INTRODUCTION TO VOLUME 1: ADDITIONS TO C–X Π-BONDS, PART 1

Aldehydes and ketones and their derived azomethines are electrophiles that are crucial to a diverse array of complexity-building bond constructions in organic chemistry. This volume seeks to build on the foundational work put forth in 1991 describing addition reactions to these versatile functional groups.

The addition of organolithium and Grignard reagents to aldehydes, ketones, and imines are textbook reactions that remain prominent in the field as prototypical methods for chain elongation and fragment assembly. Carbon–carbon bond formation occurs, often in a stereocontrolled manner influenced by resident stereochemistry, with concomitant creation of an oxygen- or nitrogen-bearing stereogenic center. Coupling reactions are also often facilitated at C═O π bonds by virtue of their capacity to participate in olefination reactions that perform admirably in the demanding confines of complex molecule assembly.

Of course, those C═O and C═N functional groups that possess protons at the α-position are susceptible to proton transfer because of the acidifying effect of the π-bond. As will be seen in other volumes, this proton transfer can be productively harnessed for many useful functionalizations at the α-position, but for the purposes of the direct additions to the carbonyl or azomethine described in this volume, the proton transfer can become a pernicious yield-diminishing pathway. Successfully engineering the desired addition mode (relative to undesired enolization) is a continuing challenge in organic chemistry. A number of our chapters detail the development and modern application of organometallic reagents that can exhibit good chemoselectivity for carbonyl or imine addition relative to undesired proton transfer. Synthetic chemists have been successful in creating and developing a toolbox of reagents and conditions where kinetic basicity is attenuated relative to the reagent's nucleophilic character, thus maximizing chemical yield and overall efficiency. Detailed here are the unique properties associated with particular families of organometallic reagents, particularly in the context of carbonyl addition, and situations in which a given organometallic species might be preferred relative to other options.

Aldehydes and ketones are 'gateway' functional groups for other transformations when conjugated to an alkene (e.g., cycloaddition, conjugate addition); therefore, the 1991 work on understanding fundamental interactions between carbonyls and Lewis acids was crucial to an entire generation of chemists interested in the general topic of Lewis acid catalysis. The update of that chapter focuses on nascent carbonyl activation modes that rely on hydrogen bonding, particularly in the context of catalytic addition reactions. Lewis acid activation of the C═X π bonds remains essential to many useful reactions described in the volume.

The interaction of C═X π bonds with neutral species such as ylides or carbenes gives rise to unique reaction pathways that can terminate in small ring formation or products of carbonyl polarity reversal (umpolung), respectively. The former reactions are useful for the synthesis of epoxides and aziridines while the latter reactions allow aldehydes to formally function as acyl nucleophiles in reactions with other π electrophiles.

It will not be a surprise to an observer of this field that a number of our chapters are not updates of the previous edition, but new topics. For example, the enantioselective synthesis of cyanohydrins or α-aminonitriles via addition of cyanide (and its surrogates) to carbonyl and imine electrophiles was a little studied process in 1991, but the intervening years have seen an dramatic uptick in research activity in this field. As a consequence and as detailed herein, access to glycolic and α-amino acid derivatives via this technique is now highly developed. Similarly, the stereoselective addition of heteroatom nucleophiles to aldehydes and imines is a chapter that is new to this edition, fueled by mild catalytic techniques that allow the resulting products to be generated in a manner that ensures their configurational stability.

The collection of chapters in this volume highlights the vibrant, dynamic nature of the synthesis enterprise and the central role played by aldehydes, ketones, and their derivatives. The intervening years since the first edition have reminded us of the versatile reactivity associated with the carbonyl functional group and taught us that much remains to be learned.

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1.01 Carbanions of Alkali and Alkaline-Earth Cations: (II) Selectivity of Carbonyl Addition Reactions

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Glossary

Chiral auxiliary A moiety that is temporarily incorporated into a substrate or reactant whose purpose is to direct the stereochemical outcome of a reaction.

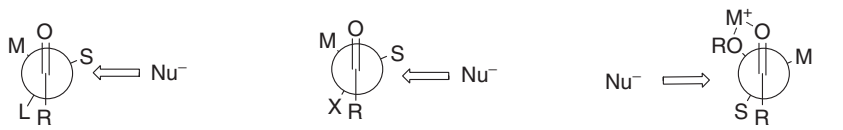
Diastereoselective reaction A reaction that preferentially generates one diastereomer over others.

Enantioselective reaction A reaction that preferentially generates one enantiomer over another.

1.01.1 Introduction

The selective nucleophilic addition of Grignard and organolithium reagents to carbonyl compounds has been the subject of extensive study since the early 1900s when McKenzie described the asymmetric synthesis of α-hydroxy acids from the corresponding chiral α-keto esters.[1] This report, as well as others,[2] is the foundation of the seminal work of Cram,[3] Prelog,[4] Cornforth,[5] Karabatsos,[6] and Felkin,[7] carried out in the 1950s and 1960s, which describes models of the stereochemical outcome of nucleophilic additions to carbonyl groups. This area continues to garner attention, with additional insights and refinements arising from theoretical studies,[8] structural studies and studies on related reactions such as CN additions (*see* Chapter 1.18) and reductions (*see* Volume 8, Chapter 8.01).

As excellent reviews of this area are available in a number of sources,[9,10] only a brief account of the relevant aspects of these models is described below. Cram's 'open-chain model' concerns the addition of a nucleophile to a simple α-alkyl-substituted carbonyl compound.[3a] Disposition of the carbonyl oxygen and the largest α-substituent (relative sizes of the substituents are designated L, M, and S) in an *anti*-relationship is preferred due to steric constraints, and nucleophilic addition occurs from the side of the smallest substituent (S) (**Figure 1(a)**). This model was found to be unreliable in the case of α-halocarbonyls,



(a) Open-chain model (b) Cornforth dipolar model (c) Cyclic chelation model

Figure 1 Historical models of nucleophilic additions to carbonyl compounds: (a) open-chain model; (b) Cornforth model; and (c) cyclic chelation model.

and Cornforth proposed that the carbonyl and carbon–halogen (or any electron-withdrawing group) dipoles prefer an *anti*-orientation, such as shown in Figure 1(b) (X=polar group). This effect overcomes any steric factors of the other α-substituents, and nucleophilic attack takes place from the less-encumbered face.[4] When an α-substituent capable of coordination is present, the 'cyclic chelation model' is invoked. The favored conformation results from formation of a chelate between the cationic reagent (M^+), the carbonyl oxygen, and the coordinating substituent. Addition then occurs from the least-hindered trajectory (Figure 1(c)).[3b]

The design of reactions based on these models, in particular the cyclic chelation-control model, can lead to high stereoselectivities. However, discrepancies between theoretical and experimental results led to the development of alternative theories. Among these, the work of Felkin and coworkers[7] has gained the most acceptance. In an open-chain model, orientation of the largest α-substituent in a conformation perpendicular to the carbonyl group is considered most relevant (Figure 2). Because the carbonyl oxygen is deemed less sterically demanding than the substituent bonded directly to the carbonyl carbon (R), conformation a is favored over b. Calculations by Anh and Eisenstein[11] support the results derived from the Felkin model; however, they propose a different course of nucleophilic attack. These workers suggest that with the carbonyl substrate in a conformation like that proposed by Felkin, the reacting nucleophile approaches not perpendicularly to the carbonyl bond, but tilted away from it. Preferential attack occurs on a trajectory closest to the smallest substituent (Figure 3(a)). Debate still continues on which of these models is most accurate in predicting the course and outcome of a given reaction.[10] For the purpose of this discussion, the term 'cyclic chelation control' will be used to describe those reactions which adhere to the model depicted in Figure 1(c). 'Felkin–Anh' or 'nonchelation control' will refer to selective additions that can be described by models such as those shown in Figure 3(a).

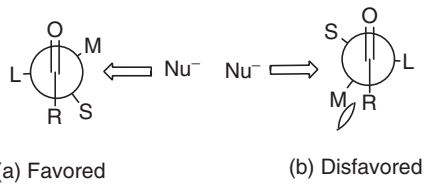


Figure 2 Felkin model of nucleophilic additions to carbonyl compounds: (a) favored conformation and (b) disfavored conformation.

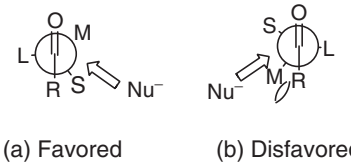


Figure 3 Felkin–Ahn model of nucleophilic additions to carbonyl compounds: (a) favored conformation and (b) disfavored conformation.

Although these models are often useful in predicting the outcome of a reaction in a qualitative sense, the degree of stereoselectivity can be affected by simple changes in reaction conditions. Solvent, temperature, and specific organometallic reagent, among other factors, play a vital role in determining which of the reaction modes predominates, and simple modification of these conditions can enhance, diminish, or even reverse stereoselectivities.[12,13]

Through the early 1990s, there was considerable research activity on the selective addition of organolithium and Grignard reagents to carbonyl compounds. Progress in the general area of selective nucleophilic addition to carbonyl compounds has exploded in the past 20 years, however, the use of alkali and alkali earth cations in these reactions has been eclipsed somewhat by advances utilizing other metal-based reagents, such as titanium and zinc (*see* Chapters 1.05 and 1.07). These reagents typically lead to high selectivities and yields, and take place under relatively mild reaction conditions. In addition, they can often be rendered catalytic. Challenges in using organolithium or Grignard reactions include: (1) their high reactivity and therefore reduced selectivity; (2) their tendency to engage in other chemistries such as deprotonation; (3) their capacity to complex with solvent and additives to form mixtures of higher-order structures that may react at different rates and with different selectivities; and (4) their difficulty in handling. Some common themes over the past 20 years in this area include understanding and controlling the nature of the reacting organometallic species as well as the carbonyl substrate, modulating the reactivity of reagents, and attempting to develop catalytic methods. This chapter focuses on the most selective methods, those that are most widely used, and recent work on the selective addition of carbon nucleophiles generated from organolithium and organomagnesium reagents to carbonyl compounds.

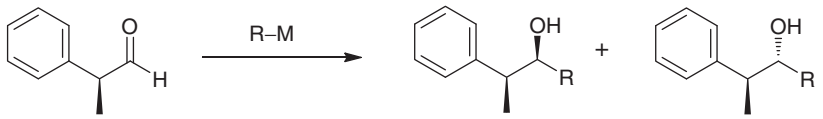
1.01.2 Additions of Achiral Reagents to Chiral Substrates

1.01.2.1 Additions to Acyclic Systems

1.01.2.1.1 1,2-Selectivity

1.01.2.1.1.1 α-Alkyl carbonyl substrates

The diastereoselective addition of organolithium and Grignard reagents to simple carbon substituted carbonyls through a Felkin–Ahn transition state typically results in modest and variable selectivities. Although specific reactions can be optimized, the product ratios are difficult to predict and depend on numerous factors including the specific substrate, specific organometallic reagent,[14] solvent, additives, and temperature.[15,16,17] General solutions to obtaining high yields of Felkin–Ahn products (e.g., **1**, equation 1) include using additives such as crown ethers that eliminate the chelation-control pathway[18] or specific metal ligands such as magnesium tosylates, rather than standard Grignard reagents.[19] Table 1 illustrates the effect of these reaction modifications of the stereoselective addition of organometallics to a simple α-methyl aldehyde.

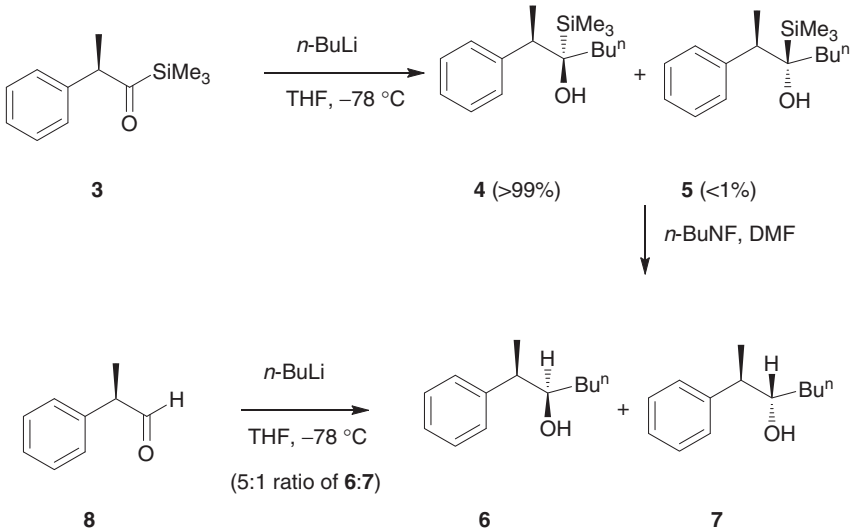


1 (Felkin–Ahn product) **2** (1)

Table 1 General conditions to favor Felkin–Ahn products (equation 1)

R–M	*Additive*	*Yield (%)*	*Ratio of 1:2*	*References*
n-Bu–Li	–	91	83:16	18
n-Bu–Li	15-crown-5	91	>97:3	18
Me–MgCl	–	>80	70:30	19
Me–MgOTs	–	76	92:8	19

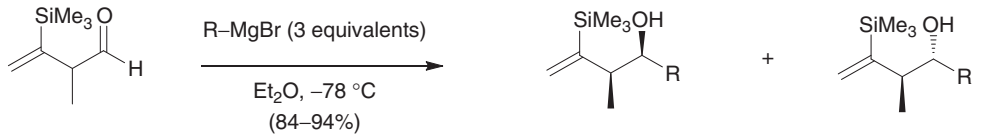
Another strategy replaces the aldehyde function with an acylsilane (Scheme 1).[20] In one representative example, treatment of the acylsilane **3** with *n*-butyllithium afforded excellent selectivity (>99%) of the Felkin–Ahn product **4**. The silane was readily replaced with hydrogen to generate the products of formal addition to the aldehyde, **6** and **7**. In contrast, addition of *n*-butyllithium to the aldehyde **8** gave products **6** and **7** in a ratio of 5:1. The authors suggest that that larger silyl group (compared with a hydrogen atom) reinforces the preference for a Felkin–Ahn type transition state.



Scheme 1 Diastereoselective addition to acyl silane **3**.

Sato and coworkers exploited the bulky trimethylsilyl group in the β-position of an aldehyde to increase the steric bulk, and therefore favor a Felkin–Ahn transition state during the course of 1,2 addition reactions.[21] Reaction of **9** with ethyl, isopropyl, or phenyl

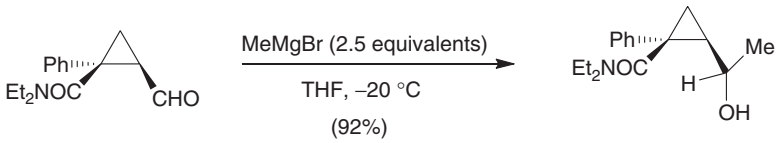
Grignard reagents produced the *syn*-product **10** exclusively; methyl Grignard afforded a 91:1 *syn*:*anti* ratio (equation 2). This methodology offers a number of options for further chemistry: oxidation of the alcohol **10** followed by reduction afforded the *anti*-product **11**, protodesilation generated the homoallylic alcohol, and a three-step sequence converted the vinylsilane into a ketone group. The steric demands of the β-trimethylsilyl group also overrode any effects of a chelating group, like a methyl ether, in the α-position.[22]



(2)

9 **10** (*syn*) **11** (*anti*)

Additions of Grignard reagents to cyclopropyl aldehydes occur with very high selectivity due to the strong conformational bias of the substrate. Reaction of cyclopropyl aldehyde **12** with MeMgBr generated the alcohol **13** almost exclusively (equation 3).[23] The conformational preference of the substrate for the s-*trans*-conformation (Figure 4) is thought to control the selectivity of the reaction.



(3)

12 **13**

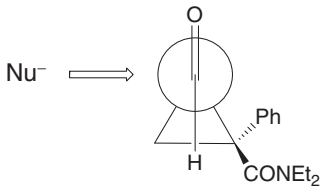
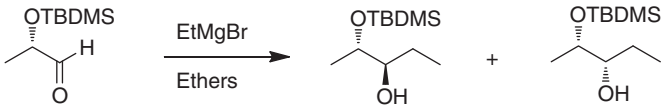


Figure 4 Proposed transition state of nucleophilic additions to **12**.

1.01.2.1.1.2 α-Heteroatom carbonyl substrates

When the carbonyl substrate contains a heteroatom in the α-position, high selectivities can sometimes be achieved by exploiting options for incorporating either strongly chelating moieties that favor the chelation-controlled transition state or nonchelating, sterically demanding protecting groups that favor the Felkin–Ahn conformation. However, as described above, ratios can vary widely and depend on the specific substrate, reagent, solvent, temperature, and the use of additives. In particular, solvents capable of competing with chelating groups often have a significant effect on diastereoselectivities, and therefore generalized solutions have not yet been achieved.[9,12,15,24] One striking example of the sensitivity to reaction conditions is the recent work that highlights an important role for solute–solvent effects.[25] Examples of the profound effects of solvent and temperature on selectivity in addition reactions to α-hydroxy aldehyde **14** is highlighted in Table 2. Modest changes in solvent (various ethers) and temperature influenced the distribution of the products **15** and **16**, and even reversed the selectivity when anisole was used. This work emphasizes the variability that is often observed in these reactions.[26]



(4)

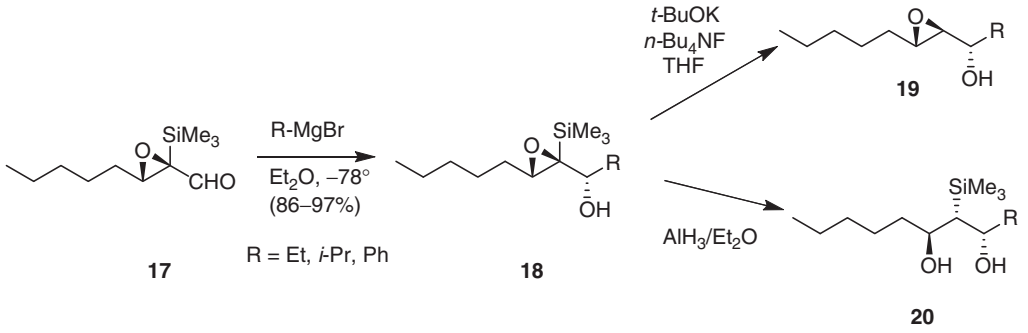
14 **15** (*anti*) **16** (*syn*)

Table 2 Effects of solvent and temperature on diastereoselectivity of reaction of EtMgBr with **14**

Solvent	*Temperature (°C)*	***15*:*16*** *(anti:syn)*
THF	–45	77:23
Et_2O	–94	81:19
Et_2O	15	60:40
Anisole	–30	39:61

Abbreviation: THF, tetrahydrofuran.

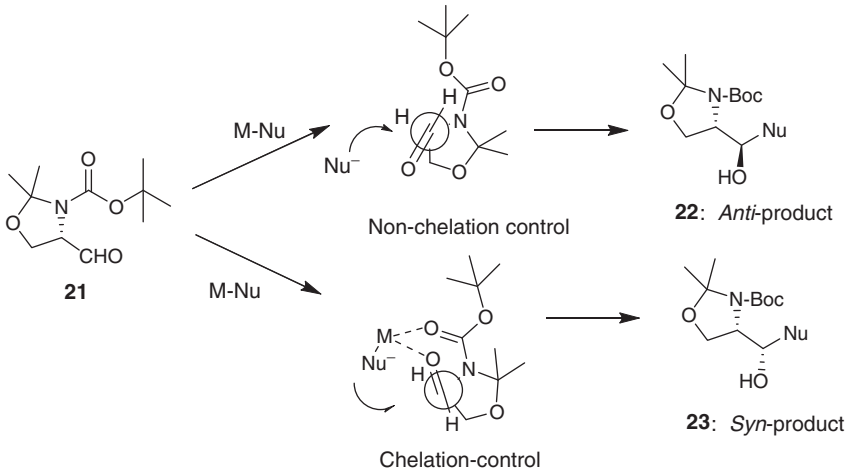
Although accurately predicting the diastereoselectivity of additions to α-hydroxy carbonyl compounds is often challenging, when the α-hydroxy substituent is constrained by incorporation into a ring, high selectivities are often observed. α-Silyl-α,β-epoxy aldehydes such as **17** reacted with organometallic reagents to afford the *anti*-epoxy alcohol (e.g., **18**) as the major product in ratios ranging from 7.9:1 to 26:1 (Scheme 2).[27] The presence of the silyl group was essential for the high selectivities observed. The products were transformed into useful intermediates through protodesilation or epoxide opening to provide compounds such as **19** or **20**, respectively.



Scheme 2 Diastereoselective addition of Grignard reagents to **17**.

In contrast to the case of α-hydroxy-aldehyde and ketone substrates, a number of consistently reliable methods to obtain either the chelation-control or nonchelation-control product from chiral α-amino carbonyl compounds have been reported via the use of appropriate nitrogen-protecting groups. These efforts have been facilitated by the increasing number of diverse amino acids (natural and unnatural) that have become available from commercial sources and via synthesis, and their use as starting materials. In general, small nitrogen substituents favor chelation-control transition states and produce the *syn*-amino alcohol products; sterically demanding protecting groups generate the *anti*-amino alcohol through a Felkin–Ahn model. Both mechanisms, and therefore poor selectivities, are usually observed when the nitrogen groups are of moderate size or when the nitrogen moiety is monoprotected. In addition to defining the reaction course, the appropriate *N*-protecting group is essential to ensure configurational stability of the aldehyde or ketone starting material.[28,29]

Garner's aldehyde, **21**,[30] prepared from serine, is a configurationally stable, differentially protected amino aldehyde that has been extensively used in the total synthesis of diverse natural products. The availability of both antipodes, the ease of deprotection, and the versatility of the aldehyde functional group allow considerable flexibility for subsequent synthetic steps. In addition, **21** is readily available on large scale, and can exhibit high stereoselectivities upon reaction with Grignard and organolithium reagents with appropriate reaction conditions.[31] *Anti*-products (e.g., **22**) result from nonchelating conditions (potentially through a Cornforth model); the *syn*-adduct (e.g., **23**) can be generated under conditions that favor chelation. Scheme 3 illustrates both transition states.



Scheme 3 Nucleophilic addition to Garner's aldehyde via nonchelation and chelation-control mechanisms.

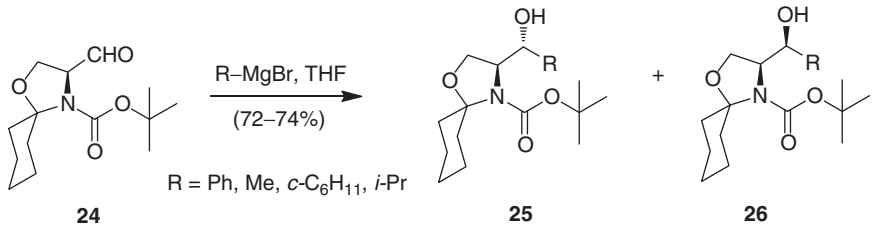
Recent examples of the versatility and limitations of nucleophilic additions to this amino-aldehyde are highlighted in Table 3. Addition of a lithium acetylide in the presence of the cation complexing agent hexamethylphosphorous triamide (HMPT) in order to favor nonchelation control afforded excellent selectivity for the *anti*-adduct. Using chelating conditions (e.g., Grignard reagent and CuI) reversed the disastereoselectivity.[32] Selectivities for acetylide additions to Garner's aldehyde are often excellent;[14] in contrast, the addition of alkyl organometallics (e.g., *n*-Bu-M) usually yields only modest disastereoselectivities. These ratios can be improved with the use of additives such as $MgBr_2$.[33] Hamada[34] and Nakagawa[35] studied the addition of aryl-metal reagents to Garner's aldehyde. Modest *anti*-selectivities were observed using the lithium reagents, and the Grignard reagents were even less selective. However, Casiraghi and coworkers reported that addition of Mg-phenolates to Garner's aldehyde afforded excellent *syn*-diastereoselectivity, presumably through a chelation-controlled mechanism.[36] Additions of dithianes were reported by Fujisawa, and under optimized conditions occurred with virtually complete stereocontrol to provide the *anti*-product.[37]

Table 3 Selectivities observed on addition of nucleophiles to Garner's aldehyde **21** (Scheme 3)

M–Nu	*Additive*	*Solvent*	*Anti:Syn*	*Yield (%)*	*References*
Li—≡—$SiMe_3$	HMPT	THF	95:5	85	32
BrMg—≡—$SiMe_3$	CuI	THF/SMe_2	5:95	86	32
n-Bu–MgBr		THF	76:24	[a]	33
n-Bu–Li		THF	70:30	[a]	33
n-Bu–MgBr	$MgBr_2$ (catalyst)	THF	88:12	[a]	33
BrMg—C$_6$H$_4$—OBn		THF	50:50	50	34
Li—C$_6$H$_4$—OBn		THF	80:20	50	34
Li—C$_6$H$_5$	HMPT	THF	80:20	33	35
BrMgO—C$_6$H$_4$—*t*-Bu		CH_2Cl_2	4:96	72	36
Li—S,S-dithiane		THF	70:30	96	37
Li—S,S-dithiane	BF_3–OEt_2/CuI	THF	>99:<1	70	37

[a]Not reported.

By replacing the *gem*-dimethyl substituent in Garner's aldehyde with a sterically more demanding *spiro*-cyclohexyl group (**24**), Joullié found improved diastereoselectivities in the addition of phenyllithium (89:11 ratio of **25** to **26** (R = Ph) compared with the 83:17 ratio obtained using Garner's aldehyde; equation 5).[38] However, she also observed a reversal of selectivity for certain Grignard reagents under the same reaction conditions. For example, addition of cyclohexyl Grignard to **24** afforded the *anti* and *syn* products in a ratio of 6:94, presumably through a chelation-controlled transition state. A rationale for this divergence was based on the reactivity of the Grignard reagent. Additions using more reactive Grignards (e.g., Me and Ph) occurred under kinetic control, before chelation occured. The less reactive reagents (e.g., *i*-Pr and *c*-C_6H_{11}) allowed the chelate to form, and proceeded through a transition state where *syn*-selective products predominated.



(5)

Garner's aldehyde, first described in 1984, continues to find wide use in the synthetic chemistry community as a starting material for the syntheses of diverse natural products and medicinally relevant compounds.[31] It is interesting to note that despite some of the modest selectivities observed in nucleophilic additions, practical syntheses can be developed. The synthetically useful

and somewhat predictable diastereoselectivities that can often be upgraded through reaction optimization and the availability of efficient separation technologies likely contribute to the continuing popularity of this starting material.

Reetz exploited the *N*,*N*-dibenzyl protecting group to enforce nonchelation-control addition of carbanions to α-amino carbonyls. Very high diastereoselectivities were observed based on a Felkin–Ahn transition state (Figure 5), regardless of the reagent or specific nature of the substrate.[39] For example, reaction of the alanal derivative (**27**; R = Me) with MeMgBr or MeLi resulted in the *syn* (**28**; R = Me) and *anti* (**29**; R = Me) products in ratios of 5:95 and 9:91, respectively. The entries in Table 4 reflect the consistency of obtaining the nonchelation-control products and the range of substrates and reagents that are amenable to this strategy. The related *N*,*N*-dibenzyl ketones afforded tertiary alcohols with similarly high diastereoselectivities. Ratios deteriorated, however, with the most reactive reagents such as allyl Grignard reagents and when the substrate contained multiple functional groups that are capable of chelation (e.g., R = CH(Me)OBn). In those examples, transmetalation to less reactive organometallics (e.g., titanium) was often a solution.[40,41] The relative ease of removal of the dibenzyl protecting group and the high *anti*-diastereoselectivity makes this strategy very effective for generating the α-amino alcohols that are often a feature of biologically active molecules.

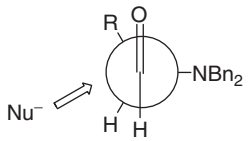
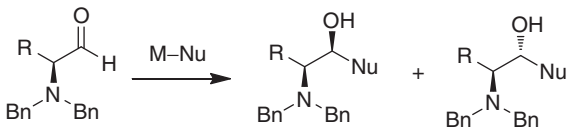


Figure 5 Transition state of nucleophilic additions to *N*,*N*-dibenzyl amino aldehydes **27**.



(6)

27 **28** (*syn*) **29** (*anti*)

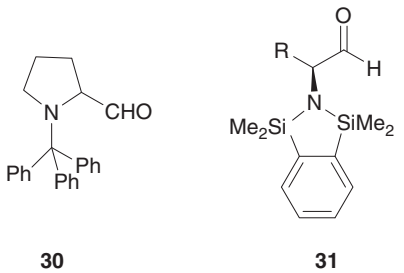
Table 4 Selectivity of nucleophilic additions to *N*,*N*-dibenzyl amino aldehydes **27**

M–Nu	*R*	*Yield (%)*	***28*** *(syn)*:***29*** *(anti)*
Me–MgI	Me	87	5:95
Me–Li	Me	91	9:91
t-Bu–Li	Me	88	<3:>97
Me–MgI	Bn	85	8:92
Allyl–MgCl	Bn	82	28:72
Me–MgI	*t*-Bu	85	10:90
n-Bu–Li	CH_2O–Si(*t*-Bu)Me_2	30	<5:>95
Me–Li	CH(Me)OBn	82	48:52
Me–MgI	CH(Me)OBn	87	15:85

The rationale for the high selectivity observed in these reactions is not completely understood.[41] However, the current line of thinking suggests that a steric model based on ground state conformational properties can be used to explain the selectivities observed. This hypothesis is supported by observations of little or no selectivity on additions of organometallic reagents to *N*,*N*-dimethylalanal and other amino-aldehydes containing less sterically demanding protecting groups.

The use of sterically demanding nitrogen-protecting groups has been applied to other α-amino carbonyl substrates. The trityl (as in **30**)[42] and the benzostabase (as in **31**) protecting groups[43] were used to direct nucleophilic additions through a Felkin–Ahn model. In both examples, high proportions of the *anti*-product using both organolithium and Grignard reagents (often >95:5) were reported (Figure 6).

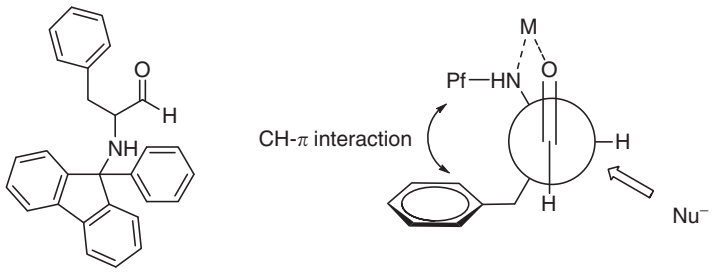
Although *anti*-α-amino alcohol products are readily accessible, the *syn* products are more difficult to consistently produce. An anomalous result reported by Park and coworkers suggested one potential strategy that relies on CH–π interactions to influence the transition state.[44] When investigating the nucleophilic addition of ethynyl Grignards to aromatic α-amino aldehydes protected with a 9-phenylfluoren-9-yl group (Pf) such as in **32** (Figure 7) the *syn*-product predominated rather than the expected *anti*-adduct. The authors propose that a CH–π interaction between the aromatic substituent and a hydrogen atom of the Pf group favor a chelation-control transition state such as the one illustrated in Figure 7. This interaction can be seen in X-ray structures of the



30 **31**

Figure 6 Structures of compounds **30** and **31**.

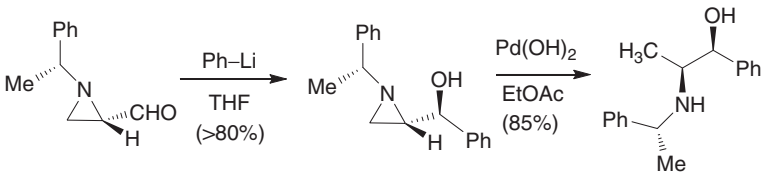
substrate, and explains the high *syn*-selectivity (9–10:1) observed with aromatic amino alcohol substrates compared with the corresponding aliphatic substrates (~2:1 ratio).



32

Figure 7 Structure of compound **32** and proposed transition state for nucleophilic addition.

The aziridine ring has also been exploited to prepare 1,2-amino alcohols from the corresponding carbonyl derivative. By 'embedding' the nitrogen lone pair into an aziridine, these substrates are chemically and configurationally stable, and can reliably participate in chelation-controlled reactions. However, this area is still evolving; the nature of the substrate (e.g., *cis* vs. *trans*-aziridine), the *N*-substituent and the specific nucleophile can drastically influence the levels of diastereoselectivities observed. Scheme 4 illustrates one example where high selectivities were reported: reaction of phenyllithium with aziridine **33** generated the aziridinyl alcohol **34** as the major isomer (>90:10). Opening of the aziridine with Pearlman's catalyst led to 1,2-amino alcohol **35** in good yield. Highest stereoselectivities were achieved by using aryllithiums instead of Grignards, tetrahydrofuran (THF) as solvent and LiCl as an additive.[45]



33 **34** (Major isomer) **35**

Scheme 4 Reaction of azirindyl aldehyde **33** with PhLi and conversion to amino alcohols.

Use of Boc-protected *trans*-aziridine aldehydes (e.g., **36**) as a substrate gave similar results, with the Grignard reaction proceeding through a chelation-control mechanism to afford high levels of the diastereomer **37**, presumably through a transition state such as shown in Figure 8.[46] Direct addition of $MgBr_2$ to the Grignard product generated the *anti*,*syn*-1-bromo,2,3-amino

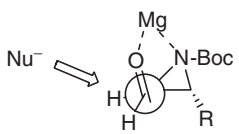
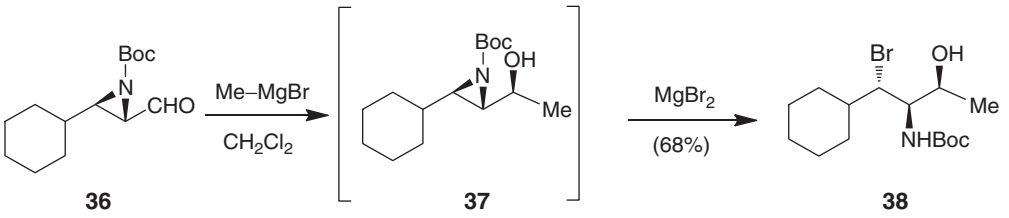


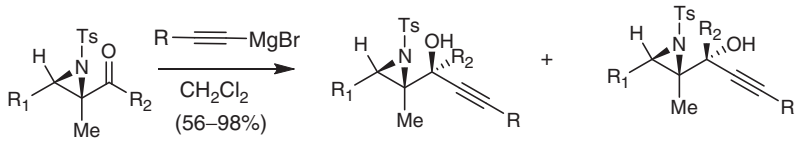
Figure 8 Proposed chelation-controlled transition state for nucleophilic addition to **36**.

alcohols **38** (equation 7). This method provides ready access to three contiguous stereocenters that can be further manipulated. The corresponding *cis*-aziridines did not react with any selectivity. Poor to modest selectivity (3–5:1) using benzyl-protected *cis*-aziridines was also reported by Pedrosa and coworkers.[47]



36 **37** **38** (7)

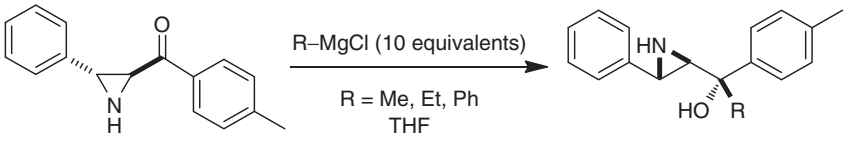
Tosyl-protected 2,2,3-trisubstitued aziridinyl aldehydes and ketones (**39**, equation 8; $R^1 = CH_2OBn$, Ph; $R^2 = H$, Me) underwent reaction with alkynyl Grignards (R = H, Me, Ph, and TMS) to generate the *syn*-aziridinol **40** as the major product and only minor amounts of the *anti*-product **41** (>97:3).[48] The authors questioned the role of chelation control in these reactions, as the addition of the complexing agent tetramethylethylenediamine had no effect on selectivities.



