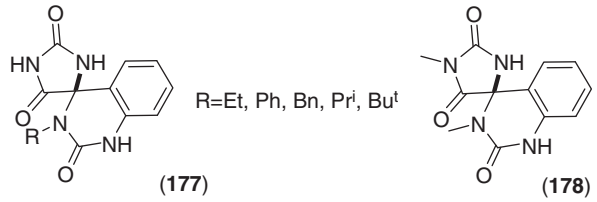
Spiroquinazolin-2-ones bearing a hydantoin pattern showed significant reducing properties of sugars potentially useful for diabetes treatment. To study the structure–activity relationships of these compounds, many synthetic routes have been explored from easily accessible and inexpensive raw materials, including ureas or thioureas.[66] The resulting hydroxy lactams (**172**) lead directly to the spirocompounds (**174**) in acidic medium by azacyclization of the *N*-acyliminium cation (**173**). An alternative route starting from isothiourea (**215**) has been developed leading to similar results (equation 50).[67]



(50)

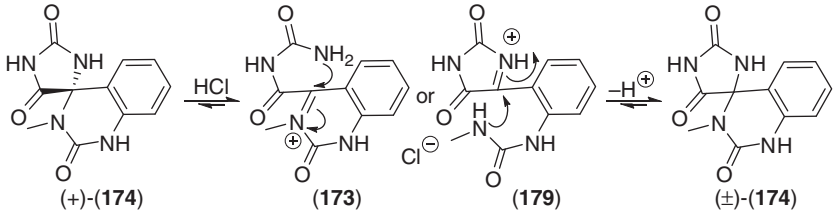
Intramolecular azacyclization in quinazoline series

The Me group linked to the nitrogen atom may be replaced by different substituents such as Et, Ph, Bn, Pr^i, and Bu^t, and the reaction was generalized to monosubstituted (**177**)[66,67] and disubstituted ureas (**178**; Scheme 5).[68]



Scheme 5 Compounds in quinazoline series.

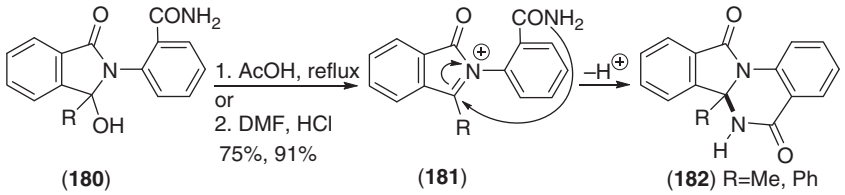
Within the same program, the search for a leader compound required the synthesis of enantiopure products. Typically, the optically resolved spiroquinazoline, via the brucine (the most effective chiral base used in this case), leads to two enantiopure isomers, and biological tests have shown that (*R*)-(+)-(**174**) was the most active. As for the racemization of the inactive enantiomer, it is performed under acidic conditions (HCl). Cleavage of the optically active *N*,*N*-aminal (**174**) can occur in two ways, providing both the *N*-acyliminium salts (**173**) or (**179**); their azacyclization leads to the racemic mixture (±)-(**174**).



(51)

Optical resolution/racemization via azacyclization in quinazoline series

Quinazolines fused to isoindolone ring (**182**) were obtained easily by intramolecular azacyclization of (**181**), isolated from the treatment of the hydroxy lactam (**180**) with an acid (equation 52).[69] It is important to note that the low nucleophilicity of nitrogen, and the steric hindrance of the cationic center (R=Me, Ph) have no impact on the profile and the yields of the azacyclization reaction.

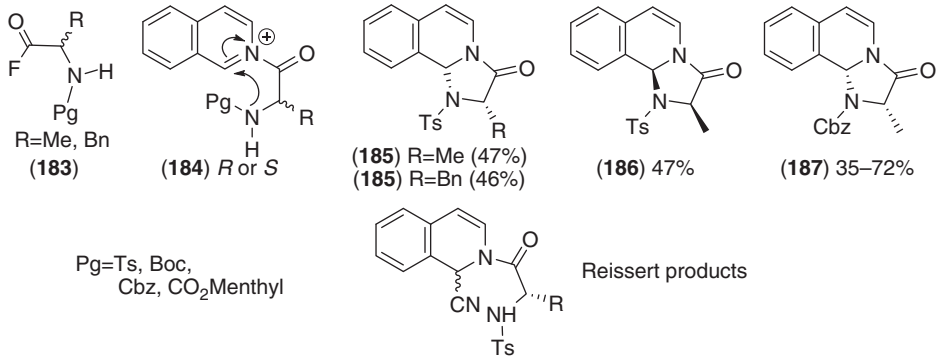


(52)

Intramolecular azacyclization in quinazoline series

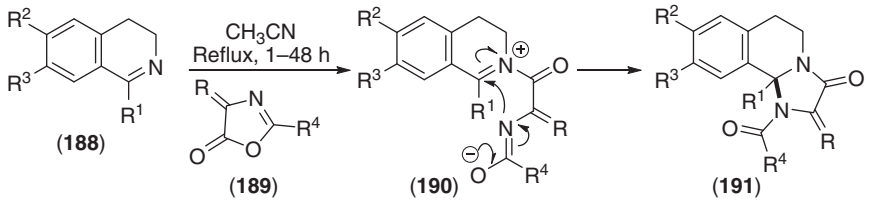
2.17.5.2 Syntheses of Quinolines and Isoquinoline Series

During the access to Reissert products by reaction between isoquinoline and TMSCN (e.g., $AlCl_3$ cat, TMSCN, −78 °C), Liebscher and collaborators have shown that chiral amino acid fluorides (**183**) *R* or *S*, used as chiral auxiliary, do not lead to the expected 1-cyanoquinolines (Reissert products; Scheme 6). The reaction leads exclusively to **225**, **226**,[70] and **227**[71] with standard yields but with excellent diastereoselectivity (>95:5) (Scheme 6). In these reactions, it seems that the competitive process of intramolecular azacyclization versus intermolecular cyanation is only taken into consideration. It should also be noted that the reaction progression can be changed in favor of the intermolecular version when the protecting group is different from the Ts or the Boc group.



Scheme 6 Intramolecular azacyclization in isoquinoline series.

Similar annulation reactions, starting from dihydroisoquinolines (**188**) and polysubstituted azalactones (**189**), provide easily and directly highly substituted imidazoloisoquinolin-3-ones (**191**) under neutral conditions, following a 'one-pot' procedure (equation 53).[72]



(53)

Intramolecular azacyclization in cascade process

The reaction mechanism suggests the passage through the cationic species (**190**) which then undergo an azacyclization reaction to provide products (**191**). Cation (**190**) is derived from the attack of the imine nitrogen of the starting dihydroisoquinoline (**190**) on the lactonic carbonyl group, followed by its opening. Finally, this approach is generalizable and has permitted quick access to a small library of heterocyclic systems, important in medicinal chemistry (Table 9).

The reaction of α-chloroformylarylhydrazines hydrochlorides (**192**) with quinoline in the presence of air (e.g., 90 °C, 2 h) leads after isomerization to a mixture of two products (**195**) and (**196**) in similar proportions (Table 10). Although the formation of **195** is explained by azacyclization of **193** followed by instantaneous oxidation of **194**, the formation of **196** requires the regression of the nitrogen cycle of *N*-acyliminium ion (**193**) in azeridine, rearrangement of the latter followed by a double cyclization and dehydrogenation. In the case of 3-methyl quinoline, this mechanism is blocked and in the reaction conditions, only the product (**195**) from the tandem azacyclization reaction of (**193**)/oxidation is isolated in good yields (Scheme 7).[73]

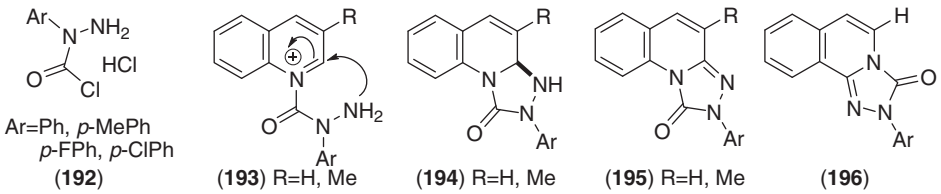
Table 9 Azacyclization in Reissert compounds with azalactones (**189**) (equation 53)

Entry	*R*	R^1	R^2	R^3	R^4	*Time (h)*	*Product*	*Yield (%)*
1	Ph–CH═	H	H	H	Ph	12	**191a**	88
2	3,4-di$OMeC_6H_3$–CH═	H	OMe	H	Ph	3	**191b**	94
3	3,4-di$OMeC_6H_3$–CH═	H	H	H	Me	24	**191c**	78
4	Ph–CH═	Ph	OMe	OMe	Ph	48	**191d**	17[a]
5	Ph–CH═	H	H	H	Me	24	**191e**	44
6	Ph–CH═	H	OMe	H	Me	3	**191f**	64
7	3,4-di$OMeC_6H_3$–CH═	H	H	H	Me	24	**191g**	47
8	Ph–CH═	Ph	OMe	OMe	Me	46	**191h**	4[a]
9	H,H	H	OMe	OMe	Ph	1	**191i**	18
10	H,H	H	OMe	H	Ph	1	**191j**	12
11	H,H	OMe	OMe	OMe	Ph	1	**191k**	34

[a]From 50% to 80% of the starting materials was recovered.

Table 10 Triazoloquinolin-3-ones from α-substituted hydrazines and quinolines (**Scheme 7**)

			Yield (%)	
Entry	*R*	*Ar*	*Product (**195**)*	*Product (**196**)*
1	H	Ph	42	32
2	H	*p*-MePh	40	35
3	H	*p*-FPh	33	33
4	H	*p*-ClPh	39	35
5	Me	Ph	82	–
6	Me	*p*-MePh	76	–
7	Me	*p*-FPh	72	–
8	Me	*p*-ClPh	40	–



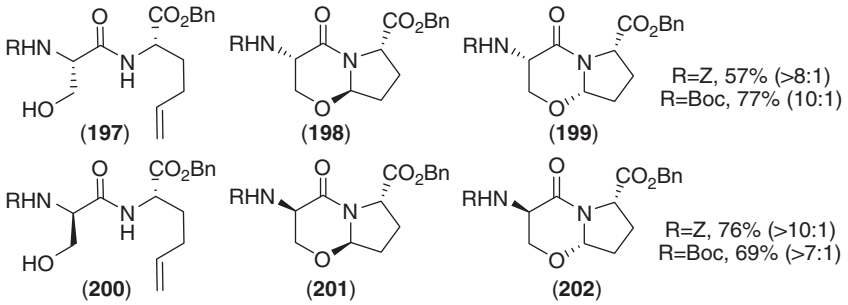
Scheme 7 Intramolecular azacyclization in isoquinoline series.

2.17.5.3 Synthesis of Peptidomimetics via Linear Amides

In the case of peptide analogs, the β-turn mimetics can bring new biological characteristics and increase the duration of their action. In this context, the nitrogen atom also offers opportunities to access to a wide variety of *N*,*N*-aminals.

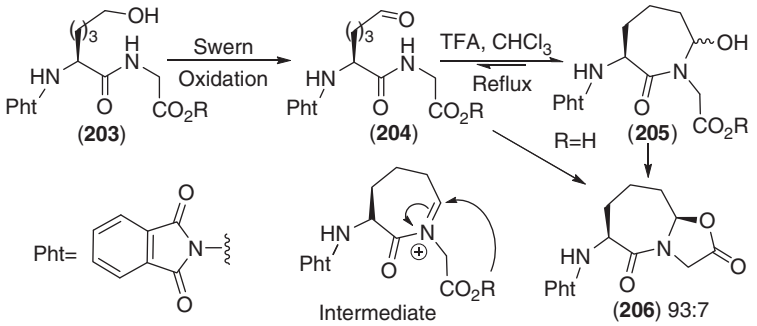
In this line, two reaction sequences provided bicyclic 5,6- and 5,7-membered *N*,*O*-acetals not mentioned above but used as models for *N*,*N*-aminals which are discussed below. Indeed, the linear amidoaldehydes cyclize easily to the corresponding hydroxy lactams in acidic conditions via a dynamic equilibrium of these two functions. These precursors of *N*-acyliminium ions are generally obtained by several methods and oxidation of olefin-amides proved to be an effective way.[74] A first application, made by Baldwin in the oxygenated series, afforded rapid access to a basic skeleton of bicyclic lactams (**Scheme 8**). Specifically, treatment of the amide-olefin (**197**) by $NaIO_{4cat}/OsO_4$ (2 equivalents) generates a crude mixture containing the amido-aldehyde. This amido-aldehyde, treated with an acid (e.g., TFA_{cat}, DCM, reflux), provides a mixture of two isomers (**198**) and (**199**) in a ratio > 8:1 (R=Z) and 10:1 (R=Boc), respectively. The chiral induction observed during the reaction is exercised by the ester group and the major product (**198**) is obtained by an oxacyclization at the opposite side of the ester group. The same observations were confirmed when (**200**) was transformed into bicyclic lactam isomers (**201**) and (**202**).[75]

A similar application uses a primary alcohol as the starting substrate (equation 54). Thus, the Swern oxidation of linear *N*-phthaloyl-amide (**203**) gives aldehyde (**204**). Refluxing **204** in a mixture $TFA/CHCl_3$ provides the expected product (**206**) in a



Scheme 8 Examples of tandem oxidation/intramolecular oxacyclization in dipeptide analogs.

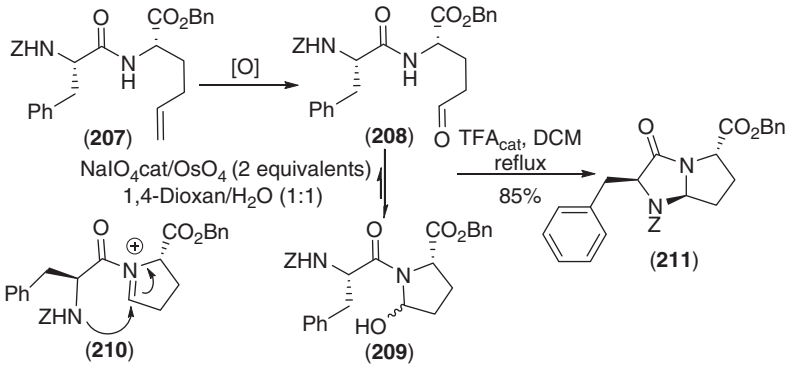
correct diastereomeric ratio of 93:7. The reaction proceeds according to a double cyclization including the *O*-cyclization of *N*-acyliminium salt intermediate with a carboxylic acid acting as an internal nucleophile (equation 54).[76]



(54)

Examples of intramolecular oxacyclization in cascade process

Similarly, the oxidation of **207** leads to **208** followed its treatment with a Brönsted acid (TFA) provides, via the *N*-acyliminium ion (**210**), bicycle (**211**) as the only product of double cyclization. To explore other conditions, salt (**210**) was generated by use of a Lewis acid (BF_3OEt_2) from the α-methoxy lactam synthesized from (**209**). This modification does not improve significantly the yield or the diastereoselectivity of the intramolecular azacyclization reaction (equation 55).[77]

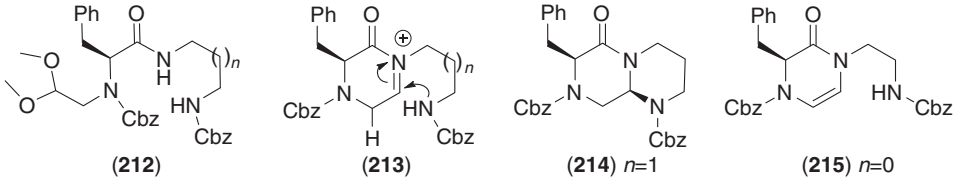


(55)

Intramolecular azacyclization in cascade process

A similarly easy approach has been applied to the synthesis of substituted octahydropyrazino[1,2-*a*]pyrimidin-6-ones (**214**) as a scaffold for the formation of bicyclic peptidomimetics (Scheme 9).[78] The rigidity of these β-turn mimetics allows better interaction of side chains with target proteins compared with the external peptidomimetic derivatives.

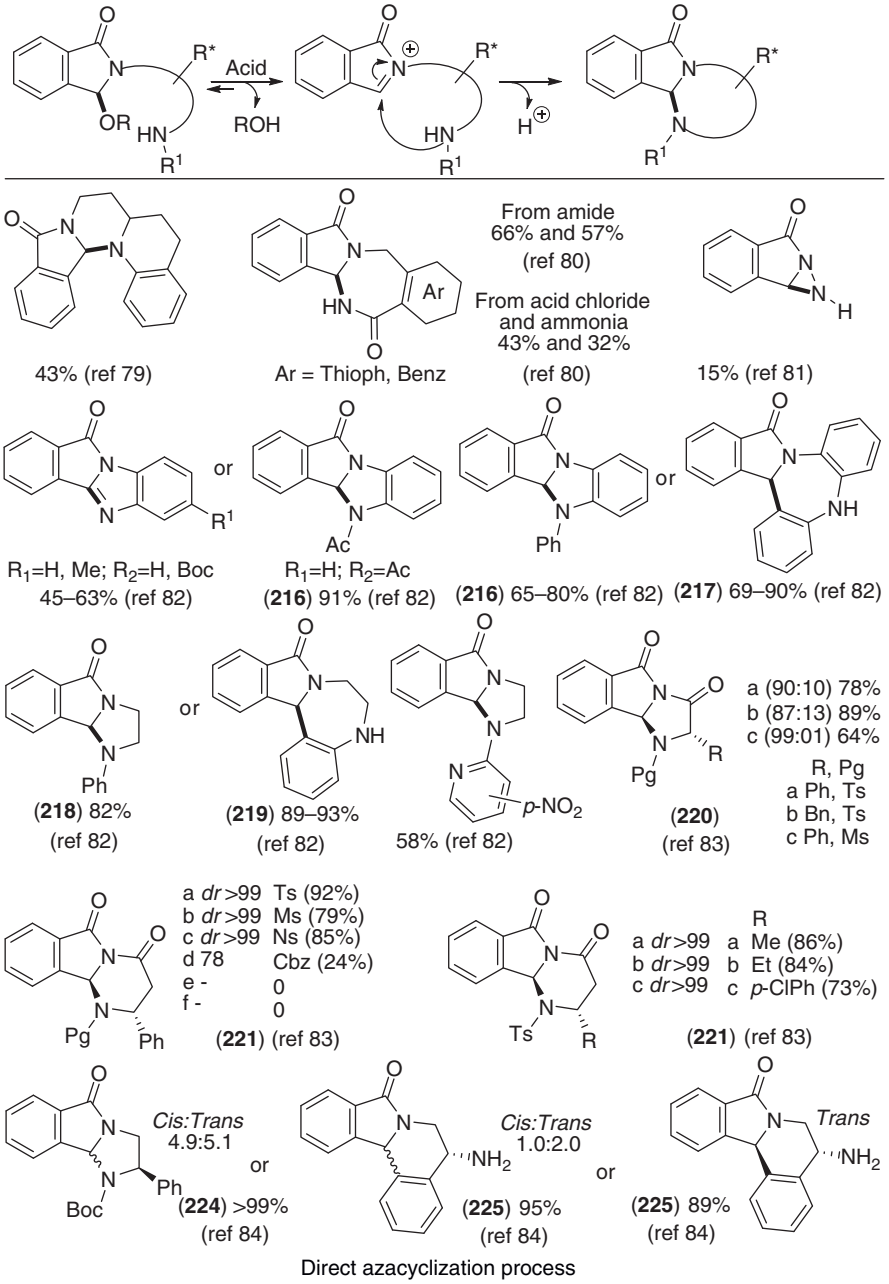
The amide (**212**, $n=1$) bearing an acetal function was reacted under the conditions of the double intramolecular cyclization reaction (e.g., HCO_2H) discussed above in equation 55, and leads to the bicyclic product (**214**) as a single diastereoisomer. It seems that the azacyclization reaction of *N*-acyliminium ion (**213**) is the result of a thermodynamic control. When $n=0$, the same reaction sequence does not provide the bicyclic product but enamidone (**215**) exclusively. This results from the very competitive deprotonation of the *N*-acyliminium ion (**213**) intermediate to the detriment of the intermolecular cyclization reaction (Scheme 9) and illustrates the ease of obtaining 5:6 bicyclic systems compared with 6:5 systems.



Scheme 9 Oxidation/intramolecular azacyclization tandem in dipeptide analogs.

2.17.5.4 Azacyclization of Isoindolinone Series

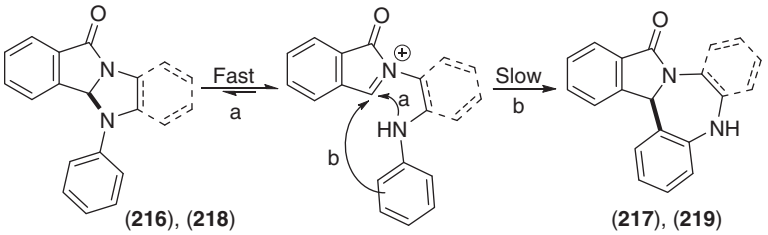
The nucleophilicity of the nitrogen atom was used in azacyclization reactions in the case of isoindolinone both in racemic and chiral series.[79–84]



(56)

The results shown in (equation 76) deserve some comments. In the case of (**216–219**), a broad screening of acidic cyclization conditions was carried out. These have not only allowed to find the best cyclization conditions but also have emphasized, in the

case of a π-cationic cyclization reaction competitive to azacyclization, a kinetic control versus a thermodynamic one (equation 57). Under well-chosen conditions, kinetic (benz)imidazo[2,1-*a*]isoindolones (**218**) and (**216**) or the thermodynamic isoindolo[1,4] benzodiazepines (**217**) and (**219**) can be isolated exclusively.[82]

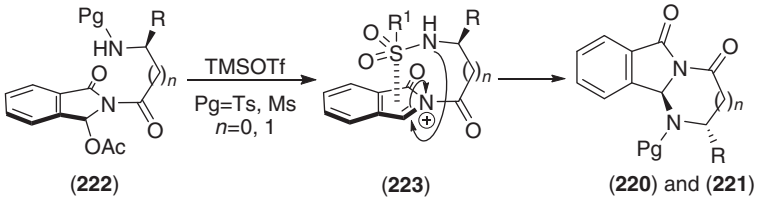


(57)

Kinetic versus thermodynamic control leading to fused *N*,*N*-aminal isoindolones

A similar kinetic versus thermodynamic control (**224** vs. **225**), depending on the nature of the acid used was also obtained in chiral series (equation 56). This fact is particularly present when the starting α-hydroxy lactam bears two nucleophiles, nitrogenated and π-aromatic systems, which are potentially competitive (equation 56).[84]

The impact of the protecting group on the intramolecular azacyclization reaction in racemic and chiral series has recently been published by Yamada.[83] In this study, AM1 calculations of all the obtained conformers were optimized and have shown that the fragments N-Pg with Pg=Ts, Ms are located on the same side of the *N*-acyliminium ion intermediate (**223**) (equation 58). This transition state provided the cyclic products (**220**) and (**221**) in *trans* configuration exclusively. With other protecting groups for which this interaction *N*-acyliminium ion/sulfone function was absent, the high diastereoselectivity of the reaction was not obtained.

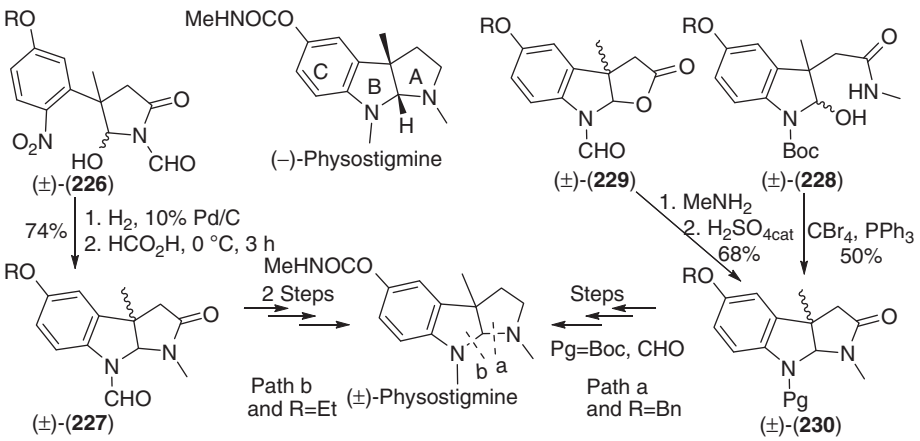


(58)

Key of the stereochemical outcome of some azacyclization process

2.17.5.5 Azacyclization in Total Synthesis

A first target was physostigmine, also called eserine, extracted from the calabar bean. The anticholinergic properties of this chiral alkaloid and its clinical use led to five synthetic approaches; and two chiral versions have been described (equation 59). In the racemic version, basically two main synthetic routes have been proposed both based on the generation of a C–N bond forming either the B ring or the A ring of physostigmine. The first approach (path b), uses the nitro group reduction/aza-intramolecular cyclization of (**226**) in tandem reaction to access to the tricyclic ring (**227**) considered as the key precursor in the synthesis of the targeted alkaloid.[85] The starting material (**226**) was obtained by regioselective reduction of a carbonyl function of the imide, and is composed of two diastereoisomers in a 3:1 ratio. The cyclic product (**227**) is also a mixture of two rotamers at the formyl group in a ratio 6.5:3.5.

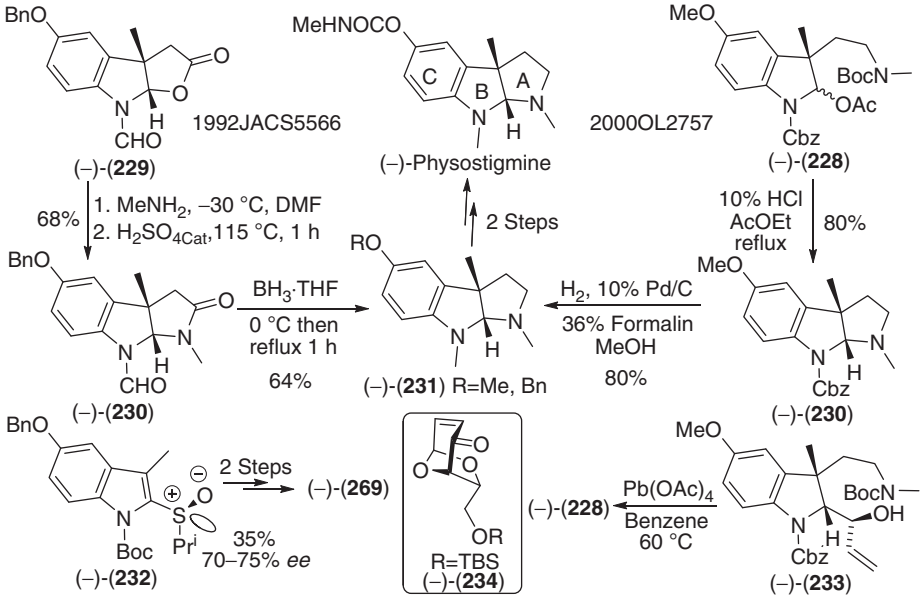


(59)

Pathways of total synthesis of racemic physostigmine

Path a corresponds to two similar approaches starting from the amide-hydroxy lactam (**228**) or lactone-amide (**229**).[86] Neutral conditions using the mixture CBr_4/PPh_3 led to the desired product (**230**) in a yield of 50%. An alternative method starting from **229** allowed quick access to target product (**230**). Cleavage of **229** by methylamine provides an amide-hydroxy lactam intermediate whose azacyclization in the sulfuric acid medium affords **270** (68% in two steps). Additional reduction manipulations of the two carbonyl groups (BH_3·THF), deprotection of the phenol group (Ra-Ni), and carbamate formation (Na_{cat}, MeNCO) lead to the racemic target physostigmine in three steps starting from **270** (68%).

The chiral (–)-butyrolacto-indoline (**229**) required for the synthesis of (–)-physostigmine (equation 60) was synthesized in two steps by transfer of chirality of chiral sulfoxides, and the best result was obtained with *S*-(–)-2-(isopropylsulfinyl)indole (**232**). The substrate *S*-(–)-(**229**) thus obtained, despite the low *ee*, is transformed into (–)-(**231**) via (–)-(**230**) in two lactamization steps followed by a double reduction.[86] The (–)-physostigmine of natural configuration is ultimately obtained after two well-known reduction steps and formation of the carbamate group on the benzene ring.

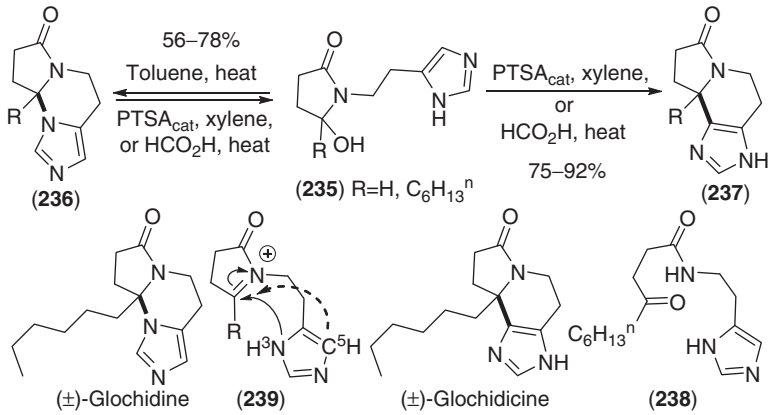


(60)

Pathways for total synthesis of (–)-physostigmine

A second total synthesis of this alkaloid (equation 60),[87] long compared with the previous one, has been designed using the chiral system (–)-(**234**). The *α*-acetoxy lactam (**228**) was obtained after oxidation of the allylic alcohol of (–)-(**273**). Treatment of **268** under acidic conditions (HCl) affords the tricyclic system (–)-(**230**) via the tandem Boc group decomposition/azacyclization (80%). Cbz deprotection sequence/*N*-methylation (by Clarke–Eschweiler reaction) of the isoindoline nitrogen is then realized in one step in 80% yield and provides the common intermediate (R = Me) (–)-(**231**) with good stereochemistry. Finally, it should be noted that two advantages are recognized to this approach compared with the previous ones, even if it is longer: (1) possible access to another bioactive alkaloid, the (–)-physovenine, isolated from the same Calabar bean and (2) the diastereomeric excesses obtained along the reaction sequence are generally better.

The study of the regioselectivity of the *N*-cyclization reaction versus *π*-aromatic cyclization of an *N*-acyliminium ion in imidazole series provided easy access to two alkaloids, the (±)-glochidine and (±)-glochidicine (equation 61).[88] In this perspective, the behavior of the *α*-hydroxy lactam (**235**) was evaluated.

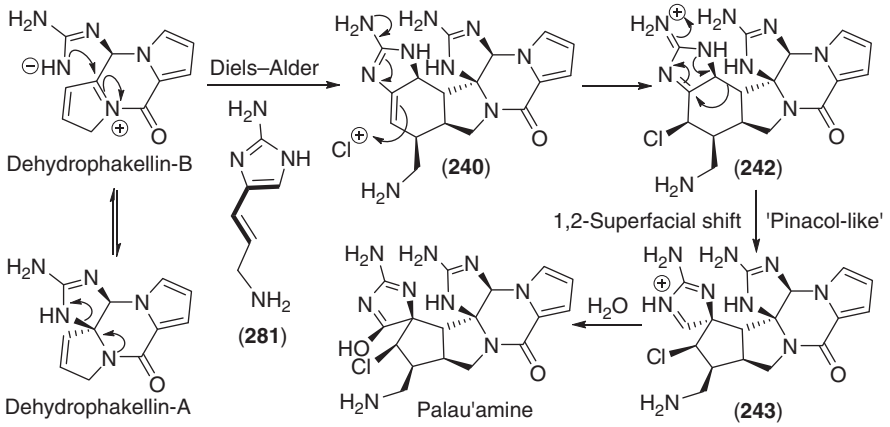


(61)

Pathways for total synthesis of (±)-glochidine and (±)-glochidicine

The results obtained after treatment of the α-hydroxy lactam (**235**) (R=H) under thermal cyclization conditions, or under protic acidic conditions (HCO_2H and PTSA), in catalytic amount or not, show that the azacyclization product (**236**) is the kinetic product, irreversible up to 50 °C in toluene. The reaction does not require acid catalysis. Beyond this temperature, the same operating conditions lead to equilibrium of this process, and the formation of compound (**277**) as the only final product of the reaction. The *N*-acyliminium ion (**239**) is the center of these kinetic versus thermodynamic transformations. The reaction conditions were identified and successfully applied to the total synthesis of alkaloids (±)-glochidine and (±)-glochidicine ($R=C_6H_{13}{}^n$). It should be noted that alcohol (**235**) cannot be isolated pure as it exists in equilibrium with its stable open form (**238**). Cyclization of the mixture leads exclusively to the tricyclic product resulting from the formation of the $C–N_3$ bond for (±)-glochidine or the $C–C_5$ bond for (±)-glochidicine.

The search for the biosynthetic mechanism of alkaloids called 'oroidiniens' (or pyrroloimidazole alkaloids), including the palau'amine and its congeners, has led to several assumptions and suggestions. In this perspective, biogenesis assumptions of these compounds have been formulated, based on the reactivity of the *N*-acyliminium ion (this is commonly called dehydrophakellin-B) in equilibrium with dehydrophakellin-A (equation 62).[89]

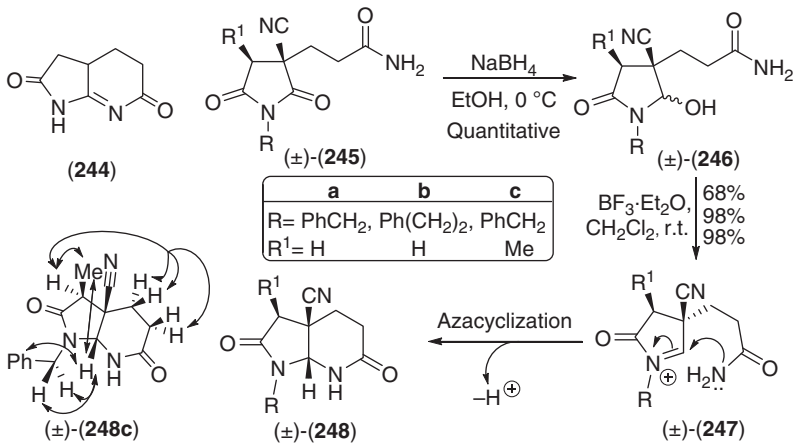


(62)

Kinnel and Scheuer's proposed biosynthesis of palau'amine

The scheme begins by a Diels–Alder reaction between the real dienophile dehydrophakellin-B and aminoimidazole (**241**), in tandem with an azacyclization reaction. The resulting chlorination of (**240**) initiates the cyclic contraction of **242** via a pinacolic type 1,2-migration, leading to the intermediate (**243**). This compound has an iminium center, which is trapped by water, thus providing the palau'amine. Other possible biosyntheses exploiting this type of scheme have been proposed.[90]

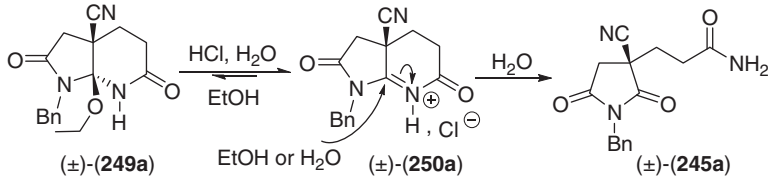
The product (**244**), issued from the defensive secretion of centipedes *Rhinocricus padbergi*, belongs to the 7-azaindole family. A synthetic approach to analogs of this product, in order to realize RSA studies, was undertaken starting from polysubstituted imides containing a primary amide (±)-(**245**) (equation 63). Their regioselective reduction leads quantitatively to a mixture of two inseparable diastereoisomers (±)-(**246**). These nonisolated compounds, treated in an acid medium (BF_3OEt_2), provide expected (±)-(**248**) via an azaintramolecular cyclization of stable *N*-acyliminium ions (±)-(**247**) in very good yields and high diastereoselectivities ($dr>95\%$).[91] Finally, oxidation attempts of (±)-(**248**) in order to access **244** have not been successful.