39 **40** (*syn*, major) **41** (*anti*, minor) (8)

A comprehensive study to understand the roles of substrate structure (aziridine stereochemistry, aziridine substitution, and *N*-protecting group) and organometallic reagent on the selectivity observed in these reactions was reported by Borhan.[49] The authors concluded that the course of the reaction is controlled by multiple, interrelated factors such as the orientation of the aldehyde, the conformation of the aziridine, the electronic nature of the *N*-substituent, and the aziridine's steric environment. General trends are that high selectivities can be achieved with benzyl-protected *cis*-aziridines, *N*-tosyl-2,3-disubstituted aziridines, and *N*-Boc-*trans*-aziridines. Modest selectivities are observed using *N*-tosyl-trans-aziridines; and little preference is observed when benzyl-protected *trans*-aziridines, *N*-Boc-*cis*- and *N*-Boc-2,3-disubstitited aziridines, and *N*-tosyl-*cis*-aziridines are substrates. Poor selectivities are likely due to a lack of conformational preference of the electrophile.

A few examples of nucleophilic addition to unprotected azirdinyl ketone **42** were reported to generate only one diastereomer, **43** (equation 9). The reaction, which requires an excess of Grignard reagent, was proposed to proceed through a magnesium chelate intermediate (**Figure 9**).[50] Further studies to explore the generality of this protocol are warranted.



42 **43** (9)

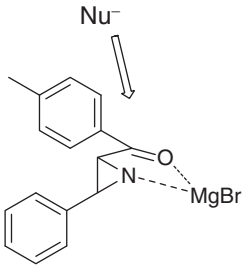
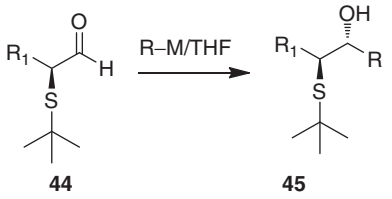


Figure 9 Transition state of nucleophilic addition to **42**.

Additions of nucleophiles to other α-heteroatom aldehydes and ketones have been less well studied. In one example, Enders reported that the addition of Grignards and organolithiums to α-sulfenylated aldehydes **44** generated the vicinal *anti*-thioether

alcohols **45** (equation 10) with high diastereoselectivity (>90% *de*) in virtually all cases examined (Table 5). Least selective examples were those that employed a highly reactive organometallic, such as allyl or methyl Grignard. [51]



44 **45** (10)

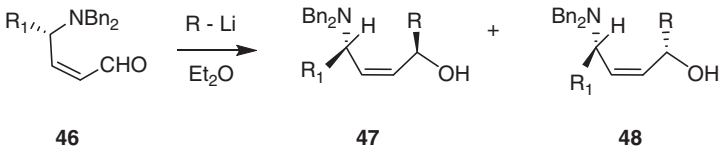
Table 5 Selectivity of nucleophilic addition to **44** (equation 10)

R[1]	*R–M*	*Yield (%)*	*de* of ***45*** *(%)*
n-Pr	Bn–MgBr	54	98
i-Pr	Bn–MgBr	68	97
c-$C_6H_{11}CH_2$	Bn–MgBr	53	98
Bn	Me–MgBr	84	82
Bn	Ph–MgBr	62	95
Bn	Ph–C≡C–Li	62	95
Bn	Allyl–MgBr	51	46

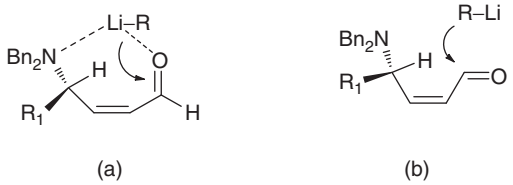
1.01.2.1.2 1,3-, 1,4- and remote asymmetric induction

Typically, nucleophilic addition reactions of Grignard or organolithium reagents to *β*-chiral or other remotely chiral acyclic carbonyl compounds yield mixtures of diastereomers that are not synthetically useful.[15,16,24] This outcome can be explained by the increasing distance of the asymmetric center from the reaction center, and therefore a reduced influence that does not strongly favor one transition state over another. However, notable exceptions exist, and this area has seen significant advances in the past several years. In many of these cases, the selectivities are controlled by conformational constraints imposed by the substrate and/or a remote functional group that chelates to the incoming nucleophile and generates a stable macromolecular transition state.[52] For the purpose of this chapter, the discussion will focus on examples of highly selective remote asymmetric inductions involving both acyclic as well as cyclic systems. Although the selectivities of these remote asymmetric inductions can be high, the specific structural requirements of the substrate are not often amenable to broadly general solutions. An exception is the case of chiral auxiliaries, which are discussed in Section 1.01.2.1.3.

Reetz reported 1,4-asymmetric induction using *N*-dibenzyl-*Z*-enals such as **46** (equation 11).[53] When treated with organolithium reagents, the product **47** was preferentially formed in very good to excellent selectivities (>80:20). This stereochemistry was rationalized by either chelation followed by intramolecular delivery of the nucleophile as in Figure 10(a) or by the possibility that the enal was conformationally locked due to 1,3-allylic strain (Figure 10(b)). A range of substituents at R was tolerated, as were a range of organolithiums (see Table 6). Under the same reaction conditions, the corresponding *E*-isomer provided no selectivity, a finding that is consistent with both chelation and conformational arguments.



46 **47** **48** (11)



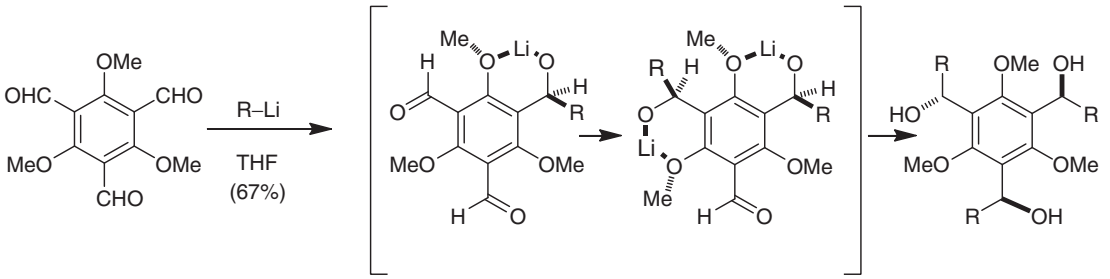
(a) (b)

Figure 10 Possible transition states for addition of nucleophiles to **46**: (a) intramolecular delivery mechanism and (b) conformationally locked mechanism.

Table 6 Selectivities of addition of organolithium reagents to **46** (equation 11)

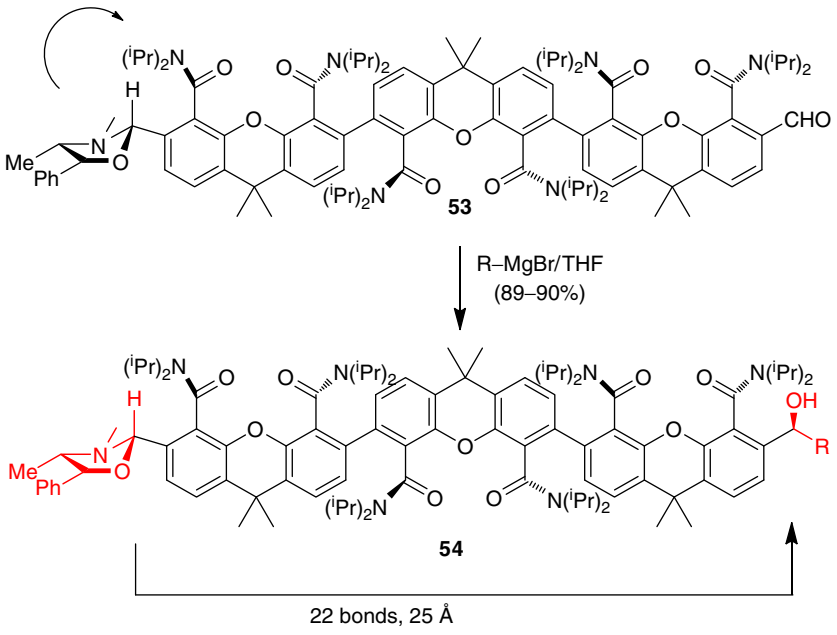
R^1	R	Yield (%)	Ratio **47:48**
Me	Me	79	87:13
Me	*n*-Bu	84	88:12
Bn	Me	81	86:14
Bn	Ph	84	91:9
i-Bu	Me	79	91:9
i-Bu	*n*-Bu	82	93:7

1,5-asymmetric induction was reported in the addition of organometallics to a crowded aromatic core.[54] This example highlights the use of densely functionalized systems that display strong conformational preferences. Although this example is not likely to find general use, it is included here as an illustration of the strategy employed. When the trialdehyde **49** was treated with excess of Ph–Li or Ph–MgBr, only the racemic *anti,syn* isomer **52** was isolated, via 1,5-asymmetric induction (equation 12). The intermediates **50** and **51**, depicting the first and second addition products, were proposed to explain the selectivity, which is based on chelation and steric control within the highly crowded aromatic core. This example of asymmetric induction without benefit of a true 'chiral' reagent or substrate relied on rigid scaffolding to control the selectivity.



49 **50** **51** **52** (12)

Clayden and coworkers used similar principles to induce what they call 'ultra-remote' stereocontrol.[55] In the most extreme example, a *tris*-xanthene system was designed to adopt a specific conformation wherein the amide groups prefer an *anti*-orientation in order to minimize the overall dipole. Incorporating a chiral oxazolidine ring into the system (**53**) influenced the conformation of the adjacent amide, and that conformational influence was transmitted through the rest of the molecule. Reaction of Et–MgBr or Ph–MgBr with **53** afforded one diasteromeric alcohol **54** with >95% diastereoselectivity (equation 13). The asymmetry at the oxazolidine ring was transmitted through 22 bonds, and a linear distance of more than 25 Å. Although this system is highly designed, it highlights a successful strategy for remote asymmetric induction through careful control of conformation.

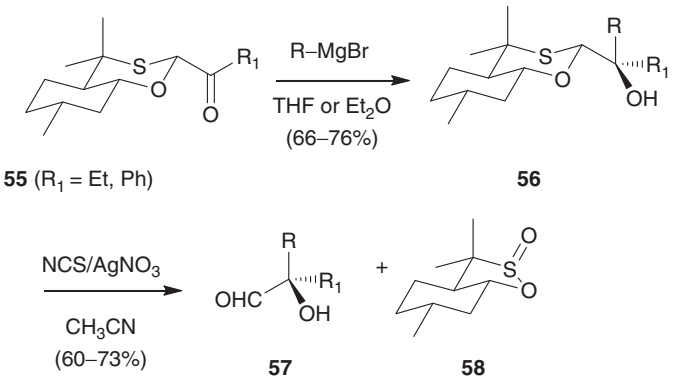


(13)

1.01.2.1.3 Chiral auxiliaries

A special class of acyclic diastereoselective reactions involves the use of chiral auxiliaries to control the absolute stereochemistry of nucleophilic additions at carbonyl centers. This process takes advantage of steric and/or electronic factors within the chiral adjuvant to selectively promote nucleophilic addition from one face of the molecule, and thereby generates one predictable diastereomer. Removal of the auxiliary, in the best cases, generates enantiomerically pure products, as well as the reusable chiral auxiliary. The end result of this process is the synthesis of enantiomerically pure products via diastereoselective reactions. Particularly effective strategies are those in which the chiral auxiliary also acts as a handle for further chemical manipulation.

Eliel has extensively studied heteroatom-containing formyl equivalents as chiral auxiliaries to control the addition of organometallics to ketones; removal of the auxiliary affords a chiral α-hydroxy-aldehyde. The chiral bicyclic 1,3 oxathiane ketone **55** (Scheme 5), synthesized from (+)-pulegone, represents the most developed system.[56] Nucleophilic addition of Grignard reagents such as MeMgBr, EtMgBr, and *n*-PrMgBr occurred with excellent diastereoselectivity to produce **56**, which on cleavage generated chiral α-hydroxy aldehyde **57** in *ee*s ranging from 90% to 100%. The sultine **58** that is formed was used to regenerate the chiral auxiliary. Either enantiomer of **57** was available by using the diastereomeric oxathiane or by reversing the order of R-group addition. A Cram cyclic chelation model for nucleophilic addition is supported by experimental evidence[57] and involves chelation of the Grignard reagent to the ketone and hard oxygen atom of the oxathiane ring (in preference to the soft sulfur atom), followed by intramolecular addition from the less-hindered side of the auxiliary (Figure 11).[58] In substrates where the ketone substituent R_1 is also capable of chelation (e.g., $R^1 = (CH_2)_xOBn$), erosion and even reversal of selectivities occurred due to competition between the auxiliary and the R^1 side chain for chelation with the organometallic reagent. In these examples, use of a bulky, nonchelating protecting group such as triisopropylsilyl (e.g., $R^1 = (CH_2)_xO$-TIPS) resulted in excellent selectivities. Further studies on more highly substituted ketone substituents and the use of organolithium reagents indicated that in certain cases, the reaction pathway can be strongly influenced by chelation as well as steric effects.[59]



Scheme 5 General scheme of reaction of **55** with Grignard reagents to generate optically active hydroxy aldehydes **57**.

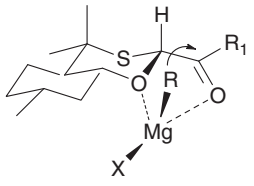
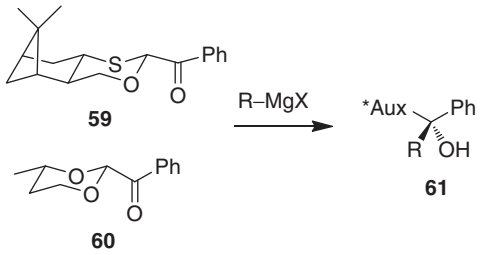


Figure 11 Proposed transition state of nucleophilic addition to **55**.

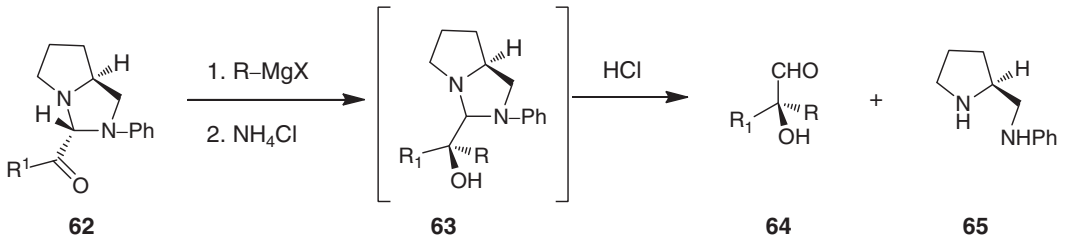
Related systems include the bridged system such as **59** (and analogs), that were prepared from the natural product (–)-myrtenal[60] and the 4-substituted-1,3-dioxane **60**.[61] High diastereoselectivities (>90% *de*) were observed on reaction with Grignard reagents (e.g., MeMgBr, EtMgBr, BnMgCl, and allylMgBr) with both, and afforded **61** (equation 14). The mechanism is proposed to occur via a Cram chelation model, analogous to that invoked in the Eliel system. The adducts were converted to α-hydroxyl aldehydes, diols, or in the case of **60**, acids. The simplicity of **60** is notable in that a single substituent, remote from the reaction center, exerts considerable influence over the course of the reaction.



(14)

These systems, particularly the chiral oxathianes, have been broadly used due to their ready availability, and the high and predictable diastereoselectivity of nucleophilic reactions. Additionally, the product of the synthetic sequence, typically an aldehyde, is a versatile moiety for further functionalization.

Chiral auxiliaries based on proline have garnered significant attention by a number of different researchers.[16] By constraining prolinol derivatives into bicyclic systems, highly structured auxiliaries are generated that can guide diastereoselective reactions to adjacent carbonyls. Furthermore, the ready availability of optically pure proline, and the ease of synthesis of these auxiliaries make this strategy particularly attractive. One such example is chiral keto-aminal **62**, developed by Mukaiyama that generated hydroxyaminals **63** on addition of Grignard additions. Hydrolysis of the product yielded the α-hydroxy aldehyde **64** and the pyrrolidine **65**, which was used to regenerate **62** (equation 15). Selectivities were typically very high, regardless of the substrate or reagent; reduced discrimination was only observed when R^1 and R were similar in size (**Table 7**).[62] Two factors are thought to control the selectivity. First, the aminal conformer **62** likely predominated due to relief of steric congestion and second, nucleophilic addition occurred through a chelation-control model as in **Figure 12** in which the Mg chelates to the nitrogen and carbonyl oxygen, and delivers the nucleophile to the less hindered face.



(15)

Table 7 Synthesis of optically active α-hydroxy alcohols from pyrrolidine **62** (equation 15)

R^1	*R–MgX*	*Solvent*	*Yield (%)*	*% ee (**64**)*
Ph	Me–MgI	Et_2O	67	95
Ph	*i*-Pr–MgI	Et_2O	82	>95
Ph	Vinyl–MgBr	THF	67	96
Me	Ph–MgBr	Et_2O	76	99
Me	Et–MgBr	Et_2O	43	78
i-Pr	Ph–MgBr	Et_2O	75	94

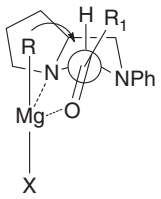
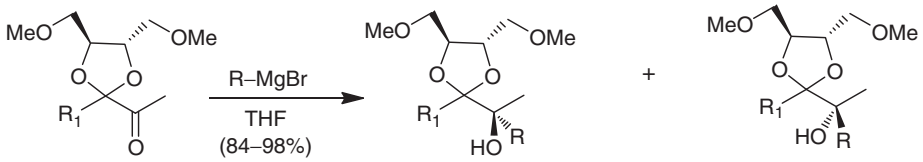


Figure 12 Mode of addition of Grignard reagents to **62**.

Employing chiral acetals as auxiliaries provides the advantage of incorporating a familiar protecting group that also acts as a stereochemical-directing group. Acetals of ketone **66**[63] reacted diastereoselectively with certain Grignard reagents (e.g., R=Et, vinyl, and Ph) to generate **67** as the predominant diastereomer in ratios of >97:3 (equation 16). The reaction was proposed

to occur through a transition state shown in Figure 13, where the organometallic reagent chelated to the carbonyl and one of the acetal ethers, and delivered the nucleophile to the least hindered face of the rigid structure. The use of a Grignard reagent was essential; organolithiums gave little selectivity. Examples of acetals derived from aldehydes are reported to be much less selective.[64]



66 (R_1 = Ph, Et) **67** **68** (16)

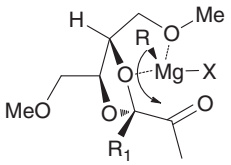
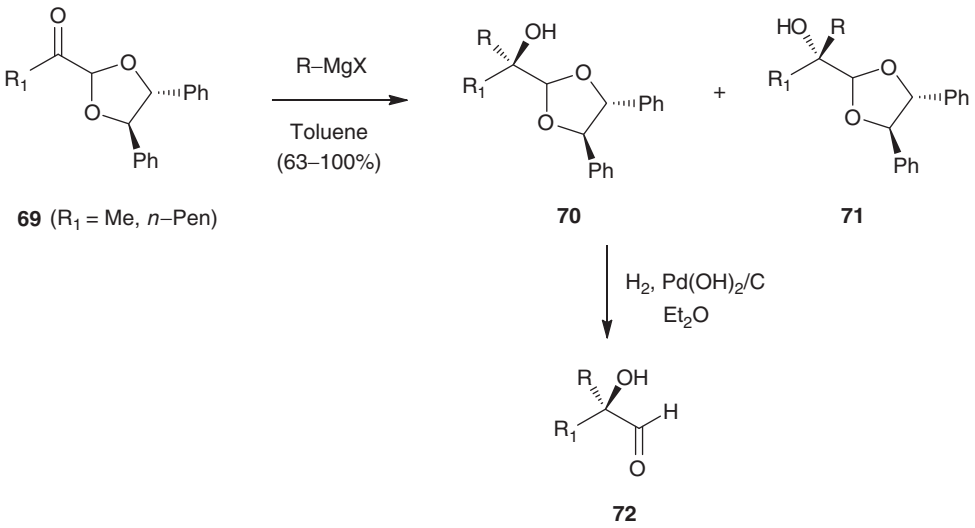


Figure 13 Transition state of addition of Grignard reagents to **66**.

In related work, diphenyl dioxolane (as in **69**, Scheme 6) was designed as a chiral ligand that would maximize stereoselectivity based on the presence of sterically demanding, nonchelating aryl groups in the auxiliary.[65] Excellent diastereoselectivities (>90:10) were observed with the use of most Grignard reagents (Ph, vinyl, *i*-Pr, Et, and Me) with the exception of allyl Grignard. The major acetal product (**70**) was readily cleaved under mild hydrogenolytic conditions to afford optically active α-hydroxy aldehyde **72**. A model to explain the selectivity is shown in Figure 14: the magnesium ion complexes to the carbonyl and one of



69 (R_1 = Me, *n*–Pen) **70** **71** **72**

Scheme 6 Nucleophilic additions of Grignard reagents to **69**, and conversion to – hydroxy aldehyde **72**.

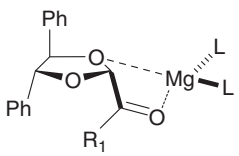
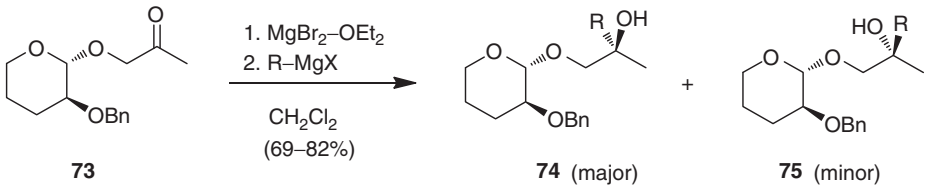


Figure 14 Model of **69** chelated to Grignard reagent.

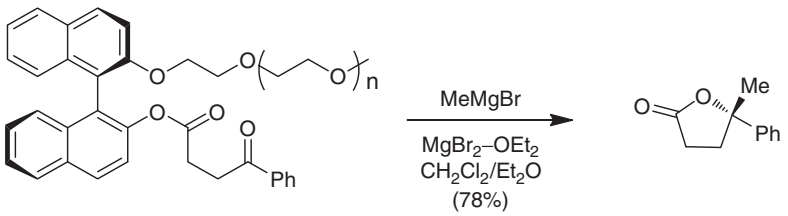
the acetal oxygens in a conformation that minimizes steric interaction with the phenyl group, and addition of the nucleophile occurs from the *exo* face to avoid to steric hindrance that is encountered from the *endo* face.

Tetrahydropyranyl groups have been employed as chiral auxiliaries to generate optically active 1,2 diols.[66] Addition of Grignard reagents (Ph, vinyl, Et, and *c*-Hex) to the ketone **73** precomplexed with $MgBr_2$ afforded excellent diastereoselectivities (>97:3) of the alcohol **74**. Allyl Grignard was the only reagent that performed with poor selectivity. The reaction is believed to occur through a chelation-controlled transition state. Hydrolysis of the auxiliary generates the diol, and either antipode of the chiral auxiliary is available from readily available materials, making this method highly versatile.



73 **74** (major) **75** (minor) (17)

Miyano and coworkers exploited axial chirality inherent in 1,1-binaphthalen-2-ols to control remote asymmetric induction, and prepared optically active diols and lactones. Equation 18 illustrates a representative example.[67] Axially chiral γ-keto-ester **76** was treated with MeMgBr in the presence of a Lewis acid and directly generated the butanolide **77** in high enantioselectivities (88% *ee*). The high disastereoselectivity is believed to be due to the cooperative chelation between magnesiu–m, the diketo-function and the pendant polyether chain, followed by nucleophilic attack from the least hindered face (Figure 15). These investigators extended the work to other polyether tethers and to 1,5-keto esters and higher homologs to form δ-lactones and diols, respectively.[68] In these examples, the specific nature of the tether often dictated the level of the diastereoselectivity.



76 (*n* = 2) **77** (18)

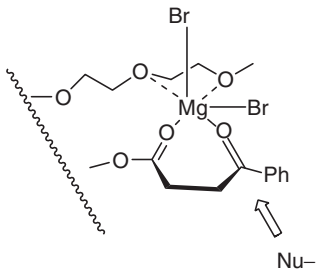
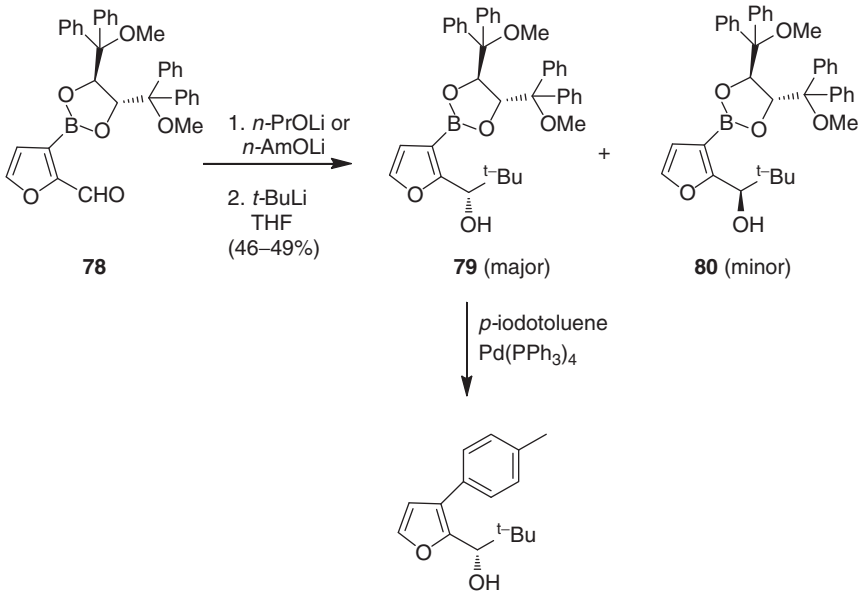


Figure 15 Mode of nucleophilic addition to **76**: $MgBr_2$ complex.

Chan and Wong extended the chiral auxiliary concept by incorporating a useful synthetic handle – a chiral boronate – to direct diastereoselective reactions.[69] Scheme 7 illustrates one example. Aldehyde **78** was treated with a bulky lithium alkoxide (*n*-PrOLi or *n*-AmOLi), then with *t*-BuLi (Scheme 7). The alcohol **79** was formed as the major isomer almost exclusively (99% *de*). A sterically demanding boronate ester was required, as was the use of a bulky lithium alkoxide as additive. A tetrahedral boronate was generated on addition of the alkoxide, and nucleophiles add from the less sterically hindered *si*-face (Figure 16). The products of the nucleophilic addition were used directly in cross coupling reactions, as shown in Scheme 7. This strategy is particularly attractive since the chiral boronate serves a dual purpose: not only is it a stereochemical-differentiating factor, but it is also a highly versatile chemical handle for further chemistry such as Suzuki reactions.



Scheme 7 Diastereoselective addition of *t*-BuLi to **78**, and subsequent Suzuki reaction.

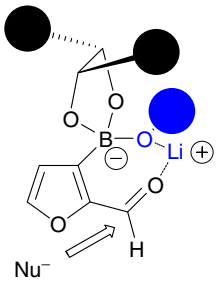
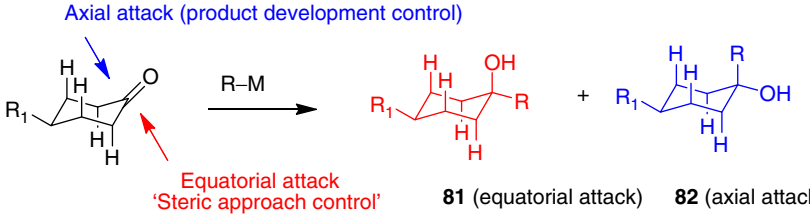


Figure 16 Mode of addition of nucleophiles to chiral tetrahedral boronates derived from **78** and a lithium alkoxide (blue).

1.01.2.2 Additions to Cyclic Systems

Compared with nucleophilic additions to acyclic carbonyls, additions to cyclic carbonyls are considerably more intricate. In acyclic systems, the configuration of the adjacent or nearby center is usually a primary influence in determining the outcome of diastereoselective reactions. In cyclic systems, the conformation of the transition state is influenced by numerous additional factors including substitution patterns on the ring, electronic effects, and torsional effects. In addition, cyclic substrates can confer a higher degree of rigidity to the transition state than acyclic substrates, and this also influences the reaction. The relative importance of each of these effects varies, and plays a role in determining the regiochemical and stereochemical outcome of the reaction.

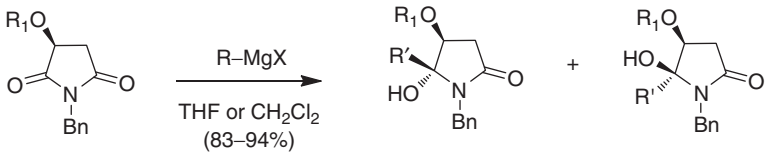
Models for the nucleophilic addition of organolithium and Grignard reagents to cyclic ketones assume that the incoming nucleophile approaches the carbonyl carbon perpendicularly to the plane of the sp^2 center (equation 19). This approach maintains maximal overlap of the orbitals in the transition state of the reaction. Whether this perpendicular nucleophilic attack occurs from an equatorial or an axial trajectory depends on the effects mentioned above. In the case of simple cyclohexanones, if 'steric approach control' influences the reaction, axial attack is hindered by the axial hydrogens at C-3 and C-5, and the nucleophile enters from the less hindered equatorial position (e.g., **81**). When 'product development control' is in effect, formation of the equatorial alcohol, via axial attack (e.g., **82**), is favored.



(19)

The mode of addition to substituted cyclohexanones depends on the nature and position of the substituents, a well as the specific nature of the organometallic reagent; however, some broad generalizations can be made. Organolithiums and Grignards, with the exception of acetylides, usually approach equatorially to yield the axial alcohols; this route is enforced as the steric bulk of the nucleophile increases. With acetylides, axial attack to form the equatorial alcohol predominates due to torsional effects. In the case of cyclopentanones, although the above generalizations predominate, there are frequent exceptions and accurate predictions are often difficult.[16,70] Given the variability in the course of the reactions with cyclic substrates, only a few examples of specialized regio- and diastereoselective systems are highlighted below.

Hydroxy-substituted malimides offer two opportunities for nucleophilic addition, and are an informative example of effects that govern regio- and stereoselectivity. Grignard reaction with protected hydroxymalimides such as **83** (equation 20) proceeded almost exclusively at the more hindered α-carbonyl group to afford **84** and **85**, albeit with little or only modest *trans*-stereoselectivity.[71] This high regioselectivity was attributed to chelation of the Grignard reagent with the ether group, and delivery of the nucleophile to the adjacent carbonyl. In concordance with this hypothesis, Grignard reaction with malimides containing a nonchelating α-substituents such as *t*-butyldimethylsilyl (e.g., **86**) afforded little or no regioselectivity. In the examples where *trans*-stereoselectivity was noted, the rigidity of the ring system favored the formation of the *trans*-product (**84**) through the *cis*-α-chelated transition state.

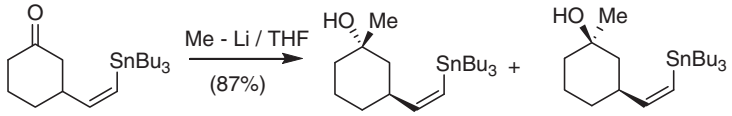


(20)

83: R_1 = Bn
86: R_1 = TBDMS

84 (*trans* isomer) **85** (*cis* isomer)

The conformation of the cyclic substrate combined with a directing effect of a stannyl group was exploited in the addition of nucleophiles to cyclopentanones and cyclohexanones. Equation 21 illustrates one specific example wherein reaction of **87** with MeLi afforded the *syn*-product **88** and *trans*-product **89** in a ratio of 99:1.[72] High degrees of selectivity (>90:10) were observed on addition of organolithiums to both five- and six-membered ring systems, and even in highly substituted ring systems. Grignard reagents were a little less effective, and produced *syn*:*anti* ratios in the 80:20 range. The selectivity is believed to arise from a tin-directed intramolecular delivery of the nucleophile, perhaps through a hypervalent tin anion, to generate the *syn* product. Supporting this hypothesis is the observation that the (*Z*)-stereochemistry of the vinyl tin moiety is essential for high selectivity, and the distance between the carbonyl center and tin atom was optimal at five bonds. This method is useful in that the tin-directing group is also a valuable tool for further chemical elaboration of the molecule.

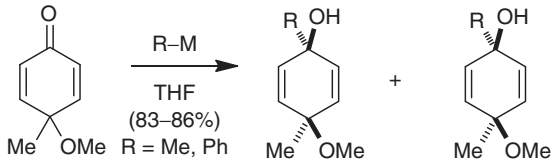


(21)

87

88 (*syn*) 99 : **89** (*anti*) 1

4,4-Disubstituted dienone **90** exhibited facial selectivity (>75:25) on reaction with methyl or phenyl Grignard reagents (equation 22) to yield the product (**91**) of nucleophilic attack on the face opposite from the C(4) oxygen substituent.[73] A careful study suggested that selectivity of these reactions was dictated by dipoles, and larger dipole moments predict greater facial selectivity. Cyclic systems such **93** and **94** (**Figure 17**) showed similar facial selectivity, that is, nucleophilic attack from the face opposite the heteroatom. In the case of **95**, attack *anti* to the sulfur, and *syn* to the oxygen substituent predominated.[74]

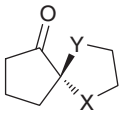


(22)

90 **91** **92**

An intriguing report suggests that regioselectivity in Grignard reactions between structurally similar carbonyls (e.g., cyclopentanone vs. cyclohexanone) could be controlled by shaped laser pulses.[75] The authors presented theoretical studies that predict shaped laser pulses can exclusively stretch the C–O bond of one carbonyl to the length required for Grignard reaction, in the

presence of a similar carbonyl. Although this report has not yet been experimentally realized, it offers an intriguing possibility for highly regioselective Grignard reactions.



93: Y=CH_2, X=O
94: Y=CH_2, X=S
95: Y=O, X=S

Figure 17 Structures of **93**, **94**, and **95**.

1.01.3 Additions of Chiral Reagents to Achiral Substrates

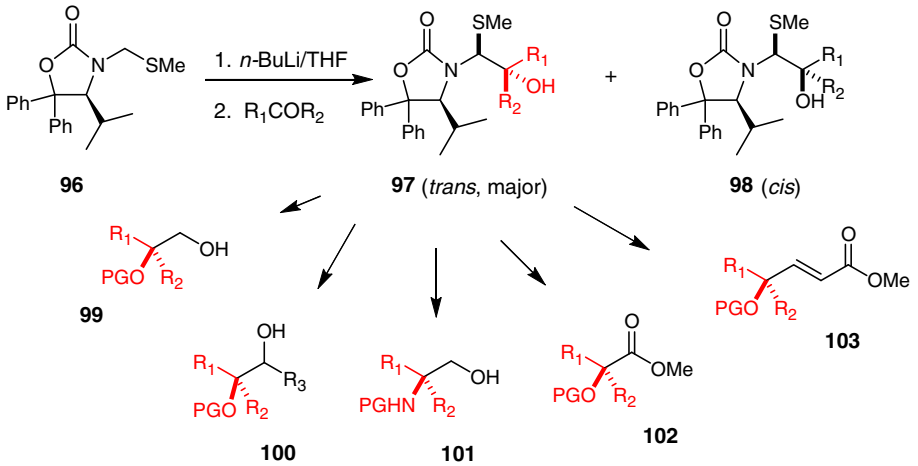
1.01.3.1 Introduction

The addition of a chiral reagent to an achiral substrate is a second strategy used by synthetic chemists to perform stereoselective reactions. This approach has the advantage of not requiring significant modification of the substrate (e.g., through protecting group manipulation) in order to achieve the desired stereoselectivity. In theory, a toolbox of chiral reagents would provide versatile and flexible methods that would be applicable to any substrate. In recent years, advances toward developing chiral reagents, some of which are catalytic, have been substantial. Two subsets of reactions of chiral reagents with achiral substrates are described, those using 'covalent chiral reagents' and those relying on 'noncovalent chiral reagents.' Covalent chiral reagents, in which the nucleophilic moiety is optically active, have found some general use, particularly when the chiral reagent acts as an auxiliary. The development of 'noncovalent chiral reagents' has seen explosive growth in the recent past and involves the use of achiral nucleophiles in a chiral environment. In these examples, close association between the nucleophile and a chiral additive generates asymmetric reagents without virtue of a formal chemical bond.

1.01.3.2 Covalent Chiral Reagents

The lack of configurational stability of many organolithium and Grignard reagents (and therefore the need to use specific conditions to maintain one configuration) and the likelihood that some of their reactions proceed through a single-electron transfer mechanism, renders converting a wide array of building blocks into chiral lithium or Grignard reagents challenging.[76,77] The most widely used covalent chiral reagents are those that can be considered 'chiral auxiliaries.' After directing the stereoselectivity of their incorporation into a substrate, they are ultimately removed. Chiral acyl equivalents are one such example; many have been reported and are based on chiral sulfur reagents and oxazolidinones and thiazolidines.[78] As most of these follow the same principles, only one example is described in detail.

Seebach developed the oxazolidinone **96** as a chiral acyl anion equivalent.[79] Deprotonation with BuLi and addition to an aldehyde or unsymmetrical ketone afforded very high levels (typically >90:10) of diastereoselectivity to produce the *anti*-isomer **97** (Scheme 8). Highest selectivities (Table 8) were observed when the aldehyde was aromatic, heteroaromatic,



Scheme 8 Reaction of chiral acyl anion equivalent **96** with carbonyl compounds and conversion to bifunctional building blocks.

Table 8 Addition of acyl anion equivalent **96** to aldehydes and ketones (Scheme 8)

R^1	R^2	*Yield (%)*	***97*:*98*** *Ratio*
Ph	H	90	93:7
Furyl	H	90	90.5:9.5
Ph–C≡C	H	80	93:7
CH_2=C(Me)	H	88	85:15
i-Pr	H	84	71:29
Ph	Me	60	91:9
Ph	*i*-Pr	85	72:28
3-pyridyl	Et	59	91:9
c-C_3H_5	Me	72	62:38

or propargylic. Modest selectivities (70:30 to 86:14) were seen using alkyl and α,β-unstaturated aldehydes as substrates; only highly reactive and sterically undifferentiated ketones afforded low selectivities. The versatility of the system was illustrated by conversion of the thioether in **97** to the corresponding alcohol, and then removal of the chiral auxiliary. Depending on the specific reaction protocol, a variety of chiral building blocks such as 1,2-diol derivatives **99** and **100**, 2-amino alcohols **101**, 2-hydroxy esters **102**, and 4-hydroxy-2-alkenoates **103** were synthesized. The diastereoselectivity is proposed to arise from a five-membered ring chelate structure of the anion (Figure 18) that approaches the carbonyl from the least sterically demanding trajectory.

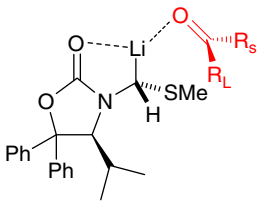


Figure 18 Transition state of addition of lithiated **96** to carbonyl substrate (red).

1.01.3.3 Noncovalent Chiral Reagents

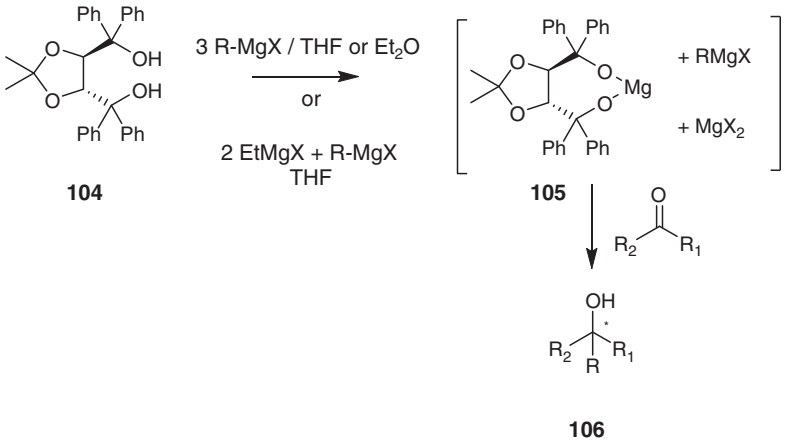
The stereoselective addition of achiral nucleophiles to prochiral carbonyl compounds in the presence of chiral additives is a conceptually elegant method for the synthesis of enantiomerically pure compounds from achiral starting materials. Advantages of this strategy include the ability to recover the chirality 'inducer,' the potential for these reactions to occur catalytically, and the elimination of steps involving introducing and removing chiral auxiliaries. Despite these advantages, this approach is challenging. The high reactivity of organolithium and Grignard reagents requires them to be appropriately tuned in order to yield high enantioselectivity but efficient reactivity. Additions to aldehyde substrates further complicate the reactivity–selectivity balance due their own high reactivity. Furthermore, the multiple, interchanging aggregates of organometallic reagents, often complexed with solvent or product, frequently confound the ability to reliably predict selectivity. On a positive note, the significant advances in understanding the aggregated structure, conformation, and reactivity of these complexed reagents suggests that the ability to design ligands and reaction systems may not be far in the future.

1.01.3.3.1 Stoichiometric reactions

The literature reveals reports on asymmetric additions of Grignard and organolithium reagents to carbonyl compounds mediated by chiral ligands dating back to the 1940s. Early on, chiral solvents and chiral additives were both employed, however only modest stereoselectivities were typically observed. In these examples, natural products-based additives such as sparteine, tartrates, prolines, and carbohydrate derivatives were frequently the source of chirality. Small modifications to reaction conditions – solvent, temperature, and stoichiometry – were often reported to have a profound and poorly understood influence on selectivities. The history of this area has been thoroughly reviewed, and therefore only the examples of the most successful and most recent work will be highlighted.[15,80,81]

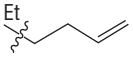
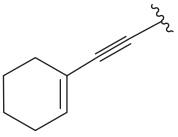
The first example of generally high (>95%) asymmetric additions of achiral Grignard reagents to achiral ketones directed by a chiral additive was reported by Seebach in the 1990s.[82] $\alpha,\alpha,\alpha',\alpha'$-tetraryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol's (TADDOL's) such as **104** are highly rigid structures that when treated with 3 equivalents of a primary alkyl Grignard reagent generate a 'chiral

Grignard reagent' (e.g., **105**). Reactions using primary Grignard reagents and aryl and heteroaryl ethyl ketones yielded tertiary alcohols (**106**, Scheme 9) with high enantioselectivity. α,β-Unsaturated ketones and acetylenic ketones afforded lower selectivities, as did the presence of steric bulk in either the substrate or reactant. Table 9 highlights the scope and limitations of this protocol.



Scheme 9 Use to TADDOL **104** to generate optically active alcohols **106**.

Table 9 Additions of grignard reagents to ketones in the presence of TADDOL-ate **105** (Scheme 9)

R	*R*[1]	*R*[2]	*Yield (%)*	*er*
Et	Ph	Me	62	99:1
Et	Cyclohexenyl	Me	56	85:15
Et	3-Pyridyl	Me	50	98:2
Et	2-Thiophenyl	Me	43	98:2
n-Bu	Ph	Me	75	>99:<1
n-Bu	Cyclohexyl	Me	Trace	62:38
Et	Benzyl	Me	22	75:25
Et	2-Furyl	Me	53	82:18
	3-Pyridyl	3-Me	58	93:7
Et		Me	88	87:13

The nature of the slow, heterogeneous reaction makes understanding the mechanism challenging. Key observations include the strong dependence on solvent (THF), the lack of dependence on the size of the aryl TADDOL substituents, and the involvement of only 1 equivalent of TADDOL in the transition state. Three different transition states (Figure 19(a), (b), and (c)) have been

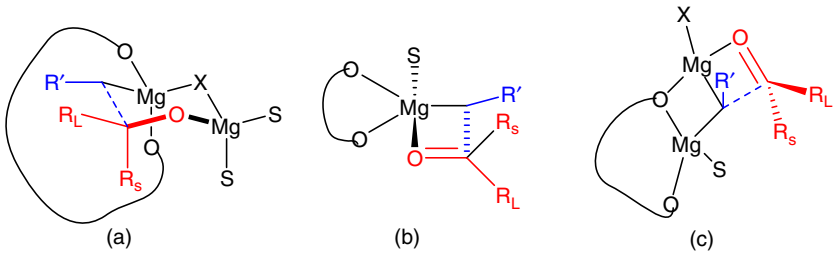
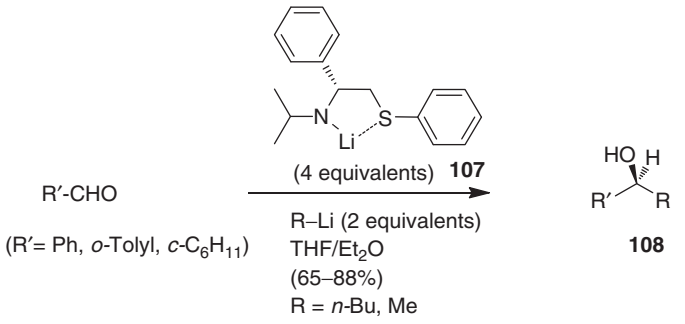


Figure 19 Three proposed transition states (a, b, c) to explain stereoselectivity of addition of TADDOL-derived R–MgX to aldehydes.

proposed. However, to date, the exact mechanism has not been elucidated. TADDOL's have also found wide use as a ligand for other metals, and are considered by some to be a 'universal' chiral auxiliary.[83]

Chiral lithium amide bases have been developed by several different research groups as an additive to promote enantioselective addition of alkyllithiums to simple alkylaldehydes to generate optically active alcohols.[81] For example, the lithiated amino sulfide **107** reacted with standard organolithium reagents (e.g., *n*-BuLi and MeLi) to generate a mixed dimer reagent that added to aldehydes. Most alcohols (**108**) produced exhibited *ees* of >86% (equation 23); but some highly hindered aldehydes performed poorly in the reaction. The stereochemistry observed was thought to be due to a transition state in which the aldehyde approaches so that the R group points away from the mixed dimer complex (**Figure 20**).[84] Replacement of the thiophenyl moiety in **107** with diphenyl phosphine also led to high enantioselectivities.[85]



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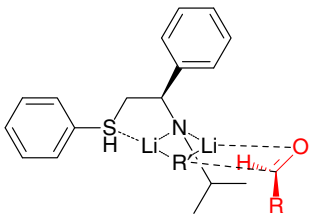
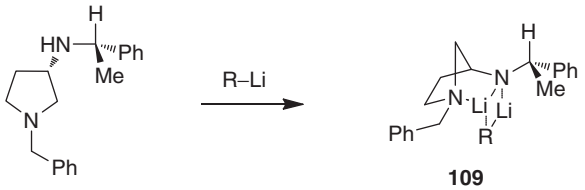


Figure 20 Mode of addition of aldehyde (red) to **107**:R-Li mixed aggregate.

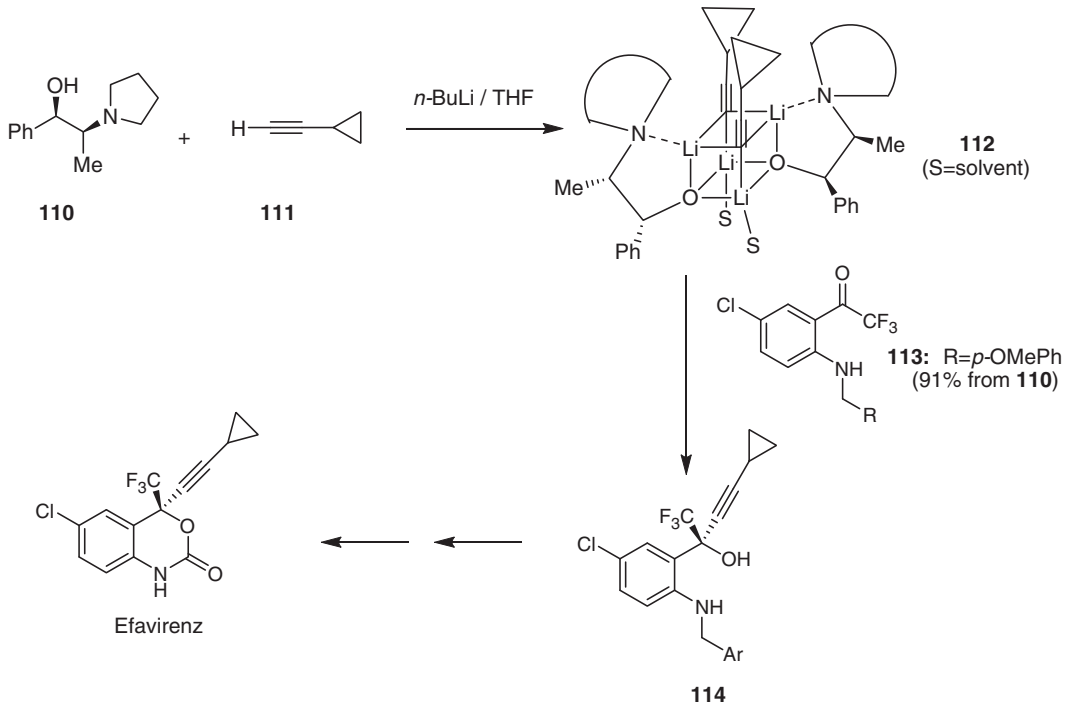
Maddaluno described a similar system that employed 3-amino pyrrolidine-based mixed aggregate systems such as **109** (equation 24). In general, the enantioselectivities were modest to good (46–80% *ee*). However, the value of the work lies in the extensive structural and computational studies that were reported in an effort to understand the nature of the reactive species, and the role of solvent and additives on the selectivity.[86]



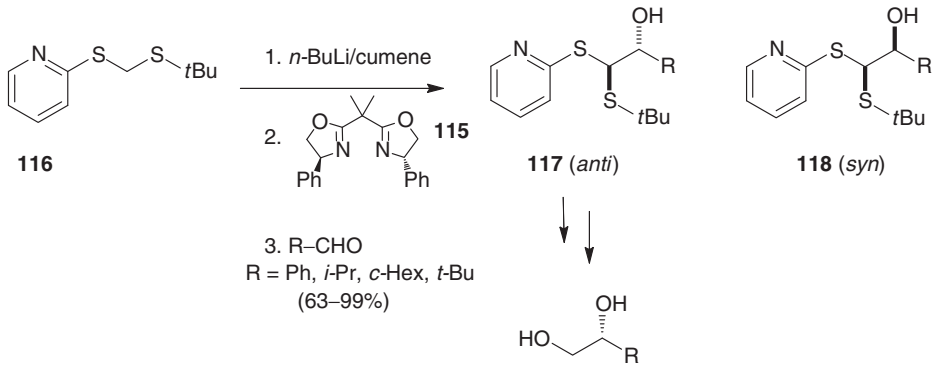
(24)

The use of mixed aggregates using an ephedrine derivative as the chiral ligand was put to practical use in the synthesis of the anti-human immunodeficiency virus drug, Efavirenz (**Scheme 10**). The chiral additive **110** was mixed with acetylene **111**, and treated with *n*-BuLi to generate the stable aggregate **112**. This chiral reagent reacted with the trifluoroketone **113** to afford the product **114** in 98% *ee*. Key to the high enantioselectivity was the 2:2 pyrrolidine alkoxide: lithium acetylide stoichiometry and an equilibration of the alkoxide–acetylide mixture before reaction to ensure that only one aggregate species (e.g., **112**) was present.[87]

Toru expanded the concept of a chiral formyl anion equivalent by using the chiral bis(oxazoline) ligand **115** to control the addition of an achiral formyl anion equivalent (unsymmetrical dithioacetal **116**) to aldehydes (**Scheme 11**).[88] Moderate to good diastereoselectivites (55:45 to 90:10) were reported in the generation of the products **117** and **118**; *ee*s ranged from 60–88%. Although the stereoselectivities are not optimal, the ease of this protocol and the ability to use very simple achiral formyl anion equivalents suggests this method, on further optimization, could find widespread use.[89]



Scheme 10 Synthesis of efavirenz using the mixed aggregate **112**.

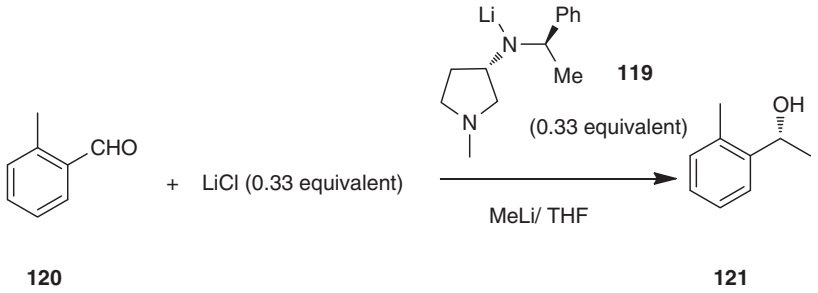


Scheme 11 Addition of a chiral formyl anion derived from **116** to aldehydes in the presence of **115**.

1.01.3.3.2 Substoichiometric reactions

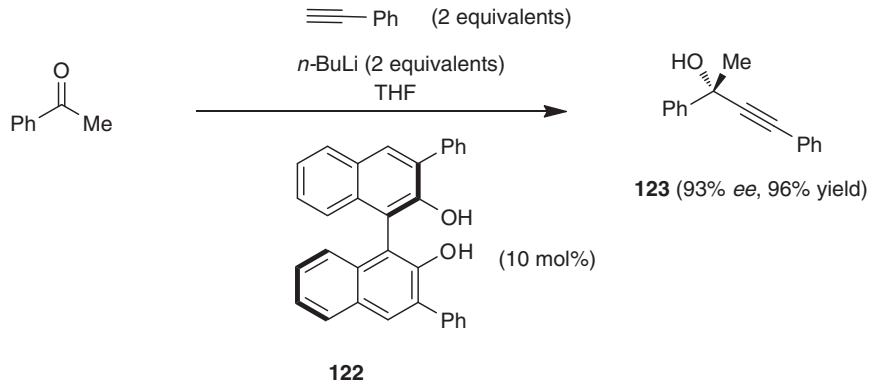
The high reactivity of organolithium and Grignard reagents, along with the heterogeneity of the reagent complexes and their aggregates, provides a particular challenge when trying to develop catalytic asymmetric addition protocols. However, any success in this area would have an enormous impact on synthetic organic chemistry.

Maddaluno and coworkers took advantage of a careful study of the aggregation phenomena of chiral lithium amide reagents during stoichiometric addition reactions to aromatic aldehydes.[90] Their analysis suggested that the alkoxide product formed after nucleophilic addition of the chiral lithium complex to the aldehyde trapped the chiral ligand–lithium complex, resulting in a change in the reagent composition and diminishing enantioselectivity. By adding LiCl, the lithium alkoxide product was removed from the reaction cycle, thereby maintaining the integrity of the chiral reactant, and allowing substoichiometric amounts of the chiral ligand to be used. A specific protocol was designed that involved preforming the chiral ligand **119**•MeLi complex, and adding it to the aldehyde substrate (*ortho*-tolualdehyde, **120**) that had been premixed with LiCl. The alcohol product (**121**) was formed with *ees* of up to 80% (equation 25). Efforts to further reduce the chiral ligand stoichiometry required the careful removal of LiCl from the commercial solutions of MeLi. Although the *ees* obtained were not as high as those achieved from stoichiometric methods (70% vs. 86%) and the reaction required some manipulation, this approach suggests directions for future work in this area.



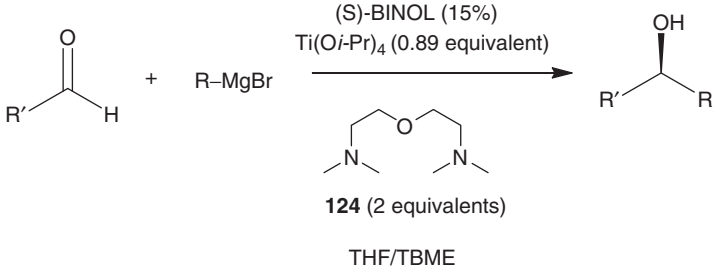
(25)

The enantioselective addition of lithium phenylacetylide to ketones was reported to be catalyzed by lithium binaphtholate **122**. Equation 26 describes a representative example where the alkynyl alcohol **123** was generated in 93% *ee* and 96% yield.[91] A wide variety of arylalkyl ketones were used as substrates and most afforded products with >85% *ee*s; however branched ketone substrates were much less effective starting materials. At this time, the method appears to be limited to acetylides as the nucleophile.



(26)

Some efforts to convert stoichiometric enantioselective Grignard additions to catalytic versions have focused on strategies to deactivate the Grignard reagent. Da and coworkers reported the use of a *bis*-amino ether analog **124** to do so.[92] In the presence of catalytic amounts of 1,1′-Bi-2-naphthol (BINOL;10–40%) and substoichiometric amounts of $Ti(OiPr)_4$ (0.9 equivalent), excellent enantioselectivities were observed on addition of Grignard reagents to aldehydes (equation 27, **Table 10**). The reaction was catalyzed by the chiral complex between (S)-BINOL and $Ti(OiPr)_4$, and deactivation of the Grignard reagent via complexation with **124** was essential for the high selectivities observed. In general, addition of bulky Grignard reagents to aromatic aldehydes afforded highest *ees*, but manipulation of conditions could improve certain reactions that incorporated smaller Grignard reagents and aliphatic aldehydes. The effects of changes stoichiometry and the scope of the reaction are illustrated in **Table 10**.

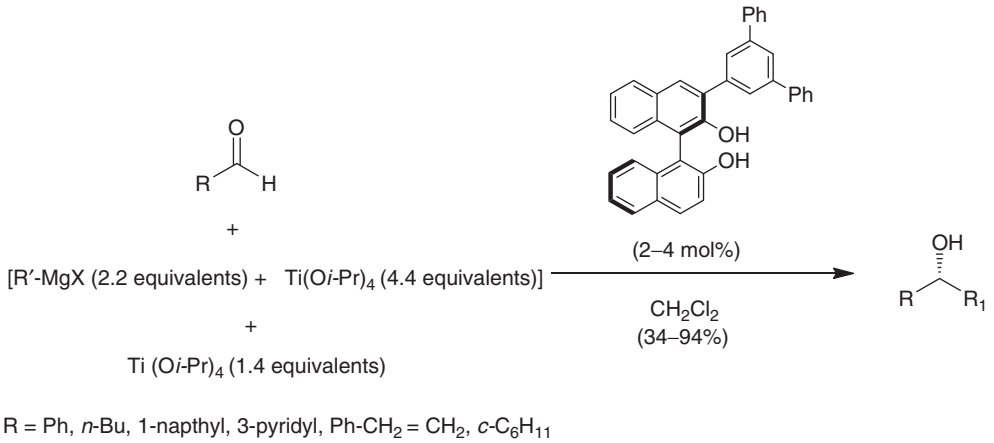


(27)

Table 10 Selectivities of addition of Grignard reagents to aldehydes in the presence of **124** (equation 27)

R	*R*[1]	*BINOL equivalent*	*Yield (%)*	*% ee*
Et	Ph	0.4	46	81
Et	Ph	0.1	39	70
t-Bu	Ph	0.15	76	98
Ph	1-Naphthyl	0.4	75	58
i-Bu	1-Napthyl	0.15	93	98
i-Bu	Cyclohexyl	0.15	27	98
n-Pentyl	Ph	0.15	53	90

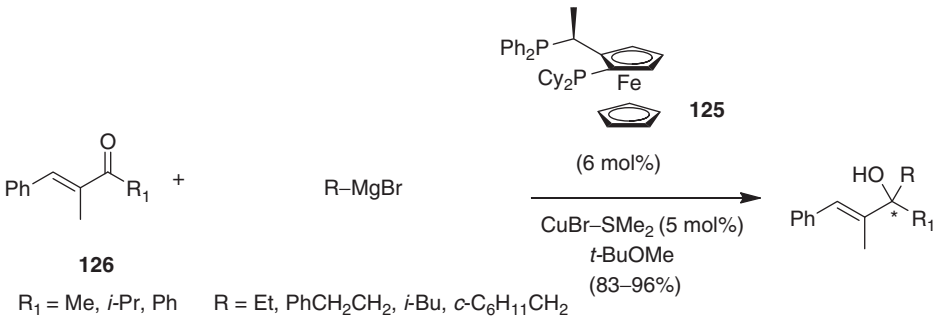
Other efforts to modify the reactivity of Grignard reagents employed Ti(O*i*-Pr)$_4$ to generate [R′-Ti(O*i*-Pr)$_4$]MgX.[93] In the presence of catalytic amount of a chiral catalyst (DPP-BINOL), Grignards (*n*-Bu, *n*-Pr, Et, Ph, and Me) added to aromatic, heteroaromatic, cycloalkyl and alkyl, and α,β-unsaturated aldehydes with excellent selectivities (80–97% *ee*, equation 28). In these examples, the reactive moiety is the titanium reagent; however the use of Grignard reagent as the origin of the nucleophile provided ready access to a large number of reagents.



(28)

Yus and coworkers also reported that BINOL ligands could catalyze the enantioselective reaction of Grignards and alkylithiums to aldehydes.[94] In the case of Grignard additions, the addition of excess equivalents (4–10) of Ti(*i*-OPr)$_4$ and 10–20 mol% of the BINOL derivatives was required. Simple nucleophiles (MeMgBr, EtMgBr, and *n*-BuMgBr) were most effective (72–96% *ee*), as were aromatic aldehyde substrates. Modest optical yields (50–70% *ee*) were observed when the substrate was an aliphatic aldehyde. The use of organolithium reagents similarly required excess Ti(*i*-OPr)$_4$ and 20 mol% of the BINOL ligand, and offered a similar scope: aromatic aldehydes and sterically undemanding organolithium reagents afforded the highest selectivities (often >90%).

Finally, copper ferrocenyl ligand catalysts such as **125** were used to promote the 1,2-addition of Grignard reagents to α-substituted α,β-unstaturated ketones **126** (equation 29).[95] Highest enantioselectivities (>90:10) were found with increasing steric bulk on the ketone and/or Grignard reagent. The presence of the α-substituent and unsaturation was essential for high regio- and stereoselectivity. This work has been extended to the use of α-bromo unsaturated ketones and aryl alkyl ketones as substrates.[96]



(29)

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1.02 Organosilicon Reagents: Vinyl-, Alkynyl-, and Arylsilanes

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Glossary

Hyperconjugation The interaction of a σ bond with a π-system.

Ipso attack The addition of an incoming group to a position on an aromatic moiety, which is already bearing a substituent other than hydrogen.

Stereospecific reaction A reaction is stereospecific if reactants varying only in configuration produce stereoisomeric products. This means that stereospecific reactions are necessarily stereoselective, but not all stereoselective reactions are stereospecific.

Wagner–Meerwein shift (migration) This is a class of 1,2-rearrangements of carbocations in which a hydrogen, alkyl group, or aryl moiety migrates one carbon to the adjacent carbocationic center to relieve ring strain or form a more stable carbocation.

1.02.1 Introduction

Organosilanes are well known for their participation in the Hosomi–Sakurai reaction[1] and the Hiyama coupling,[2] and are typically employed as bench-stable carbanion equivalents. Several reviews of organosilanes and, in particular, allylsilanes exist and readers are recommended to see related chapters in this work.[3] This review focuses on the use of vinyl-, alkynyl-, and arylsilanes as silicon-stabilized carbanion surrogates. These reagents have seen less use than the corresponding allylsilanes and this is probably owing to the decreased reactivity of vinyl-, alkynyl-, and arylsilanes as compared to allylsilanes (vide infra). Despite the generally low reactivity of these reagents as compared to archetypal organometallic reagents, organosilanes are an important class of reagents in carbon–carbon bond forming reactions. This is due to their predictable reactivity profile in additions to C–X π-systems, regularly resulting in high stereo- and regioselectivities. The origin of this selectivity is typically attributed to the electronic nature of silicon as will be discussed below. The following sections will provide an overview of the fundamental concepts in this field and highlight recent advances, especially in stereoselective, asymmetric synthesis.

1.02.2 Characteristics of Organosilicon Compounds

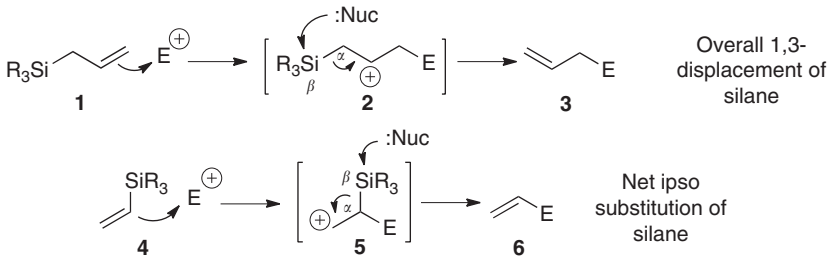
This section will give insight into the underlying stereoelectronic factors that impart high stereo- and regioselectivity when using vinyl-, alkynyl-, and arylsilanes and will define the tools that are used in the prediction and rationalization of reaction outcomes.

First, silicon stabilization and its consequences are detailed. A section describing general reactivity trends, including a comparison of organosilicon species, follows this. Finally, stereochemical models for the observed reactivity patterns in vinylsilane additions are outlined.

1.02.2.1 Hyperconjugation (β-Silicon Effect)

Hyperconjugation, exemplified by the donation of electron density from a filled σ orbital to an empty p orbital, plays a central role in organosilicon chemistry. This kind of orbital interaction results in stabilization of carbanions, carbocations, and radicals by a nearby silicon moiety and arises from the electronic nature of silicon, namely its larger size, low-lying orbitals, and its diminished electronegativity.[4] For vinylsilanes and related scaffolds the β-silicon effect, the stabilization of vicinal carbocations, is arguably the most important of these phenomena.

During the nucleophilic addition of organosilanes to electrophiles, a silicon-stabilized carbocation is typically generated (Scheme 1, cations **2** and **5**). A carbocation β to a silicon atom is stabilized by hyperconjugation, more specifically by the contribution of electron density from the Si–C σ bond to the carbocation p-orbital (Figure 1). Since silicon is more electropositive than carbon, the Si–C σ bond is polarized toward carbon, further strengthening this stabilizing effect. In fact, the magnitude of this stabilization has been calculated to be 38 kcal mol^{-1} of which 29 kcal mol^{-1} arises from hyperconjugation and the remainder is ascribed to inductive and field effects.[5] Compared to the β-stabilization of a methyl group (13 kcal mol^{-1}) there is a significant increase in the stabilization of a carbocation by a β-silicon atom. Additionally, in the solvolysis of constrained systems a β-silicon atom imparts a rate enhancement of up to 10^{12} as compared with a hydrogen atom, which is one of the largest kinetic effects measured to date (only Sn and Ge provide larger effects).[6,7] Often this phenomenon is simply referred to as the β-silicon effect or the vertical effect and it plays a fundamental role in the prediction and rationalization of reaction outcome for the nucleophilic addition of organosilicon reagents to C–X π-systems as will be detailed below.



Scheme 1 General reactivity of allylsilanes and vinylsilanes with electrophiles. E, electrophile; Nuc, nucleophile.

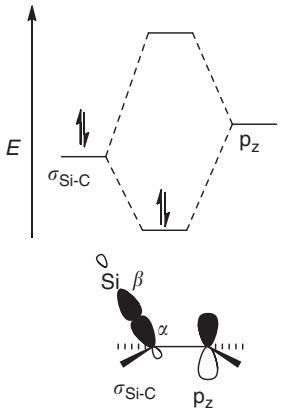


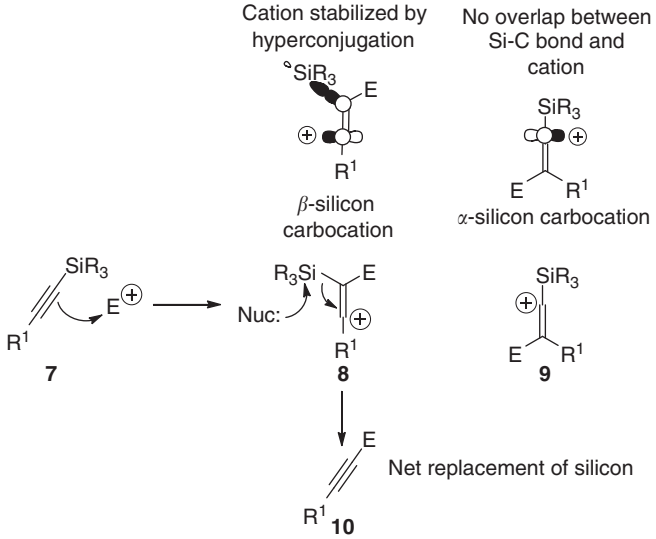
Figure 1 Orbital diagram and depiction representing the β-silicon effect.

There are several factors that influence the magnitude of the β-silicon effect.[4] First, this effect is dependent on the overlap of the Si–C σ bond to the p-orbital of the carbocation, and in order to achieve maximum stabilization these two orbitals must achieve coplanarity. This means that any conformational restraints, which restrict orbital alignment, will decrease the β-silicon effect.[8] Second, if the R groups bound to silicon are electron withdrawing, they will decrease the electron density in the Si–C σ bond, which will ultimately lead to diminished stabilization of the intermediate carbocation.[9] Similarly, the electron density of the olefin, as well as other donating groups proximal to the carbocation, can moderate or override the β-silicon effect.[10] Finally, the coordination at the silicon atom also influences the β-silicon effect, as silicon-'ate' complexes are more electron rich than the

corresponding neutral silicon species, leading to increased stabilization of the carbocation. The coordination around silicon can also alter the elimination process associated with the addition of a vinyl- or allylsilane to an electrophile (Scheme 1, **2**→**3**, **5**→**6**).[11] An understanding of these concepts is important for the rationalization of the regioselective and stereoselective outcomes of organosilane additions to electrophiles.

The impact of the β-silicon effect on the nucleophilic addition of organosilanes to electrophiles is twofold. First, as mentioned above, hyperconjugation imposes a geometrical constraint on the reactive conformations available to the intermediates, as the maximum stabilizing effect occurs when the Si–C σ bond and p-orbital are coplanar. This is an important aspect in reaction stereochemistry and will be discussed in more detail in Section 1.02.2.3. Additionally, under acidic conditions the formation of a β-silicon-stabilized carbocation is generally energetically favored over a methyl or hydrogen stabilized cation. Thus, the β-silicon effect generally enforces regiochemical fidelity in the nucleophilic addition of organosilanes to electrophiles, as the site of reactivity is a consequence of which carbocation is the most stable. In intermolecular reactions this results in substitution of the silane for alkynyl- and vinylsilanes, in which the silane is directly bound to the olefin, and net 1,3-displacement for allylsilanes and related scaffolds (Scheme 1).