(63)

Access to defensive secretion of millipede *Rhinocricus padbergi* core

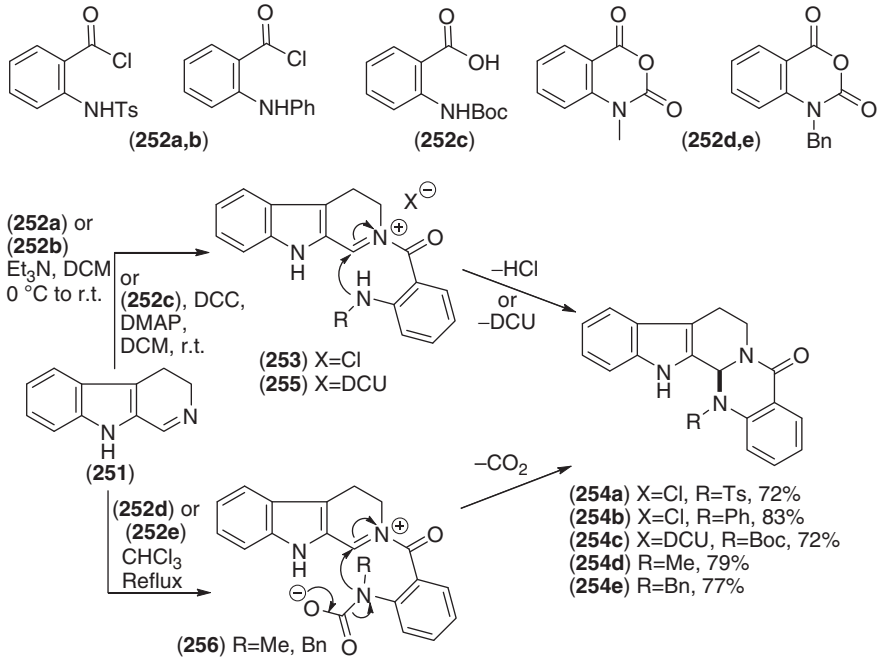
The reactivity of compound (±)-(**249**), obtained from the trapping of (±)-(**240**) by ethanol, was studied in order to access the corresponding product (**244**). All attempts of intermolecular trapping by nucleophiles derived from the *N*-acyliminium ion (±)-(**240**), obtained from (±)-(**249**) in an acid medium, have been inconclusive except in the case of ethanol and water. In the latter case, only imide (±)-(**245**) resulting from the hydrolysis of (±)-(**250a**) was isolated (equation 64).



(64)

Mechanistic pathways leading to substituted imides (±)-(**245**) versus **244**

In a project dedicated to the synthesis of potential anticancer luotonines, the rutaecarpines were chosen as intermediates that can provide these products in few steps including, in particular, the Witkop–Winterfeldt oxidation reaction as the second key step.[92] Rutaecarpine synthesis is performed by an *N*-alkylation/intramolecular cyclization tandem process from imine (**251**) and an acylating agent with a protected aromatic nitrogen (equation 65).



(65)

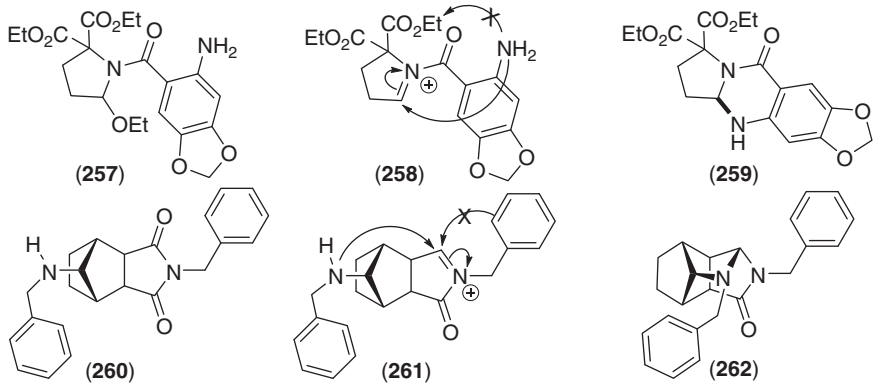
Rutaecarpines including the Topo-I poison natural evodiamine (**254d**)

The acylation of imine (**251**) by the anthranilic acid chlorides (**252a,b**) in the presence of triethylamine generates **253,** which undergoes an azacyclization reaction instantly to give the derivatives of rutaecarpine alkaloid (**254a,b**). Treatment of **251** with the *N*-Boc anthranilic acid (**252c**) in peptide-coupling conditions using DCC catalyzed by DMAP leads to quinazolino-*β*-carboline (**254c**). In the latter case, the formation of an *N*-acyliminium ion intermediate (**255**) having the DCU as anion should be noted.

Without having a short and efficient synthesis to access *N*-methyl and *N*-benzyl anthranilic acids, isatoic *N*-methylated (**252d**) or *N*-benzylated (**252e**) anhydrides were used in refluxing chloroform. Expected products Evodiamine (**254d**),[93] as anticancer and topoisomerase-I poison, and (**254e**) were thus obtained in good yields. Finally, this approach has the advantage of using very reactive substrates and is currently the most direct and shortest method that leads to this type of products.

2.17.5.6 Particular Azacyclization Reactions

Regarding the specific methods, the behavior of the amino ether (**257**) is quite interesting. Indeed, its treatment in acid medium (e.g., HCl, benzene, r.t.) yields the azacyclization product (**259**) as the exclusive product of the reaction (**Scheme 10**).[94] It seems that only the *N*-acyliminium ion (**258**) is taken into consideration and no trace of coupling product between the amine and ester is isolated from the reaction even if the polycyclic *N*,*N*-aminal (**259**) is reversible in acidic medium.

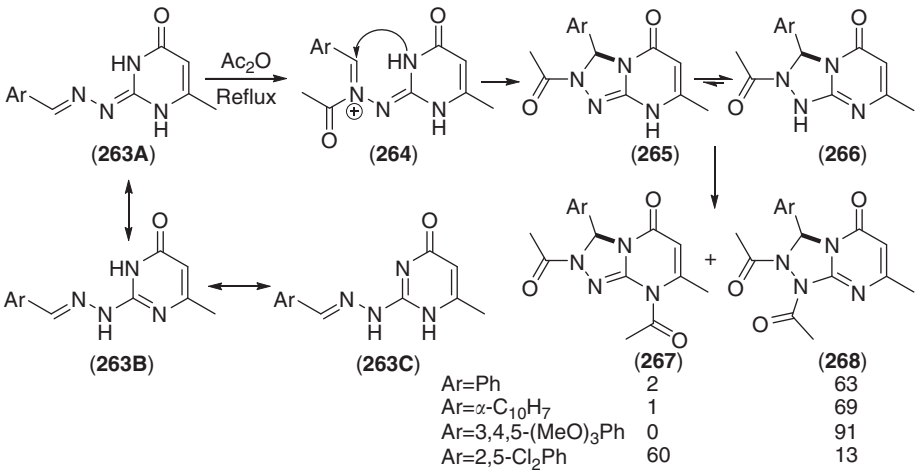


Scheme 10 Azacyclization as effective reaction in a competitive context.

Another example is that of the *N*-acyliminium ion (**261**) bearing two nitrogen and carbon nucleophiles. Its reaction does not lead to the π-cyclization product, more stable and irreversible, but to the reaction providing only the bridged cyclic product (**262**).[95] A congested cycle seems to be preferred in this cyclization reaction. It is also worth noting that the cyclic *N*,*N*-aminal (**262**) is formed in one step directly from imide (**260**) and that the final hydrolysis conditions cause the cyclization of **261** (e.g., $LiAlH_4$, THF, r.t., 96 h, 35%).

The treatment of hydrazono-pyrimidones (**263**) with acetic anhydride at reflux leads to a mixture of two separable triazolo[4,5-*a*]pyrimidine-4-ones (**267**) and (**268**), in different ratios but in good yields (equation 66).[96]

The existence of the three tautomeric forms **A**, **B**, and **C** of the starting hydrazones (**263**) was demonstrated by NMR and their reaction with acetic anhydride provides the *N*-acyliminium ions (**264**) which, after cyclization, lead to products (**265**), in equilibrium with their tautomeric forms (**266**). The acylation of the latter then gives the *N*-acylated products (**267**) and (**268**). These results also show that the azacyclization reaction is regiospecific as only the attack of N_3 takes place, and the most stable cyclized product seems to be in most cases that initiated via intermediate (**266**).

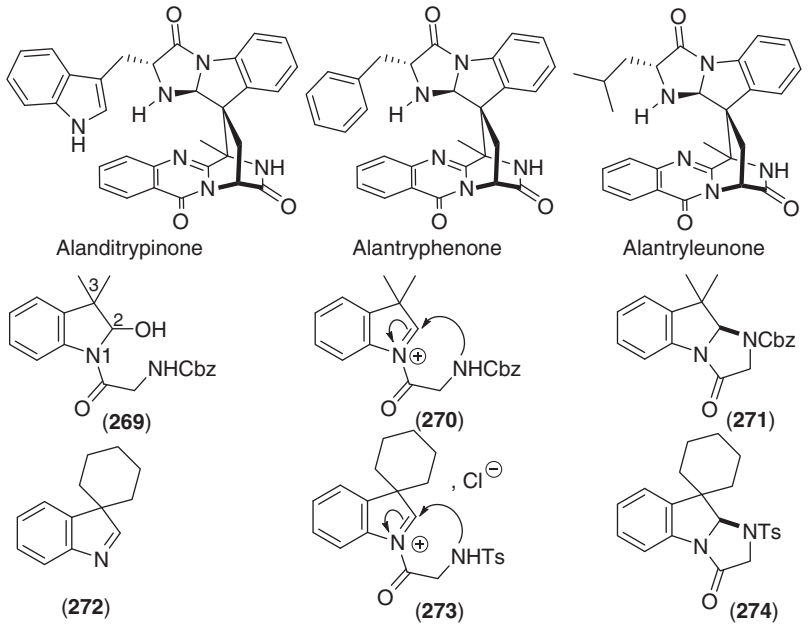


(66)

Tautomerism impact on azacyclization in polynitrogen heterocycles

Spiroimidazoloindolines are important units encountered especially in the structure of alkaloids of the spiroquinazoline family with various biological activities, such as alanditrypinone and alantryphenone. For a long time, a major challenge has been the establishment of an experimental procedure for introducing imidazoloindoline patterns on oxindole or their derivatives bearing two substituents in the C_3-position. The following scheme summarizes two strategies that have been developed and are directly applicable to the total synthesis or hemisynthesis of these spiroalkaloids (**Scheme 11**).[97]

The regioselective reduction of *N*-acylated oxindole (BF_3OEt_2 (excess), Et_3SiH (6 equivalents), DCM, −78 °C, 79%) leads to dimethyl carbinol (**279**). Its acid treatment (PTSA.H_2O, benzene, 80 °C, 30 min, 98%) provides imidazoloindoline (**271**) by intramolecular azacyclization reaction of (**270**). A similar *N*-acyliminium ion (**273**) was obtained according to a protocol in an even shorter duration. The generation of the similar *N*-acyliminium ion (**273**) has produced a tricyclic ring system (**274**) according to a short protocol. The reaction between the spiroindoline (**272**) and the appropriate acid chloride, the 2-(4-methyl-phenyl-sulfonamido) acetic acid chloride, in refluxing xylene gives the target system (**274**) in 62% yield.



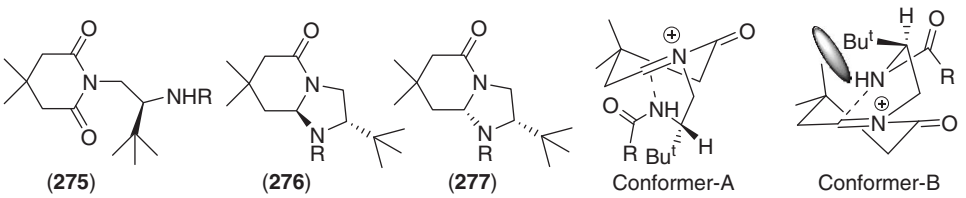
Scheme 11 Azacyclization in imidazoloindolines as model substrates.

The general procedure of regioselective reduction of imides to hydroxy lactams and the generation of *N*-acyliminium ion in the presence of an acid was applied to imides (**275**). Thus, their treatment by DIBAL-H or superhydride ($LiEt_3BH$) in cold DCM (−78 °C) provides directly and unexpectedly, a mixture of cyclic products (**276**) and (**277**) with ratios depending on the nature of the protecting group of the nucleophilic nitrogen (Table 11; Scheme 12).[98]

Table 11 Reductive azacyclization of imides (**275**) using super hydride (Scheme 12)

Entry	*Substrate*	*R*	*Product (**276**) (2S,4S)*	*Product (**277**) (2S,4R)*	*Yield (%)*[a,b]
1	**275a**	Boc^t	75	25	77
2	**275b**	Cbz	74	26	75
3	**275c**	Ac	61	39	63
4	**275d**	$COCF_3$	56	44	68
5	**275e**	SO_2Me	39	61	87

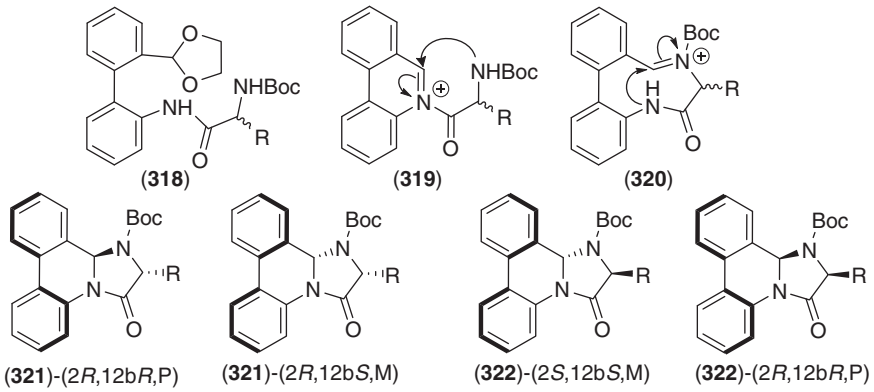
[a]The ratio was as determined by ^1H NMR analysis of the crude mixture.
[b]Total yield of the isolated products (**276**) and (**277**).



Scheme 12 Azacyclization in imidazoloindolines as model substrates.

The stereoselectivity observed for entries 1 and 2 (Table 11) is probably due to steric hindrance of Boc and Cbz^t groups, which disadvantages the conformer B and leads to the formation of (**276**) derivative. The less hindered groups trifluoroacetyl (entries 3 and 4) result in a lower stereoselectivity. In the case of methylsulfonyl (SO_2Me) protecting group (entry 5), it can be assumed that electrostatic repulsion between the oxygen atoms of the tetrahedral group SO_2 and lactamic C=O supports conformation A, leading to a reversal stereoselectivity compared with acetyl group.

The last azacyclization example discussed in this chapter focuses on obtaining chiral-fused biaryl compounds using the Meyers's standard protocol and describes the case of a particular *N*-acyliminium ion (Scheme 13).



Scheme 13 Cascade cyclizations of α-amino acid-based biaryls including azacyclization.

Thus, three pairs of enantiopure biaryls (**278**) were synthesized, and then treated with PTSA in acetone at room temperature. Depending on the chirality of the starting substrate, the products are obtained as two diastereoisomers (**281a**,**b**) and (**282a**,**b**) in different ratios (Table 12) with one major diastereoisomer.[99]

Table 12 Results of the cascade cyclizations of α-amino acid based biaryls (**278**) (Scheme 13)

Entry	*Substrate*	*R*	*Product (**321**)*	*Yield (%)*[a]	*Product (**322**)*	*Yield (%)*[a]	dr (***321:322***)	*Yield (%)*[b]
1	**318(*R*)**	Me	(2*R*,12b*R*,*P*)	16	(2*R*,12b*S*,*M*)	30	35:65	46
2	**318(*S*)**	Me	(2*S*,12b*R*,*P*)	33	(2*S*,12b*S*,*M*)	17	66:34	50
3	**318(*R*)**	Bu^i	(2*R*,12b*R*,*P*)	05	(2*R*,12b*S*,*M*)	30	14:86	35
4	**318(*S*)**	Bu^i	(2*S*,12b*R*,*P*)	51	(2*S*,12b*S*,*M*)	10	84:16	61
5	**318(*R*)**	Bn	(2*R*,12b*R*,*P*)	07	(2*R*,12b*S*,*M*)	40	15:85	47
6	**318(*S*)**	Bn	(2*S*,12b*R*,*P*)	43	(2*S*,12b*S*,*M*)	09	83:17	52

[a]Isolated yields of each product obtained after flash column chromatography on silica gel.
[b]Total yield of the isolated products (**281**) and (**282**).

These chiral biaryl *N*,*N*-aminals are formed by intramolecular azacyclization reaction of the *N*-acyliminium ion (**279**) generated *in situ*. The participation of the macrocyclic *N*-acyliminium ion (**280**) was rejected by conducting additional experiments, performed in anhydrous ethanol that played the role of external nucleophile. In these conditions, besides compounds (**281**) or (**282**), a α-ethoxy lactam, issued from the trapping of the *N*-acyliminium ion (**279**) by ethanol, is isolated in a large amount. Finally, in this chirality transfer study in biaryl systems, it has been shown that the cyclization of biaryl amide-acetals (**278**)***R*** is kinetically controlled, and the formation of the two diastereoisomers is performed by retaining the axial chirality.

2.17.6 Thia- and Selenacyclization of *N*-Acyliminium Ions

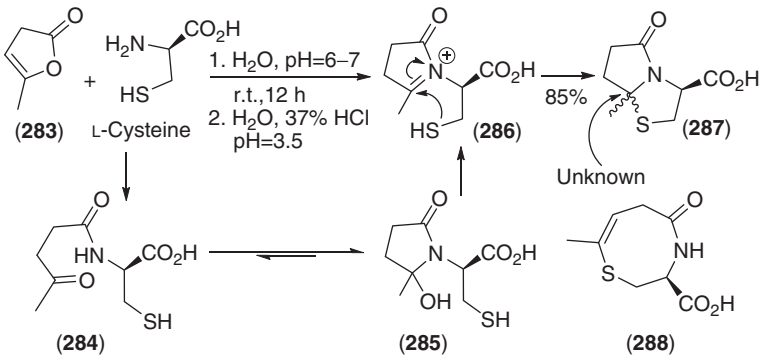
Although oxygen, sulfur, and selenium belong to the same column of the periodic table, there are many differences between these elements, especially concerning the C_{sp3}–O, C_{sp3}–S, and C_{sp3}–Se bonds. It should be noted in particular that, due to the large size of these two elements, the C–S (1.82 Å) and C–Se (1.98 Å) bonds are longer than the C–O bond (1.43 Å). On the contrary, they are less energetic than the C–O bond (E = 358 kJ mol^{-1}), with binding energies of E = 272 and 234 kJ mol^{-1}, respectively. For these reasons, combined with the orbital instability of these two atoms, linked to the presence of free orbitals unlike oxygen, organic compounds with C–S and C–Se bonds are more reactive and extremely important in organic synthesis.