This reactivity pattern is exemplified by comparison of the vinyl cations **8** and **9** generated by the addition of an electrophile onto an alkynylsilane **7** (Scheme 2). In α-silyl carbocation **9** the Si–C σ bond cannot achieve coplanarity with the cation, and therefore stabilization by hyperconjugation cannot be realized. In contrast, in β-silicon cation **8** the Si–C σ bond can align with the carbocation, resulting in stabilization of the carbocation via hyperconjugation. This forces a single site of reactivity for the electrophilic addition via the most stable intermediate, namely the β-silicon stabilized carbocation, and leads to the observed product **10** where there has been a net substitution of silicon.



Scheme 2 Addition of an alkynylsilane **7** to an electrophile (E^+) resulting in alkyne **10**.

Ipso attack and net substitution of silicon is also generally observed in arylsilanes. It is commonly accepted that reactions of arylsilanes with electrophiles proceed via an electrophilic aromatic substitution pathway. Thus, the reason that the substitution of the silyl group is usually faster than replacement of a hydrogen atom is a consequence of the additional stabilization imparted to the intermediate cation by the β-silicon effect (Figure 2, compare **11** and **12**).

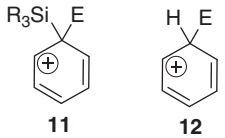


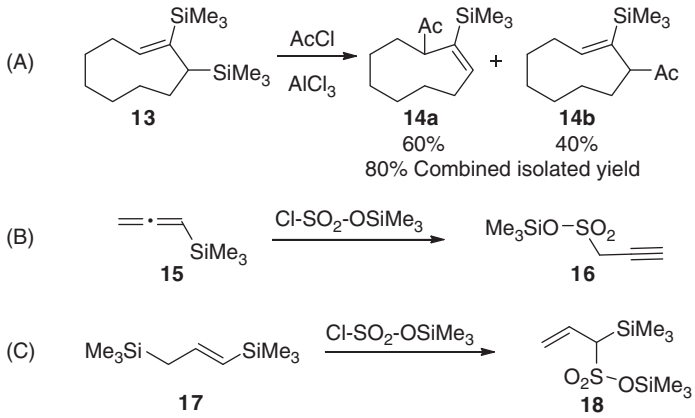
Figure 2 Cationic intermediates in electrophilic aromatic substitution reactions. Intermediate **11** is further stabilized by the β-silicon effect.

1.02.2.2 Reactivity

1.02.2.2.1 Comparison of organosilane species

As alluded to above allyl- and propargylsilanes are generally more reactive than the related vinyl-, aryl-, and alkynylsilanes. This can be difficult to quantify since it depends on a variety of experimental factors including solvent, functional groups bound to

silicon and Lewis acid employed. Furthermore, there are few direct comparisons of organosilane species. Therefore, only general trends will be presented here. First, silyl enol ethers are about an order of magnitude more reactive than allylsilanes.[12] Allylstannanes have been shown to be more reactive than allenylstannanes and this trend is expected to apply to the corresponding allylsilanes over allenylsilanes.[13] Allylsilanes are expected to be more reactive than vinylsilanes. For example, in the intramolecular competition between the allyl- and vinylsilanes found in bissilane **13**, the substrate reacts as an allylsilane, yielding product **14** (Scheme 3).[14] The observation of two double-bond isomers **14a** and **14b** in this reaction can be ascribed to the flexibility of the nine-membered ring system, which allows two conformations of the allylsilane with correct orbital alignment to be attainable. Furthermore, allenylsilane **15**[15] and bissilane **17**[16] also both react as allylsilane equivalents further indicating a preference for the allylsilane reaction manifold over the vinylsilane pathway.



Scheme 3 Reactivity differences between allyl-, allenyl-, and vinylsilanes.

The basis for the increased reactivity of allylsilanes, as compared with allenyl-, alkynyl-, vinyl-, and arylsilanes can be traced back to the connectivity of the silicon atom to the π-system. In the case of allyl- and propargylsilanes, the silicon atom is able to rotate freely around the plane of the olefin. This leads to a conformation where the Si–C σ bond can overlap with the π-system, effectively raising the highest occupied molecular orbital of this system via hyperconjugation (Figure 3). This results in the ground state destabilization of these species and increased reactivity.[17] For vinylsilanes and the related scaffolds, this orbital overlap cannot be attained in the ground state, as the silicon atom is locked perpendicular to the π-system, which is consistent with the diminished reactivity observed for these substrates.

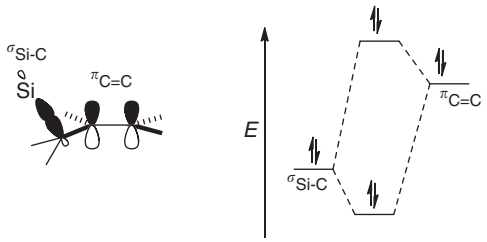
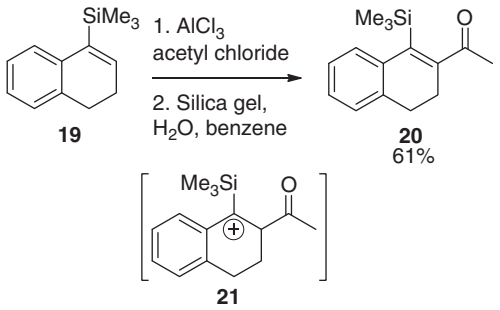


Figure 3 Molecular orbital diagram of the origin of ground state destabilization in allylsilanes and related structures.

1.02.2.2.2 Comparison of β-silicon effect to other stabilizing effects

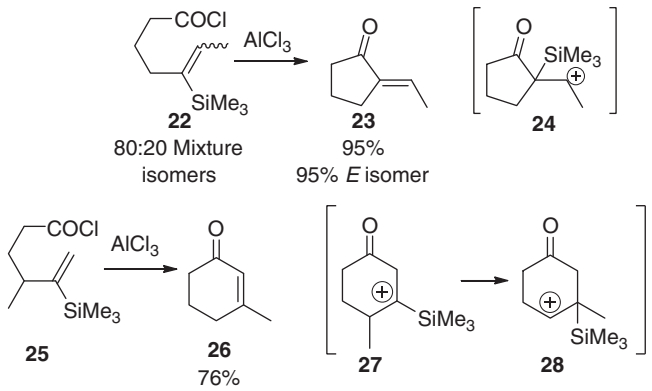
As mentioned earlier, the β-silicon effect generally imposes predictable regioselectivity in the addition of organosilanes to electrophiles, as the site of reactivity in these reactions is a direct consequence of the stability of the intermediate carbocation. For vinyl-, alkynyl-, and arylsilanes, this normally results in net replacement of the silane by the electrophile, as the β-silicon-stabilized cation is favored. However, the β-silicon effect is not overarching and can be overridden. This can complicate the use of β-silicon effect for the prediction of reaction outcome, especially in intramolecular cases. For example, in vinylsilane **19** the phenyl group and silicon moiety are exerting opposite directing effects (Scheme 4). As evidenced by the observed product **20** in which the silyl group remains, the benzylic cation **21** is more stable than the secondary β-silicon-stabilized cation that would be predicted by invoking the β-silicon effect.[10] Thus, net substitution of silicon is not observed when a more stable cation can be generated.

Further insight into the factors governing regiochemistry, namely the relative stability of carbocation species, is found in a study by Nakai.[18] Subjecting acid chloride **22** to Lewis acid yielded cyclized product **23**, as is easily predicted by implementing the



Scheme 4 Reactivity of vinylsilane **19**.

β-silicon effect. However, for the related acid chloride **25**, the regioselectivity of the reaction was completely reversed and cyclized cyclohexenone **26** was the sole product. In order to rationalize the observed results, Nakai and coworkers suggest that the relative stabilities of the intermediate carbocations predict the mode of cyclization. As confirmed by the reaction outcome, when acyl chloride **22** is used secondary β-silicon stabilized carbocation **24** is the preferred intermediate, and therefore more stable than the tertiary α-silyl carbocation that would be generated by the opposite sense of vinylsilane addition (corresponding to carbocation **27**) (Scheme 5). In the case of substrate **25**, a primary β-silicon stabilized carbocation would be the intermediate predicted by the β-silicon effect. However, the more stable tertiary α-silyl carbocation **27** is formed instead. Wagner–Meerwein shift of the methyl group in intermediate **27** leads to carbocation **28**, which after desilylation and isomerization yields the observed product.

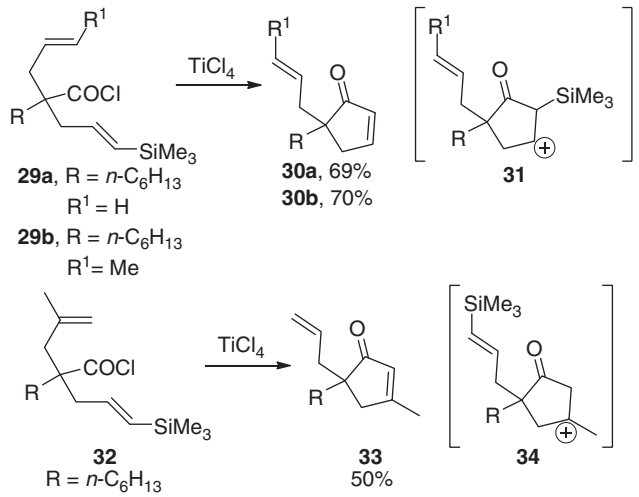


Scheme 5 Intramolecular additions of vinylsilanes to acid chlorides reveal that the carbocation stability impacts the mode of cyclization.

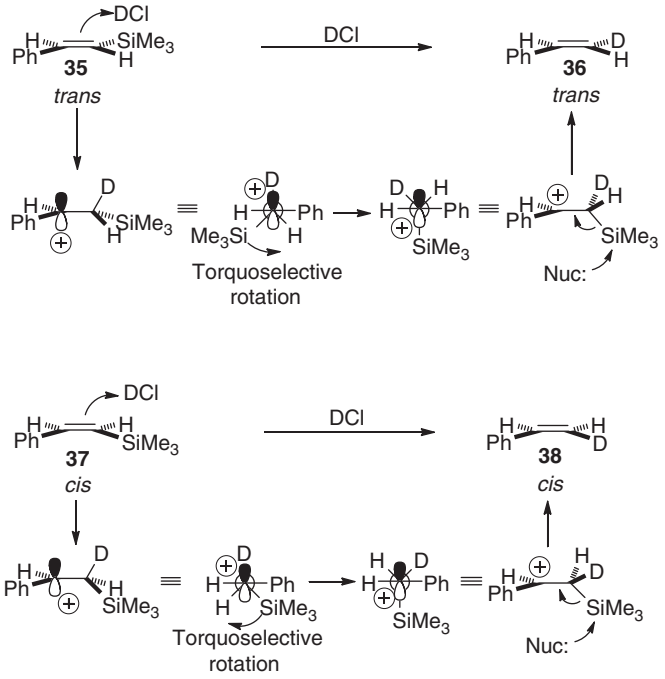
In an analogous study, Kuwajima examined the intramolecular addition of vinylsilanes to acid chlorides for substrates with a pendant olefin, which allows for further comparisons between alkyl cations and silicon stabilized cations to be drawn.[19] Subjecting acid chloride **29** to Lewis acid yielded pentenone **30**, the product predicted by the β-silicon effect, through silicon stabilized carbocation **31** (Scheme 6). Notably, substrate **32** gave rise to product **33**, which was attributed to the selective attack from the pendant olefin onto the acid chloride to yield carbocation **34** followed by quenching of the cation, and subsequent protodesilylation of the vinylsilane. This indicates that the formation of a tertiary trialkyl carbocation **34** is more stable than a secondary β-silicon stabilized carbocation. Similar reactivity patterns have been observed in intermolecular reactions of vinylsilanes and acid chlorides, as well as other cyclization reactions.[20] Taking the previous study by Nakai into consideration, in the absence of stereoelectronic or other restrictions, intramolecular cyclization reactions of vinylsilanes form carbocations with the following preferences: tertiary trialkyl > secondary β-silyl > tertiary α-silyl, secondary dialkyl > primary β-silyl. Clearly, the stability of the intermediate carbocations dictates the regioselectivities in the nucleophilic addition of organosilanes to C–X π-systems, and is an important factor to keep in mind when trying to predict the outcome of such reactions.

1.02.2.3 Stereochemical Outcome and Rationalization

Vinylsilanes generally undergo stereospecific additions to electrophiles. For example, the addition of deuterium chloride to *trans*-trimethylsilyl styrene **35**, was reported to furnish the *trans*-product **36** exclusively, whereas the *cis* styrene **37** was found to yield solely *cis* product **38** (Scheme 7).[21] The stereospecificity of this reaction is attributed to a torquoselective rotation, where the silyl group rotates via the least motion path from the plane of the double bond to attain coplanarity with the carbocation. Desilylation of the carbocation then yields the product, in which the double-bond geometry has been retained.

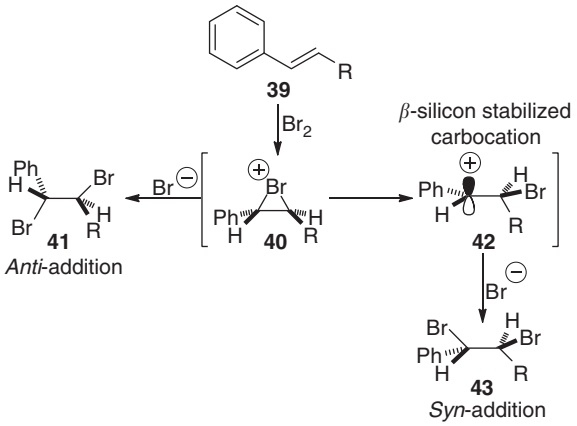


Scheme 6 Intramolecular competition between an alkene and a vinylsilane in the addition to an acid chloride.



Scheme 7 Origin of regioselectivity in electrophilic additions to vinylsilanes.

By exploiting the torquoselective rotation accompanied by β-silicon stabilization, Brook and coworkers were able to determine the relationship between the electronegativity of the substituents on silicon and the magnitude of the β-silicon effect. Substituted styrene **39** can undergo electrophilic bromination via two competing reaction manifolds (**Scheme 8**).[22] The first route is through the bromonium ion **40**, which after the attack of bromide on this intermediate leads to *anti*-addition of bromine across the double bond and furnishes *anti*-dibromide **41**. Exclusive observation of this pathway is reported for styrenes with other donating groups, such as methyl. In the other reaction manifold the β-silicon effect will cause bromonium **40** to open to the β-silicon stabilized carbocation **42**. This occurs with concommitant rotation of the silyl group to assume coplanarity with the cation and forces the attack of the bromide to occur opposite to the silyl group, giving rise to the *syn*-dibromide **43**. Thus, more of the *syn*-dibromide should be observed as the strength of β-silicon effect increases. Brook and coworkers then measured the ratio of *syn*-addition to *anti*-addition of bromine for a variety of silyl groups and found that a decrease in electronegativity of the substituents on silicon leads to an increase in *syn*-addition (**Table 1**). This is an effective procedure for the evaluation of the magnitude of the β-silicon effect for various silyl derivatives, though more than 100% of the *syn*-bromide cannot be realized and thus the method cannot discriminate between electron-rich silyl groups.

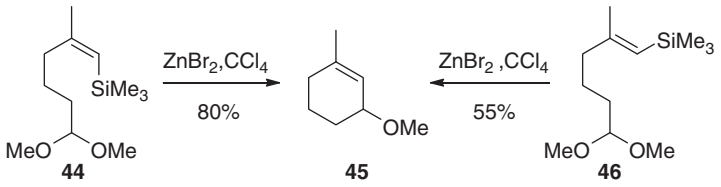


Scheme 8 Method for comparing the electronegativity of the silyl moiety and the magnitude of the β-silicon effect. *See* **Table 1** for R_3.

Table 1 Results of the bromination of vinylsilane **43** (**Scheme 8**)

R	% syn-*addition*	*Electronegativity*
$SiMe_3$	100	2.05
$SiMe_2F$	87	2.23
$SiMeF_2$	40	2.41
SiF_3	17	2.59

Although intermolecular vinylsilane additions to electrophiles are often stereospecific, as demonstrated by the above example, electronic effects can override the β-silicon effect. In intramolecular reactions the use of the β-silicon effect for prediction of reaction outcome can also be complicated by steric demands. As an illustration of this, when vinylsilane **44** and isomeric vinylsilane **46** were subjected to Lewis acid they yielded the same product *Z*-cyclohexene **45**. Furthermore, vinylsilane **44** cyclizes to give the product faster and in better yield than the isomeric vinylsilane **46** (**Scheme 9**).[23] The results indicate that there is relaxation of the torquoselectivity normally adhered to in vinylsilane additions. This comes at the price of the yield for vinylsilane **46**, and arises because it is unreasonable to generate the corresponding *E*-cyclohexene product.

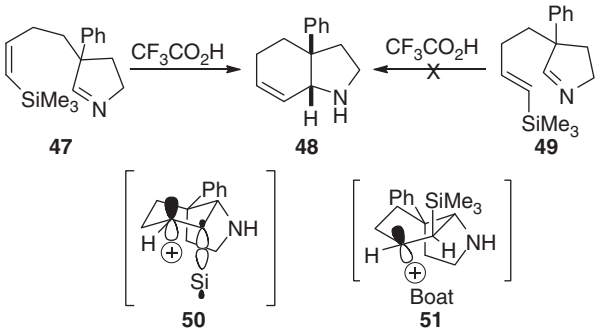


Scheme 9 Under Lewis acid catalysis the *E*- and *Z*-isomers of vinylsilane **44** and **46** give the same product **45**.

Another illustration of the disparate results that can obtained for isomeric vinylsilanes was disclosed by Overman et al. in their route toward the alkaloid epielwesine using intramolecular cyclization of vinylsilanes onto iminium ions.[24] When the *cis*-vinylsilane **47** was treated with trifluoroacetic acid in acetic acid at 82 °C for 2 h, cyclized product **48** was isolated in 90% yield (**Scheme 10**). When the *trans*-vinylsilane **49** was subjected to the same conditions no product was observed even after 48 h. These contrasting outcomes presumably occur because in *cis*-vinylsilane **47**, the silyl group can stabilize the incipient cationic charge and achieve coplanarity with the intermediate cation, as shown in transition state **50**. This is not possible due to conformational restrictions for the cyclization of *trans*-vinylsilane **49**.

1.02.3 Vinylsilanes

Inter- and intramolecular addition of vinylsilanes to electrophiles is a well-established tool for making carbon–carbon bonds in organic chemistry. In the intermolecular mode the reaction normally proceeds with retention of stereochemistry, although this is not always the case for intramolecular cyclizations.

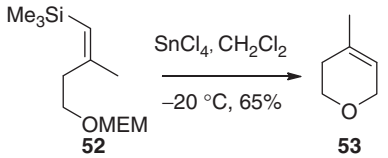


Scheme 10 Only one of the isomeric vinylsilanes **47** and **49** can cyclize.

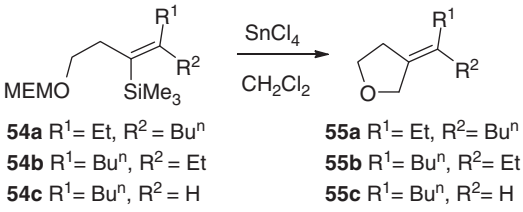
Vinylsilanes have been successfully added to acyl halides, acetals, and iminium ions, and have been used to direct the course of the Nazarov cyclization. The area has been well reviewed,[3g,h,25] and only recent advances will be presented here.

1.02.3.1 Acetal- and Carbonyl-Mediated Reactions

Intramolecular acetal-mediated cyclizations have been developed as an efficient method for preparing five- to seven-membered oxacycles,[26] an example being the $SnCl_4$-mediated cyclization of vinylsilane **52** into dihydropyran **53** (Scheme 11).[27] Depending on the structure of the substrate, the reaction can proceed by an *endo* or *exo* mode with respect to both the vinylsilane and the intermediate oxonium ion, and this can also affect the stereoselectivities obtained. For example, (*Z*)- and (*E*)-isomers **54a** and **54b** both yielded a 40:60 mixture of **55a**:**55b** (81% and 86% yield, respectively), whereas **54c** cyclized in excellent stereoselectivity to give **55c** (81%, *dr* 97:3) in which the stereochemistry of the olefin has been retained (Scheme 12).

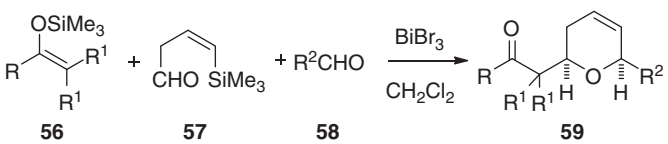


Scheme 11 Cyclization of vinylsilane **52**.



Scheme 12 Cyclization of substituted vinylsilanes **54a–c**.

The general reaction type outlined in Scheme 11 has been expanded to include efficient two- and three-component silyl-Prins reactions, affording dihydropyrans. $BiBr_3$-mediated Mukaiyama aldol addition of a silyl enol ether or silyl ketene acetal **56** to aldehyde **57** generated a sensitive homoallylic alcohol (Scheme 13). This material was not isolated but instead a second aldehyde **58** (R^2CHO) was added together with additional $BiBr_3$ (10 mol%) to give *cis*-2,6-disubstituted dihydropyran **59** in good yield and excellent selectivities (Table 2).[28] When using the less nucleophilic silyl enol ethers it was necessary to preactivate the Lewis acid or increase its concentration in order to favor the reaction for completion. The stereochemical outcome is rationalized by invoking

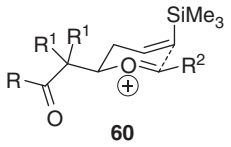


Scheme 13 Three-component silyl-Prins reaction generating dihydropyran **59**.

(*E*)-oxocarbenium ion **60** in which the axial silyl group is oriented so as to provide optimal stabilization for the developing positive charge (Figure 4).[29] Attempts to prepare *trans*-2,6-disubstituted tetrahydropyrans by using an (*E*)-vinylsilane gave only trace amounts of cyclization products, in line with the stereoelectronic requirements for this reaction, as the Si–C σ bond cannot attain the necessary coplanarity with the *p*-orbital of the carbocation.

Table 2 Three-component synthesis of dihydropyran **59** (Scheme 13)

Entry	*R*	R^1	R^2	*Yield (%)*	*dr (cis:trans)*
1	MeO	Me	$PhCH_2$	64	>99:1
2	Ph	Me	n-C_5H_{11}	76	>99:1
3	Ph	H	n-C_7H_{15}	44	>19:1
4	Bu^t	H	Ph	80	>19:1



60

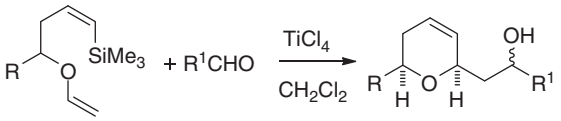
Figure 4 Transition state for the three component silyl-Prins reaction.

In an alternative entry to the dihydropyran ring system, vinylether **61** was subjected to a $TiCl_4$-mediated aldol reaction with aldehyde **58**, and the intermediate oxocarbenium ion was then trapped intramolecularly by the vinylsilane tether to give **62** (Table 3 (Scheme 14)).[30] For these reactions, the *cis*-2,6 stereochemistry was excellent and it is reasonable to assume that its origin is due to the stereoelectronic effect detailed above. However, the diastereoselectivity at the hydroxyl stereocenter was poor (entries 3 and 4). When the silyl-Prins reaction was performed on a (*Z*)-4-(trimethylsilyl)but-3-en-1-ol derivative $InCl_3$ proved to be the best catalyst, but when the sequence was expanded to an aldol/silyl-Prins protocol this Lewis acid only resulted in recovered starting material. However, it was found that $TiCl_4$ successfully promoted the formation of dihydropyran **62**.

Table 3 Aldol/silyl-Prins reaction to give dihydropyran **62** (Scheme 14)

Entry	*R*	R^1	*Yield (%)*	*dr*[a]
1	H	$PhCH_2$	53	3.2:1
2	H	n-C_5H_{11}	48	1.7:1
3	Me	n-C_5H_{11}	42	3.7:1
4	Ph	c-C_6H_{11}	52	1.8:1

[a]Only the *cis*-2,6-dihydropyran isomer **62** was detected. *dr* refers to the hydroxyl stereocenter.



61 **58** **62**

Scheme 14 Aldol/silyl-Prins reaction sequence to dihydropyran **62**.

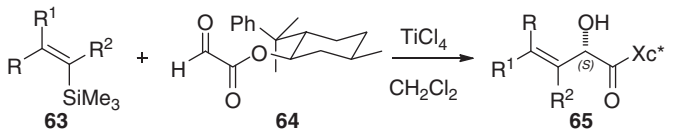
Due to its efficiency and high diastereoselectivity the silyl-Prins reaction has been used as a key step in the synthesis of several natural products containing a 2,6-disubstituted-pyran unit.[31]

The possibility to use vinylsilanes for regio- and stereoselective intermolecular carbon–carbon bond formation is an attractive feature, although the number of available electrophiles is somewhat limited due to the low reactivity of these reagents. In a pioneering study it was shown that vinylsilanes can be added to methyl glyoxylate to give the corresponding α-hydroxy-β,γ-unsaturated esters with complete retention of the olefin stereochemistry.[32] Furthermore, when using the 8-phenylmenthol-derived glyoxylate **64** as the substrate, alcohol **65** was obtained in good yields and with preservation of the original alkene geometry (Table 4 (Scheme 15)). Both (*Z*)- and (*E*)-monosubstituted vinylsilanes **63** (entries 1, 2 and 3, 4, respectively) and (*E*)-disubstituted **63** (entry 5) performed well, whereas the (*Z*)-isomer (**63**, R=Me, R^1=H, R^2=Me) gave a mixture of the addition

product and the product derived from a carbonyl-ene reaction. When comparing the 2-phenyl substituted vinylsilanes to the 2-Bu^n ones (entries 1,3 and 2,4, respectively) the yields for the latter are somewhat lower, which is consistent with these silanes being less reactive. The new stereogenic center is introduced with high diastereoselectivity and its absolute stereochemistry (2*S*) implies that the vinylsilane adds to the *Si* face of the chelated carbonyl moiety. It was noted that the choice of Lewis acid had a profound influence on the reaction outcome. Although the use of $TiCl_4$ promoted the addition of most vinylsilanes onto the glyoxylate, the use of $SnCl_4$ favored a carbonyl-ene reaction manifold instead.[33]

Table 4 Asymmetric addition of vinylsilane **63** to glyoxylate **64** (**Scheme 15**)

Entry	*R*	R^1	R^2	*Yield (%)*	*dr (%)*
1	Ph	H	H	89	>99
2	Bu^n	H	H	83	>99
3	H	Ph	H	99	>99
4	H	Bu^n	H	74	>99
5	H	Me	Me	95	>99

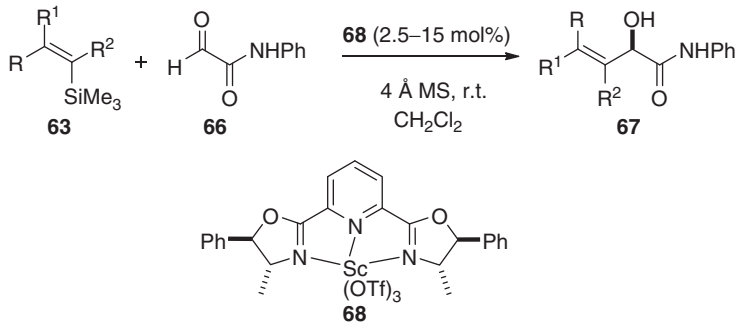


Scheme 15 Asymmetric construction of alcohol **65** using 8-phenylmenthol-derived glyoxylate **64**.

More recent efforts have focused on developing enantioselective Lewis acid-catalyzed additions of vinylsilanes to electrophiles. Screening of several Sc(III)-pybox complexes revealed that (*R*,*R*)-norephedrinepybox catalyst **68** was most efficient in promoting the addition of vinylsilane **63** to glyoxamide **66**, affording alcohol **67** in high yield and *ee* (**Table 5**, entry 1 (**Scheme 16**)).[34] For most substrates examined, the olefin stereochemistry was retained throughout the reaction with the exception being (*Z*)-phenylvinylsilane (**63**, R=Ph, R^1=H, R^2=H). When this reagent was added to **66** the corresponding (*E*)-allylic alcohol was

Table 5 Catalytic asymmetric addition of vinylsilane **63** to glyoxylate **66** (**Scheme 16**)

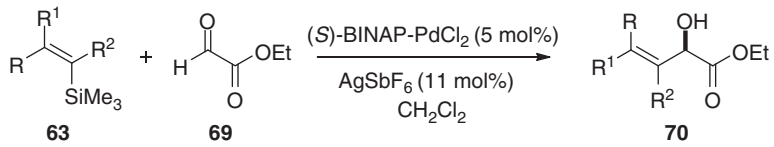
Entry	*R*	R^1	R^2	*Yield (%)*	*ee (%)*
1	H	Ph	H	92	99
2	H	4-Me-C_6H_4	H	89	98
3	H	4-F-C_6H_4	H	83	99
4	H	Bu^n	H	63	98
5	Bu^n	H	H	49	97
6	Me	Ph	H	92	98
7	Me	Me	H	64	98
8	Me	Me	Me	45	99



Scheme 16 Scandium-catalyzed addition of vinylsilane **63** to glyoxylate **66**.

obtained in 89% yield and 99% *ee*, which is the same outcome as for (*E*)-phenylvinylsilane (entry 1). It was speculated that the reason for this anomaly could be traced to the stability of the intermediate benzylic cation, which apparently is stable enough to allow for C–C bond rotation and formation of the thermodynamic product, although such rotation will reduce the effect of the *β*-silicon stabilization. In this study it was also noted that the alkyl substituted vinylsilanes gave a lower yield compared with the aryl substituted ones, although the enantioselectivity was not compromised (compare entries 4, 5, 7, 8 with 1–3, 6). Although amides are generally considered difficult to derivatize, it has been shown that *N*-phenylcarboxamides similar to **67** can be activated (Boc_2O) and then hydrolyzed (H_2O_2, LiOH) to the carboxylic acid without racemization, thus adding considerable application to this protocol.[35]

A similar asymmetric addition to ethyl glyoxylate has been achieved using a chiral dicationic Pd(II)-(*S*)–BINAP complex (Scheme 17, catalyst in Scheme 23).[36] The addition proceeds well for a range of substrates, affording alcohol **70** in good to high yields and high *ee*s (Table 6). Addition of (*Z*)-phenylvinylsilane (**63**, R=Ph, R^1=H, R^2=H) resulted in a minor erosion of the olefin stereochemistry, whereas all other vinylsilanes reacted with retention of alkene geometry. To clarify the mechanism of this reaction a crossover experiment was performed. The outcome indicated that the transfer of the silicon moiety is intramolecular, and it was concluded that this rules out the possibility of vinylpalladium intermediates. The scope of the silicon substituents was also investigated; with trialkyl and dialkyl phenyl silyl groups performing best whereas trialkoxy- and alkyl dialkoxysilanes were less efficient, which is the expected trend when the vinylsilane is the active nucleophile.



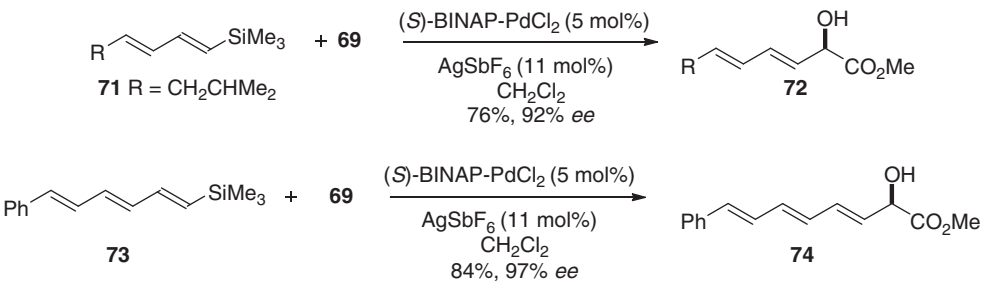
Scheme 17 Asymmetric addition of vinylsilane **63** to ethyl glyoxylate **69** using a Lewis acid catalyst.

Table 6 Asymmetric addition of vinylsilane **63** to ethyl glyoxylate **69** (Scheme 17)

Entry	*R*	*R^1*	*R^2*	*Yield (%)*	*ee (%)*
1	H	Ph	H	84	98
2	H	4-MeO-C_6H_4	H	83	95
3	H	4-CF_3-C_6H_4	H	55	97
4	H	Bu^n	H	64	91
5	Ph	H	H	79[a]	96
6	Bu^n	H	H	60	95
7	Me	Me	Me	73	99

[a] Z/*E* 96:4.

The dicationic Pd(II)-(*S*)–BINAP complex was also a competent catalyst for the addition of (*E*,*E*)-dienylsilane **71** and (*E*,*E*,*E*)-trienylsilane **73** to glyoxylate **69**, affording alcohols **72** and **73** in high yields and *ee*s (Scheme 18). Clearly, this catalyst system is capable of delivering a range of highly functionalized and enantioenriched allylic alcohols, compounds, which are valuable building blocks in organic synthesis.

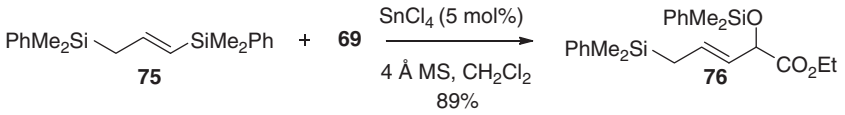


Scheme 18 Catalytic asymmetric addition of polyenes to glyoxylate **69**.

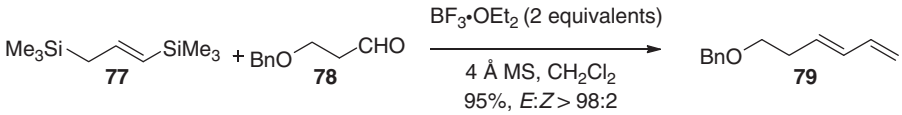
A general enantioselective vinylation of aldehydes using trialkoxy- or alkyldialkoxysilanes catalyzed by a CuF-DTBM –SEGPHOS complex has been described.[37] Although this reaction is formally an alkenylation of carbonyl groups using vinylsilanes, mechanistic investigations indicate a more complicated picture. It has been suggested that an alkenylcopper intermediate,

generated by transmetalation, is the true nucleophilic species and that the vinylsilane is thus not relevant in the enantiodifferentiating step. Consequently, this chemistry will not be further discussed in this chapter.

In an attempt to improve the reactivity of vinylsilanes, 1,3-bis(silyl)propenes (e.g., **75**) have been designed and investigated.[38] More specifically, it was envisioned that such reagents should enjoy increased reactivity due to the allylsilane moiety, whereas retaining the regioselectivity of the vinylsilane functionality. Indeed, addition of 1,3-bis(silyl)propene **75** to ethyl glyoxylate **69** gave silyl ether **76**, formally the result of an addition of a vinylsilane to **69** (Scheme 19).[39] When silane **76** was subjected to TMSOTf the corresponding diene, (*E*)-ethyl penta-2,4-dienoate, was obtained in quantitative yield and as a single double-bond isomer. Following this result, the procedure has been modified into a direct synthesis of terminal (*E*)-dienes from aldehydes using mild and nonbasic reaction conditions, as exemplified by the addition of **77** to aldehyde **78**, affording diene **79** in good yield and selectivity (Scheme 20).[40]



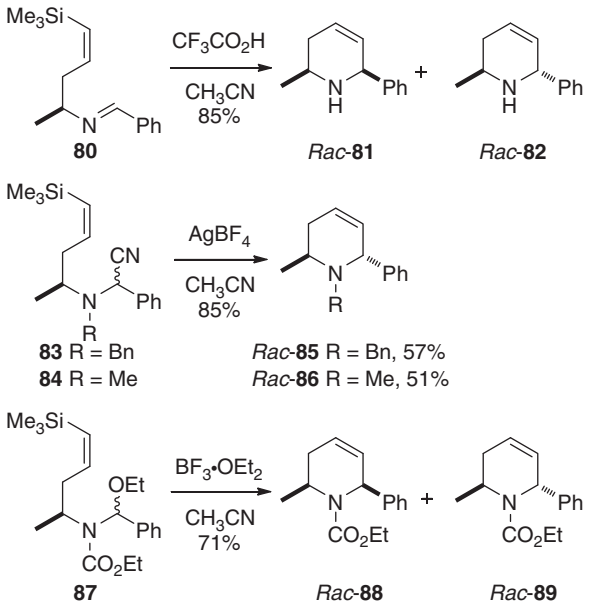
Scheme 19 Addition of 1,3-bis(silyl)propene **75** to glyoxylate **69**.



Scheme 20 Direct synthesis of dienes using 1,3-bis(silyl)propene 77.

1.02.3.2 Iminium Ion Initiated Cyclizations

Intramolecular cyclizations of vinylsilanes onto iminium ions and *N*-acyliminium ions to generate tetrahydropyridines were pioneered by Overman, and have since been used with great success in organic synthesis.[26] In most cases the iminium ion has been generated by condensation of an amine with formaldehyde, although examples in which other aldehydes are used have been described. The *N*-acyliminium ions, however, are typically derived from the corresponding aminals or by oxidation. The stereochemical outcome from these reactions is not always straightforward to rationalize (Scheme 21).[41] Acid-mediated cyclization of imine **80** afforded tetrahydropyridines *rac*-**81** and *rac*-**82** as a 1:1 mixture, the racemization apparently occurring before the cyclization event. In contrast to this, the iminium ions generated from **83** and **84** cyclized with complete diastereoselectivity to



Scheme 21 Intramolecular additions of vinylsilanes onto iminium ions.

give *trans*-2,6-disubstituted tertrahydropyridines *rac*-**85** and *rac*-**86**, respectively, but again with accompanying racemization. However, later studies have shown that similar iminium ions generated from secondary amines can indeed be cyclized using Brønsted acids or $InCl_3$ to afford the corresponding tetrahydropyridines with complete diastereoselectivity and no racemization.[42,43] Finally, the *N*-acyliminium ion derived from **87** gave *rac*-**88** and *rac*-**89** as a 1:1 mixture. Again for this case it was later shown that an enantioenriched 2-substituted sulfonamide could be cyclized to the corresponding 2-substituted *N*-Ts-tetrahydropyridine with only minor loss of enantiomeric purity.[44]

The stereochemical outcome in these cyclizations, i.e., the formation of *trans*-2,6-disubstituted tetrahydropyridines *rac*-**85** and *rac*-**86** in the cyclization of **83** and **84**, and the lack of selectivity in the cyclization of **80** and **87**, together with the reversed selectivity as compared with the corresponding cyclization of oxocarbenium ions (compare Scheme 13 and Scheme 21) is puzzling and has been studied in some detail.[26,41,45,46] The salient features that have emerged are summarized in Figure 5. For an *in situ*-generated iminium ion the reaction starts from **A** (R^1 = alkyl), in which the R group occupies a pseudoequatorial position whereas the R^2 moiety has a pseudoaxial orientation to avoid a steric interaction with the silane. The cyclization can then proceed by the addition of the vinylsilane onto the iminium ion to give an intermediate carbocation that is stabilized by the axially oriented trimethylsilyl group in β-position, followed by elimination to give **C** (**A**→**C**). Alternatively, an ensuing stepwise aza-Cope rearrangement generates the same stabilized carbocation, and this intermediate then collapses to give structure **B**. The allylsilane moiety in **B**, being more nucleophilic than the vinylsilane in **A**, can now add to the iminium ion to give the *trans*-2,6-disubstituted tetrahydropyridine **C** (**A**→**B**→**C**). The racemization that has been observed in some cases can then be a consequence of the aza-Cope rearrangement proceeding from structure **D** (addition to the opposite face of the iminium) and this will eventually afford *ent*-**C**. Quantum-mechanical investigations have also revealed that for aldimines generated from primary amines (**A**, R^1 = H) the transitions states for the aza-Cope rearrangement are of comparable energy when the R^2 groups have a pseudoaxial orientation or pseudoequatorial one (not shown in Figure 5), and since these two conformers will result in the diastereomeric *trans*- and *cis*-2,6-tetrahydropyridines, respectively, this nicely accounts for the observed experimental outcome.

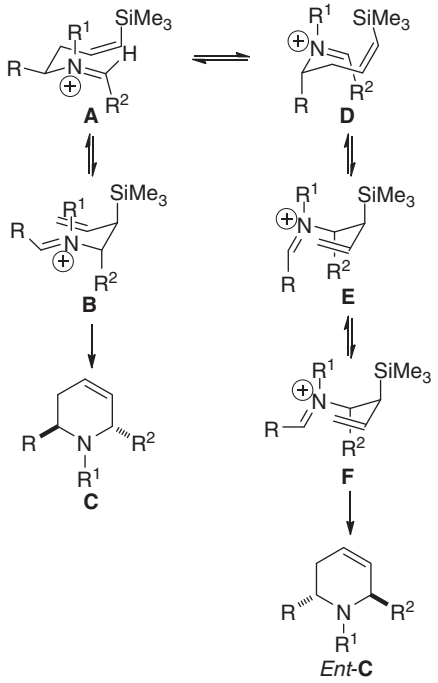
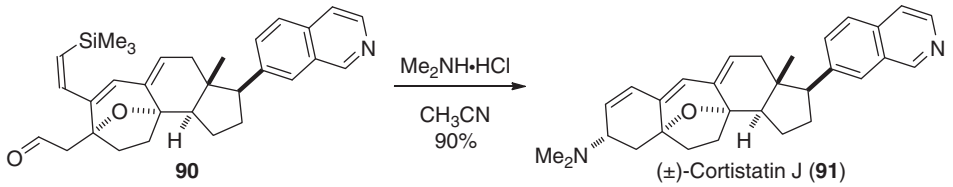


Figure 5 Proposed mechanism for the intramolecular cyclization of vinylsilanes to N–H and *N*-alkyl iminium ions, accounting for the observed racemization and low diastereoselectivity.

The intramolecular cyclization of vinylsilanes onto iminium ions has been used with great success in the synthesis of natural products,[3i,26] and a single example will suffice to illustrate the potential of the methodology in complex molecular settings. In the last step of a total synthesis of the marine steroidal alkaloid (±)-cortistatin J (**91**), aldehyde **90** was subjected to dimethylamine hydrochloride to give the target molecule as a single diastereomer in excellent yield (Scheme 11).[47] It should be noted that the mechanism discussed above (Figure 5) is not operative in this case since the reaction proceeds in an *exo* mode with respect to the iminium ion, precluding any involvement of an aza-Cope rearrangement. Thus, the conversion of **90** into **91** represents a direct addition of the vinylsilane onto the iminium ion (Scheme 22).



Scheme 22 Use of an intramolecular vinylsilane addition onto an iminium ion in the total synthesis of (±)-cortistatin (**91**).

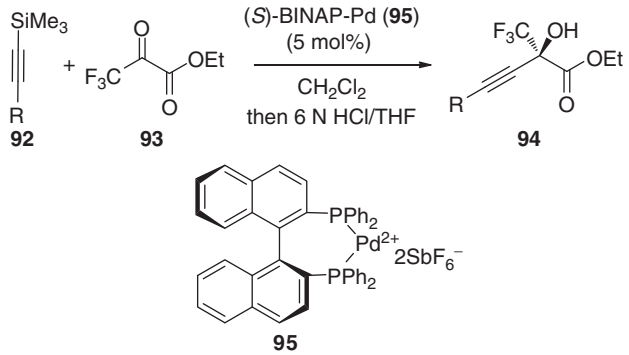
1.02.4 Alkynylsilanes

Alkynysilanes are used as nucleophiles in addition reactions to C=X bonds. Lewis acid-catalyzed additions to aldehydes,[48] acid chlorides,[49] acetals,[50] stabilized carbocations,[51] and quinolines[52] have been realized. This section aims to highlight recent advances in stereoselective transformations using alkynylsilanes, where the alkynylsilane does not undergo a transmetalation event.

1.02.4.1 Lewis Acid-Catalyzed Additions

1.02.4.1.1 Enantioselective approaches

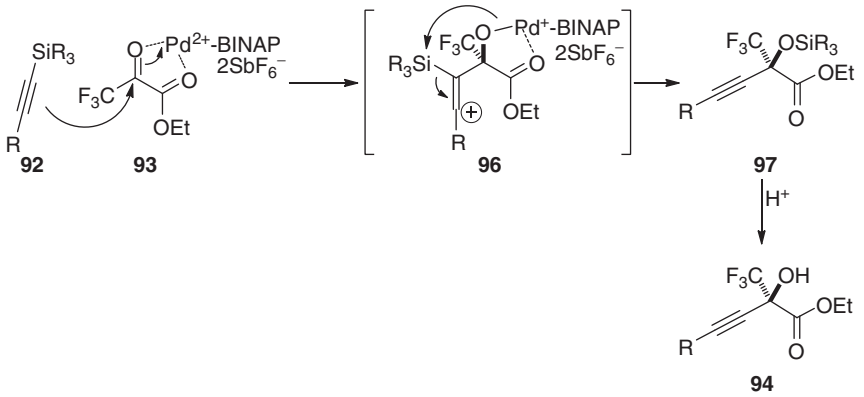
Recent efforts have focused on catalytic, asymmetric addition of alkynylsilanes to electrophiles, although the number of electrophiles is limited due to the low reactivity of the alkynylsilane reagents. Mikami and coworkers recently reported the asymmetric addition of alkynylsilanes **92** to trifluoropyruvate **93** to yield α-trifluoromethyl-substituted tertiary alcohols **94** using Pd(II)-catalysis (Scheme 23).[53] This reaction gives good yields and enantioselectivities for a variety of alkynylsilanes, including aryl- and alkyl-terminated alkynylsilanes (Table 7). The reaction also worked well for a variety of polyynes, including a tetrayne (61% yield, 96% *ee*). The mechanism of the reaction was studied by NMR and it was revealed that there was no transmetalation of the alkyne to the Pd catalyst. Thus, in the proposed mechanistic cycle the cationic Pd catalyst acts a Lewis acid, further activating the trifluoropyruvate toward nucleophilic attack by the alkynylsilane (Scheme 24). This yields a β-silicon stabilized carbocation **96**, which is quenched by internal silyl transfer to the silylether **97**. Acidic work up then furnishes the observed alcohol **94**. An advantage of this procedure is that there is no need to pregenerate a metal acetylide. The authors further demonstrated that the products could be readily transformed into chiral allenes and chiral allylic alcohols, broadening the significance of these results. In an interesting extension of this work, more electron-rich R groups (**92**, R=C_5H_4–4-OMe) were explored. It was found that the reaction course alters for these substrates and stable oxetenes can be produced instead.[54]



Scheme 23 Asymmetric addition of alkynylsilane **92** to pyruvate **93** using Pd(II)-catalysis.

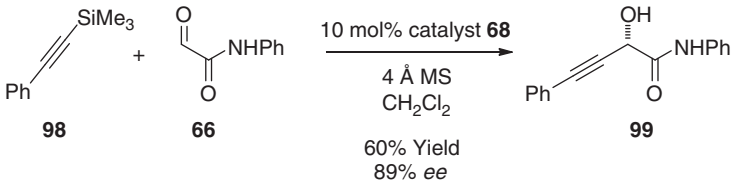
Table 7 Yields and *ee* for the asymmetric addition of alkynylsilanes to pyruvate **93** (Scheme 23)

Entry	*R*	*Yield (%)*	*ee (%)*
1	–C_6H_4–4-CF_3	70	98
2	–mesityl	86	98
3	–Me	69	>99
4	–cyclohexyl	94	>99
5	–benzyl	75	90



Scheme 24 Proposed mechanism for the asymmetric addition of alkynylsilanes **92** to pyruvate **93**.

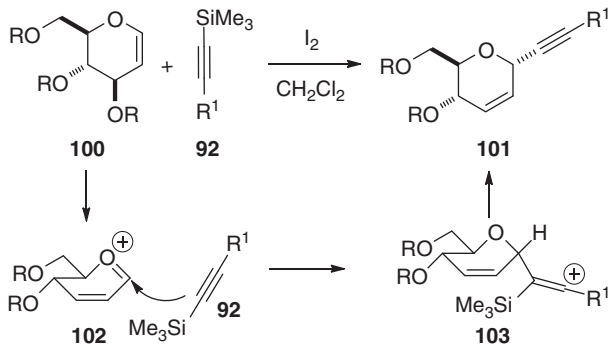
In a related type of catalytic, enantioselective reaction, the Evans group has reported the addition of alkynylsilane **98** to glyoxamide **66** using a Lewis acid catalyst **68** (Scheme 25, catalyst depicted in Scheme 16).[34] This proceeded in moderate yield and good enantioselectivity. However, only one example using an alkynylsilane was demonstrated.



Scheme 25 Asymmetric addition of alkynylsilane **98** to glyoxamide **66**.

1.02.4.1.2 Diastereoselective methodologies

There have been many disclosures of the addition of alkynylsilanes to sugar derivatives to append an alkyne onto the sugar scaffold.[55] This has been accomplished for pyranoses,[56] pentose glycals,[57] aldehydes producing pseudoglycals *in situ*,[58] furanosides,[59] and D-glucals using a variety of Lewis acid catalysts, including molecular iodine,[60] and $InBr_3$.[61] Thus, a single example will be used to demonstrate the utility of this type of carbon–carbon bond formation. Addition of alkynylsilane **92** to D-glucal **100** using I_2 as a catalyst has been described (Scheme 26).[60] This results in only α-glycoside linkages (1,4-*syn*) and good yields of the alkynyl sugars **101** (Table 8). It is believed that the reaction goes through the enonium ion **102**. Attack on this intermediate by alkynylsilane **92**, directed by overlap of the π-orbitals of the enonium ion and the acetylene, then yields a silicon stabilized carbocation **103**, which is quenched by loss of silicon to furnish product **100**. Additionally, when R=MeO and $R^1=SiMe_3$ for alkynylsilane **92** then the bis-glycosylated acetylene can be isolated in 87%. In general, alkynylsilanes give higher diastereoselectivity for this transformation than the corresponding allylsilanes and this is believed to be stereoelectronically driven.[55b] Interestingly, when pentose sugars were used 1,4-*anti* selectivity was observed. This has been described for other additions of alkynylsilanes to pentoses and is presumed to arise from stereoelectronic effects.[57] A related application of these conditions is the addition of alkynylsilanes to simple cyclic allylic acetates.[62] Using I_2 as a catalyst the products can be obtained in good yields.

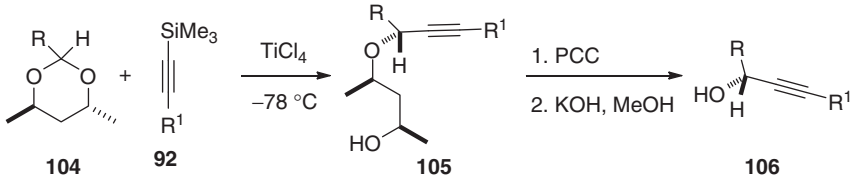


Scheme 26 Addition of alkynylsilanes **92** to D-glucals **100**.

Table 8 Addition of alkynylsilanes **92** to glucals **100** (Scheme 26)

Entry	*R*	*R^1*	*Yield (%)*
1	AcO	Ph	90
2	AcO	Bu^n	87
3	AcO	$SiMe_3$	85
4	AllylO	Bu^n	83

As described for vinylsilanes, acetals have also been exploited as competent electrophiles in nucleophilic addition reactions of alkynylsilanes under Lewis acidic conditions. Johnson et al. have described the synthesis of chiral propargylic alcohol **106** using a chiral auxiliary (Scheme 27).[63] Subjection of chiral acetal **104** to a Lewis acid affords an oxonium intermediate, which is subsequently attacked by the alkynylsilane **92**. This furnishes the chiral alkynyl ether **105** in good yields and good to moderate *dr* for a variety of alkyl substituents. Treating this product with PCC to oxidize the free alcohol and then KOH in MeOH liberated the chiral propargylic alcohol **106** in excellent yields and good to moderate *ee*. Comparable diastereoselective additions to acetals using substrate control have been used to access a variety of substituted tetrahydropyrans.[64]

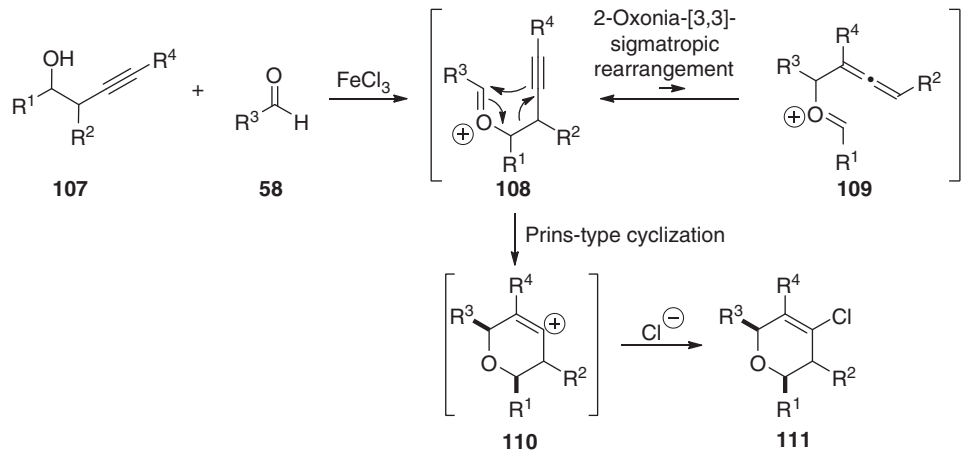


104 **92** **105** **106**

Scheme 27 Construction of chiral propargylic alcohols from alkynylsilanes.

1.02.4.1.3 Alkynylsilane Prins reaction

In intramolecular reactions, the presence of an alkynylsilane moiety can often influence the cyclization mode of the reaction.[3d] Miranda et al. reported that primary homopropargylic alcohols (**107**, $R^1=R^2=R^4=H$) react with an aldehyde in the presence of a Lewis acid via a Prins cyclization (Scheme 28).[65] However, for secondary homopropargylic alcohols (**107**, $R^1\neq H$, $R^4=H$) using the same conditions the oxonia [3,3]-sigmatropic rearrangement became the dominant reaction manifold (**107**→**108**→**109**), yielding a mixture of products. As the stability of the intermediate carbocation **108** determines the reaction manifold it was reasoned that by using a silyl-terminated alkyne (i.e., $R^4=SiMe_3$) the desired Prins reaction could be favored via a silicon-stabilized carbocation for secondary alcohol substrates. This was indeed the case and the $FeCl_3$-catalyzed Prins reaction proceeded in good yields and excellent diastereoselectivity for a variety of secondary homopropargylic alcohols **107** (Table 9). Only for the more sterically hindered isobutyl aldehyde (**58**, $R^3=Bu^i$) was a lower diastereoselectivity observed. The reaction proceeds with the preservation of silicon, as it is mechanistically unreasonable to generate the corresponding cyclic alkyne. Unfortunately, the reaction was only successful for alkyl aldehydes, and no reaction was observed with aryl aldehydes. More recently, Yadav reported a similar silylalkyne Prins cyclization using I_2 as the catalyst.[66] The reaction shows similar diastereoselectivity and substrate scope.



107 **58** **108** **109** **110** **111**

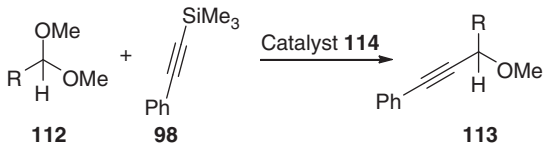
Scheme 28 The alkynylsilyl Prins reaction and competing [3,3]-sigmatropic rearrangement.

Table 9 Results for the silylalkynyl Prins reaction (Scheme 28)

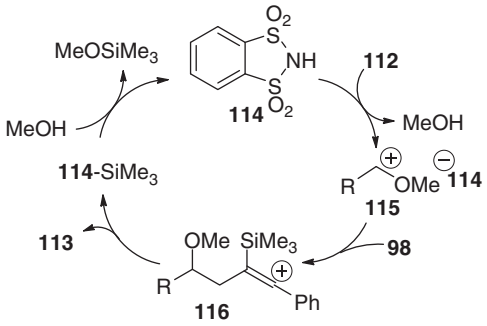
Entry	R^1	R^2	R^3	R^4	*dr*	*Yield (%)*
1	Me	H	cyclohexyl	$SiMe_3$	99:1	65
2	Me	H	Bu^s	$SiMe_3$	99:1	82
3	Me	H	Bu^i	$SiMe_3$	50:50	80
4	Me	Me	cyclohexyl	$SiMe_3$	99:1	62

1.02.4.2 Brønsted Acid Catalysis

The use of Brønsted acids catalysis for the addition of alkynylsilanes to electrophiles has also been explored. Barbero et al. recently detailed the catalytic addition of alkynylsilane **98** to acetal **112** using Brønsted acid **114** (Scheme 29, catalyst depicted in Scheme 30).[67] This proceeded for several aromatic acetals and one alkyl acetal in moderate yields (Table 10). Unfortunately, the catalyst loadings are quite high for this process. The authors propose that the catalyst **114** protonates acetal **112** to give cation **115**. This cation is attacked by the silylalkyne **98**, which is then decomposed by the catalyst **114** to give the silylated catalyst **114**-$SiMe_3$ and the product **113**. Reaction of silylated catalyst **114**-$SiMe_3$ with methanol then regenerates catalyst **114**.



Scheme 29 Addition of alkynylsilanes to acetals using Brønsted acid catalysis.



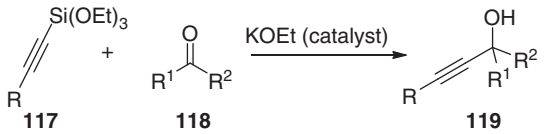
Scheme 30 Proposed catalytic cycle for the addition of alkynylsilanes to acetals using Brønsted acids.

Table 10 Addition of alkynylsilanes to acetals using Brønsted acid catalysis (Scheme 29)

Entry	*R*	*mol% catalyst*	*Yield (%)*
1	Ph	20	65
2	4-MeO-C_6H_4	30	65
3	4-NO_2-C_6H_4	30	54
4	$(CH_2)_4Me$	30	55

1.02.4.3 Base-Catalyzed Reactions

There has been a recent resurgence of interest in base-catalyzed alkynylsilane additions to aldehydes and ketones.[68] This includes the use of fluoride sources[69] and Lewis bases (such as phosphazene,[70] phenoxide,[71] and alkoxide[72]), and one example will be highlighted here. Scheidt and coworkers have described the addition of various alkynylsilanes **117** to aldehydes and ketones **118** using a catalytic amount of KOEt (Scheme 31).[73] The reaction has a broad substrate scope and even results in good yields for sterically hindered or enolizable ketones (Table 11). For ketones it is necessary to add a catalytic amount of 18-crown-6 in order to facilitate catalytic turnover. The authors suggest that either the KOEt or the deprotonated product serve as the catalyst. It was found that the triethoxysubstituted silane was also crucial for obtaining the desired reactivity.



Scheme 31 Addition of alkynylsilanes to aldehydes and ketones using Lewis base catalysis.

Table 11 Results from the addition of alkynylsilanes to aldehydes and ketones using Lewis base catalysis (**Scheme 31**)

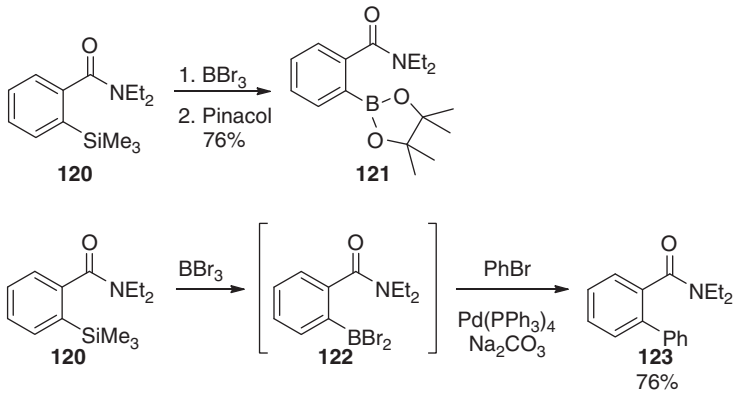
Entry	*R*	*R*^{1}	*R*^{2}	*Yield (%)*
1	Bu^n	H	Ph	74
2	Bu^n	Me	Bu^t	73
3	Bu^n	Ph	CH═CHPh	54
4	Ph	H	4-MeO-C$_6$H$_4$	77

1.02.5 Arylsilanes

1.02.5.1 General Reactivity

Although arylsilanes have seen extensive use as bench-stable carbanion surrogates, many of these reactions occur via transmetalation of the arylsilane to a metal species. This section will focus on the use of arylsilanes as carbanion equivalents in reactions where there is no transmetalation step. Often in the case of arylsilanes the silyl group is added both to boost reactivity in the electrophilic aromatic substitution, as well as to act as a directing group, ensuring the desired regioselectivity.

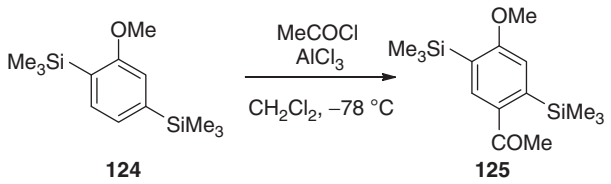
This strategy has recently been applied to the synthesis of pinacol borane **121** from arylsilane **120**, which was synthesized by directed *ortho*-metalation (**Scheme 32**).[74] Here, the silyl moiety was used to direct the site of borylation and it was found that a two-step procedure first generating the dihaloborane and then adding pinacol delivered desired boronic ester **121** in good yield and as a single regioisomer. As these organoboranes are competent substrates for the Suzuki coupling reaction, the authors also explored a one-pot coupling procedure where the arylsilane **120** was converted to dihaloborane **122** *in situ*, followed by directed subjection to Suzuki coupling, resulting in biaryl **123** in good yield. Interestingly, the authors also explored nitration of similar substrates in this study and found that when there was a methoxy group *meta* to the silane the expected *ipso*-substituted product was not observed.



Scheme 32 Synthesis of boronic esters from arylsilanes and one pot borylation-Suzuki reaction.

As mentioned above in arylsilane additions there are cases where *ipso* attack and subsequent substitution is not seen.[75] This phenomenon occurs when the β-silicon effect is not the dominant electronic factor. For example, when the silyl moiety is *meta* to a methoxy group, the intrinsic *ortho*/*para* directing capability of the methoxy group overrides the *ipso* directing ability of the silane, as shown in the reaction of arylsilane **124** with acetyl chloride and $AlCl_3$. Here, electrophilic aromatic substitution results in *para* substitution of the aryl ring with retention of silanes, giving ketone **125** (**Scheme 33**).[76]

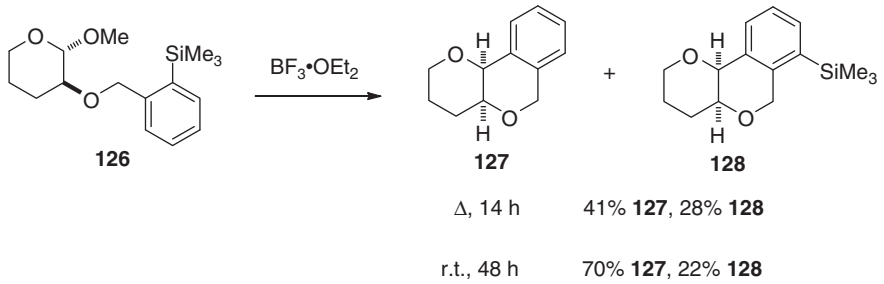
Similarly, in the cyclization reaction of arylsilane **126** with Lewis acid, two products were isolated (**Scheme 34**).[77] One was the expected *ipso*-substituted product **127**, whereas the other product **128** had cyclized and retained the silyl group. Deuteration of the starting material in the *para* position led to 100% D incorporation for both products. This indicates that **127** does not arise from



124 **125**

Scheme 33 Failure of the *ipso* substitution rule in the acylation of bissilane **124**.

protodesilylation of **128**. Attempts to cyclize a substrate that did not contain a silyl group were unsuccessful. Thus, the silyl activation is attributed to two opposing cyclization pathways. In one pathway, the silyl group activates the aryl ring as expected by stabilizing the intermediate carbocation and enforcing substitution of the silane. In the other reaction manifold the silyl group activates the aromatic ring to cyclize by a steric effect. The authors attribute this increased activity to the torqued Si–C=C–CH_2 dihedral angle, which may boost the electrophilicity of the aryl moiety. Also, the authors note the silyl group locks the benzyl group's π-system parallel to the intermediate oxonium ion, further increasing the reactivity.



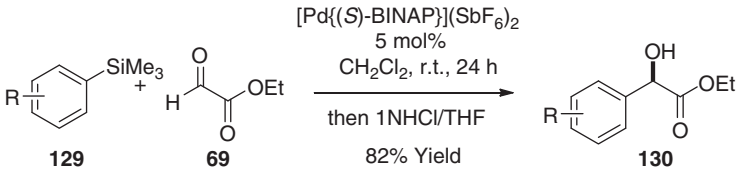
126 **127** **128**

Scheme 34 Intramolecular Friedel–Crafts of arylsilane **126**, yielding two cyclized products.

1.02.5.2 Lewis Acid-Catalyzed Reactions

1.02.5.2.1 Enantioselective reactions

Recently, Mikami reported the catalytic asymmetric addition of arylsilanes to glyoxylate (Scheme 35, catalyst in Scheme 23).[78] This reaction is regiospecific and occurring with only *ipso* attack and substitution, which is probably due to transition state stabilization imparted by the silicon and the other donating groups. Good yields and enantioselectivities were obtained for a variety of electron-rich aromatic and heteroaromatic substrates (Table 12). All of the examples using aromatic substrates have an electron-donating moiety in *ortho*- or *para*-position, although the authors demonstrated that alkylation of ethyl glyoxylate with other electron-rich aromatic compounds lacking silyl activation gave lower yield, enantioselectivity and regioselectivity. The authors propose that the Pd(II) species acts as a Lewis acid catalyst activating glyoxylate **69** for attack from arylsilane **131**



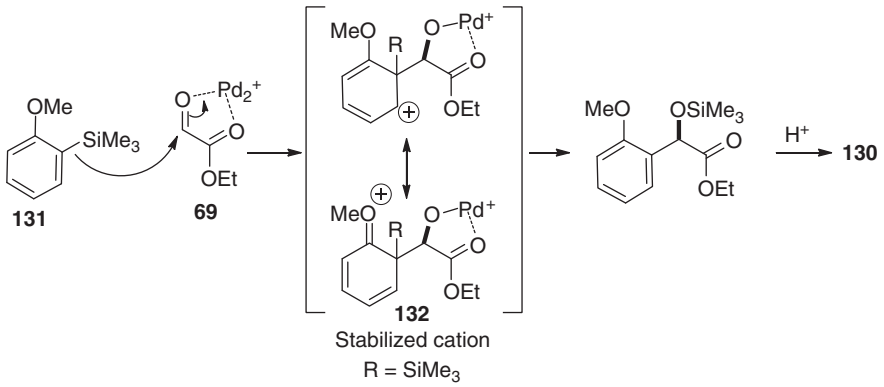
129 **69** **130**

Scheme 35 Catalytic, asymmetric addition of arylsilane **129** to glyoxylate **69**.

Table 12 Yields and *ees* for the asymmetric addition of arylsilane **129** to glyoxylate **69** (Scheme 35)

Entry	*R*	*Yield (%)*	*ee (%)*
1	*o*-OMe	82	>99
2	*p*-OBn	71	97
3	*p*-Me_2N	85	97
4	*o*-OMe, *m*-F	69	97

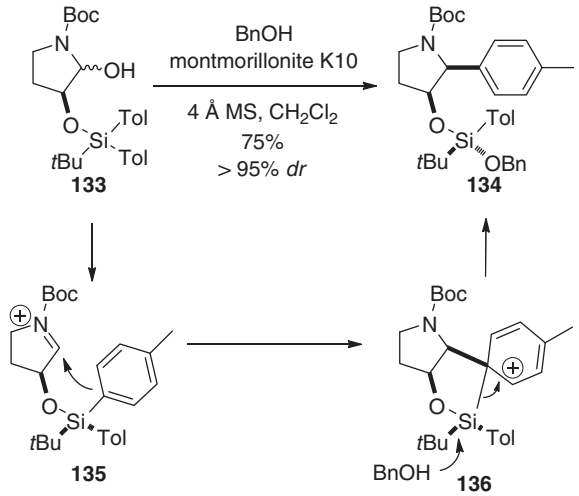
(Scheme 36). This results in a stabilized carbocation **132**, which is quenched by internal attack and the resulting silyl ether is hydrolyzed to yield alcohol **130**. Using ^{1}H and ^{31}P NMR it was determined that no arylpalladium intermediate arising from transmetalation was observed, supporting the proposed mechanism. Several other examples of arylation of carbonyls using arylsilanes as the nucleophiles are known.[37b,c] However, mechanistic and kinetic studies for these protocols favor the generation of a copper-aryl species through transmetalation, and thus the arylsilane is not acting as the nucleophile in the enantiodifferentiating step.



Scheme 36 Proposed mechanism for the nucleophilic addition of arylsilane **129** to glyoxylate **69** using Pd(II) catalysis.

1.02.5.2.2 Diastereoselective reactions

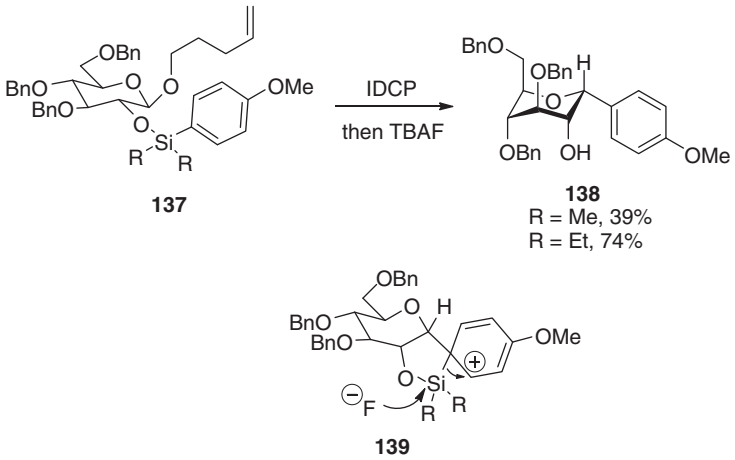
Several intramolecular transfers of an aryl moiety from a silyl protecting group or silyl tether to a neighboring electrophilic site have been explored.[79] For example, the diastereoselective synthesis of α-aryl β-hydroxy cyclic amine **134** from hemiaminal **133** has been reported by Toomoka et al. (Scheme 37).[80] This reaction takes place highly stereoselectively via internal delivery of the nucleophile to generate the *cis*-α-aryl β-hydroxy cyclic amine **134**. The starting aminal and the aminal derived from the attack of the added benzyl alcohol are in equilibrium with the *N*-acyliminium ion **135** under Lewis acidic conditions. Intramolecular Friedel–Crafts reaction onto this electrophile by one of the aryl groups on silicon then yields the β-silicon stabilized cation **136**. Attack of the alcohol on this intermediate generates the product in a highly diastereoselective manner. It was further demonstrated that the products could be readily elaborated into biologically relevant molecules such as *cis*-α-phenyl-β-hydroxypiperidine derivatives.



Scheme 37 Internal delivery of an aryl group from a silicon tether onto acyl iminium species **135**.