2.17.6.1 Thiacyclization of *N*-Acyliminium Cations

The first example of thiacyclization was highlighted in a study on carcinogenicity of lactones, especially when they are unsaturated and are reacted with L-cysteine.[100]

The reaction of the 4-hydroxypent-3-enoic acid lactone (**283**) with L-cysteine was initially investigated by Cavallito and Haskell, and the structure 1,4-thiazocinione (**288**) was hastily attributed to the reaction product.[101]

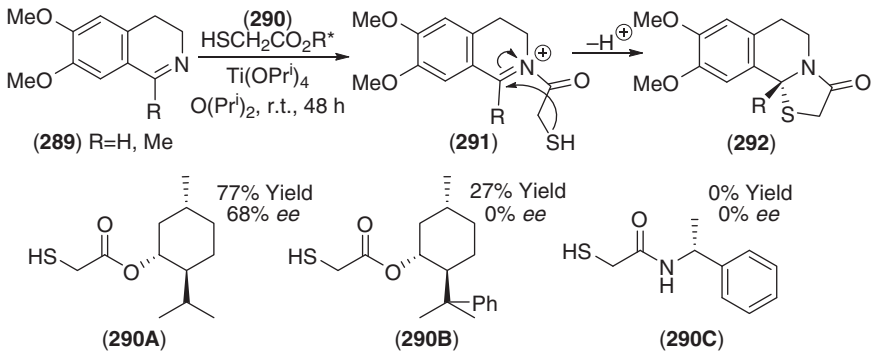
The synthetic potential of this reaction, in general, and of this cyclization, in particular, was revisited 23 years later, and has permitted to correct the structure (**288**) initially proposed. Indeed, the reaction mechanism search has shown that the product of condensation between lactone (**283**) and L-cysteine was pyrrolo[2,1-*b*]thiazole (**287**) obtained by intramolecular thiacyclization of the *N*-acyliminium ion (**286**). This is the result of dehydration of the hydroxy lactam (**285**) in equilibrium with the ketoamide (**284**), which can be isolated and characterized (equation 67).



(67)

Reaction of 4-hydroxypent-3-enoic acid lactone (**283**) with L-cysteine

In a project using sulfur-containing cyclic intermediates for the synthesis of alkaloids, Rozwadowska and collaborators[102] undertook asymmetric synthesis of dihydrothiazolo[2,3-*a*]-isoquinolinones (**292**) and the corresponding sulfoxides (equation 68).

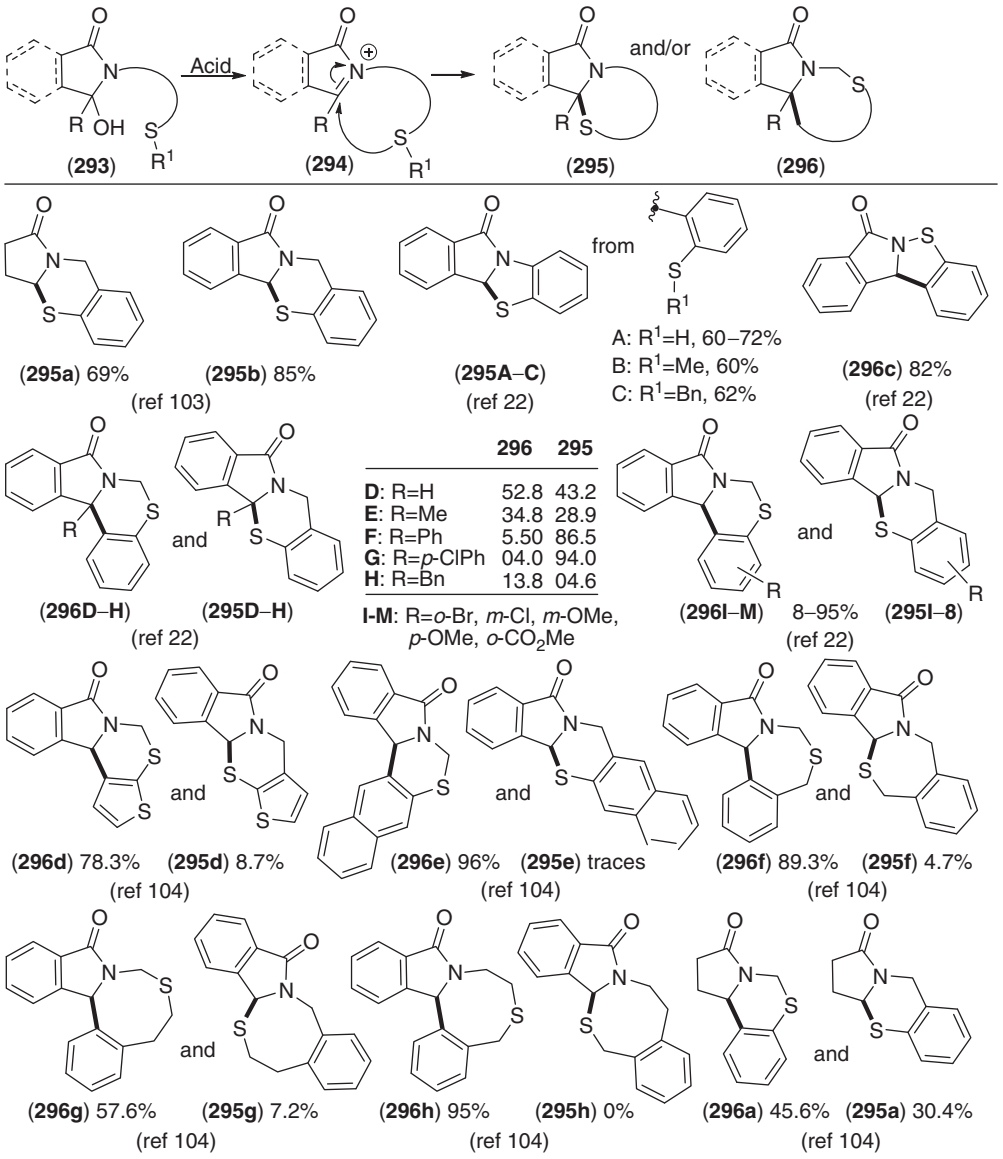


(68)

Enantioselective thiacyclization in dihydroisoquinoline system

The protocol used consists in the reaction of 3,4-dihydroisoquinoline (**289**) with a chiral thioglycolic ester (**290**), which begins by the formation of the salt (**291**) followed by its intramolecular thiacyclization. After an extensive screening of operating conditions (solvent, temperature, catalyst, and the nature of chirality inducer), the use of $Ti(OPr^i)_4$ in isopropylic ether seems to be the best condition to accede the target tricyclic system (**292**). The best yields (77%) and *ee* (68%) were obtained when the (–)-methyl thioglycolate (**290A**) was used, and a simple recrystallization from anhydrous ethanol gave enantiopure (*R*)-(+)-(**292**). Curiously, no chiral induction was observed with the two other thioglycolic esters (**290B**) and (**290C**), typically employed elsewhere for their excellent induction.

On the basis of the following reaction sequence, the nucleophilicity of sulfur atom has been extensively explored subsequently on α-hydroxy pyrrolidine and isoindoline lactams in acidic medium, in the presence of a solvent or not (equation 69).[22,103,104]



(69)

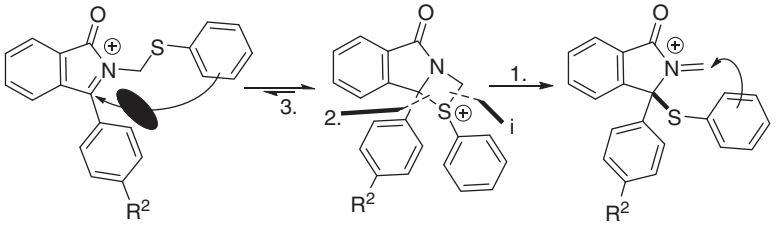
Thiacyclization process in pyrrolidine and isoindoline series[22,103,104]

In the context of thioether bond formation and/or cleavage in fused *N*,*S*-heterocyclic systems, the research group has reported preliminary results on pyrrolo[1,3]benzothiazines and isoindolo[1,3]benzothiazine. Thus, the treatment of *ω*-carbinol lactam (**293a**) in an acidic medium (e.g., Neat TFA, r.t., 24 h) led to pyrrolidino[1,3]benzothiazine (**295a**). The reaction is regioselective and proceeds via the tandem thiacyclization of the intermediate *N*-acyliminium ion, followed by debenzylation of the cyclic *N*,*S*-acetal salt formed. Under the same conditions, the *α*-hydroxy lactam (**293b**) furnishes the cyclization product (**295b**) following the same reaction sequence (85%).[103]

The reaction sequence has been applied to the synthesis of isoindolo[1,2-*b*]benzothiazolin-6-(10b*H*)-one (**295A**) starting from the *N*-arylated phthalimide with a sulfur atom in the ortho position, and protected by a methyl or benzyl, or in its free form. In the latter case, the crude reaction mixture resulting from the reduction of the imide is treated with 20% HCl or TFA for 12 h at room temperature. Under these conditions, only **295A** is isolated in good yields of 60% and 72%, respectively.[22] When the sulfur atom is protected by a methyl or benzyl, the *ω*-carbinol lactams issued from the reduction of imides are isolated, and their cyclization under acidic conditions affords thiacyclization products, via an *N*-acyliminium ion, followed by dealkylation. Although debenzylation releases a stable benzyl carbocation, the demethylation provides an unfavorable carbocation. The reaction in this case takes place anyway, and the product (**295A**) is obtained in a yield comparable to that observed in the two other cases. With particular *α*-hydroxy lactam (**293c**) with the phenylthio group attached directly to the nitrogen lactam, the cyclization reaction leads only to a single *π*-cationic cyclization product (**296c**), regardless of the employed acid-operating conditions.

Moreover, in an acid medium, 2,3-dihydro-3-hydroxy-*N*-(phenylthiomethyl)-1 *H*-isoindol-1-one leads to an inseparable mixture of two cyclic products (**296D**) and (**295D**) (5.5:4.5); the reaction mechanism is detailed in equation 14.[22] Therein, the azasulfonium ion formed by heterocyclization isomerizes to an endocyclic *N*-acyliminium ion precursor of (**296D**) by π-cationic cyclization and an exocyclic *N*-acyliminium ion precursor of (**295D**) by intramolecular thiacyclization. The impact of the substitution at the angular carbon on the intermediate azasulfonium salt formation, as well as on the two cyclization reactions was studied starting from the same hydroxy lactams (**293B-E**) with Me, Ph, *p*-ClPh, and Bn substituents.

The results show several important facts: (1) In the case of methyl substituents (**293B**) and benzyl (**293E**), a competitive deprotonation reaction takes place and leads to the major product in the case where R = Bn. (2) The more hindered the angular carbon, the more the thiacyclization reaction leading to products (**295C,D**) favored at the expense of π-cyclization. This high selectivity can be explained by a favorable approach of the cationic center by the aromatic of the form **298C,D** at the expense of form **297C,D** (equation 70).

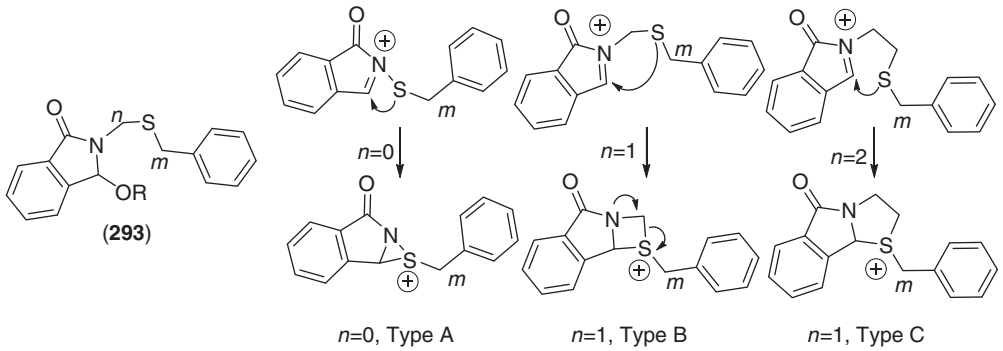


(70)

Thia- versus π-cyclization and *N*-acyliminium ion geometry in the case of **293C,D**

In the same study, it was shown that the isomerization process of the azasulfonium ion is sensitive to the nature of the substituent on the benzene ring. Moreover, the substitution in the ortho position exclusively promotes π-cyclization to the detriment of the thiacyclization. In the case of the metasubstitution, a mixture of two or four regioisomers was isolated. Although the thiacyclization reaction accompanies the π-cationic cyclization in the case of substituent Cl, only the π-cyclization is observed in the case of the substituent MeO, demonstrating that the electronic distribution is an important factor for this isomerization.[104] In the case where the benzene ring is replaced by a thiophene[105] or β-naphthalene,[106] the isomerization of the azasulfonium ion occurs and leads to two cyclization products (**296d,e**) and (**295d,e**); however, with only traces of product (**295e**).

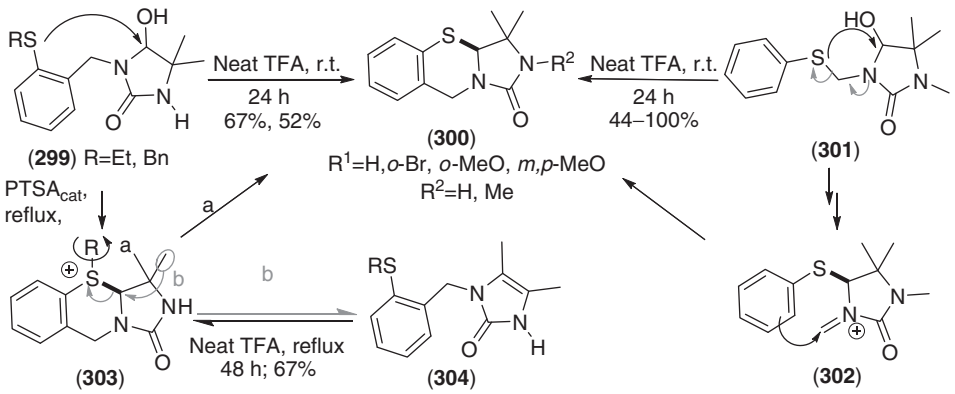
Systematic research on the guiding factors of this cascade reaction led to examine the influence of the size of the ring formed. In this context, it appears that the length (n) of the carbon chain between the lactam nitrogen and the sulfur atom plays a pivotal role in the cyclization reaction, while m has no influence (**Scheme 14**). Indeed, in all cases where $n = 1$, the intramolecular thionation/isomerization of *N*-acyliminium ion/π-cationic cyclization domino reaction is effective. However, when $n = 0$ or $n = 2$, only the direct π-cyclization products of endocyclic *N*-acyliminium ion are obtained. The type B azasulfonium ion, considered as the intermediate required for providing the thiacyclization product (**295**), is the only species capable of generating an exocyclic *N*-acyliminium ion because of the donor effect of the lactam nitrogen atom. In the case $n = 0$ (type A cation) and $n = 2$ (type C cation), no conjugation is possible, and therefore only the π-cyclization product is to be considered.



Scheme 14 Aza-sulfonium ions as potential intermediates in the domino cyclization process.

This method has been generalized to nonaromatic *N*-acyliminium ions issued from succinimide (equation 69). In this case, pyrrolobenzothiazines (**296a**) and (**295a**) are obtained in good yields, in a ratio of 5.5:4.5, similar to that observed in the isoindolinone series. This synthesis also provides a chemical verification of the same structure (**295a**) obtained by direct thiacyclization.

Given the unexpected behavior observed during the acid treatment of the functional groups discussed in Section 2.17.6.1 (equation 69), the domino process has been studied in the imidazolinone series. This choice is due to the fact that these entities involving two different nitrogen sites N_1 and N_3 are able to provide several *N*-acyliminium ion precursors with the nucleophilic part attached to two different nitrogen sites (equation 71).[107]



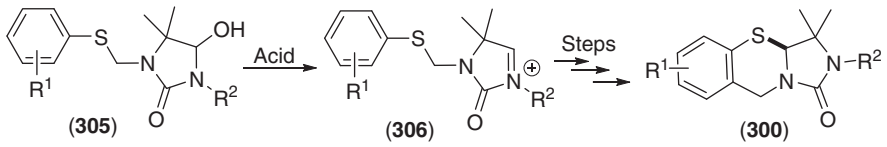
(71)

Direct and indirect thiacyclization initiated by acid in imidazolinone series

In a first series, the phenylthiomethyl group is carried by N_1, and to simplify the study nitrogen N_2 is protected by a methyl group. The α-hydroxy lactams obtained by reduction (**301**) were treated under acidic conditions (e.g., Neat TFA) and lead to **300** formed by the same domino 'one-pot' process as before (equation 71). However, the reaction is selective and only products (**300**) resulting from the intramolecular π-cyclization of exocyclic *N*-acyliminium ions (**302**), resulting from the cleavage of the aza-sulfonium intermediates are isolated, and no trace of the resulting endocyclic *N*-acyliminiums is detected. Note that the nature of the substituents R^1 (R^1=H, *o*-Br, *o*-MeO, *m,p*-MeO) does not change the nature of the reaction, but significantly impacts the final yield.