A related approach was recently reported by Martin and coworkers for the stereoselective synthesis of aryl α-*C*-glycosides, such as sugar **138** (Scheme 38).[81] Few stereoselective methods for the construction of aryl α-*C*-glycosidic linkages are reported, as there is a thermodynamic preference for the β-configuration of the glycosidic linkage. In the strategy employed here, internal addition of the nucleophile provides the desired 1,2-*cis* configuration. The reaction proceeds through a similar mechanism to the above case

by Tomooka, in which a β-silicon stabilized carbocation **139** is generated and subsequently decomposed on the addition of TBAF to yield product **138**. Several sets of *p*-methoxyphenyl-substituted silyl groups were tested, and without an activating methoxy group on the phenyl ring no reaction was observed. In general when R = Et the reaction gave higher yields than when R = Me, as demonstrated for substrate **137**. This strategy was also applied to *C*-furanosides as described by Martin et al.[59]



137 **138** R = Me, 39% R = Et, 74% **139**

Scheme 38 Synthesis of α-glycosidic linkages using internal delivery of an arylsilane. IDCP, Iodonium dicollidine perchlorate.

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1.03 Organoaluminum Reagents

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Glossary

Chiral sulfoxide In general, the racemization barrier of sulfoxide (RSOR′) is high enough to prevent stereoinversion at sulfur atom (from 35 to 42 kcal mol^{-1} for $\Delta H^{\#}$, and from -8 to $+4$ cal $(mol\ K)^{-1}$ for $\Delta S^{\#}$). Accordingly, chiral sulfoxides are isolated as thermodynamically stable compounds and utilized as conventional chiral auxiliaries in asymmetric organic syntheses.

Davis's imine They are chiral imines prepared from carbonyl compounds and chiral *p*-toluenesulfinamide developed by Dr. Franklin A. Davis. They can be applied to diastereoselective 1,2-addition of various nucleophiles.

Ellman's imine They are chiral imines prepared from carbonyl compounds and chiral 2-methyl-2-propanesulfinamide developed by Dr. Jonathan A. Ellman.

Erythro*/*threo One definition for diastereomeric compounds which possess two contiguous stereocenters. In the Fischer projection, the *erythro* isomer is defined as two identical substituents that are oriented on the same side and the *threo* isomer is defined as that on the opposite side. This definition comes from the names of diastereomeric aldoses – erythrose and threose.

MABR, MAPH, ATPH A series of bulky aluminum Lewis acid MAD derivatives introduced by Dr. Hisashi Yamamoto: methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR), methylaluminum bis(2,6-diphenylphenoxide) (MAPH), and aluminum tris(2,6-diphenylphenoxide) (ATPH).

MAD Methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) was first reported as a bulky organoaluminum Lewis acidic reagent by Dr. Hisashi Yamamoto and Dr. Keiji Maruoka. Compared with typical Me_3Al, the Lewis acidity of MAD is decreased, however, the bulky environment of MAD enables the unique reactivity and selectivity in 1,2-additions of various nucleophiles to carbonyl compounds.

Meerwein–Ponndorf–Verley (MPV) reduction In 1925, Meerwein and Verley independently reported the reduction of aldehydes with primary alcohol in the presence of aluminum ethoxide. Later, Ponndorf investigated the reduction of ketones with secondary alcohols and $Al(OiPr)_3$. This reaction is called 'the Meerwein–Ponndorf–Verley (MPV) reduction' and believed to undergo via a six-membered transition state consisted of carbonyl compounds, alcohols, and aluminum alkoxides.

Passerini reaction A three-component reaction between carboxylic acid, carbonyl compound, and isocyanide. The Passerini reaction provides a straightforward way to α-acyloxyamides. The reaction mechanism is believed to involve the addition of isocyanide to the complex of carboxylic acid and

carbonyl compound, and the following rapid acyl transfer to give the desired product.

TADDOL The chiral ligand was first developed by Dr. Dieter Seebach. Various TADDOL (this name is derived from selected letters of 'α,α,α′,α′-TetraAryl-1,3-Dioxolan-4,5-DimethanOL') derivatives can be prepared from chiral tartaric acid. A number of metal–TADDOL complex-catalyzed asymmetric reactions have been reported to date, and the TADDOL family has established itself as privileged chiral ligands.

1.03.1 Introduction from the View Point on the Preparation of Organoaluminum Reagents

In 1972, the first comprehensive book on the chemistry of organoaluminum reagents, involving the details of preparations and reactions, was published by Mole et al.[1] A vast number of investigations have been demonstrated to date for the purpose of emphasizing synthetic power of the organoaluminum reagents. Even during this decade, several reviews on the chemistry of organoaluminum reagents have been published one after another,[2–5] and this fact eloquently tells how important and fundamental the chemistry is in modern organic chemistry.

As summarized in Chapter 1.3 of Comprehensive Organic Synthesis I (COS I) written by Hauske,[6] various organoaluminum reagents are readily available as organometallic compounds with various protocols such as the insertion of metallic aluminum into organic halides, the carboalumination of unsaturated C–C bonds and the aluminum–metal exchange. For example, the early reviews on the preparation of alkenyl- and alkynyl organoaluminums were described by Normant and Alexakis[7] and Zweifel and Miller,[8] respectively. Furthermore, Yamamoto described the reviews on the preparations and reactions of allyl-[9a] and crotylaluminum[9a] reagents. However, the preparation of arylaluminum reagents still remains elusive.[4,10] To this end, Uchiyama et al.[11–13] and Wunderlich and Knochel[14] recently demonstrated the novel generation of arylaluminum reagents through the aluminum base mediated by a deprotonative-directed alumination. Transmetallation of organolithium or organomagnesium reagents with aluminum salts can also generate the corresponding arylaluminum compounds.[15–18] In 2010, Knochel et al. discovered the more direct preparation of various arylaluminum reagents by an aluminum insertion into aryl halides in the presence of LiCl and catalytic amount of metal chlorides such as $TiCl_4$, $InCl_3$, $BiCl_3$, and $PbCl_2$.[19] As a result, a variety of organoaluminum reagents have become easy-to-access compounds by using the recent techniques. Compared with other organometallic reagents, significant features of such organoaluminum reagents, bearing a sp^2 aluminum center, should be its strong Lewis acidity arising from the presence of one vacant p-orbital.[2–5] Organoaluminum reagents make coordination bonds with Lewis basic heteroatoms such as oxygen and nitrogen to complete electron octets, and thus, are sufficiently activated to react with various electrophiles. Organoaluminum reagents can act not only as Lewis acid catalysts but also as nucleophilic reagents themselves, that is, aliphatic or aromatic substituents on aluminum center can migrate to be incorporated into products. Among the reactions of organoaluminum reagents, this chapter will deal with the 1,2-addition to C–X π-bond systems (carbonyl compounds and imines) providing general and powerful routes for C–C bond formations. In COS I, stereoselectivity, enantioselectivity, regioselectivity, and chemoselectivity will be emphasized.[6] As COS I reviewed the detailed examples of 1,2-addition of organoaluminum reagents reported before 1991, this COS II will focus on the advancements over the past two decades.

1.03.2 Uncatalyzed 1,2-Addition of Organoaluminum Reagents

1.03.2.1 Addition to C–O π-Bonds

1.03.2.1.1 Stereoselective addition to β-keto carbonyl or sulfinyl compounds

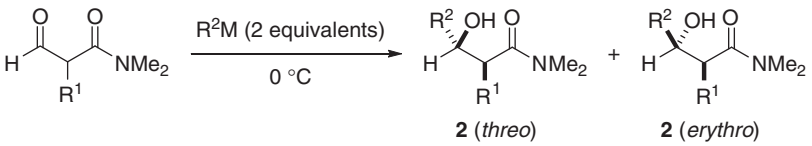
As with other organometallic reagents, the reaction of ketones and aldehydes with organoaluminum compounds furnishes the corresponding alcohols. One of the seminal reports regarding the stereocontrol of 1,2-addition is the examination of reactions of α-substituted β-keto carbonyl compounds performed by Oshima and Utimoto et al.[20] Treatment of α-formyl amides **1** with alkylaluminum dichloride or arylaluminum dichloride afforded *threo*-α-alkyl β-hydroxy amides **2** with high diastereoselectivity (Table 1). In contrast, the diastereoselectivity was drastically decreased in the reaction using trialkylaluminums (entries 1 and 4).

In general, alkylaluminum dichloride reagents possess weaker nucleophilicity but stronger Lewis acidity compared with trialkylaluminum. Accordingly, the key factor to achieve high *threo* selectivity should be the formation of a six-membered chelate complex with another organoaluminum reagent (Scheme 1). The nucleophilic species would approach from the opposite side of the α-alkyl side chain to avoid steric repulsion, thus giving the corresponding *threo*-α-alkyl β-hydroxy amides **2**.

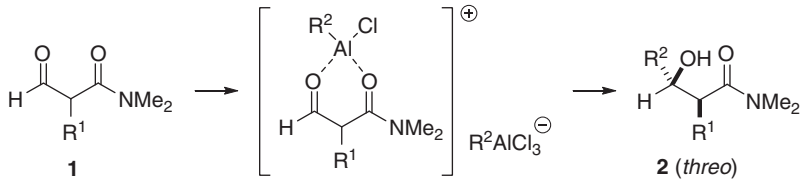
Furthermore, the same research group surveyed the stereochemical relationship in the 1,2-addition to α-methyl β-keto amides or esters **3**.[20] Treatment of **3** with organoaluminum reagents provided a series of α-methyl β-hydroxy amides or esters **4** with high diastereoselectivity (Table 2).

Likewise, the reaction of cyclic β-keto ester **6** with Me_3Al gives the methylated product **7** with high diastereoselectivity (Table 3, entry 1).[21] Interestingly, however, the opposite diastereomer **8** was selectively obtained after longer reaction times at room temperature (Table 3, entry 3). This result suggests that, in the early stage of this reaction, the kinetically favored product **7** was selectively formed, and the isomerization of **7** gradually proceeded to give the thermodynamically favored product **8**.

Table 1 Diastereoselective addition of aluminum chloride to α-formyl amides **1**

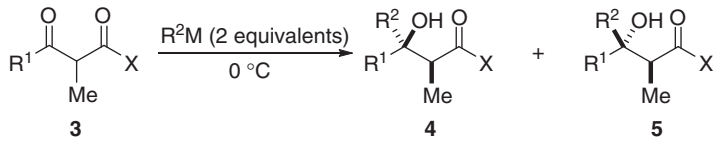


Entry	*R^1*	*R^2M*	*Yield (%)*	Threo/erythro
1	Me	Me_3Al	45	59/41
2		Me_2AlCl	38	93/7
3		$MeAlCl_2$	66	97/3
4		Et_3Al	60	35/65
5		Et_2AlCl	84	90/10
6		$EtAlCl_2$	63	96/4
7		$PhAlCl_2$	53	93/7
8	Et	$MeAlCl_2$	56	97/3
9		$EtAlC1_2$	40	99/1
10		$PhAlCl_2$	46	96/4
11	*i*-Pr	$MeAlCl_2$	62	99/1
12		$EtAlC1_2$	72	99/1
13		$PhAlCl_2$	55	99/1



Scheme 1 Six-membered chelate model of organoaluminum reagent and α-formyl amides **1**.

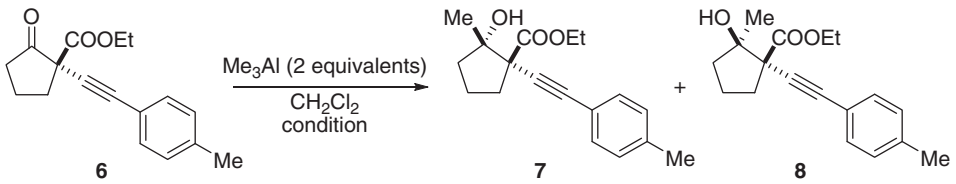
Table 2 Diastereoselective 1,2-addition of organoaluminum reagents to α-methyl β-keto amides or esters **3**



Entry	*R^1*	*X*	*R^2M*	*Yield (%)*	***4/5***
1	Ph	NMe_2	Me_3Al	90	>99/1
2			Et_2AlCl	88	>99/1
3			(*n*-Bu≡)$_3$Al	84	>99/1
4	Me	NMe_2	Et_3Al	18	>99/1
5			Et_2AlCl	76	>99/1
6	Et		Me_3Al	81	>99/1
7	*t*-Bu		Me_3Al	87	>99/1
8	Ph	OEt	Me_3Al	90	>99/1
9			Et_3Al	54	>99/1
10	Et		Me_3Al	–	80/20

Figure 1 represents the plausible mechanism for kinetically controlled methylation onto **6** which might prefer conformer **6A** due to the steric hindrance between ethoxycarbonyl group and hydrogen atom on the cyclopentane ring of conformer **6B**. Thus, the selective formation of Me_2Al alkoxide of **7** can be rationalized in terms of the sterically controlled approach of monomeric or dimeric Me_3Al from the less hindered side of carbonyl group. Subsequently, epimerization between the Me_2Al alkoxide of **7** and of

Table 3 Reaction of cyclic β-keto ester **6** and Me_3Al



Entry	*Condition*	*Yield (**7**+**8**) (%)*	***7/8***
1	0 °C, 30 min	83	96/4
2	0 °C, 60 min	72	89/11
3	0 °C, 60 min then r.t., 120 h	88	12/88

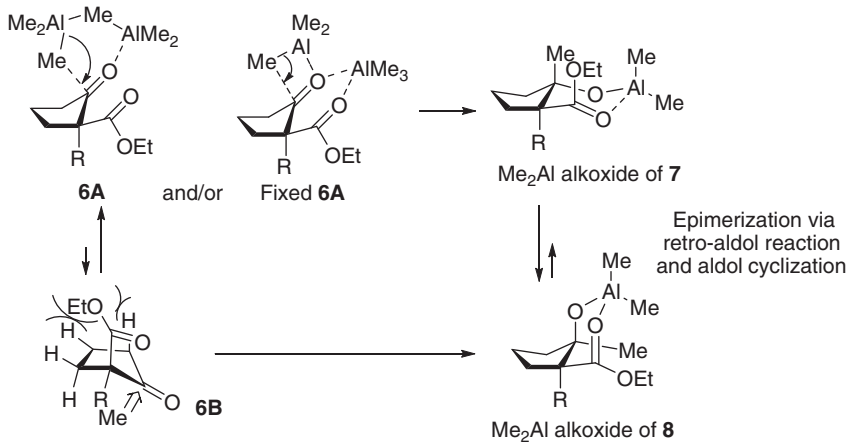
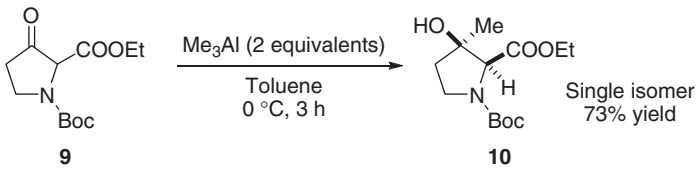


Figure 1 Plausible mechanism for kinetically controlled methylation of cyclic β-keto ester **6**.

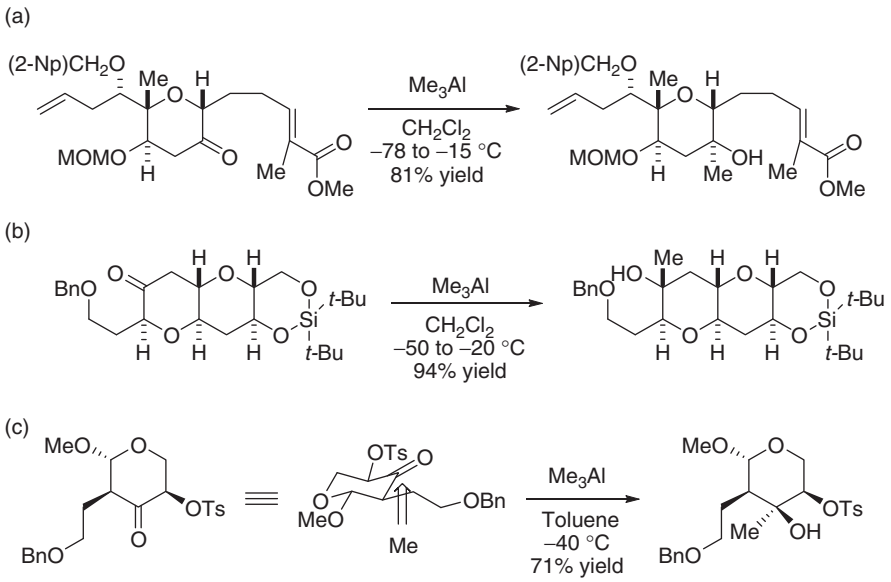
8 via retro-aldol-type ring opening followed by aldol-type cyclization and ring conversion to furnish a thermodynamically favored product 8.[21]

The methylation reaction of *N*-Boc protected five-membered cyclic β-keto ester 9 also gives the corresponding product **10** which is the frequently crucial structural motif of biologically active and natural products (Scheme 2).[22]



Scheme 2 Reaction of *N*-Boc protected five-membered cyclic β-keto ester **9**.

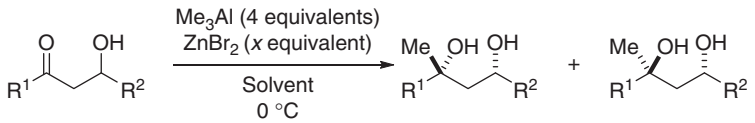
Indeed, conformationally constrained cyclic carbonyl compounds are prone to undergo the diastereoselective methylation using Me_3Al. This protocol has often been utilized in the total syntheses of natural compounds.[23] Recent representative examples are the synthesis of LMN-ring fragment of the Caribbean ciguatoxin C-CTX-1 reported by Inoue et al. in 2007 (Scheme 3a),[24] the total synthesis of gambierol reported by Mori et al. in 2010 (Scheme 3b),[25] and the total synthesis of (–)-salinosporamide A reported by Chiba et al. in 2011 (Scheme 3c).[26]



Scheme 3 Examples of diastereoselective 1,2-addition of Me_3Al in total synthesis.

In addition to the steric environment, the influence of a chelate formation between substrates and organoaluminum compounds plays an important role in the diastereoselective 1,2-addition. In particular, the reaction of acyclic substrates demands this chelation control to construct the rigid conformation of substrates as shown in Oshima and Utimoto's research (Table 2).[20] In 1996, Ruano et al. investigated the stereoselectivity in the methylation reactions of several β-hydroxy ketones **11** with Me_3Al (Table 4).[27] The major products were *syn*-diol **12** with moderate-to-high diastereoselectivity and the addition of $ZnBr_2$ improved the diastereoselectivity due to the increased stability of half-chair conformation **11b** compared with **11a** (Figure 2).

Table 4 Methylation reactions of β-hydroxy ketones **11** with Me_3Al



11 *syn*-**12** *anti*-**12**

Entry	R^1	R^2	X	*Solvent*	*Yield (%)*	Syn/anti
1	*t-Bu*	*i*-Pr	0	Toluene	52	65/35
2	*t-Bu*	*i*-Pr	2	CH_2Cl_2	66	79/21
3	Ph	Me	2	CH_2Cl_2	75	88/12
4	*p*-Tol	Et	2	CH_2Cl_2	72	75/25
5	*n*-Pr	*i*-Pr	2	CH_2Cl_2	78	66/34
6	*i*-Bu	*i*-Ph	2	CH_2Cl_2	65	65/35
7	*i*-Bu	*i*-Pr	2	CH_2Cl_2	66	60/40

In addition, the diastereofacial-controlled 1,2-addition of organoaluminum reagents to chiral β-ketosulfoxide has been the subject of extensive studies to give chiral tertiary alcohol. The pioneering survey using optically active (*R*)-β-ketosulfoxide **13** was conducted by Fujisawa et al. in 1988 (Table 5).[28]

Later, Carreño et al. developed modified procedures using $ZnCl_2$ as additive to provide chiral tertiary alcohol **14** with higher diastereoselectivity (Table 6).[29] In addition, the same research group discovered that the methylation of chiral five-membered β-ketosulfoxide **15a** afforded the corresponding alcohol **16a** as an essentially single isomer without any additives (Scheme 4a), whereas the addition of $ZnCl_2$ was necessary to achieve high stereoselectivity in the case of six-membered β-ketosulfoxide **15b** (Scheme 4b).[30] Furthermore, Ruano et al. reported asymmetric methylation of chiral acyclic α-methyl-β-ketosulfoxides with Me_3Al and Me_2AlCl in 2004.[31]

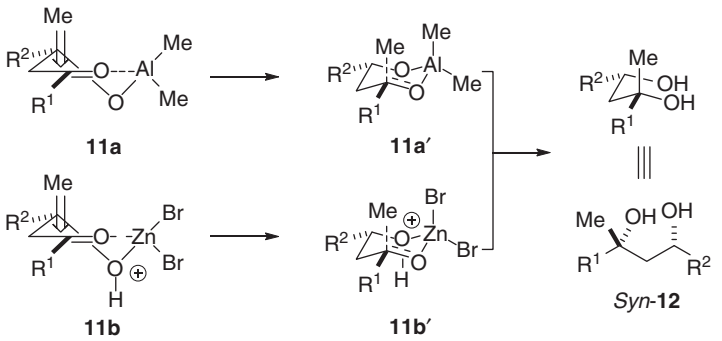
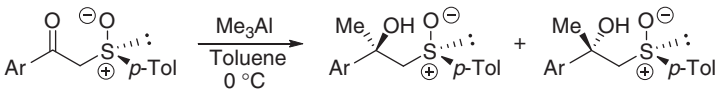
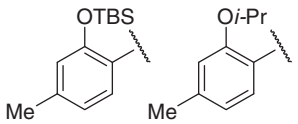


Figure 2 The chelate model between β-hydroxy ketones **11** and $ZnBr_2$.

Table 5 Diastereoselective 1,2-addition of Me_3Al to chiral β-ketosulfoxide **13**

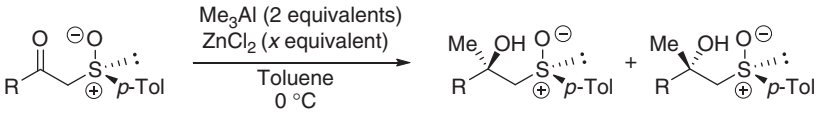


Entry	*Ar*	*Yield (%)*	*(S)/(R)*
1	Ph	66	74/26
2	*p*-Tol	50	84/16
3	**X**	71	87/13
4	**Y**	48	96/4

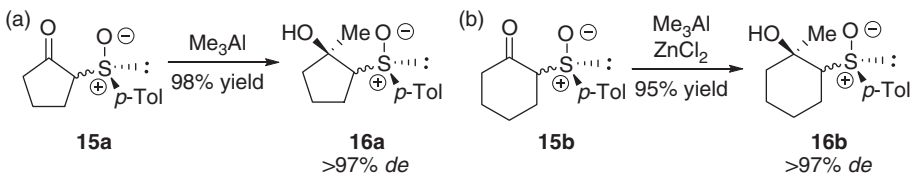


X **Y**

Table 6 Improvement of yield and diastereoselectivity in the presence of $ZnCl_2$

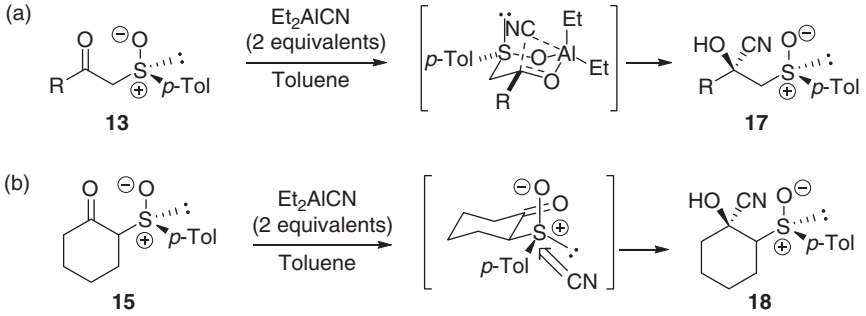


Entry	*R*	x	*Yield (%)*	*(S)/(R)*
1	Ph	0	40	76/24
2	Et	0	15	72/28
3	Ph	1.6	70	90/10
4	*p*-MeO-C_6H_4	1.6	90	67/33
5	Et	1.6	90	87/13
6	*i*-Pr	1.6	96	87/13
7	*t*-Bu	1.6	89	95/5



Scheme 4 Methylation of chiral cyclic β-ketosulfoxide **15**.

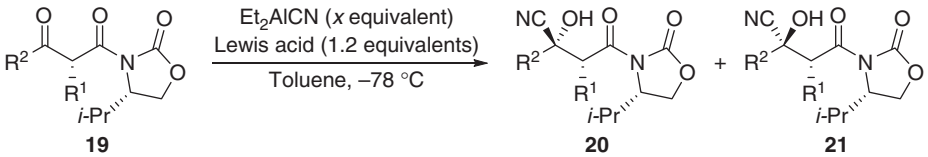
The stereoselective hydrocyanation of chiral acyclic β-ketosulfoxides **13** using Et_2AlCN has been explored, providing optically active cyanohydrins **17** derived from ketones (Scheme 5a).[32] Cyclic β-ketosulfoxides **15** can also be utilized for this transformation (Scheme 5b).[33]



Scheme 5 Diastereoselective hydrocyanation of chiral β-ketosulfoxides **13** and **15** using Et_2AlCN.

The diastereoselective 1,2-addition to β-keto amides **19** bearing chiral oxazolidinone auxiliary has been described in Table 7.[34] The reactions of β-keto amides without α-substituent ($R^1 = H$) resulted only in the recovery of the starting materials even in the presence of chelating Lewis acid such as $ZnCl_2$ (entries 1–4). The lack of reactivity of these compounds can be attributed to the high stability of the generated enolic form. However, the reactions of α-methyl-β-keto amides **19** ($R^1 = Me$) proceeded to give a mixture of **20** and **21** with poor diastereoselectivity (entries 5 and 6). However, this selectivity was dramatically improved under the influence of chelating Lewis acid, $ZnBr_2$ or Et_2AlCl (entries 7–13), providing **20** as a major isomer. The determination of absolute stereochemistry of **20** suggested that the 1,2-addition of cyanide took place from the opposite side of α-methyl group of **19** which coordinates to the Lewis acid metals thus forming six-membered rigid chelates.

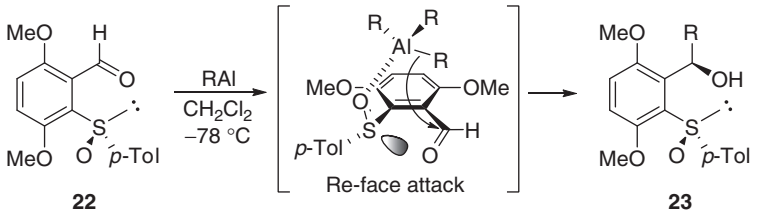
Table 7 Diastereoselective 1,2-addition of Et_2AlCl to chiral β-keto amides **19**



Entry	*R^1*	*R^2*	x	*Lewis acid*	*Yield (%)*	***20/21***
1	H	Me	2	None	No reaction	–
2	H	Ph	2	None	No reaction	–
3	H	Me	4	$ZnBr_2$	No reaction	–
4	H	Ph	4	$ZnBr_2$	No reaction	–
5	Me	Me	2	None	77	50/50
6	Me	Ph	2	None	63	80/20
7	Me	Me	4	$ZnBr_2$	77	94/6
8	Me	Ph	4	$ZnBr_2$	82	98/2
9	Me	Me	4	Et_2AlCl	77	94/6
10	Me	Ph	4	Et_2AlCl	79	95/5
11	Me	*p*-Cl-C_6H_4	4	$ZnBr_2$	60	98/2
12	Me	*p*-MeO-C_6H_4	4	$ZnBr_2$	27	98/2
13	Me	*p*-Tol	4	$ZnBr_2$	65	98/2

As another application of asymmetric 1,2-addition to substrates involving chiral auxiliary, Carreño and Urbano et al. examined nucleophilic additions of alkylaluminum reagents to benzaldehyde **22** bearing a chiral sulfinyl group (Table 8).[35a] The effective association between the aluminum atom and oxygen atom of sulfinyl moiety could be required to determine the stereochemical outcome of the alkylated products **23**. Stereoselective hydrocyanation of δ-ketosulfoxide with Et_2AlCN has been studied by using similar remote stereocontrol.[35b]

Table 8 Additions of alkylaluminum reagents to benzaldehyde **22** bearing a chiral sulfinyl group

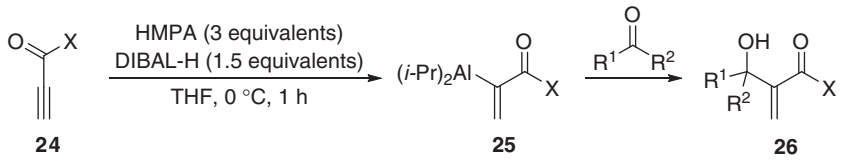


22 **23**

Entry	*RAl*	*Yield (%)*	*Major/minor (**23**)*
1	Me_3Al	92	>98/2
2	Me_2AlCl	84	97/3
3	Et_3Al	64	>98/2

1.03.2.1.2 Preparation and reaction of vinyl, allyl, and allenyl organoaluminum reagents

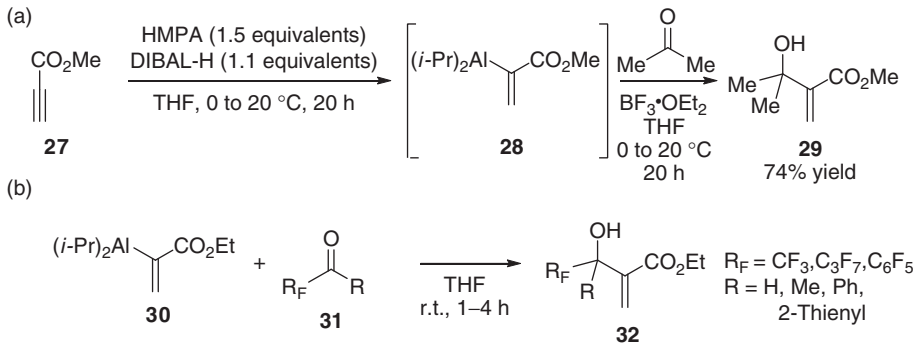
In 1987, Tsuda et al. introduced the regioselective preparation of various vinylaluminum reagents **25** by the hydroalumination of α,β-acetylenic carbonyl compounds **24** with DIBAL-H in the presence of HMPA (Scheme 6).[36]



24 **25** **26**

Scheme 6 Hydroalumination of α,β-acetylenic carbonyl compounds **24** with DIBAL-H.

During recent two decades, this pioneering manipulation has been well utilized in the 1,2-addition to carbonyl compounds to furnish the Baylis–Hillman-type[37] adducts **26** (Scheme 7). For instance, in 1994, Kündig et al. reported the efficient synthesis of radical trapping reagent, methyl 2-(*tert*-butyl)acrylate **29** and its analogs by performing the boron Lewis acid-promoted 1,2-addition of vinylaluminum reagent **28** to ketones (Scheme 7a).[38] In 1998, Ramachandran developed the protocol to prepare highly functionalized and fluorinated compounds **32** by demonstrating the reaction of perfluoroalkyl and -aryl aldehydes and ketones **31** with vinylaluminum reagent **30** (Scheme 7b).[39] It should be noted that this reaction proceeded without the presence of Lewis acid catalyst.[40]

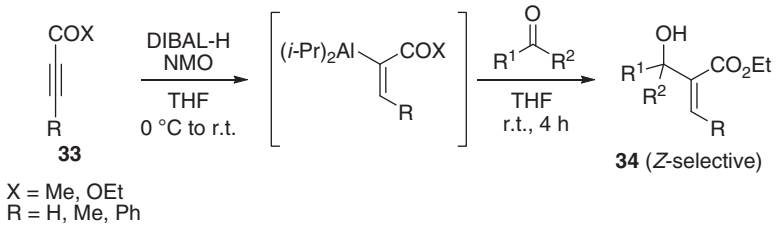


27 **28** **29** 74% yield

30 **31** **32**

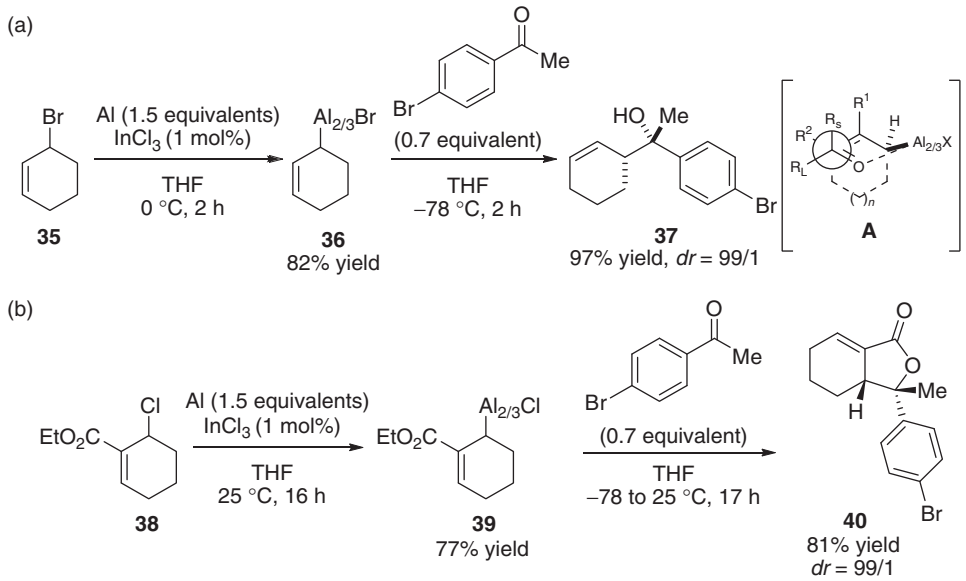
Scheme 7 1,2-Addition of vinylaluminum reagent **28** and **30**.

The disadvantage of this protocol is the essential use of HMPA, a known cancer-causing reagent. To refrain from the use of hazardous HMPA, several alternative reagents, such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU),[41a] 1,3-dimethylimidazolidin-2-one (DMEU or DMI),[41b] and quinuclidine *N*-oxide (QNO),[41c] have been reported in the literature. Ramachandran et al. devised the use of trimethylamine *N*-oxide (NMO) to prepare various vinylaluminum reagents **33** which can react with aldehydes and ketones to afford the corresponding products **34** (Scheme 8).[42] Reactions with β-substituted acetylenes (R = Me, Ph) provide the corresponding *Z* adducts **34** with high diastereoselectivity.



Scheme 8 Reactions of vinylaluminum reagents prepared from β-substituted acetylenes **33**.

Very recently, Knochel et al. developed novel procedures to prepare allylic aluminum reagents from allyl halides and aluminum powder,[19] and examined their application in the diastereoselective 1,2-addition to various carbonyl compounds.[43] For example, 3-bromocyclohexene **35** is converted to the corresponding allylic aluminum reagent **36** and reacts with 4′-bromoacetophenone to give allylic alcohol **37** in good yield and with excellent diastereoselectivity (Scheme 9a). This diastereoselectivity can be rationalized by a chair-like transition state **A** (Scheme 9a). With this procedure, organoaluminum reagents bearing ester moiety **39** can be prepared from allylic chloride **38** without suffering from the intramolecular addition to ester functionality (Scheme 9b). The reaction of this functionalized organoaluminum reagent **39** and 4′-bromoacetophenone provides bicyclic lactone **40** as a single diastereomer.



Scheme 9 Knochel's procedure to prepare allylic aluminum reagents **36** and **39** from allyl halides and aluminum powder and its applications in diastereoselective 1,2-addition to ketone.

The similar protocol enables the preparation of allenylaluminum reagents **42** from secondary propargylic bromides **41**. The reaction of these organoaluminum compounds **42** with aldehydes and ketones gave the tertiary homopropargylic alcohols **43** in a *syn* stereoselective manner (Scheme 10).[44]

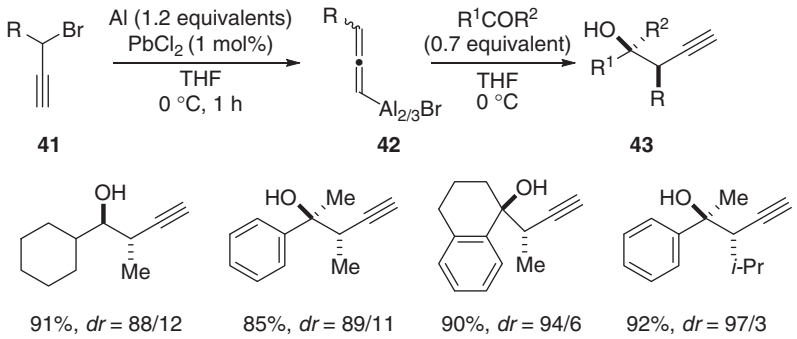
This *syn* selectivity can be explained with the possible cyclic transition state **44** (Figure 3). Transition state **44a** to give *syn* products would be favored compared with another transition state **44b** for steric reasons.

1.03.2.1.3 1,2-Addition to other carbonyl compounds

Other than aldehydes and ketones, new classes of carbonyl compounds were recently discovered to react with organoaluminum reagents.

For example, Demir et al. introduced the reaction of aryl phosphonates **45** and organoaluminum reagents (Scheme 11a).[45] This method provides a straightforward entry for the synthesis of secondary and tertiary α-hydroxy phosphonates **46**, which are important building blocks of enzyme inhibitors. Micouin et al. reported the direct synthesis of ynones **49** by the reaction of acid chlorides **47** and dimethylalkynylaluminum reagent **48** (Scheme 11b).[46]

In the course of utilizing pentamethylcyclopentadiene (Cp^*H),[47] Yorimitsu et al. performed the synthesis of β,γ-unsaturated ketones **53** from acid chlorides **50** via C–Cp^* bond formation and cleavage (Scheme 12a).[48] First, treatment of aromatic acid chloride **50** with Cp^*Li affords the corresponding aryl pentamethylcyclopentadienyl ketones **51**. The following reaction of the



Scheme 10 Reaction of allenylaluminum reagents **42** with carbonyl compounds.

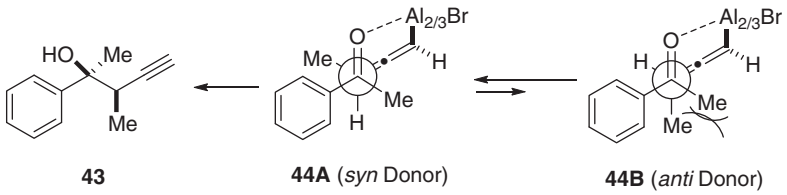
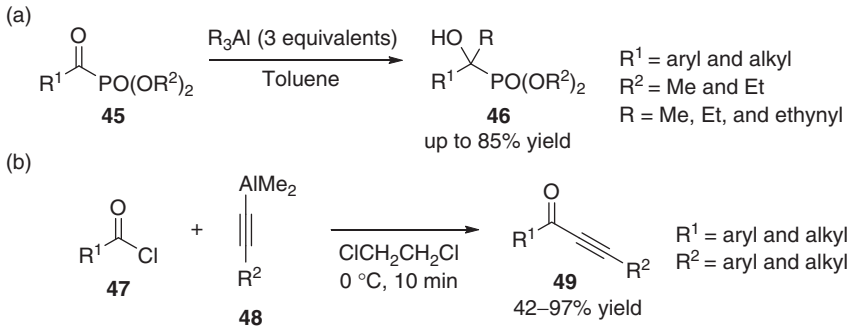
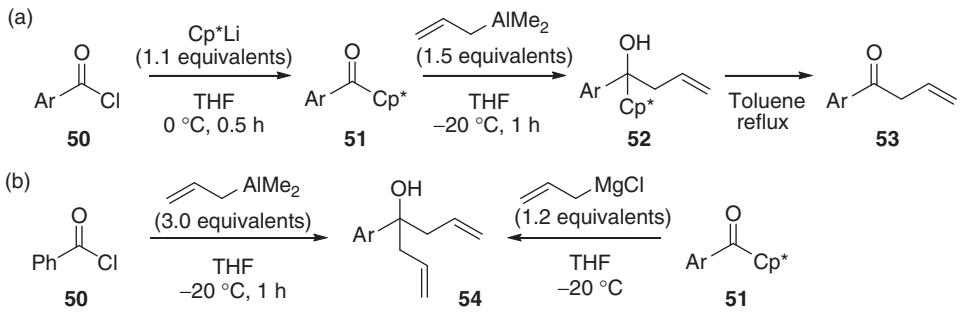


Figure 3 Diamine-based chiral ligands **78** and **79** for the asymmetric addition of arylaluminum reagents.



Scheme 11 1,2-Addition to other carbonyl compounds **45** and **47**.

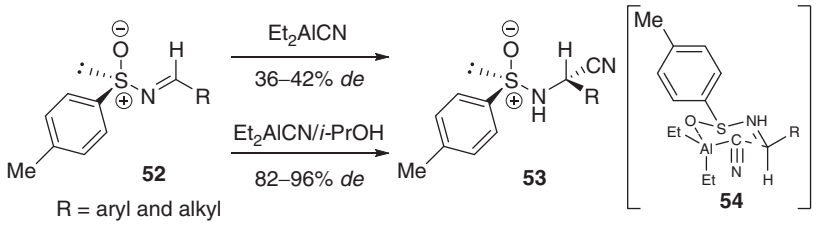
ketones **51** with allylaluminum reagent, which can be prepared from allylmagnesium bromide and Me_2AlCl, furnishes the tertiary homoallyl alcohol **52**. Finally, the removal of Cp^*H from **52** in toluene of reflux leads to the dominant formation of the desired aryl allyl ketones **53**. It should be noted that both the reaction of acid chloride **50** with allylaluminum reagents and the reaction of ketone **51** with allylmagnesium bromide resulted in the exclusive formation of undesired diallylated alcohol **54** (Scheme 12b).



Scheme 12 Reaction of pentamethylcyclopentadienyl ketones **51** with allylaluminum reagent.

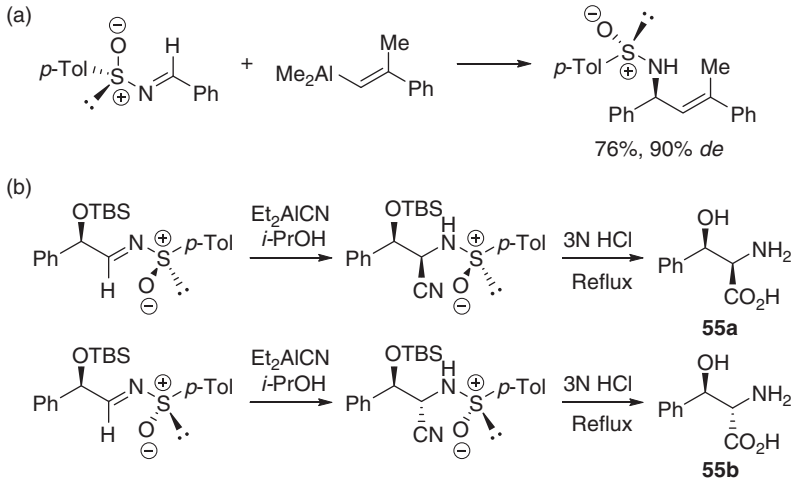
1.03.2.2 Addition to C–N π-Bonds

Asymmetric 1,2-addition of organoaluminum reagents to imines provides a straightforward strategy to prepare optically active amine functionalities. Chiral sulfinylimines have been recognized as attractive electrophiles to give the corresponding chiral amines with high stereoselectivity. In addition, this protocol possesses several advantages such as the electron-withdrawing activation of imine function, ease of diastereomer separation by using column chromatography, and the facile N–S bond cleavage to remove chiral auxiliary. Chiral sulfinylimines have been widely studied, in particular, by Davis et al. who developed *N*-(*p*-tolyl)sulfinylimines[49] and by Ellman et al. who developed *N*-(*tert*-butyl)sulfinylimines,[50] respectively. In 1994, Davis et al. demonstrated the pioneering work using *N*-(*p*-tolyl)sulfinylimines **52** and Et_2AlCN, giving amine **53**, whereas moderate diastereoselectivity (Scheme 13).[51] Formation of **53** is consistent with complexation of Et_2AlCN with sulfinyl oxygen via chair-like transition state **54**. Later, the addition of *i*-PrOH in this system was found to be very effective to improve diastereoselectivity due to the *in situ* formation of Et(*i*-PrO)AlCN.[52]



Scheme 13 Reaction of chiral *N*-(*p*-tolyl)sulfinylimines **52** and Et_2AlCN.

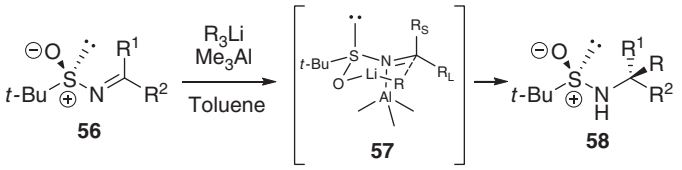
Representative examples of the reactions utilizing Davis's imines with organoaluminum reagents are shown in Scheme 14. Wipf et al. reported diastereoselective addition of vinylaluminum reagent, prepared from alkyne and Me_3Al, to Davis's imine (Scheme 14a).[53] Davis et al. demonstrated the selective synthesis of both diastereomers of amino acid **55a** and **55b** by switching the stereochemistry of the chiral sulfinyl group (Scheme 14b).[54] Applications of the present procedures in the asymmetric synthesis of natural compounds have also been performed.[55]



Scheme 14 1,2-Addition of organoaluminum reagent to Davis's imine.

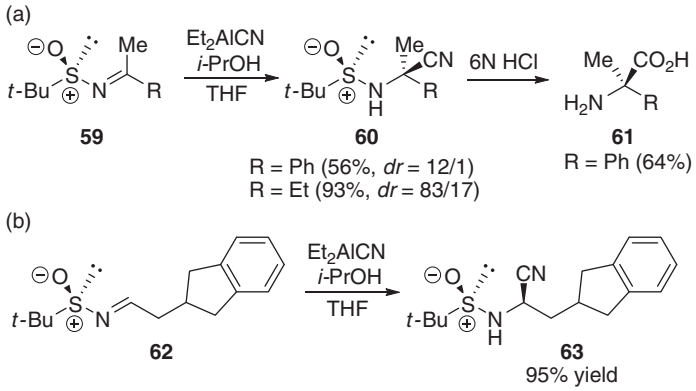
Meanwhile, the Ellman group has applied *N*-(*tert*-butyl)sulfinylimines to the asymmetric 1,2-addition mediated by organoaluminum compounds to synthesize optically active amines. They have investigated 1,2-asymmetric addition of various organolithium compounds to these imines **56**, and found that addition of Me_3Al improved both the chemical yield and diastereoselectivity of products **58** (Table 9).[56] This result can be explained as Me_3Al plays an important role both for Lewis acidic activation of imines and for formation of chair-like transition state **57**, wherein the bulky *tert*-butyl group is oriented in the equatorial position. This plausible model was supported by two experimental studies:[56a] (1) the treatment of sulfinyl imines **56** with a toluene solution of the mixture of Me_3Al and organolithium reagent did not give any products; thus, the 1,2-addition should not proceed via an migration of substituent on lithium aluminate intermediate, but likely occurred from the organolithium species to complex of imines **56** and Me_3Al. (2) The reactions conducted in ethereal solvent led to the dramatic decrease of chemical yields and selectivity, consistent with both Lewis acidic activation of imines **56** as well as organolithium coordination.

Table 9 1,2-Addition of organolithium compounds to Ellman's imine **56**



Entry	R^1	R^2	R^3	Me_3Al *(equivalent)*	*Yield (%)*	dr
1	Me	*i*-Pr	Ph	0	65	94/6
2	Me	*i*-Pr	Ph	1.1	93	97/3
3	Me	Ph	Bu	0	26	99/1
4	Me	Ph	Bu	1.1	86	98/2
5	Me	Bu	Ph	0	67	63/37
6	Me	Bu	Ph	1.1	93	89/11
7	Bu	Ph	Me	1.1	>95	99/1
8	Me	*i*-Pr	Bu	1.1	61	99/1
9	Bu	*i*-Pr	Me	0	54	82/18
10	Bu	*i*-Pr	Me	1.1	82	91/9

The 1,2-addition of organoaluminum reagents to Ellman's imines are also examined (Scheme 15). Davis et al. studied the asymmetric hydrocyanation reaction of the chiral *tert*-butanesulfinyl ketimines **59** with a mixture of Et_2AlCN and *i*-PrOH, providing chiral α-amino acid derivatives **61** (Scheme 15a).[57] Mabic and Cordi also demonstrated the addition of Et_2AlCN to *tert*-butanesulfinyl aldimines **62** to convert to **63** (Scheme 15b).[58]

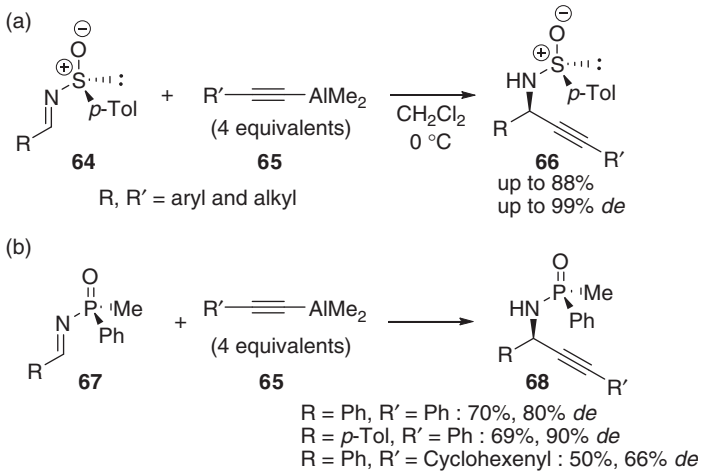


Scheme 15 Asymmetric hydrocyanation reaction of Ellman's imines **59** and **62**.

Other types of chiral imines bearing a proper chiral auxiliary on the nitrogen atom have been used for the asymmetric 1,2-addition of organoaluminum reagents. Royer et al. investigated the diastereoselective alkynylation of *N*-tolylsulfinylimines **64** (Davis imines) and dialkylalkynylaluminums **65** (Scheme 16a).[59a] In conjunction with this study, they evaluated the use of chiral phosphinoylimines **67** instead of **64**, and the corresponding propargyl amines **68** were obtained in up to 90% *de* (Scheme 16b).[59b]

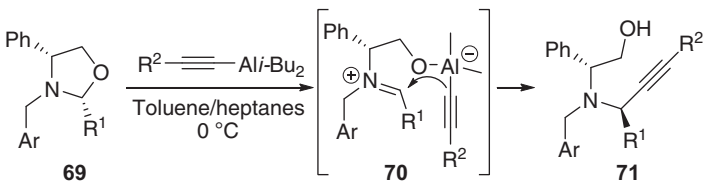
Husson et al. performed the synthesis of enantiomerically pure propargylamines **71** by the reaction of chiral oxazolidines **69** and dialkylalkynylaluminum reagents (Table 10).[60] Lewis acid-catalyzed hemiaminal cleavage at the C–O bond occurs to generate reactive iminium intermediate **70**. The following addition of alkynyl groups would give the desired products **71** with high diastereoselectivity. Later, the modification and application of this protocol have been reported.[61]

Nitrones are also used as amine precursors via nucleophilic addition of organoaluminum species. Desvergnes et al. performed the asymmetric 1,2-addition of dimethylalkynylaluminum reagents to carbohydrate-derived chiral nitrones **72** (Scheme 17).[62] This procedure enables a diastereoselective access to optically active *N*-hydroxy pyrrolidine derivatives **74** having four stereogenic centers. The stereochemical outcome of 1,2-addition on *Re*-face can be rationalized by taking the classical polar Felkin–Anh model **73**.

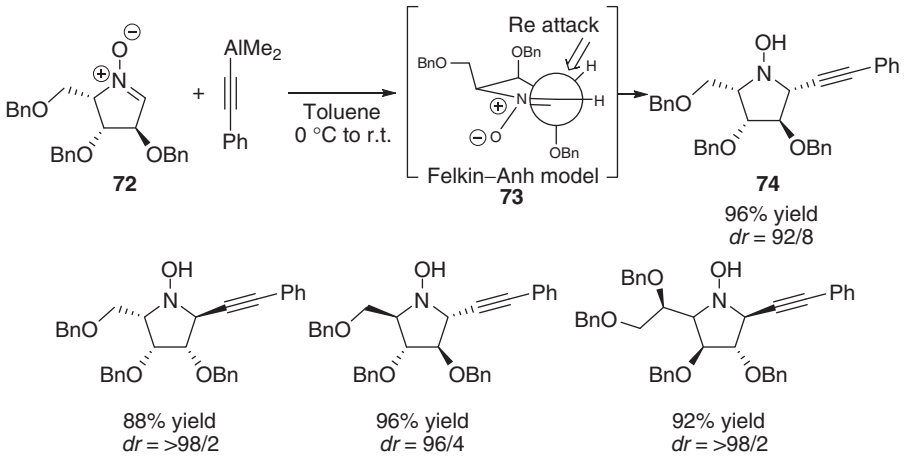


Scheme 16 Diastereoselective alkynylation of chiral imines **64** and **67**.

Table 10 Reaction of chiral oxazolidines **69** and dialkylalkynylaluminum reagents



Entry	*Ar*	*R^1*	*R^2*	*Yield (%)*	de *(%)*
1	Ph	Me	C_5H_{11}	69	94
2	Ph	Me	Ph	79	91
3	Ph	$(CH_2)_2Ph$	C_5H_{11}	69	>97
4	Ph	$(CH_2)_2Ph$	Ph	77	>97
5	Ph	Me	*t*-Bu	69	78
6	Ph	$(CH_2)_2Ph$	*t-Bu*	72	91
7	3,4-$(MeO)_2C_6H_3$	Me	Ph	71	92
8	3,4-$(MeO)_2C_6H_3$	$(CH_2)_2Ph$	Ph	75	96

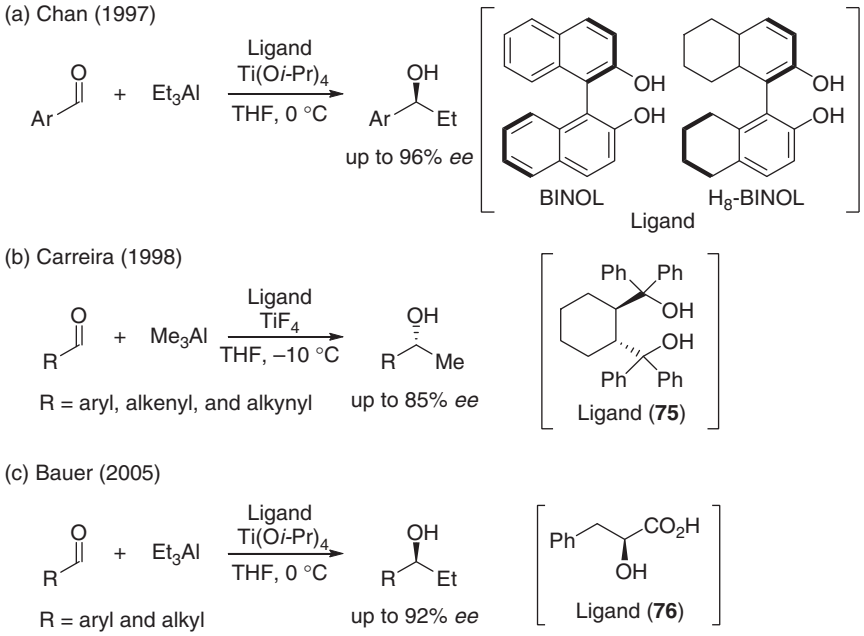


Scheme 17 Asymmetric 1,2-addition of alkynylaluminum reagents to chiral nitrones **72**.

1.03.3 Enantioselective 1,2-Addition of Organoaluminum Reagents to Carbonyl Compounds Catalyzed by Chiral Metal Complex

1.03.3.1 Titanium-Catalyzed Asymmetric 1,2-Addition to C–O π-Bonds

The development of chiral metal complex-catalyzed enantioselective 1,2-addition of organoaluminum reagents have attracted considerable attention in this decade. The main stream in this arena should be the chiral titanium complex-catalyzed asymmetric 1,2-addition to aldehydes and ketones to furnish enantiomerically enriched alcohols which are important structural motifs in organic chemistry (Scheme 18).



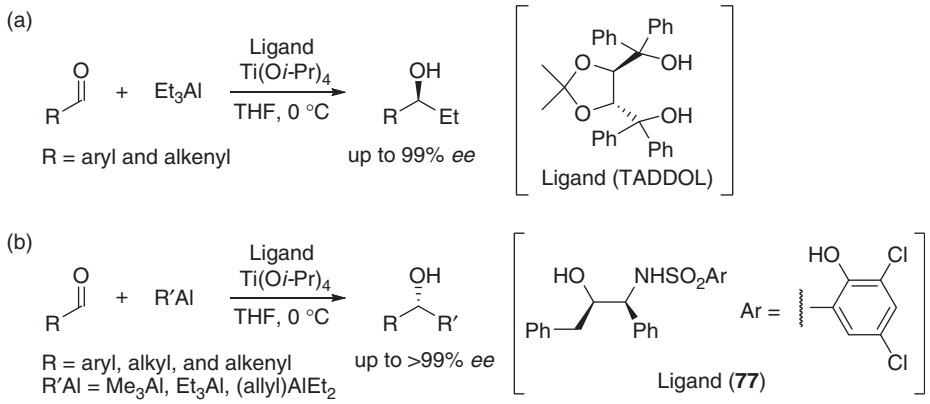
Scheme 18 Chiral titanium complex-catalyzed asymmetric 1,2-addition.

In 1997, Chan et al. reported the first example of asymmetric 1,2-addition of organoaluminum reagents to carbonyl compounds. The catalytic system composed of chiral 1,1′-bi-2-naphthol (BINOL) or 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol (H_8-BINOL) and Ti(O*i*-Pr)$_4$ was found to be effective for the enantioselective ethylation of aromatic aldehydes to give optically active secondary alcohol (Scheme 18a).[63] In 1998, Carreira et al. discovered chiral complex of titanium fluoride and *trans*-1,2-cyclohexanedimethanol **75** as an effective catalyst for the enantioselective 1,2-addition of Me_3Al to aldehydes (Scheme 18b).[64] In 2005, Bauer et al. reported the titanium-mediated enantioselective 1,2-addition of Et_3Al to aromatic and aliphatic aldehydes in the presence of a chiral α-hydroxy acid **76** (Scheme 18c).[65] In this catalytic system, the asymmetric methylation using Me_3Al resulted in the lower enantioselectivity than ethylation (up to 80% *ee*).

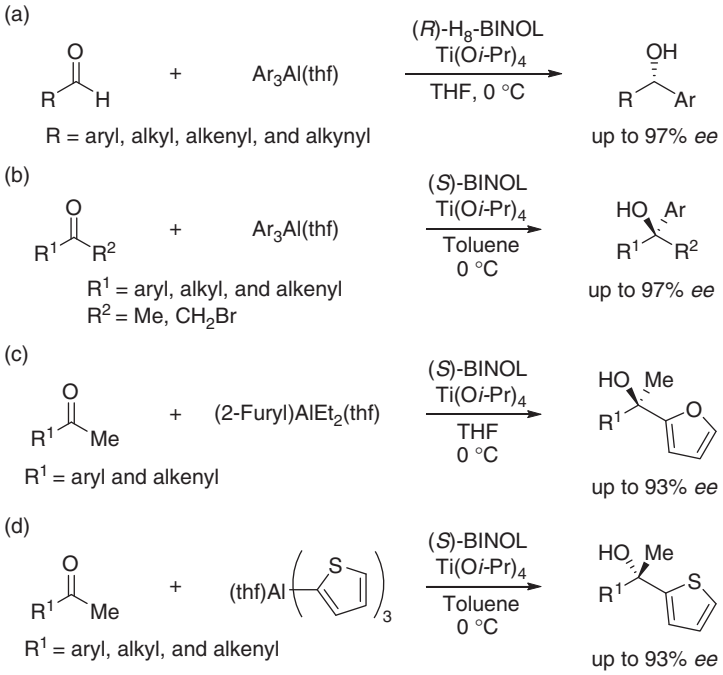
In particular, the extensive studies on enantioselective 1,2-addition of organoaluminum reagents to carbonyl compounds have been demonstrated by Gau et al. (Schemes 19–22). In 2000, they first reported titanium(IV)–TADDOLate complex-catalyzed enantioselective addition of Et_3Al to aldehydes (Scheme 19a).[66a] In 2001, they discovered *N*-sulfonylated amino alcohol **77** catalyzed the asymmetric addition of Me_3Al, Et_3Al, and (allyl)$AlEt_2$ to aldehydes (Scheme 19b).[66b]

Later, Gau et al. realized the titanium-catalyzed enantioselective incorporation of aryl substituent into carbonyl compounds by employing a series of arylaluminum reagents.[67] In 2006, they discovered that titanium complex prepared between Ti(O*i*-Pr)$_4$ and H_8-BINOL efficiently worked for arylations of aldehydes with triaryl(tetrahydrofuran)aluminum reagents [$AlAr_3$(thf)], which can be readily prepared according to Oliver's procedure (Scheme 20a).[67a,68] In 2007, they also conducted highly enantioselective aryl additions of $AlAr_3$(thf) to ketones catalyzed by titanium complex of Ti(O*i*-Pr)$_4$ and BINOL (Scheme 20b).[67b] In 2008, asymmetric synthesis of various tertiary 2-furyl alcohols, important precursors leading to a wide variety of bioactive compound, was reported by using this protocol (Scheme 20c).[67c] In a similar fashion, they reported the direct asymmetric catalytic 1,2-addition of thienylaluminum to ketones in the asymmetric synthesis of (*S*)-tiemonium iodide (Scheme 20d).[67d]

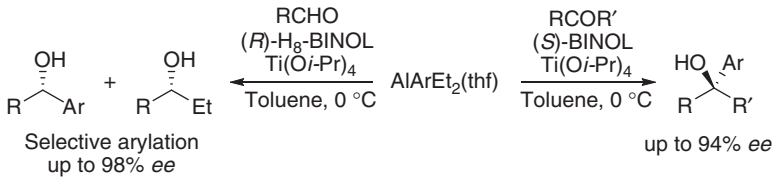
Furthermore, Gau et al. investigated the synthesis of novel aryldiethylaluminum reagents [$AlArEt_2$(thf)] derived from $AlEt_2Br$(thf) with ArMgBr, and evaluated the reactivity in the asymmetric 1,2-addition to aldehydes and ketones (Scheme 21).[69] Ti(O*i*-Pr)$_4$–H_8–BINOL complex-catalyzed arylation of aldehydes with these reagents proceeded to give the corresponding chiral alcohol, although ethyl additions simultaneously occurred in minor extent. However, asymmetric arylations of ketones catalyzed by Ti(O*i*-Pr)$_4$–BINOL complex produced optically active tertiary alcohols as a sole product with high enantioselectivity. They also



Scheme 19 Asymmetric 1,2-addition reported by the Gau et al.



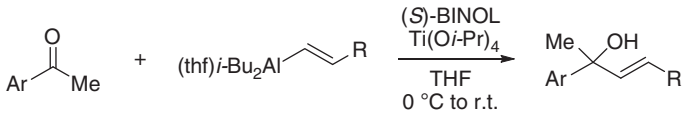
Scheme 20 Titanium-catalyzed enantioselective 1,2-addition of arylaluminum reagents.



Scheme 21 Reaction of novel aryldiethylaluminum reagents [AlArEt$_2$(thf)].

found that treatment of ketones with dialkylvinylaluminum reagents in the presence of titanium complex resulted in the formation of tertiary allylic alcohols (Scheme 22).[70]

Finally, Gau et al. have explored the usage not only of BINOL-based chiral ligands but also of diamine-based chiral ligands such as **78** and **79** for the asymmetric addition of arylaluminum reagents (Figure 4).[71]



Scheme 22 Reaction of dialkylvinylaluminum reagents.

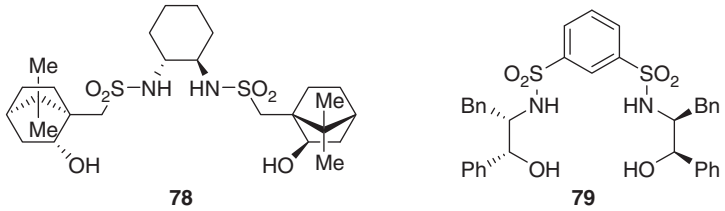
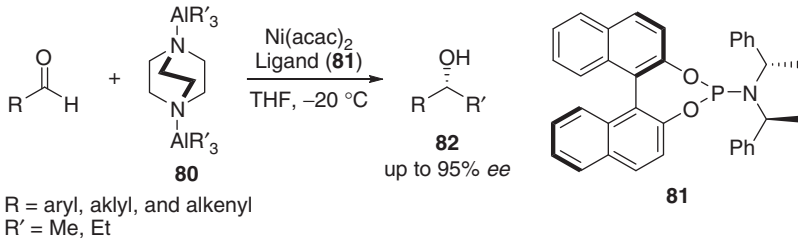


Figure 4 Plausible cyclic transition state **44** to explain *syn* selectivity of the 1,2-addition of **42**.

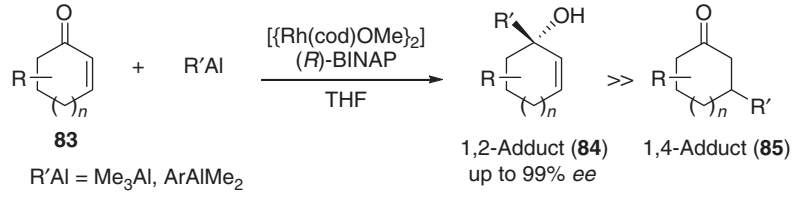
1.03.3.2 Other Metal-Catalyzed Asymmetric 1,2-Addition to C–O π-Bonds

In 2005, Woodward et al. developed the remarkably robust and stable aluminum complex **80** prepared from R_3Al (R = methyl and ethyl) and DABCO (1,4-diazabicyclo[2,2,2]octane) and applied this compound as nucleophile in the nickel-catalyzed asymmetric 1,2-additions to aldehydes (Scheme 23).[72] When this novel reagent **80** was added to THF solution of aldehydes in the presence of $Ni(acac)_2$ and chiral phosphoramidite ligand **81**, the resulting alcohols **82** were obtained in high *ee*.



Scheme 23 Nickel-catalyzed 1,2-addition with stable DABCO–aluminum complex **80**.

In 2007, Zezschwitz et al. reported rhodium-catalyzed enantioselective 1,2-addition of organoaluminum reagents to cyclic enones **83** (Scheme 24).[73] Under the present reaction condition, catalyzed by the metal complex of Rh and BINAP, the 1,2-addition occurred in preference to the 1,4-addition, thus giving cyclic tertiary alcohol **84**. Use of $ArAlMe_2$ led to the transformation into the corresponding arylated product **84** (R′ = Ar) in high *ee*'s.



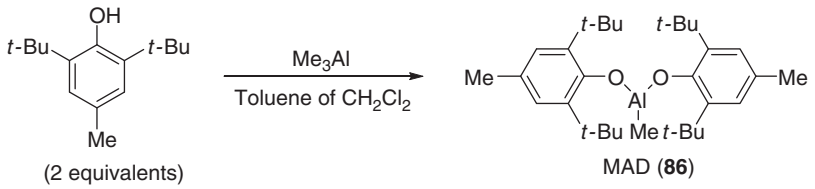
Scheme 24 Rhodium-catalyzed 1,2-addition to α,β-unsaturated ketones **83**.

1.03.4 Rational Design of Organoaluminum Lewis Acid for Selective 1,2-Addition

1.03.4.1 Achiral Organoaluminum-Catalyzed Selective 1,2-Addition

It has been revealed that the precise molecular modification of aluminum Lewis acid allows a variety of catalytic organic reactions to proceed in highly unique and selective manner.[2–5] In this context, Yamamoto et al. introduced methylaluminum

bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) **86** as a bulky organoaluminum Lewis acidic reagent first reported in 1985.[74] MAD can be readily prepared with a simple operation from Me_3Al and sterically hindered phenol ligands (Scheme 25).[75]



Scheme 25 Preparation of MAD **86**.

Compared with Me_3Al, the Lewis acidity of MAD should be decreased due to the coordination of electron-donating aryloxide groups, however, the bulky environment of MAD can prevent the formation of dimeric, trimeric, or higher oligomeric structures as typical organoaluminum reagents. In addition, a series of related bulky aluminum Lewis acids, methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR) **87**, methylaluminum bis(2,6-diphenylphenoxide) (MAPH) **88**, and aluminum tris(2,6-diphenylphenoxide) (ATPH) **89** were synthesized (Figure 5).[76]

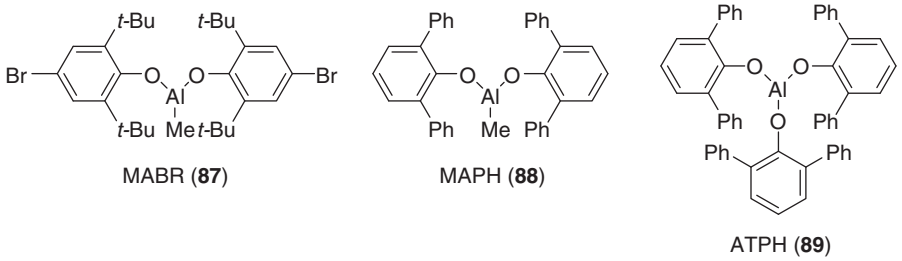
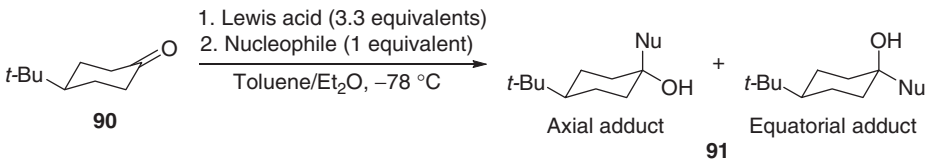


Figure 5 Various bulky aluminum Lewis acids related with MAD **86**.

The characteristic aspect of these bulky aluminum Lewis acids leads to the acquisition of new reactivity and selectivity in 1,2-additions of various nucleophiles to carbonyl compounds. For example, one of the earliest report is the 1,2-addition of organometallic species to 4-*tert*-butylcyclohexanone **90** (Table 11).[74] In the presence of MAD, the alkylated products **91** were obtained as an axial adduct exclusively (entries 2, 4, 6, and 8).

Table 11 1,2-Addition of 4-*tert*-butylcyclohexanone **90** to give an axial adduct **91**



Entry	*Lewis acid*	*Nucleophile*	*Yield (%)*	*Axial/equatorial*
1	None	MeLi	–	21/79
2	MAD	MeLi	84	99/1
3	None	EtMgBr	95	52/48
4	MAD	EtMgBr	91	100/0
5	None	*n*-BuMgBr	58	44/56
6	MAD	*n*-BuMgBr	67	100/0
7	None	AllylMgBr	86	52/48
8	MAD	AllylMgBr	90	91/0

This diastereoselectivity was rationalized as shown in Figure 6. A 1:1 complex of **90** and MAD might be preferred to a sterically favored isomer **92a**, wherein the nucleophile attacks from the less hindered side to give the corresponding axial adduct.