Structural confirmation of imidazolo[1,3]benzothiazine (**300**) was carried out by spectroscopic methods and X-ray diffraction (R^1=H, R^2=Me). Moreover, an unequivocal synthesis was initiated from imidazolones (**299**) with an unsubstituted N_2 group, and the thiol group is protected by benzyl and ethyl cleavable groups. Thus, treatment of (**299**) with a catalytic amount of PTSA in refluxing toluene for 48 h provides 58% of imidazolones (**304**) (equation 71) resulting from a methyl group transposition[1–4] at the intermediate *N*-acyliminium ion. Moreover, it is well known[1–4] that enamidones under acidic conditions can generate *N*-acyliminium ions. In more drastic conditions (e.g., Neat TFA, reflux, 48 h), the cyclization of imidazolone (**304**) with R=Et affords (**300**) in a good yield (67%) (the migration of a methyl group takes place). This result confirms the structure of the imidazolo[1,3]benzothiazine (**300**) (R^1=H, R^2=Me), and also demonstrates that the transformation of imidazolone (**304**) in the corresponding tricyclic azasulfonium salt (**303**) is reversible in acid medium (equation 71).[107]

Precursors **305** of other *N*-acyliminium ions (**306**), bearing the phenylthiomethyl group on N_1 and not on N_2 nitrogen of the imidazolone core, were subjected to the same acidic conditions as above (equation 72). Surprisingly, the cyclization products (**300**) are isolated, identical to those obtained by direct cyclization of α-hydroxy lactams (**299**), or according to a domino reaction process of α-hydroxy lactams (**301**) under acidic conditions (equation 72). A wide screening of operating conditions (Table 13) showed that the best protocol for a cyclization reaction to provide compound (**300**) (condition D, Table 13) corresponds again to the use of TFA in the absence of any solvent, but in specific proportions (1.5 ml per 1 mmol of starting substrate).



(72)

Indirect thiacyclization initiated by acid from bridged α-hydroxy lactams

With the right protocol on hand (condition D, Table 13), the reaction is tolerant with respect to the nature of the aromatic and its substituents in the meta position (good yields from 55% to 77% were obtained with *m*- and *m,p*-substitutions)

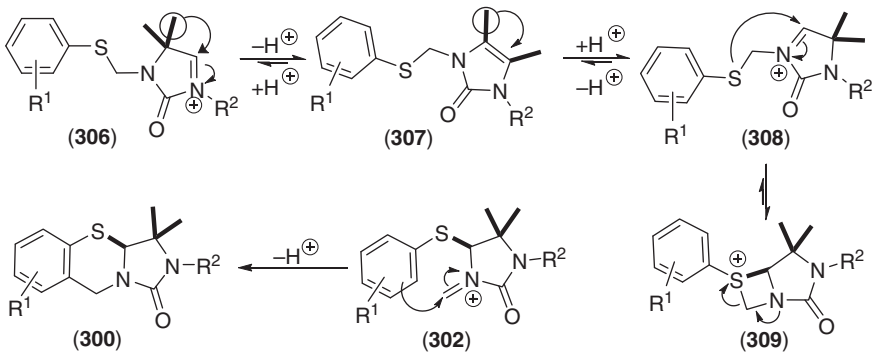
Table 13 Cascade *N*-acyliminium endocyclic–exocyclic isomerization/π-cyclization[a]

Entry	*Substrate*[b]	R^1	R^2	*Conditions*	*Product*	*Yield (%)*
1	**305a**	H	H	**A**	**300a**	–[c]
2	**305a**	H	H	**B**	**300a**	–[c]
3	**305a**	H	H	**C**	**300a**	–[d]
4	**305a**	H	H	**D**	**300a**	56
5	**305b**	H	H	**D**	**300a**	92
6	**305c**	*o*-Br	H	**D**	**300c**	21
7	**305d**	*o*-MeO	H	**D**	**300d**	29
8	**305e**[e]	*m*-MeO	H	**D**	**300e**	77[e]
9	**305f**	*p*-MeO	H	**D**	**300f**	–[c]
10	**305g**	*p*-Cl	H	**D**	**300g**	–[c]
11	**305h**	β-Napht	H	**D**	**300h**	61
12	**305i**	*m,p*-MeO	H	**D**	**300i**	55
13	**305j**	H	Me	**D**	**300j**	87
14	**305k**	H	Bn	**D**	**300k**	95

[a]Reaction conditions **A**: $PTSA_{cat}$, toluene, reflux, 24 h; **B**: BF_3OEt_2 (2 equivalents), DCM, 20 °C, 24 h; **C**: TFA (2 equivalents), DCM, 20 °C, 24 h; **D**: Neat TFA (1.5 ml for 1 mmol of α-hydroxy lactam), 24 h.
[b]The substrates **305a** and **305c–i** have group R^2 = Boc.
[c]Only the thiophenol resulting from the thioether cleavage was isolated.
[d]The unprotected starting material as α-hydroxy lactam **305b** was recovered and was accompanied with the disulfur compound namely 4-phenylthio-1-phenylthiomethyl-5,5-dimethylimidazolidin-2-one.
[e]In the case of the *m*-methoxy derivative **300e** (entry 8), the reaction was performed with total regioselectivity in favor of the C_2-position of benzene.

(entries 8, 11, and 12); the *ortho*-substitution (entries 6, 7) is characterized by low yields that do not exceed 29% and the latter regardless of the used protocols. This yield drops dramatically to 0% when the benzene ring is only *para*-substituted (entries 9, 10). This clearly demonstrates the impact of the electronic structure of the benzene ring on the cyclization reaction kinetics. Finally, the introduction of an alkyl group R^2 on the imidazolidine ring at N_3 has proved to be advantageous on the reaction yield (entries 13, 14).

Equation 73 represents a plausible mechanism to explain the domino process of exclusive production of polycyclic *N,S*-acetals (**300**). The formation of intermediates (**307**) from the *N*-acyliminium ions (**306**) is possible by the transposition of a group. The literature describes such transformations on related structures.[108] These intermediates (**307**) can be isolated when R^1 = H and R^2 = Et or Bn. In the acidic medium, they are in equilibrium with the *N*-acyliminium ion (**306**) and, by transposition of the second methyl group, with cation (**308**), also accessible when the linear α-hydroxy lactams (**301**) are treated in acid medium (equation 71).[107]



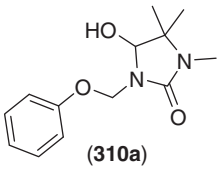
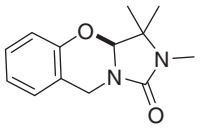
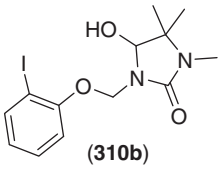
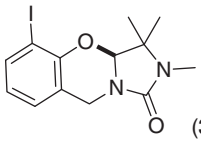
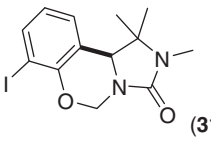
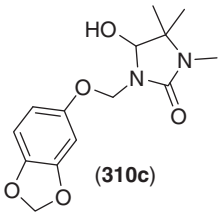
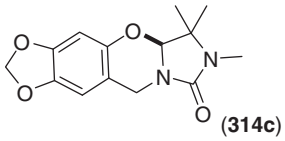
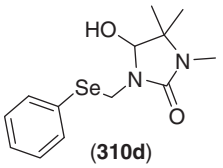
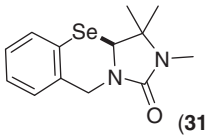
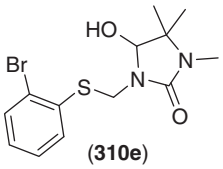
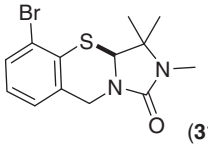
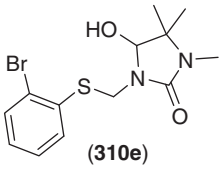
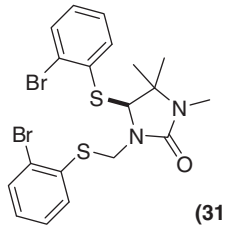
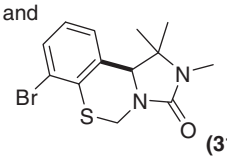
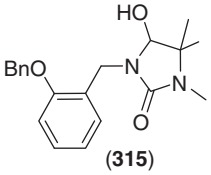
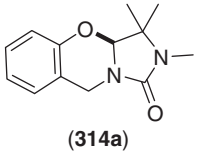
(73)

Indirect thiacyclization initiated by acid from bridged α-hydroxy lactams

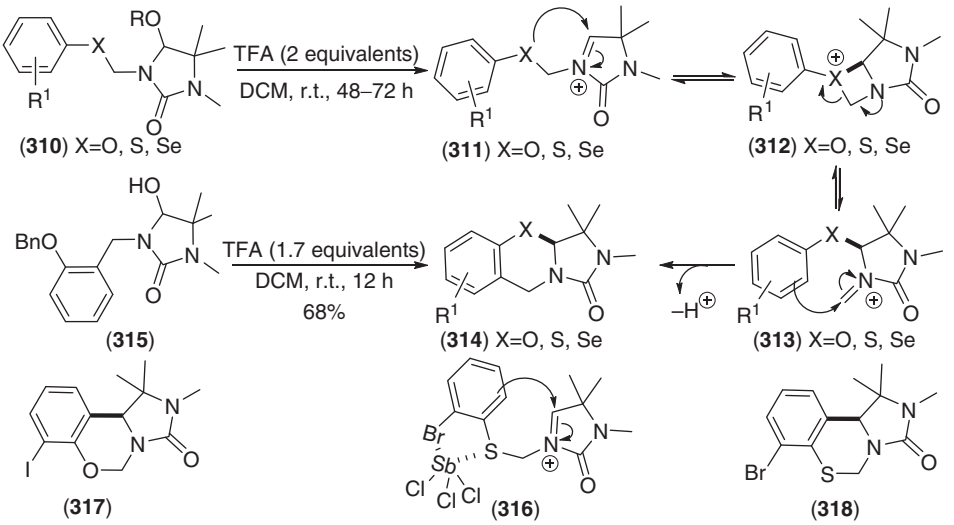
2.17.6.2 Generalization of Heterocyclization in the Imidazolidine Series (O, S, and Se)

This domino process has been generalized to the heteroatoms oxygen and selenium in the imidazolidinone series. Thus, the treatment of α-hydroxy lactam (**310**) by TFA under controlled conditions specified in Table 14 led to cyclization products (**314**), (**317**), and (**318**) (equation 74).[21]

Table 14 Thia-, oxa- and selenacyclization in imidazolidinone series (equation 74)

Entry	*N-tethered group in substrate (**310**)/(**315**)*	*Conditions*[21]	*Product*	*Yield (%)*
1	 (**310a**)	TFA (2 equivalents), DCM, r.t., 48–72 h	 (**314a**)	68
2	 (**310b**)	TFA (2 equivalents), DCM, r.t., 72 h	 (**314b**) and  (**317b**)	13 13
3	 (**310c**)	TFA (2 equivalents), DCM, r.t., 72 h	 (**314c**)	40
4	 (**310d**)	Neat TFA, r.t., 24 h	 (**314d**)	91
5	 (**310e**)	Neat TFA, r.t., 48 h	 (**314e**)	89[a]
6	 (**310e**)	$SbCl_3$ (2 equivalents), DCM, –30 °C, 72 h	 (**319e**) and  (**318e**)	11.8 55.2
7	 (**315**)	Neat TFA, r.t., 48 h	 (**314a**)	89

[a]This product is described also in reference 107.



(74)

Oxa- and selenacyclization processes in imidazolidinone series

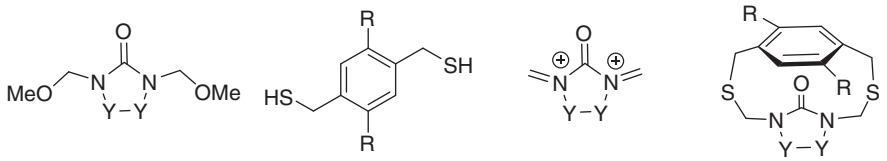
Concretely, the α-hydroxy lactams (**310a–c**) lead exclusively to the *O*-cyclization products, resulting from the domino process with the exception of case (**310b**) wherein R = H and R^1 = *o*-I. In this case (entry 2), the reaction leads to a mixture of two regioisomeric inseparable products (**314b**) and (**317b**) in a ratio of 1:1 and in low yield (26%). The structure of the *O*-cyclization product (**314a**) was chemically confirmed by unequivocal synthesis starting from the α-hydroxy lactam (**315**) (entry 7).

In the case of selenium (**310d**) (entry 4) and sulfur (**310e**) (entry 5) derivatives, in pure TFA without solvent the domino process is also exclusive and the cyclization reaction leads only to product (**315d**) (91%) or (**315e**) (89%). The presence of a bromine atom on the aromatic ring is in contradiction to the low yield, on the one hand, and the selectivity, on the other hand, obtained in the case of the iodine derivative (entry 2).

In addition, the use of different reaction conditions using thiophile agents such as $SbCl_3$ in large excess as the Lewis acid catalyst (entry 6) has inversed the reaction progression. Indeed, only π-cyclization products of endocyclic *N*-acyliminium (**318e**) (55.2%) and disulfide (**319e**) (11.8%) are observed. They result from the cleavage of the thioether function followed by trapping of the resulting sulfur moiety by the same endocyclic *N*-acyliminium ion which has not been cyclized. The nucleophilicity of the sulfur atom is lost by complexation with $SbCl_3$ together with the bromine atom, providing intermediate (**316**) wherein only the π-cyclization reaction is still possible (equation 74).

2.17.6.3 Thia- and Selenacyclization of Double *N*-Acyliminium Cations

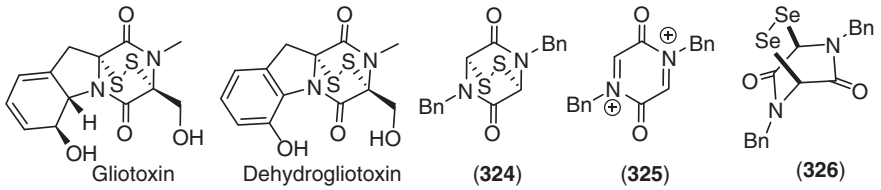
Compounds generating double *N*-acyliminium ions such as (**321**), in the imidazolidinone and benzimidazolidinone series, have allowed quick and easy access to the corresponding cyclophanes (**322a,b**) and (**323a,b**) (Scheme 15).[109]



Scheme 15 Thia-macrocyclization via double *N*-acyliminium cations.

Condensation of bis-*N*,*O*-acetals (**319**) with the bis-thiols (**320**) (R = H, Me) was tested. A diluted solution (1%) of TFA in DCM is sufficient to form bis-*N*-acyliminium ions (**321**), and under high dilution conditions, at reflux, 40% of the macrocycle (**322a**) are obtained. With BF_3OEt_2 (2–4 equivalents) at room temperature or reflux, heterocycles (**323a,b**) are obtained with better yields (43–71%) than their imidazolidine analogs (**322a,b**). Cross experiments have revealed that the macrocycles (**322a,b**) are unstable in acidic medium unlike benzimidazolidine analogs (**323a,b**). The difference in stability of intermediate bis-ions (**321**) in both the heterocyclic series could explain this, as well as obtaining better yields in the benzimidazolidine series.

Very recently, another bis-cation (**325**), in the piperazine series, was generated from a simple model similar to bioactive gliotoxin and dihydrogliotoxin alkaloids (Scheme 16). It was then used for the first synthesis of epidiselenodiketopiperazine (**326**) in three steps starting from the epidithiodiketopiperazine (**324**).[110]



Scheme 16 Selenacyclization via an original bis-*N*-acyliminium cation.

Specifically, the opening of the cyclic *N,S*-acetal (**324**) with $NaBH_4$ provides a dithiol which is alkylated in bis-thiomethyl ether by iodomethane. The treatment of the latter by bromine generates salt (**325**), which is trapped by a diselenide dianion generated *in situ* (e.g., Se, $NaBH_4$, EtOH, DMF, r.t., 1.5 h). The product (**326**) is obtained with an overall yield of 33%.

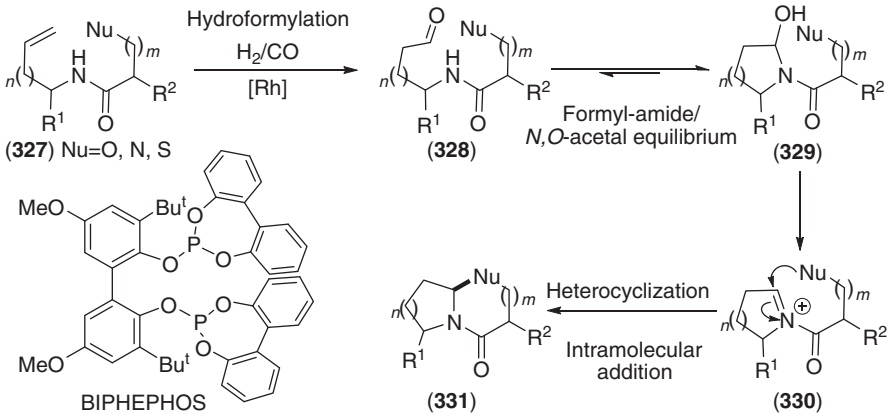
2.17.7 Common Approaches Using Oxa-, Aza-, and Thiacyclizations

Research on general methods using an *N*-acyliminium ion trap by oxygen, nitrogen, and sulfur as internal nucleophile was the subject of several investigations.

2.17.7.1 Cyclohydrocarbonylation/nucleophilic Addition Domino Reaction

The cyclohydrocarbonylation (CHC) reaction was first described by Ojima,[111] and involves the hydroformylation of a functionalized alkene to yield an aldehyde. In the context of reactions involving *N*-acyliminium salts, the alkene chain is substituted by a nitrogen chain (amine, amide, or carbamate), itself connected to a terminal nucleophile. In a first step, a hemiaminal function was formed and the key substrate (**327**) is the typical starting material of this reaction.

Depending on the reaction conditions, the process can be stopped at the hemiaminal (**329**), or by elimination, and the *N*-acyliminium ion (**330**) can be formed leading to enamide after loss of a proton (product not shown in the figure). In the case of the presence of strong nucleophiles, a cyclization reaction takes place giving the bicyclic system (**331**). If the nucleophile is a π-alcyne, π-olefin, π-allene system, alkaloids from the pyrrolizidine, indolizidine, and quinolizidine family are formed among other products. Moreover, when the nucleophile is a heteroatom, an intramolecular heterocyclization takes place and leads to the formation of bicyclic lactams of different sizes (equation 75).



(75)

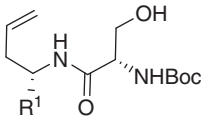
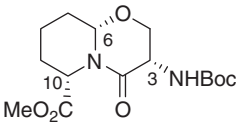
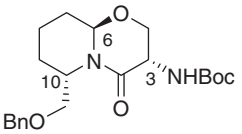
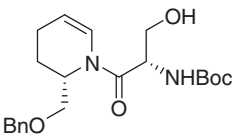
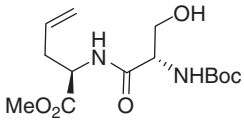
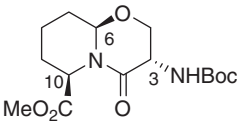
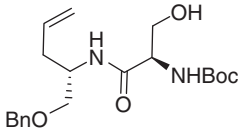
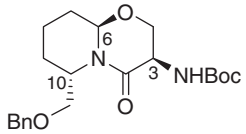
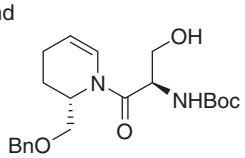
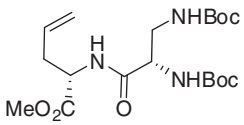
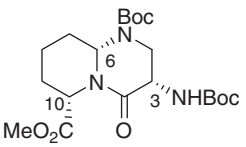
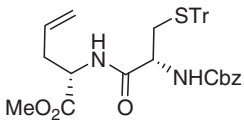
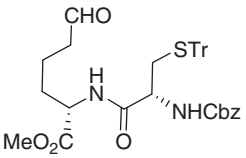
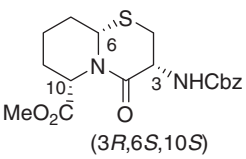
Concept of the domino process CHC/heterocyclization

When amino-alcohols, amino-thiols, and diamine derivatives are used for the synthesis of linear starting substrates (**329**), the bicyclic lactams (**331**) can carry up to three stereogenic centers obtained in a single step. In this light, Ojima's team described the use of this domino process for fast and efficient preparation of amino-acid peptidomimetics of azabicycloalcane type.[112]

Practically, dipeptides having a terminal double bond and one nucleophilic function are hydroformylated in the presence, or absence, of an acid catalyst, using $Rh(acac)(CO)_2$ as the formylation catalyst, and the biphephos as the most effective ligand. The results obtained are dependent on the nature of the substituent at the starting substrate, and of the size of the bicycle formed at the end of the process (Table 18). (Note also from the table, the formation of ene-lactams (entries i, iii).)

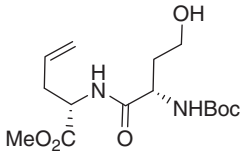
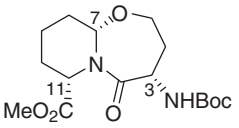
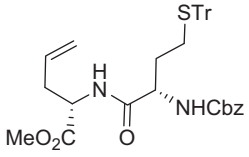
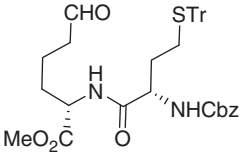
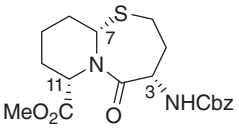
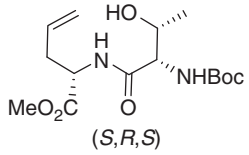
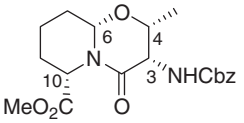
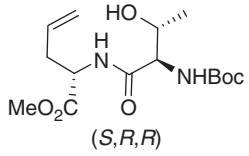
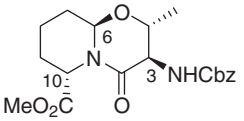
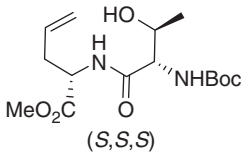
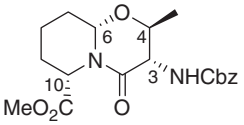
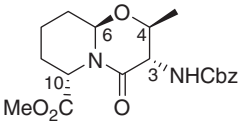
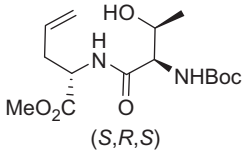
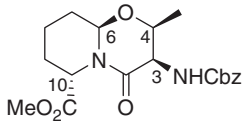
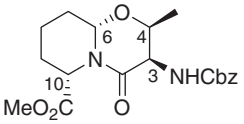
The results described in Table 18 show that the CHC associated with the heterocyclization reaction of an *N*-acyliminium ion is effective under mild conditions and that the catalysis by Rh-biphephos is extremely efficient. The process leads to the azabicyclo [n.m.0]alcanes amino-acid derivatives and their analogs with high yields and diastereoselectivity in most cases (Table 15).

Table 15 Cyclohydrocarbonylation (CHC) associated with heterocyclization (equation 75)

Entry	*Starting substrate*	*Conditions*	*Product*	*Yield (%)*
1	 (*S*,*S*) R^1=CO_2Me, CH_2OBn	$Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), H_2 (2 atm), CO (2 atm), toluene, PTSA (10 mol%), 65 °C, 20 h	 (3*S*,6*S*,10*S*)	96[a]
			 (3*S*,6*S*,10*S*)	82
			and  (*S*,*S*)	6
2	 (*R*,*S*)	$Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), H_2 (2 atm), CO (2 atm), toluene, PTSA (10 mol%), 65 °C, 20 h	 (3*S*,6*R*,10*R*)	90[a]
3	 (*R*,*S*)	$Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), H_2 (2 atm), CO (2 atm), toluene, PTSA (10 mol%), 65 °C, 20 h	 (3*R*,6*R*,10*S*)	80
			and  (*S*,*R*)	7
4		$Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), H_2 (2 atm), CO (2 atm), toluene, PTSA (10 mol%), 65 °C, 20 h	 (3*S*,6*S*,10*S*)	95
5	 (*S*,*R*)	1. $Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), H_2 (2 atm), CO (2 atm), MeOH, 65 °C, 20 h 2. TFA_{cat}, DCM, r.t., 30 min	 (*S*,*R*)	86[b]
			 (3*R*,6*S*,10*S*)	89

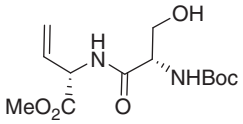
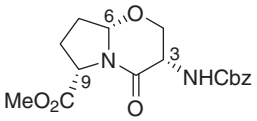
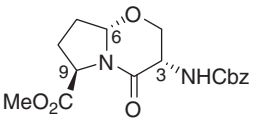
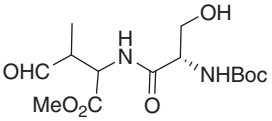
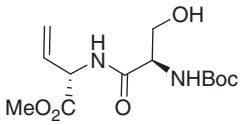
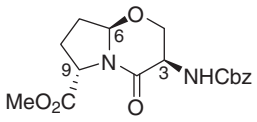
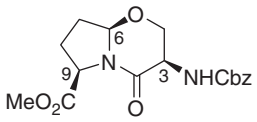
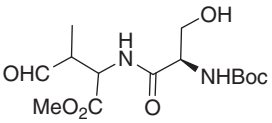
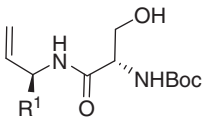
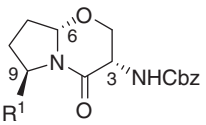
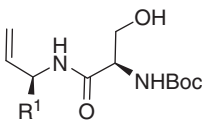
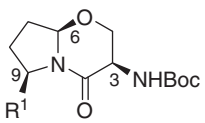
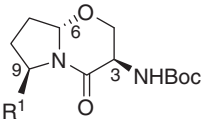
(*Continued*)

Table 15 Continued

Entry	*Starting substrate*	*Conditions*	*Product*	*Yield (%)*
6	 (*S*,*S*)	$Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), H_2 (2 atm), CO (2 atm), toluene, PTSA (10 mol%), 65 °C, 20 h	 (3*S*,7*S*,11*S*)	87
7	 (*S*,*S*)	1. $Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), H_2 (2 atm), CO (2 atm), MeOH, 65 °C, 20 h 2. $MeSO_3H$ (1 mol%), DCM, 30 °C, 1 h and then Et_3SiH (2 equivalents) in TFA	 (*S*,*S*)	93[b]
			 (3*S*,7*S*,11*S*)	90[c]
8	 (*S*,*R*,*S*)	$Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), H_2 (2 atm), CO (2 atm), toluene, PTSA (10 mol%), 65 °C, 20 h	 (3*S*,4*R*,6*S*,10*S*)	85
	or		or	
	 (*S*,*R*,*R*)		 (3*R*,4*R*,6*R*,10*S*)	94
9	 (*S*,*S*,*S*)	$Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), H_2 (2 atm), CO (2 atm), toluene, PTSA (10 mol%), 65 °C, 20 h	 (3*S*,4*S*,6*S*,10*S*)	69
			and	
			 (3*S*,4*S*,6*R*,10*S*)	17
10	 (*S*,*R*,*S*)	$Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), H_2 (2 atm), CO (2 atm), toluene, PTSA (10 mol%), 65 °C, 20 h	 (3*R*,4*S*,6*R*,10*S*)	78
			and	
			 (3*R*,4*S*,6*S*,10*S*)	10

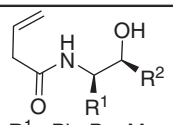
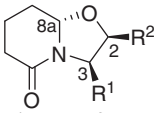
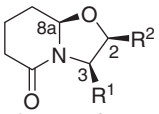
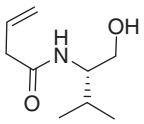
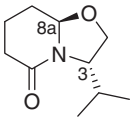
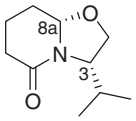
(*Continued*)

Table 15 Continued

Entry	*Starting substrate*	*Conditions*	*Product*	*Yield (%)*
11	 (*S*,*S*)	$Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), H_2 (2 atm), CO (2 atm), toluene, PTSA (10 mol%), 65 °C, 20 h	 (3*S*,6*S*,9*S*)	45
			and	
			 (3*S*,6*S*,9*R*)	21
			and	
			 (*S*)	21[d]
12	 (*S*,*R*)	$Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), H_2 (2 atm), CO (2 atm), toluene, PTSA (10 mol%), 65 °C, 20 h	 (3*R*,6*R*,9*S*)	42
			and	
			 (3*R*,6*R*,9*R*)	16
			and	
			 (*R*)	23[d]
13	 (*S*), (*S*,*S*), (*R*,*S*) R^1= H, Me, CH_2OBn	$Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), H_2 (2 atm), CO (2 atm), toluene, PTSA (10 mol%), 65 °C, 20 h	 R^1=H: (3*S*,6*S*) R^1=Me: (3*S*,6*S*,9*S*) R^1=CH_2OBn: (3*S*,6*R*,9*R*)	70[e] 94 87
14	 (*S*,*R*), (*R*,*R*) R^1= Me, CH_2OBn	$Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), H_2 (2 atm), CO (2 atm), toluene, PTSA (10 mol%), 65 °C, 20 h	 R^1=Me: (3*R*,6*R*,9*S*) R^1=CH_2OBn: (3*R*,6*R*,9*R*)	45 42
			and	
			 R^1=Me: (3*R*,6*S*,9*S*) R^1=CH_2OBn: (3*R*,6*S*,9*R*)	34 41

(*Continued*)

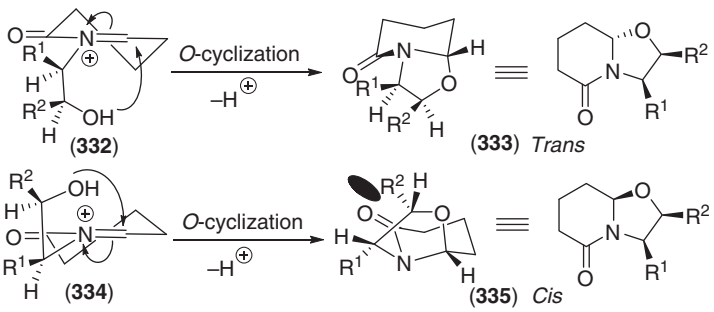
Table 15 Continued

Entry	*Starting substrate*	*Conditions*	*Product*	*Yield (%)*
15	 R^1= Ph, Bn, Me R^2= H, H, Ph	$Rh(acac)(CO)_2$ (1 mol%), BIPHEPHOS (2 mol%), H_2/CO 1:1 (5 bar), THF, PTSA (10 mol%), 70 °C, 12 h	 R^1= Ph, R^2= H (3*R*,8a*S*) R^1= Bn, R^2= H (3*R*,8a*S*) R^1= Me, R^2= Ph (2S,3R,8aS) and	85.5 81 71[f]
			 R^1= Ph, R^2= H (3*R*,8a*R*) R^1= Bn, R^2= H (3*R*,8a*R*) R^1= Me, R^2= Ph (2*S*,3*R*,8a*R*)	8.5 9 7[f]
16		$Rh(acac)(CO)_2$ (1 mol%), BIPHEPHOS (2 mol%), H_2/CO 1:1 (5 bar), THF, PTSA (10 mol%), 70 °C, 12 h	 (3*S*,8a*R*) and	78.3
			 (3*S*,8a*S*)	12.7

[a]The reaction is also effective in toluene without PTSA addition with comparable yield.
[b]The reaction was conducted in two separate steps and additional conditions were needed.
[c]The N,S-acetal bicyclic product was used for the synthesis of omapatrilat,[113] an efficient ACE inhibitor developed by the Bristol–Myers Squibb company.
[d]Total racemization at the carbone atom adjacent to the nitrogen atom was observed in both cases.
[e]The major product (3*S*,6*S*) was accompanied with 6% of the (3*S*,6*R*)-diastereomer.
[f]In this case, the PTSA (10 mol%) was replaced with PPTS (5 mol%).

Furthermore, if the reaction is effective in the oxygen and nitrogen series, in the sulfur series (entries 5 and 7) it occurs in two distinct steps, with the help in the second step of an acid, associated (entry 7) or not (entry 5) with a reducing agent. In contrast, the domino process under controlled conditions is generalized to optically pure 5,6-, 6,6- and 6,7-bicyclic lactams with two, three, or even four stereocenters, and can be used on a large scale (entry 7).

In these studies, particular attention was paid to the understanding of the reaction mechanism, including the key factors behind the diastereoselectivity, even the diastereospecificity in the second heterocyclization step. In particular, the size of the six- or seven-membered *X*,*O*-heterocycle ring formed seems to highly impact the transition state leading to these systems.



(76)

Diastereoselectivity outcome of oxacyclization

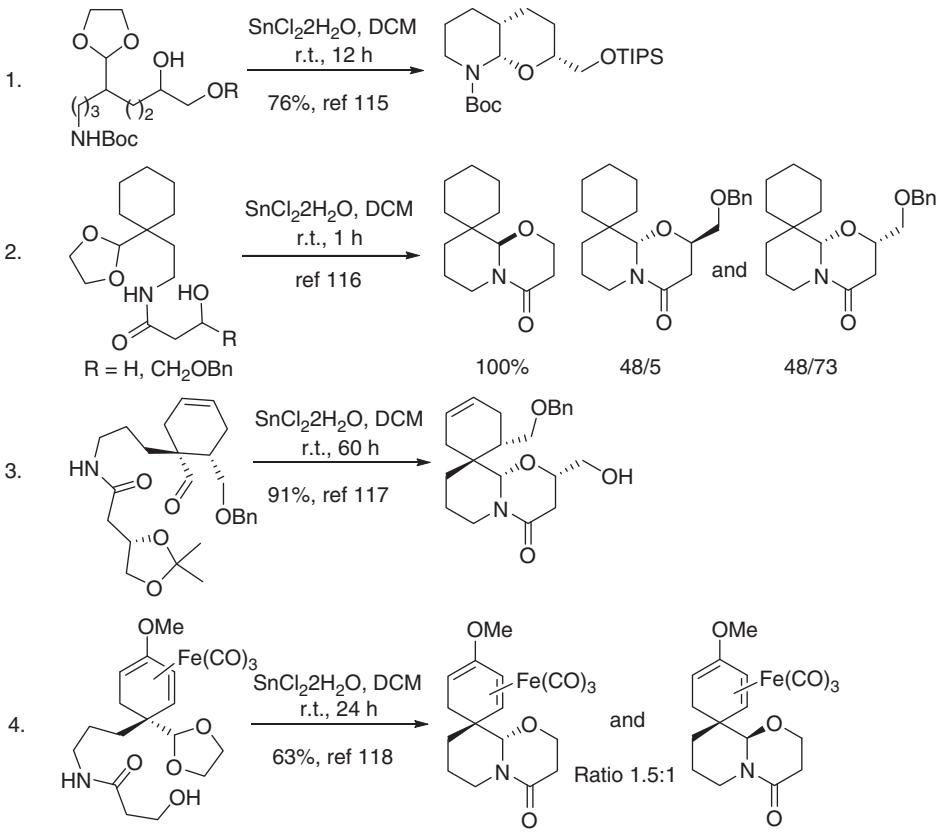
This domino reaction has been applied to vinylacetamides (entries xv and xvi), and the best results are obtained with a ratio catalyst/ligand/substrate 1:2:100.[114] The high stereoselectivity observed in the cyclization of alcohol on the *N*-acyliminium ion can be explained using the state transitions described in equation 76. The addition of nucleophiles to *N*-acyliminium ion intermediate

is realized under stereoelectronic control. Two transition states (**332**) and (**334**) are possible, but transition state (**332**) is the most important because an axial approach of the alcohol function to this *N*-acyliminium ion produces a less steric hindrance. This axial attack of the alcohol on intermediate (**332**) then leads to the bicyclic ring system (**334**) (oxazolopiperidone), whose hydrogens are in *trans* configuration.

This approach for the synthesis of oxazolopiperidones (entries 15 and 16) has advantages over other existing methods. In particular, it is fast as the compounds are in most cases obtained in two 'one-pot' steps, with good yields and excellent diastereoselectivities and lead directly to the *trans* compounds.

2.17.7.2 Deacetalization/nucleophilic Addition Domino Reaction

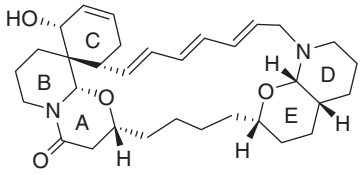
The research work reported here was made based on those dedicated to the synthesis of natural products using tin chloride ($SnCl_2 2H_2O$) as the acid promoter. The deacetalization reaction, followed by equilibrium between the aldehyde-amide formed and the corresponding α-hydroxy lactam is followed at the end of the process by intramolecular heterocyclization via an *N*-acyliminium ion (equation 77).[115–118]



(77)

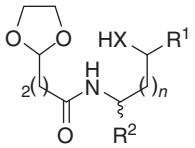
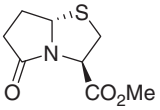
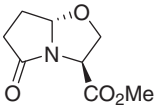
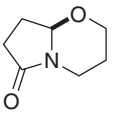
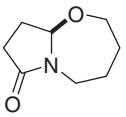
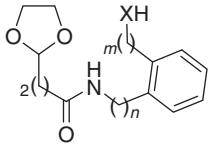
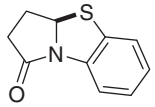
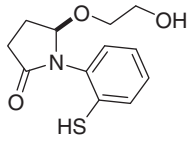
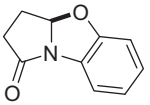
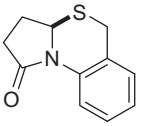
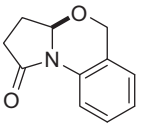
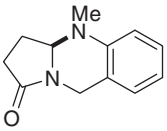
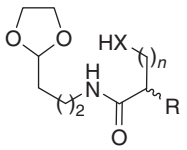
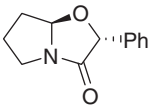
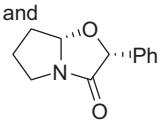
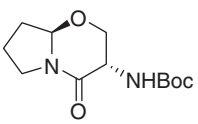
Tin(II) chloride dihydrate-mediated deacetalization-bicyclization sequence[115–118]

As shown in equation 77, the procedure used is quite simple (e.g., $SnCl_2 2H_2O$, DCM, r.t.) and can often provide enantiomerically pure complex products. Among these, the scaffolds DE (octahydropyrano[2,3-*b*]pyridine) and ABC (spirooxaquinolizidinone) of the marine alkaloid upenamide are synthesized (**Scheme 17**).[115–118] This procedure has been explored by Taylor's team detailing in particular four series of acetal-amide bearing oxygen, nitrogen, or sulfur nucleophiles on the amide function, separated by a spacer aromatic or not.[119] All corresponding results are summarized in **Table 16**.



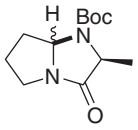
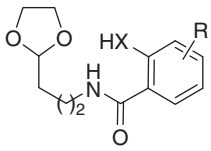
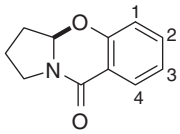
Scheme 17 Structure of upenamide.

Table 16 Results from the domino deacetalization/heterocyclization

Entry	*Substrate*	*Conditions*	*Product*	*Yield (%)*	*References*
1		$SnCl_2 2H_2O$, DCM, r.t., 72 h R^1=H, R^2=CO_2Me *n*=1, X=S		70	
		$SnCl_2 2H_2O$, DCM, r.t., 12 h R^1=H, R^2=CO_2Me *n*=1, X=O		34	
		$SnCl_2 2H_2O$, DCM, r.t., 12 h R^1=H, R^2=H *n*=2, X=O		56	119
		$SnCl_2 2H_2O$, DCM, r.t., 12 h R^1=H, R^2=H *n*=3, X=O		57	
2		$SnCl_2 2H_2O$, DCM, r.t., 48 h *n*=0, *m*=0, X=S	 and 	31[a] 14	
		$SnCl_2 2H_2O$, DCM, r.t., 48 h *n*=0, *m*=0, X=O		NR[a]	
		$SnCl_2 2H_2O$, DCM, r.t., 18 h *n*=0, *m*=1, X=S		86	119
		$SnCl_2 2H_2O$, DCM, r.t., 24 h *n*=0, *m*=1, X=O		80	
		$SnCl_2 2H_2O$, DCM, r.t., 18 h *n*=1, *m*=0, X=NMe		43	
3		$SnCl_2 2H_2O$, DCM, r.t., 18 h *n*=0, R=Ph, X=O, ratio 2:1	 and 	43 46	119
		$SnCl_2 2H_2O$, DCM, r.t., 12 h *n*=1, R=NHBoc, X=O		55	

(*Continued*)

Table 16 Continued

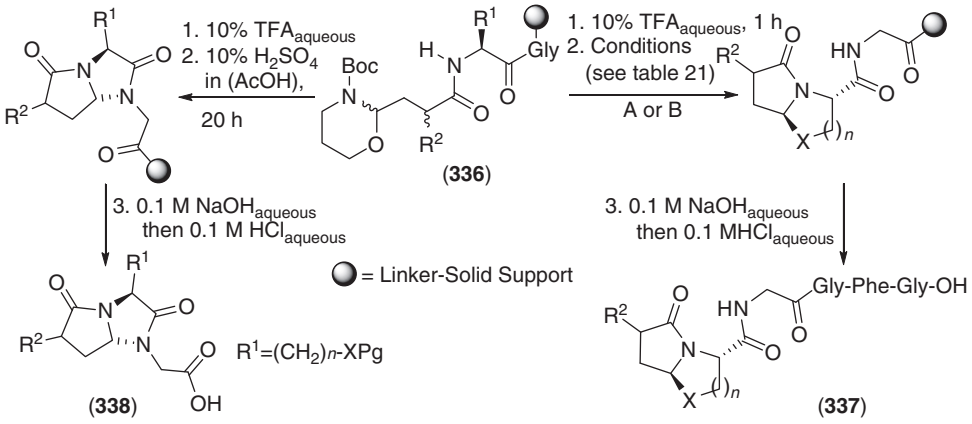
Entry	*Substrate*	*Conditions*	*Product*	*Yield (%)*	*References*
		$SnCl_2 2H_2O$, DCM, r.t., 12 h n=0, R=Me, X= NBoc, Inseparable α:β=1:3			
4		$SnCl_2 2H_2O$, DCM, r.t., 12 h	 2-F 2-Me 3-Cl 1-Pri,4-Me 2,3-Benzene 3,4-Benzene	77 98 98 87 84 65 56	119

[a]The reaction did not occur and all starting materials were recovered.

The results obtained by the implementation of this domino reaction deserve a few remarks. If the process works in almost all cases without major difficulties, the reaction time is variable in different series or even in the same series sometimes. Though the domino process yields are moderate to low in the case of 5,5-bicycles (entries 1 and 3), they are good to very good in the case of 5,6-bicyclic systems, as well as in aromatic series than in nonaromatic series (entries 2 and 4) (Table 16).

2.17.7.3 Domino Deacetalization/heterocyclization Reaction in Solid Phase

This deacetalization/intramolecular heterocyclization of an *N*-acyliminium ion sequence in a cascade process has been further developed on solid support. In this perspective, a general strategy for the synthesis of bicyclic dipeptides in solid phase (PEGA800 resin with a functionalized amine) is presented (equation 78).[120]



(78)

Solid-phase synthesis based on *N*-acyliminium ion heterocyclization

Depending on the nature of the side chain (R^1), the intermediate *N*-acyliminium ions can undergo nucleophilic attack from the functional group (–OH, $–NH_2$, –SH, and $–CONH_2$) of the side chain, or from –CONH– of the peptide backbone. Under these conditions, a wide range of oxa-, aza-, and thiabicycloalcanes is obtained with excellent purity and diastereoselectivity.

Specifically, treatment of mixed acetal (**336**) with TFA gives the aldehyde in equilibrium with the corresponding α-hydroxy lactam. After its transfer in nonaqueous solution (conditions A or B; Table 17), the newly deprotected heteroatom produces the heterocyclization reaction, and after resin cleavage provides the expected bicyclic pyrrolidinic systems (**337**) with different degrees of purity ranging from 91% to more than 95% (Table 17).

A series of bicyclic bis-lactams (**338**) was synthesized starting from the same acetal dipeptides (**336**) under hard acidic conditions (e.g., 10% H_2SO_4 in AcOH). In this approach where R^2=H (devoid of nucleophilicity) and where the water is eliminated from the reaction mixture, an *N*-acyliminium ion intermediate is formed and the amide backbone of the peptide is

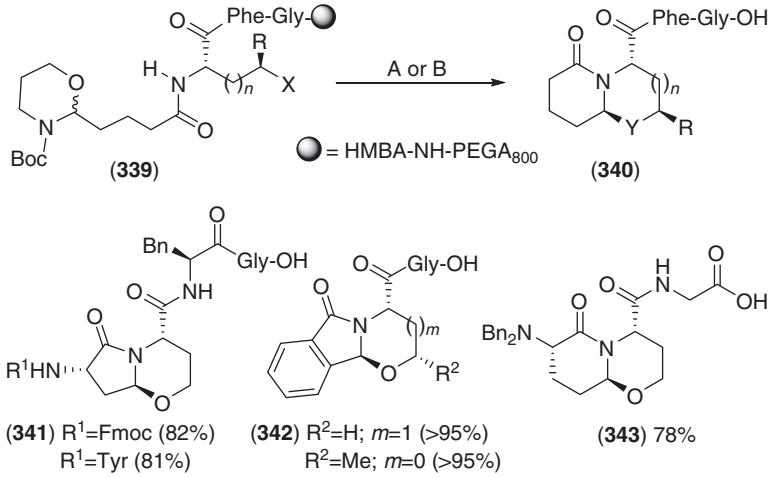
Table 17 Solid-phase synthesis based on *N*-acyliminium ion heterocyclization (equation 78)[a,b]

Entry	*Substrate*	$R^1=(CH_2)_n$–*XPg*	R^2	*n*	*X*	*Product*	*Purity (%)*[c]
1	**336a**	CH_2–OTrt	H	1	O	**337a**	Complex
2	**336b**	$(CH_2)_2$–OTrt	H	2	O	**337b**	>95[d]
3	**336c**	$(CH_2)_2$–OTrt	Bu^i	2	O	**337c**	>95[d]
4	**336d**	$(CH_2)_2$–OTrt	Bn	2	O	**337d**	>95[d]
5	**336e**	CH_2–STrt	H	1	S	**337e**	91
6	**336f**	CH_2–STrt	Bu^i	1	S	**337f**	94[d]
7	**336g**	CH_2–STrt	Bn	1	S	**337g**	>95[d]
8	**336h**	CH_2–NHBoc	H	1	NH	**337h**	>95[d]
9	**336i**	CH_2–NHBoc	Bu^i	1	NH	**337i**	91[d]
10	**336j**	CH_2–NHBoc	Bn	1	NH	**337j**	91[d]
11	**336k**	$(CH_2)_2$–NHBoc	H	2	NH	**337k**	>95
12	**336l**	$(CH_2)_3$–NHBoc	H	3	NH	**337l**	>95
13	**336m**	$(CH_2)_4$–NHBoc	H	4	NH	**337m**	Complex

[a]All reactions were run at 20 °C.
[b]Reaction conditions: Condition **A**: TFA; Condition **B**: 10% H_2SO_4 in AcOH.
[c]Product purity was determined by RP-HPLC.
[d]Product was formed as a 1:1 epimeric mixture.

forced to cause a second cyclization via a nitrogen atom as the internal nucleophile (equation 78). The reaction can be generalized to different groups R^1 (R^1 = Pr, Pr^i, Bu, Bu^s, Bu^i, CH_2-Cy, and $(CH_2)_2$-Cy) and the products are obtained with purities ranging from 91% to more than 95%. Bicyclic bis-lactams close to (**338**) but containing fused 5,6 and 5,7 rings were also obtained using the same approach, with yields of 89% and 93%, respectively.

Piperidinones fused to oxazine, thiazine, and diazine rings (**340**) were also obtained using the same procedure starting from supported mixed acetals (**339**) (equation79). The influence of the azine ring size (n variable) on the heterocyclization process and the nature of the substituent have been studied and are not, *a priori*, the limiting factors of this sequence (**Table 18**).[121]



(79)

Solid-phase synthesis sequence including the heterocyclization reaction

Table 18 Solid-phase synthesis of fused piperidones based on heterocyclization (equation 79)

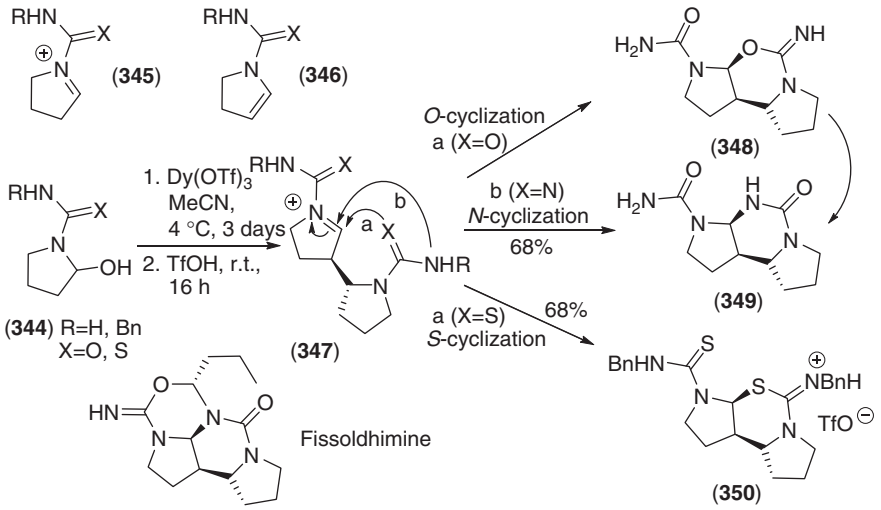
Entry	*Substrate*	*X*	*R*	*Y*	*n*	*Conditions*[a]	*Product*	*Purity (%)*
1	**339a**	OBu^t	H	O	0	B	**340a**	>95
2	**339b**	OBu^t	Me	O	0	A or B	**340b**	>95
3	**339c**	OTrt	H	O	1	A or B	**340c**	>95
4	**339d**	NHBoc	H	NHBoc	0	A	**340d**	>95
5	**339e**	NHBoc	H	NHBoc	1	A	**340e**	86
6	**339f**	NHBoc	H	NHBoc	2	A/B	**340f**	0
7	**339g**	STrt	H	S	0	A or B	**340g**	>95

[a]Conditions **A**: (i) 10% TFA (aqueous); (ii) 0.1 mol l^{-1} NaOH (aqueous). Conditions **B**: (i) 10% TFA_{aq}; (ii) 50% TFA in DCM; (iii) 0.1 mol l^{-1} $NaOH_{aq}$.

As shown in Table 18, the reaction can also be applied in the series of bicyclic piperidinones in the same way as in the pyrrolidinone series in both conditions using TFA as the heterocyclization promoter. Again, the reaction is generalized to the oxygen, sulfur, and nitrogen heteroatoms. In addition, this protocol is extended effectively to the synthesis of optically pure **341** and **342**. These products are generally obtained in good yields and with high purity (86–95%).

2.17.7.4 Heterocyclization in Alkaloid Biosynthesis

Alongside this study in supported solid phase, one of the approaches to afford the tricyclic core of the alkaloid fissoldhimine consists in a biogenetically inspired heterodimerization followed by heterocyclization via an *N*-acyliminium ion (equation 80).



(80)

Alternative biosynthetic hypothesis for fissoldhimine alkaloid formation

In this context, treatment of pyrrolidin-2-ols derivatives (**344**) with a Lewis acid (e.g., lanthanide triflate) or a Brønsted acid leads to the corresponding *N*-substituted 2-pyrrolines (**346**) via cationic species (**345**). *N*-acyliminium cations (**347**) produced, according to intramolecular oxacyclization, the unstable tricyclic iminoether (**348**). It isomerizes spontaneously by cleavage/cyclization leading to the skeleton of the alkaloid fissoldhimine (**349**) as a single diastereoisomer. The latter may be obtained directly via azacyclization reaction of the cationic species (**347**). Moreover, in the case of *N*-benzylated thiourea, a similar process in a 'one-pot' procedure provides the thiacyclization product (**350**), isolated as a triflate salt (68%) and as a unique diastereoisomer.[122]

During this domino process, examination of the stereochemical profile of a starting *N*-phenyl urea was carried out using several Lewis acids ($Sc(OTf)_3$, BF_3OEt_2) and Brønsted acids (CSA, HCl, TFAA), in catalytic or subcatalytic quantity, using different solvents. Under these conditions, the reaction product is isolated with high diastereoselectivity ranging from 65:35 to 95:5 in the best case, with an average yield of approximately 75%, showing that the stereochemistry of the reaction depends strongly on the nature of the substituent.

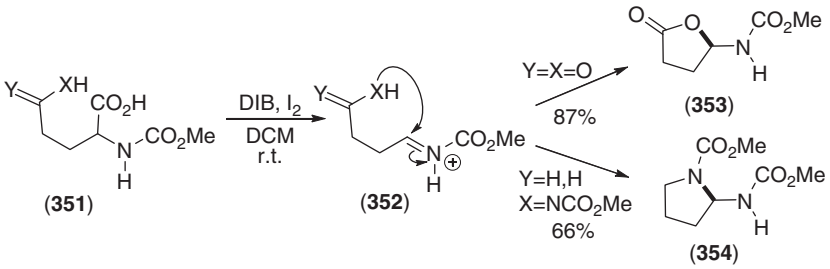
2.17.8 Common Reactions to Oxa- and Azacyclizations

As mentioned at the beginning of this review (equation 4),[7,8] the generation of an *N*-acyliminium ion from an *α*-amino acid by oxidative decarboxylation, or electrochemically, under mild conditions, is especially one of the most effective approaches.

2.17.8.1 Oxidative Decarboxylation Reaction

This oxidative decarboxylation reaction occurs in tandem with a radical reaction. The couple iodosylbenzene iodine ($PhIO/I_2$) or diacetoxyiodobenzene/iodine (DIB/I_2) is usually used, but the best results are obtained with the second reagents couple (equation 81).[123]

In this context, the intramolecular trapping of the *N*-acyliminium ion (**352**) was studied with L-ornithine and L-glutamic acid derivatives. All reactions were conducted in dry solvents (15 ml) at room temperature under nitrogen-containing DIB (2 mmol) and iodine (0.5 equivalent) per mmol of amino acid (**351**).



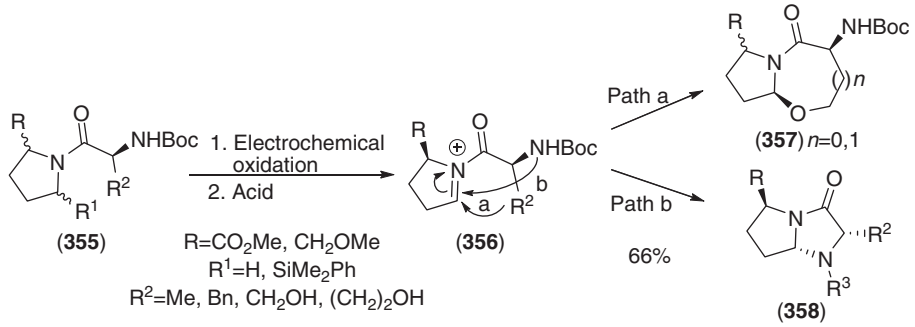
(81)

N-acyliminium intermediate trapping by oxygen and nitrogen nucleophiles

Thus, the decarboxylation of substrate (**351**) (X=Y=O) leads to furanone (**353**) as a single product of the reaction (87%), while amide (**351**) (X=NCO$_2$Me; Y=H,H) provides regioselectively pyrrolidine (**354**) in a slightly lower yield (66%). The reaction is easy to carry out, is done at room temperature, and provides the desired products in high yields and therefore, it was subsequently applied to the synthesis of azasugar and alkaloid analogs, as important families of natural compounds.

2.17.8.2 Electrochemical Oxidation Reaction

A second technique used to generate *N*-acyliminium ions consists of an electrochemical anodic oxidation reaction of amides or lactams. In particular, this reaction applied to properly functionalized dipeptides leads to peptidomimetic scaffolds. This direct route allows the *N*-acyliminium ion formation *in situ* that can be trapped by an oxygen or nitrogen nucleophile. Successful performance of the reaction depends on the intensity and current density, the nature of the electrolyte support and electrodes, the solvent and the number of Faradays used per mole during the electrochemical process.



(82)

Electrochemically generated *N*-acyliminium intermediates trapped by oxygen and nitrogen nucleophiles

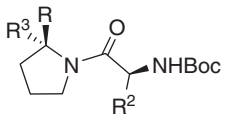
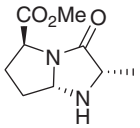
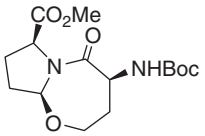
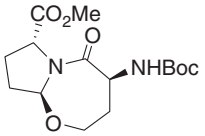
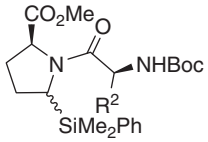
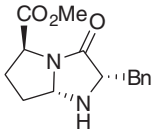
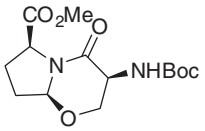
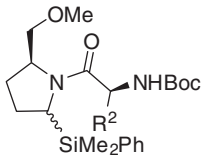
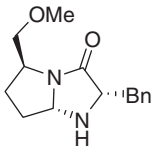
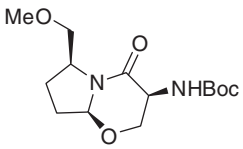
The anodic oxidation of unsubstituted pyridones (**355**) under controlled conditions, in the presence of an acid or not, provides, by interception of the *N*-acyliminium ion intermediate, bicyclic lactams (**357**) and (**358**) in diastereospecific manner, with usual yields ranging from 48% to 52% (entry 1, **Table 19**).[124]

The average yields in some cases are attributed to the presence of several oxidizable sites in α-position of a nitrogen atom on the starting substrates. It was also observed that the presence of a silyl group in the chosen position decreases significantly the oxidation potential of this position (−0.5 V). Applying this observation to silylated substrates (entries 2 and 3) leads, in a single step, to the removing of the silyl group and the generation of an *N*-acyliminium ion. The latter was trapped by an oxygen or nitrogen nucleophile, and consequently generates bicyclic dipeptides that incorporate a heteroatom. The yields obtained in these cases are generally better, and the products are diastereospecifically obtained.[125,126]

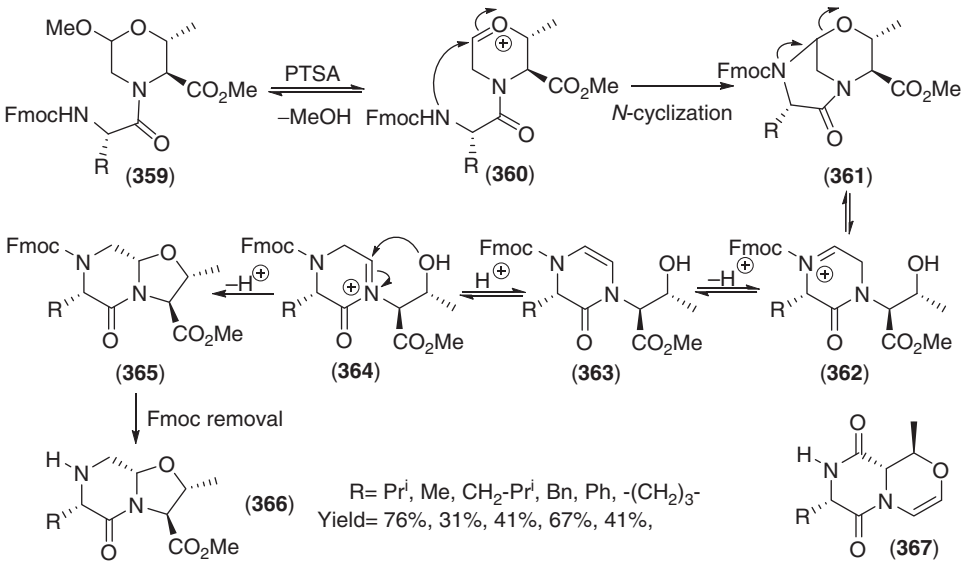
2.17.8.3 Oxa- and Azacyclization in These Complex Processes

Other general approaches have been developed for specific needs, particularly in medicinal chemistry. Among them, an interesting one, corresponding to an oxacyclization following azacyclization of an *N*-acyliminium ion, was explored by Trabocchi and coworkers in their quest for obtaining bicyclic skeletons of pharmaceutical interest.[127] Thus, the treatment of *N*-acylated morpholine acetals by *N*-Fmoc amino acid residues (**359**) leads to two different bicyclic scaffolds (**366**) and (**367**) according to the procedure used. When the PTSA is utilized in stoichiometric amount (e.g., PTSA (1 equivalent), toluene, 4 Å MS, reflux, 2 h), a 'one-pot' procedure provides bicyclic lactams (**366**) with a yield ranging from 31% to 76% (equation 83). No defined product was isolated with cyclopropyl-substituted amino acid.

Table 19 Peptidomimetics by heteroatom *N*-acyliminium trapping (equation 82)[124–126]

Entry	*Substrate*	*Conditions*	*Product*	*Yield (%)*	*References*
1		i. Pt anode, 0.03 mol l^{-1} $Bu^n_4NBF_4$, 21 mA, 5% MeOH/MeCN ii. 2.5 F mol^{-1} iii. BF_3OEt_2, Et_2O, −78 °C up to 0 °C		56	
	R^2 = Me, $(CH_2)_2OH$ R = H, CO_2Me R^3 = CO_2Me, H	i. Pt anode, 1 mol l^{-1} $Bu^n_4NBF_4$, 21 mA, 5% Pr^iOH/MeCN ii. 3.8 F mol^{-1}		48	124
		i. Pt anode, 1 mol l^{-1} $Bu^n_4NBF_4$, 21 mA, 5% Pr^iOH/MeCN ii. 3.8 F mol^{-1}		52	
2		i. RVC anode,[a] Pt wire electrode, 0.03 mol l^{-1} $Bu^n_4NBF_4$, MeOH, 21 mA ii. 2.1 F mol^{-1}; 82% iii. BF_3OEt_2, Et_2O; 75%		61.5	
	R^2 = Bn R^2 = CH_2OH				125
		i. RVC anode, Pt cathode, 0.03 mol l^{-1} $Bu^n_4NBF_4$, MeOH, 21 mA ii. 2.1 F mol^{-1}; 76% iii. 1% TFA, DCM; 81%		61.5	
3		i. RVC anode, Pt wire cathode, 0.03 mol l^{-1} $Bu^n_4NBF_4$, MeOH, 21 mA ii. 2.3 F mol^{-1}; 78% iii. BF_3OEt_2, Et_2O; 71%		55.4	
	R^2 = Bn R^2 = CH_2OH	RVC anode, Pt wire cathode, 0.03 mol l^{-1} $Bu^n_4NBF_4$, MeOH, 2.3 F mol^{-1}, 10% CF_3CH_2OH, MeCN		80	126

[a]Reticulated vitreous carbon (RVC) was used as an electrode material.

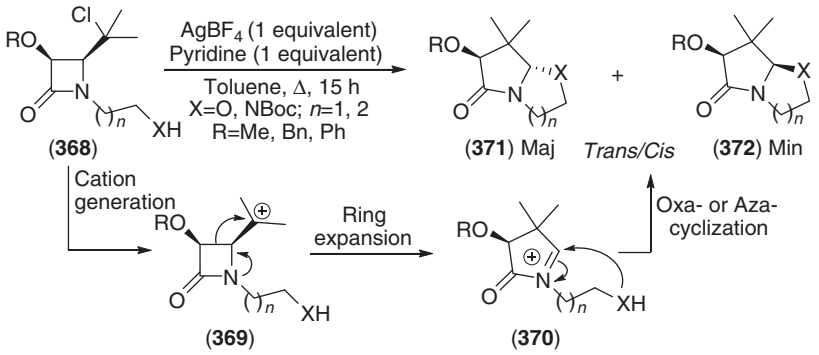


(83)

Stepwise process to bicyclic 2-oxopiperazines

The formation of bicyclic systems (**366**) can be explained by protonation of the acetal and formation of intermediate (**360**). This oxonium ion undergoes intramolecular azacyclization to give unstable *N,O*-bridged bicyclic acetal (**361**). Its cleavage in (**362**), deprotonation in (**363**), and protonation in (**364**) leads to the bicyclic *N,O*-acetal (**365**) in a last step of intramolecular oxacyclization. The ultimate products (**366**) are then generated after deprotection of the Fmoc group (equation 83).

De Kimpe and colleagues. have also developed an original and diastereoselective method to access bicyclic γ-lactams via the expansion of monocyclic β-lactams (equation 84).[128]

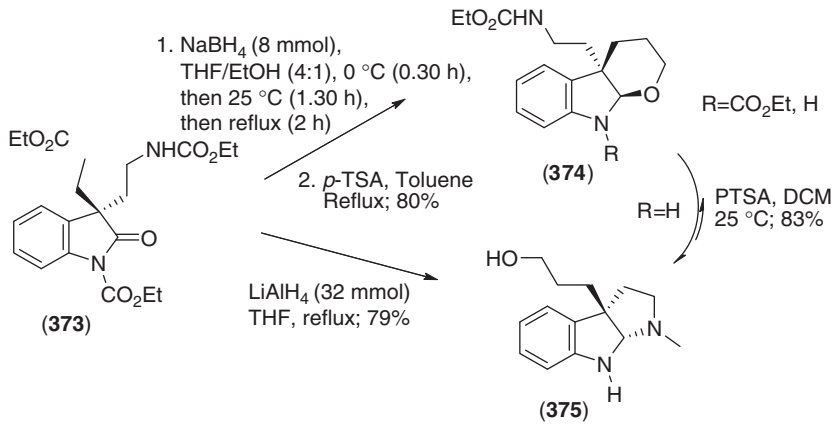


(84)

Stepwise process to bicyclic 2-oxopyrrolidines

Indeed, *cis*-(**368**) was diastereoselectively transformed ($AgBF_4$ (1 equivalent), pyridine (1 equivalent), toluene, reflux) into *trans*-(**371**) and majorly into *trans*-(**372**) (X=O, *trans*/*cis*=63–72/28–37). The formation of these products is the result of the generation of carbocation (**379**), which transposes instantly to the corresponding *N*-acyliminium ion (**380**) that is trapped by the oxygen of the alcohol function (equation 84). Similarly, the *trans* aza-analogs (X=NBoc) of these bicyclic γ-lactams (**371**) and (**372**) are prepared under the same conditions starting from the *cis*-(**408**) (X=NBoc; *trans*/*cis*=70–80/20–30). In this study, it was shown that the diastereoselectivity is higher in the nitrogenated series (X=NBoc) than in the oxygenated one (X=O), and that within the same series, the diastereoselectivity is more important when $n=2$ even if the overall yields are similar, ranging from 48% to 71%.

In a recent approach that targets the synthesis of tetrahydropyrrolo[2,3-*b*]indole core of physostigmine alkaloid, extracted from the calabar bean *Physostigma venenosum* (see Section 2.17.5.5 on the azacyclization in total synthesis), a kinetic versus thermodynamic original equilibrium was explored (equation 85).[129]

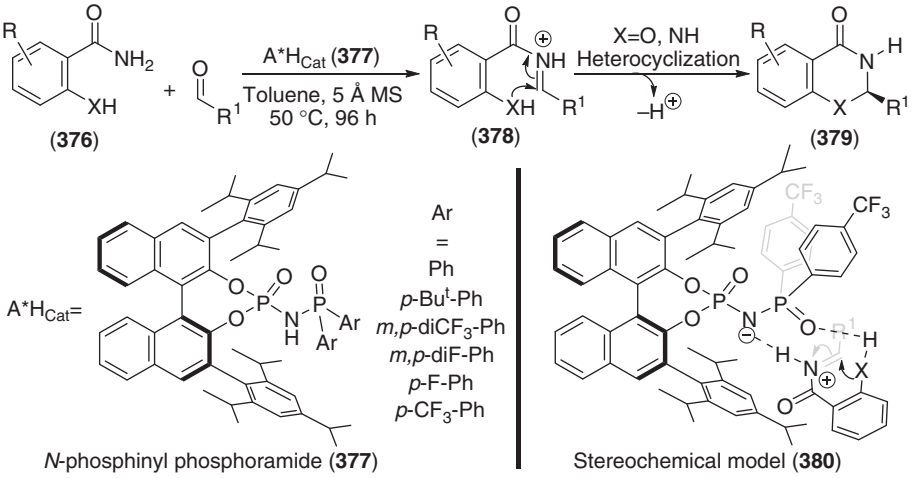


(85)

Preparation of tetrahydropyrroloindole and pyranoindole scaffolds

Thus, it has been shown that **373** can lead to pyranoindole (**374**) or pyrroloindole (**375**) under different reducing conditions. Under mild reducing conditions, it was necessary to use a large excess of hydride ($NaBH_4$) (8 equivalents), and add PTSA to the reaction mixture to generate **374** from the intermediate primary alcohol. In contrast, in the case of $LiAlH_4$, also used in large excess (32 equivalents), it was not necessary to add an acid at the end of the reduction reaction, because only the azacyclization reaction is obtained. In this study, it was shown that treatment of tetrahydropyrroloindole (**375**) in acidic medium (e.g., PTSA, DCM, 25 °C) leads to pyranoindole (**374**) in 83% yield. The equilibrium between these two indole systems (**375**) and (**374**) is largely in favor of (**374**), which is considered as the thermodynamically most stable product of the reaction. These experimental facts were corroborated by calculations of MP2/6–311+G(3*df*,2*p*)//HF-6–31+G(*d*,*p*) that show a ΔG difference in favor of **375** ($\Delta G_{375-374} = -4.1$ kcal mol^{-1}).

A recent work realized by List's team, based on *N*-acyliminium ion heterocyclization, was dedicated to the direct and enantioselective asymmetric synthesis of aldehyde *N*,*O*-acetals (equation 86).[130,131]



(86)

Enantioselective *N*,*O*-acetalization of aldehydes with *N*-phosphinyl phosphoramide

In fact, the reaction of **376** (X=O, R=*p*-Me) with the isovaleric aldehyde in the presence of a catalytic amount (10 mol%) of chiral phosphoric acid ((*S*)-TRIP) at 50 °C provides benzoxazine (**379**) obtained in an *R*/*S* ratio of 3:1 in favor of bicyclic (*R*)-*N*,*O*-acetal. A wide screening showed that, as in the nitrogen atom series leading to enantiopure [1,3]benzdiazines,[130] the *N*-phosphinyl phosphoramide (**377**) with Ar=*p*-CF$_3$-Ph greatly accelerates the reaction progression while operating a remarkable facial differentiation. Thus, only one enantiomer is isolated (*ee*>95:5), and a stereochemical model of reaction **380** has been proposed in equation 86.

The reaction was successfully generalized to different aldehydes with yields ranging from 50% in very few cases to 98% in the best case. Similarly, the enantiomeric excess with this catalyst is very good, and achieved 98.5:1.5 in the best case. Ultimately, the usefulness of this enantioselective approach was demonstrated by the one-step synthesis of chlorothenoxazine starting from 2-hydroxybenzamide and 3-chloropropanal, with an overall yield of 80% (e.g., catalyst **377** with Ar=*p*-CF$_3$-Ph (10 mol%), toluene, 5 Å MS, 50 °C, 96 h). This product of pharmaceutical interest, known for its remarkable analgesic properties, is isolated with reasonable enantioselectivity (*ee*=86:14), which becomes excellent (*ee*=96.5:3.5) after a simple recrystallization from dry methanol.

2.17.9 Concluding Remarks

Considerable efforts have been employed by the chemist community for the development of novel and effective methodologies to provide polycyclic *N*,*X*acetals (X=Carbone, heteroatom). In this chapter, the progress made especially by using the heteroatom oxygen, nitrogen, sulfur, and selenium as internal nucelophiles in the synthesis of natural and nonnatural systems with interests including their use as synthetic intermediates is summarized.

The introductory paragraph highlights the significance of *N*-acyliminium chemistry, especially in the intramolecular construction of carbon–heteroatomic bonds in light of the so documented and largely established carbon–carbon bond forming reactions using the same chemistry. In the next, each heteroatom was treated in separate sections. In each section, the preparation of *N*-acyliminium precursor, the conditions of the implementation of the heterocyclization process, and its application to the synthesis of valuable synthetic intermediates, peptidomimetics, natural products, and/or scaffolds utilized in large scale for industrial uses, either in racemic or asymmetric version has been described.

Ultimately, several developed approaches seemed to be promising and sometimes extendable. However, there are a number of limitations and problems which must be overcome. Among them, substrate limitations are still problems especially in sulfur and more effectively in selenium series, which have now opened new horizons of this chemistry. This constitutes also new synthetic challenges for the community to accede cyclized *N*,*X*-acetal-containing compounds.

Acknowledgments

The authors thank Dr. David F. Perry, Director of Development and International Affairs at HEI, for proofreading the manuscript. The authors also thank the many talented researchers in this field for their contributions, and the University of Le Havre and HEI for their technical assistance.

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