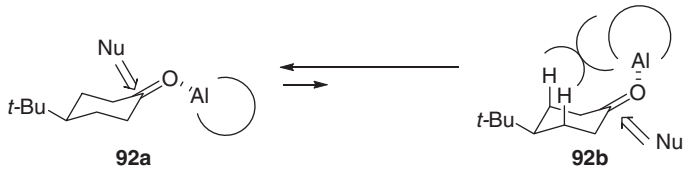
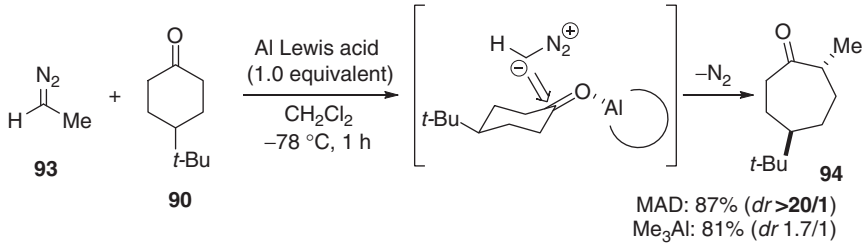


Figure 6 Possible explanation furnishing an axial adduct **91**.

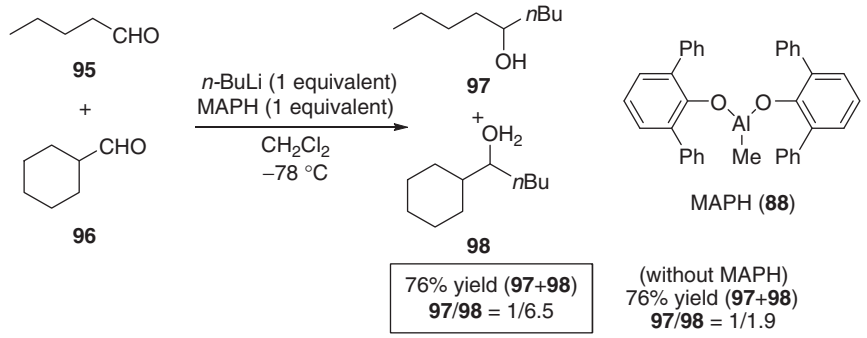
By applying this concept to the diastereofacial selection in nucleophilic addition to cyclic ketones, they also demonstrated the leading work concerning diastereoselective ring expansion with diazo compounds.[77] In the presence of stoichiometric amount of MAD, the reaction of diazoethane **93** with 4-*tert*-butylcyclohexanones **90** gave the substituted cycloheptanone **94** with high diastereoselectivity (Scheme 26). Also in this case, bulky MAD might allow diazoethane to attack carbonyl group with high diastereofacial selectivity. It should be noted that the use of Me_3Al exhibited a poor diastereoselectivity.



Scheme 26 Reaction of diazoethane **93** with 4-*tert*-butylcyclohexanones **90**.

Other representative applications on the selective 1,2-addition reactions using bulky organoaluminum reagents are the chemoselective 1,2-addition by utilizing their discriminating abilities between two sterically different carbonyl electrophiles such as ketone versus aldehyde,[78] aldehyde versus aldehyde,[79] and ketone versus ketone.[80]

For example, with the treatment of an equimolar mixture of valeraldehyde **95** and cyclohexanecarboxaldehyde **96** along with 1 equivalent of *n*BuLi in the presence of bulky organoaluminum reagent, MAPH resulted in the formation of the corresponding carbinol **97** and **98** in a ratio of 1:6.5 (Scheme 27).[79a] However, lower selectivity was observed in the reaction in the absence of MAD. This result indicates that MAPH is capable of stabilizing the sterically less hindered carbonyl group of valeraldehyde **95** toward the nucleophilic addition of *n*BuLi by selective coordination with **95**.

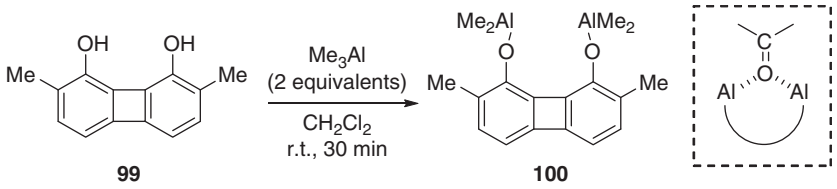


Scheme 27 Chemoselective 1,2-addition between **95** and **96** utilizing MAPH **88**.

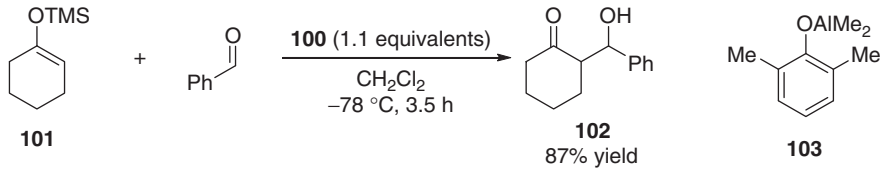
As other designer organoaluminum Lewis acid possessing unique reactivity, Maruoka et al. developed bis(organoaluminum) reagent **100** from rigid 1,8-biphenylenediol **99** and Me_3Al (Scheme 28).[81a] The rational molecular design of **100** was elaborated to realize efficient simultaneous coordination of carbonyl groups with two aluminum metal centers.[81]

Maruoka et al. evaluated the activity of bidentate organoaluminum Lewis acid **100** in a variety of 1,2-addition to carbonyl compounds. For example, the Mukaiyama aldol reaction of 1-trimethylsiloxy-1-cyclohexene **101** and benzaldehyde gave the aldol product **102** in the presence of **100**, where monodentate organoaluminum Lewis acid **103** did not exhibit any catalytic activities under the same reaction condition (Scheme 29).[81a]

To demonstrate the highly specific ability for carbonyl activation of **100**, Maruoka et al. surveyed the Mukaiyama aldol reaction of a mixture of acetophenone **104** and its dimethyl acetal **105** with ketene silyl acetal **106** promoted by bidentate aluminum Lewis acid **100** (Scheme 30).[81b] As a result, acetophenone **104** was exclusively converted to the corresponding product **107**, and

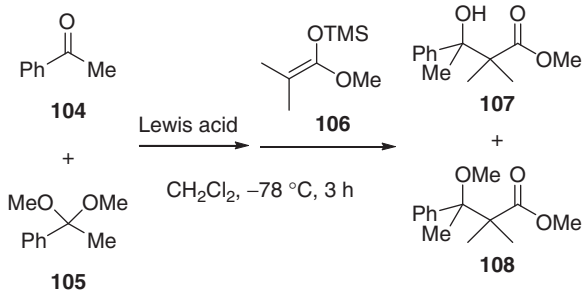


Scheme 28 Design of bis(organoaluminum) reagent **100** toward efficient simultaneous coordination of carbonyl groups with two aluminum metal centers.



Scheme 29 Use of bidentate organoaluminum Lewis acid **100** in 1,2-addition.

unreacted acetal **105** was recovered, whereas the lower chemoselectivity of products **107** and **108** were observed under the influence of typical Lewis acids such as TMSOTf or $Bu_2Sn(OTf)_2$.



Lewis acid	Yield (**107**+**108**)	**107**/**108**
TMSOTf	81%	57/43
$Bu_2Sn(OTf)_2$	75%	16/84
100	88%	>99/1

Scheme 30 Chemoselective Mukaiyama aldol reaction of ketone **104** and its dimethyl acetal **105**.

1.03.4.2 Chiral Organoaluminum-Catalyzed Enantioselective 1,2-Addition

Chiral oraganoaluminum complexes have been found to be effective Lewis acid catalysts in asymmetric 1,2-addition of various nucleophilic reagents.[2–5] Selected examples in the field of asymmetric synthesis utilizing chiral organoaluminum reagents are shown below.

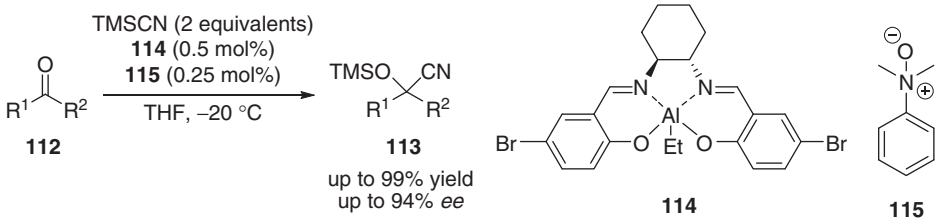
1.03.4.2.1 Formal [3 + 2] cycloaddition reaction via aldol reaction of oxazole and aldehyde

In 1998, Suga et al. demonstrated the reaction of 2-aryl-5-methoxyoxazoles **109** and aromatic aldehydes **110**-catalyzed chiral aluminum complex of (*R*)-BINOL and Me_3Al, providing optically active *cis*-2-oxazoline-4-carboxylates **111** (Scheme 31).[82] This formal [3 + 2] cycloaddition undergoes through the aldol-type nucleophilic addition of **109** to **110** and the following cyclization. Later, Evans et al. also reported a similar reaction using a chiral cationic aluminum complex.[83]

Scheme 31 Formal [3 + 2] cycloaddition reaction via aldol reaction of oxazole **109** and aldehyde **110**.

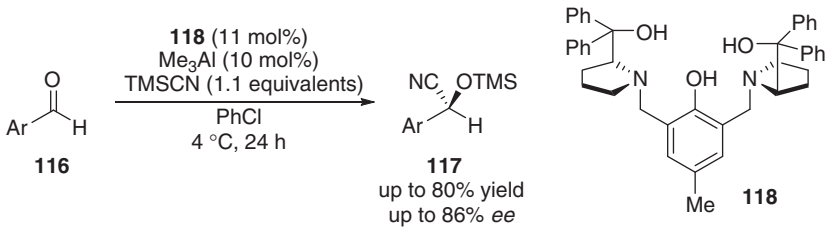
1.03.4.2.2 Cyanosilylation of carbonyl compound

In 2004, Feng et al. reported enantioselective cyanosilylation of ketones **112** catalyzed by chiral organoaluminum complex **114** (Scheme 32).[84,85] Their strategy involves the simultaneous activation of electrophiles **112** by chiral Lewis acid **114** and of nucleophiles (TMSCN) by achiral Lewis base **115**.



Scheme 32 Enantioselective cyanosilylation of ketones **112**-catalyzed by chiral organoaluminum complex **114**.

Furthermore, in 2005, Trost et al. described the enantioselective addition of TMSCN to aromatic aldehydes **116** catalyzed by chiral aluminum Lewis acid catalyst based on their inventive chiral ligand **118** (Scheme 33).[86]

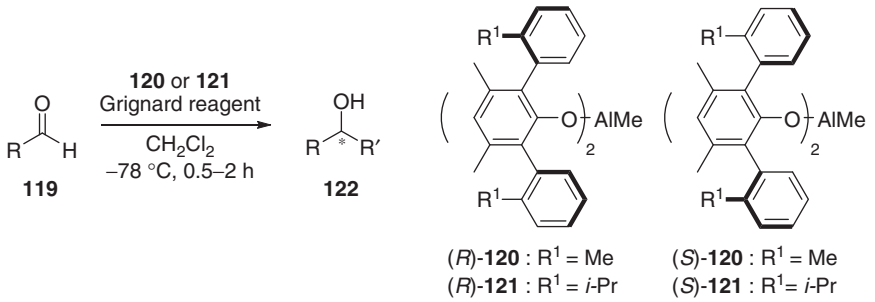


Scheme 33 Enantioselective addition of TMSCN to aromatic aldehydes **116**-catalyzed by chiral aluminum Lewis acid.

1.03.4.2.3 Chiral organoaluminum-promoted asymmetric 1,2-addition of Grignard reagent

Yamamoto and Saito examined the control of enantioselectivity in 1,2-addition of Grignard reagents to a variety of aldehydes **119** under the influence of axially chiral organoaluminum reagents **120** and **121** (Table 12).[87]

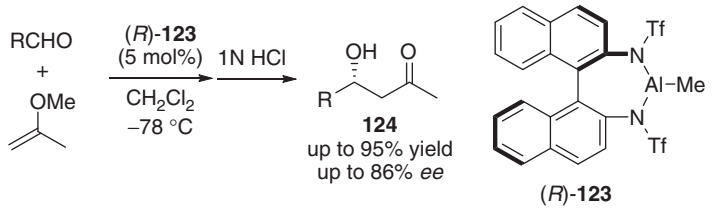
Table 12 Chiral organoaluminum-promoted asymmetric 1,2-addition of Grignard reagent



Entry	*Aldehyde*	*Lewis acid (equivalent)*	*R'MgX*	*Yield (%) (**122**)*	ee *(%)*
1	*n*-BuCHO	(*S*)-**120** (3)	MeMgI	99	52 (*S*)
2	CyCHO	(*S*)-**120** (3)	MeMgI	99	84 (*S*)
3	*t*-BuCHO	(*S*)-**120** (3)	MeMgI	90	86 (*S*)
4	PhCHO	(*S*)-**120** (1,2)	MeMgBr	83	42 (*R*)
5	PhCHO	(*R*)-**121** (1,2)	MeMgBr	61	65 (*S*)
6	PhCHO	(*R*)-**121** (1,2)	*n*-BuMgCl	99	73 (*S*)

1.03.4.2.4 Carbonyl-ene reaction

In 2004, Maruoka et al. demonstrated enantioselective hetero-carbonyl-ene reaction of aldehydes and 2-methoxypropene catalyzed by chiral organoaluminum complex (*R*)-**123**, giving the corresponding chiral *β*-hydroxymethylketones **124** (Scheme 34).[88]

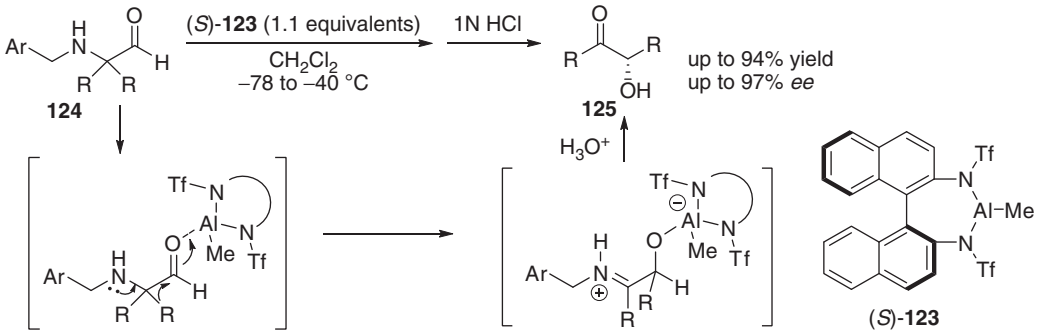


Scheme 34 Enantioselective hetero-carbonyl-ene reaction of aldehydes and 2-methoxypropene.

1.03.4.2.5 Asymmetric reactions involving intramolecular 1,2-skeletal rearrangement

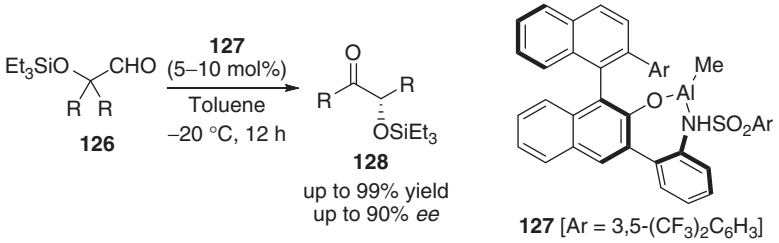
1,2-Skeletal rearrangement such as Wagner–Meerwein rearrangement often occupy a unique place in organic synthesis, due to its feasibility of giving hard-to-access organic molecules by using any other strategies. In this context, Maruoka et al. has devised a series of asymmetric 1,2-skeletal rearrangements, involving C–C bond cleavage and intramolecular 1,2-addition to carbonyl group, promoted by chiral organoaluminum complexes.

In 2003, they surveyed the enantioselective skeletal rearrangement of symmetrically *α*,*α*-disubstituted *α*-amino aldehydes **124** using chiral organoaluminum complex (*S*)-**123** to give optically active *α*-hydroxy ketones **125** (Scheme 35).[89]



Scheme 35 Enantioselective 1,2-rearrangement of symmetrically *α*,*α*-disubstituted *α*-amino aldehydes **124**.

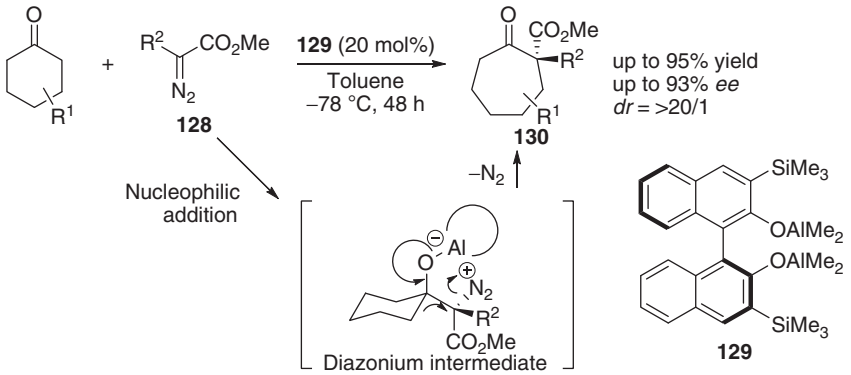
They successfully demonstrated the enantioselective 1,2-skeletal rearrangement of *α*,*α*-disubstituted *α*-siloxy aldehydes **126** catalyzed by newly developed axially chiral organoaluminum Lewis acid **127** (Scheme 36).[90] Later, they investigated the related mechanistic study shedding light on the reason for the expression of this migration aptitude in the 1,2-migration by using achiral organoaluminum species.[91]



Scheme 36 Enantioselective 1,2-rearrangement of *α*,*α*-disubstituted *α*-siloxy aldehydes **126**.

In 2011, Maruoka et al. reported desymmetrizing asymmetric ring expansion of substituted cyclohexanones with *α*-diazoacetates **128**-catalyzed chiral bis-aluminum Lewis acid **129**. This procedure gave the corresponding seven-membered products **130** with high enantio- and diastereoselectivity (Scheme 37).[92] This reaction involves (1) the nucleophilic addition of **128** to

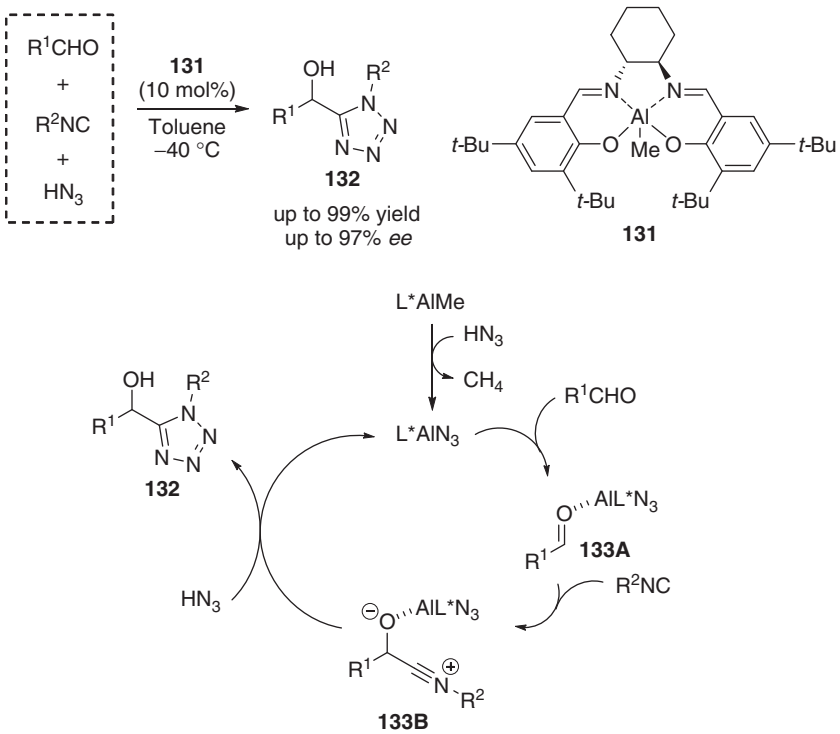
acid-activated cyclohexanones and (2) the subsequent 1,2-skeletal rearrangement of diazonium intermediate with the evolution of nitrogen. It should be noted that this protocol overcame the difficulty of stereocontrolled addition to symmetric ketones without a prochiral face.



Scheme 37 Desymmetrizing asymmetric ring expansion of substituted cyclohexanones with α-diazoacetates **128**.

1.03.4.2.6 Multicomponent reaction including 1,2-addition

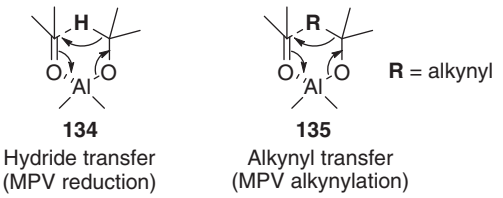
Multicomponent reactions, as represented by Ugi reaction and Biginelli reaction, are attractive strategies for the selective construction of complex organic molecules from several simple starting materials in a single operation. Recently, Wang and Zhu et al. reported asymmetric synthesis of 5-(1-hydroxyalkyl)tetrazoles **132** from aldehydes, isocyanide, and hydrazoic acid via chiral salen–organoaluminum complex **131**-catalyzed asymmetric Passerini-type reaction (Scheme 38).[93] Nucleophilic addition of isocyanide to the activated aldehyde **133a** would give the nitrilium ion **133b** and the subsequent reaction between **133b** and hydrazoic acid should result in the formation of the desired compounds **132**.



Scheme 38 Asymmetric Passerini-type reaction.

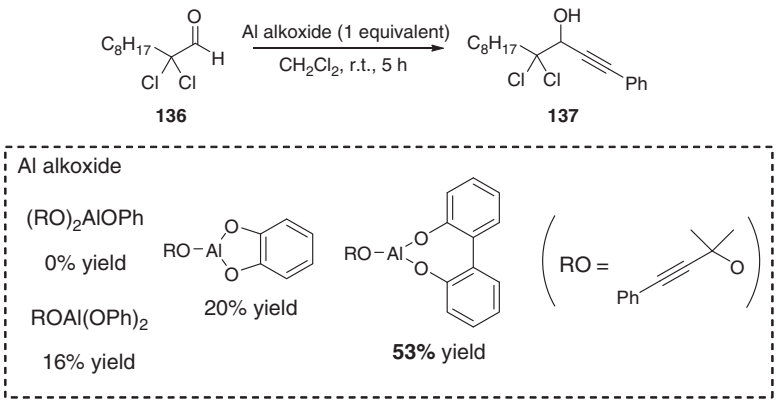
1.03.4.2.7 MPV alkynylation of aldehydes

The MPV reduction of carbonyl compounds is believed to proceed via a six-membered transition state **134** consisting of carbonyl compounds, secondary alcohols, and aluminum alkoxides (Scheme 39). Maruoka et al. developed a novel carbonyl alkynylation procedure based on the MPV reaction system involving alkynyl transfer via a six-membered transition state **135**.[94]



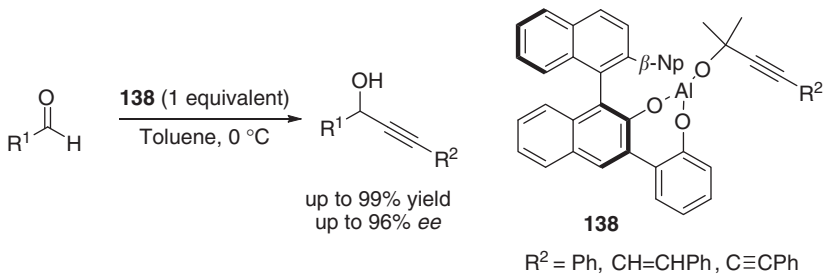
Scheme 39 A six-membered transition state of MPV reaction.

They discovered the remarkable ligand acceleration effect of 2,2′-biphenol in the alkynylation of aldehydes **136** to give the corresponding propargyl alcohol **137** (Scheme 40).



Scheme 40 MPV alkynylation using organoaluminum reagents.

With this observation, the asymmetric variant of this protocol has also been developed by using an axially chiral aluminum alkoxide **138** (Scheme 41).[94]



Scheme 41 Asymmetric MPV alkynylation using chiral organoaluminum reagent **138**.

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1.04 Regio-, Diastereo-, and Enantioselective Addition of Organocopper Reagents onto C=O and C=N Bonds

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Glossary

Chelate A chemical compound in the form of a heterocyclic ring, containing a metal ion attached by coordinate bonds to at least two nonmetal ions.

Contact ion pair/solvent separated ion pair (CIP/SSIP) It is the description of the solvatation state of an ion pair. In the CIP form the anion and the cation are intimately linked, whereas in the SSIP form they are separated by solvent molecules.

Felkin model The Felkin model predicts the stereochemistry of nucleophilic addition reactions to carbonyl groups. Felkin argued that the Cram model suffered a major drawback: an eclipsed conformation in the transition state between the carbonyl substituent (the hydrogen atom in aldehydes) and the largest α-carbonyl substituent. He demonstrated that by increasing the steric bulk of the carbonyl substituent from methyl to ethyl to isopropyl to isobutyl, the stereoselectivity also increased, which is not predicted by Cram's rule.

Hemiaminal Any organic compound having both an amino and a hydroxy functional group attached to the same carbon atom.

Hoffmann test A chemical test aimed at determining the congurational stability of species bearing a stereogenic C–metal bond in a given transformation and under defined conditions.

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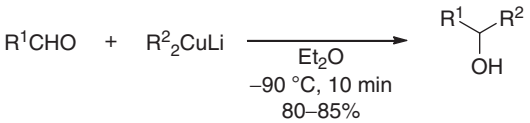
Metalloenamine Any compound in which a metal atom is bonded to the nitrogen atom of an enamine.
Metallotropic equilibrium The move of a metal center from one part of a p-bonded system to another part with concomitant rearrangement of the pi-system (e.g., double C–X bonds with X═C, O, N, S…, or triple bonds).

1.04.1 Introduction

Copper is an abundant and cheap transition metal that is implicated, under various forms, in the achievement of many complex transformations. Among them, carbometalation reactions, oxidative coupling reactions, and conjugate nucleophilic addition to α,β-unsaturated acceptors have received most of the attention (*see* Chapters 4.15, 3.10, and 4.04 for an overview on theses topics). A tremendous amount of effort has been provided by numerous research groups during the past 15 years to rationalize and develop these transformations.[1] That may explain why, in the mind of many synthetic chemists, organocopper reagents are most strongly associated with these particular reactions. Their application to other transformations has, in comparison, been far less described. Therefore, there are relatively few studies devoted to the direct addition of Cu(I) organometallic reagents to C–O or C–N double bonds.[2] Historically, it can easily be explained by the fact that organocopper or cuprate reagents are commonly obtained by transmetalation from highly reactive organometallic species (RLi, RMgX, RZnX, R_3Al, etc.) that are themselves efficient for such transformations (*see* Chapters 1.01, 1.03, 1.05, 1.07, and 1.08 for an overview on these topics). However, the increasing need to design new stereoselective transformations led to a growing interest for this metal. Indeed, organocopper reagents possess unique properties that represent precious assets for the development of highly efficient diastereo- and/or enantioselective processes. This class of organometallic reagents is essentially limited to the Cu(I) oxidation state, whatever the stoichiometry of the complex (organocopper RCu or organocuprate R_2CuX), as organocopper(II) compounds are known to be unstable[1] and that the existence of organocopper(III) species is only postulated as transient reaction intermediates. In strong contrast with classical organometallic reagents cited above, Cu(I) is a very soft Lewis acid, which has interesting consequences. One of them is that it is possible to tune this Lewis acid property by a judicious choice of ligands and/or by the nature of the associated cation, which may allow an efficient control of the chemo-, the regio- , or stereoselectivity for a given transformation. Another relevant point is that, in the context of the nucleophilic addition to a carbonyl derivative, its affinity for the resulting hard Lewis base alkoxide product will be very low. The Cu(I) complex will thus be easily released in the reaction mixture, which will grant efficient catalytic processes. These two properties will highlight most of the copper-mediated reactions presented in the following section. The first part will be devoted to stoichiometric copper-mediated transformations, and catalytic processes will be presented thereafter. The period up to the end of 1980s has previously been reviewed by Lipshutz in the first edition and will not be covered in detail herein.

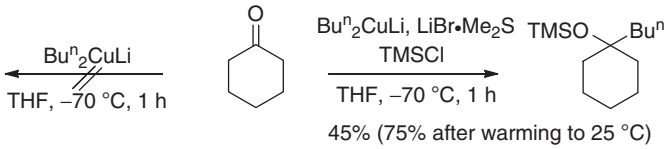
1.04.2 1,2-Additions to Aldehydes and Ketones

The 1,2-addition of organocopper reagents to saturated aldehydes is a well-established and efficient synthetic protocol. The first example was reported in 1972 by Posner and coworkers, who showed that methyl or butyl Gilman cuprates (R_2CuLi, R═Me, Bu^n) cleanly add in less than 10 min to aromatic or aliphatic aldehydes at temperatures as low as −90 °C (equation 1).[3]



R^1 = Hex^n, Ph; R^2 = Me, Bu^n (1)

In contrast, the addition to saturated ketones is more difficult and requires relatively high temperatures to occur.[2] For example no addition is observed after 1 h by reacting Bu^n_2CuLi with cyclohexanone in THF or Et_2O at −70 °C (**Scheme 1**).[4] This drawback



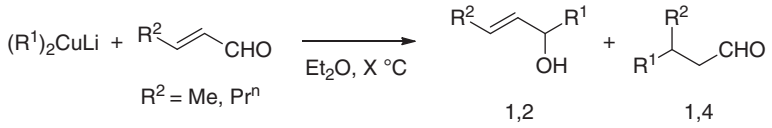
Scheme 1

can be bypassed by the use of additives. Among them, trimethylsilyl chloride (TMSCl) is known to dramatically increase the reactivity of organocopper reagents, on both 1,2- and conjugate addition reactions.[1] In the presence of this additive, Bu_2CuLi gives 45% yield of addition product after 1 h at −70 °C, and this yield can be increased by up to 75% by gradual warming up of the reaction media to room temperature.

1.04.2.1 Regioselectivity

The use of conjugated aldehydes or ketones as electrophiles is challenging due to possible competition between the direct (1,2) and the conjugate (1,4) addition modes. Three main factors have an influence on the regioselectivity: (1) the nature of the organocopper reagent, (2) steric constraints, and (3) the presence of additives. Organocopper reagents are very popular for their ability to regioselectively add onto α,β-unsaturated carbonyl derivatives to provide the 1,4-addition product. However, this rule suffers two exceptions: in contrast to alkyl, aryl, and vinyl-copper reagents, allyl and alkynyl analogs have an intrinsic propensity to the direct 1,2-addition mode, furnishing generally the corresponding homoallylic alcohols in high yields, as long as aldehyde reactants are involved. An outstanding example was given by Normant and coworkers in 1981, in a study that aimed at determining the regioselectivity of addition of Gilman reagents to conjugated aldehydes (Table 1):[5]

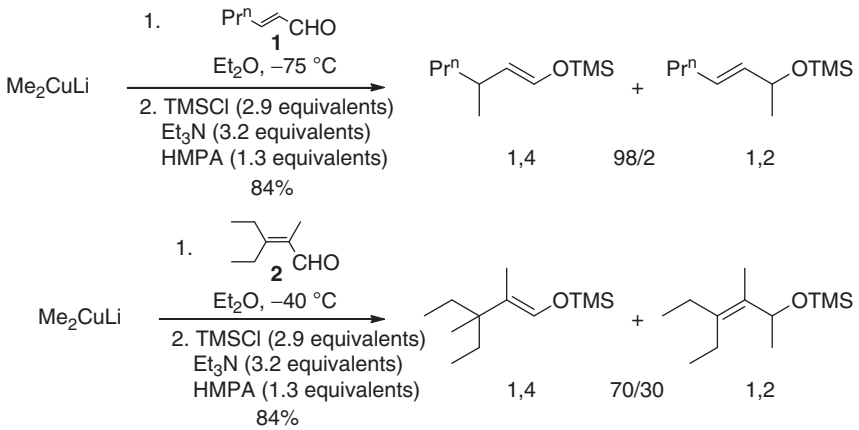
Table 1 Addition of Gillman reagents to conjugated aldehydes



No.	*R^1*	*X (°C)*	*Yield (%)*[a]	*1,2/1,4*
i	Bu^s	−70	65	55/45
ii	$Me_2C{=}CHCH_2CH_2$	−75	95	0/100
iii	$CH_2{=}CHCH_2$	−45	72	100/0
iv	(*Z*)-$Bu^nCH{=}CH$	−45	77	0/100
v	Ph	−70	66	0/100
vi[b]	Bu^n—≡	20	79	100/0

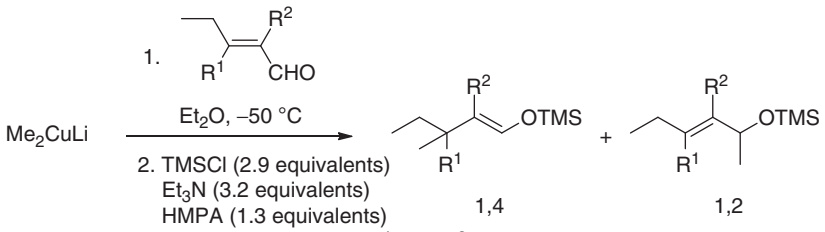
[a]Isolated yield.
[b]Reaction conducted in THF instead of Et_2O.

Steric factors can also affect regioselectivity. Normant and Clive[6] have shown that the 1,2-selectivity increases along with the steric constraints induced either by the presence of α- and/or β-substituent on the electrophile or by the substitution pattern of the copper reagent. For example, the addition of primary alkylcuprate reagents onto a given enal is 1,4-selective whereas the use of secondary alkyl analog leads to a mixture of regioisomers, as illustrated in Table 1 (entries i and ii). Furthermore, dimethyl cuprate adds regioselectively in Et_2O onto aldehyde **1** mainly through a 1,4-addition mode at temperatures as low as −75 °C, whereas a higher reaction temperature is required for the use of aldehyde **2**, and the transformation yields a mixture of 1,4- and 1,2-addition products (Scheme 2).[7]



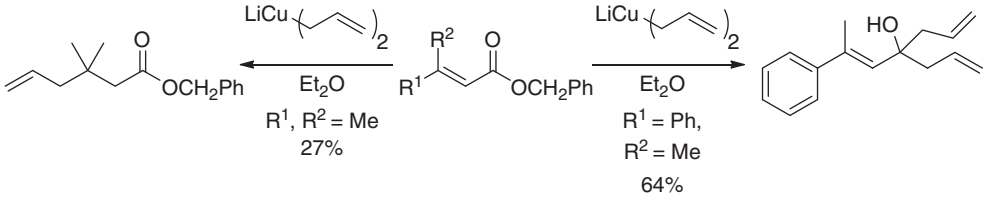
Scheme 2

However, steric hindrance may not be only responsible for the regioselectivity outcome as Normant and coworkers have shown that the 1,4/1,2-addition ratio decreases for the use of α-substituted enals compared with β-substituted ones (equation 2 and Scheme 2).[7]

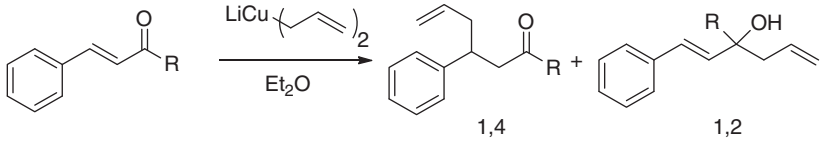


(2)

The same trend (influence of the nature of the organocopper reagent and steric constraints) is observed for the use of α,β-unsaturated carbonyl compounds. Unfortunately, in the case of allyl copper reagents, the regioselectivity of the addition is hardly predictable and sometimes low with these electrophiles, as illustrated in Scheme 3 and equation 3:[8]



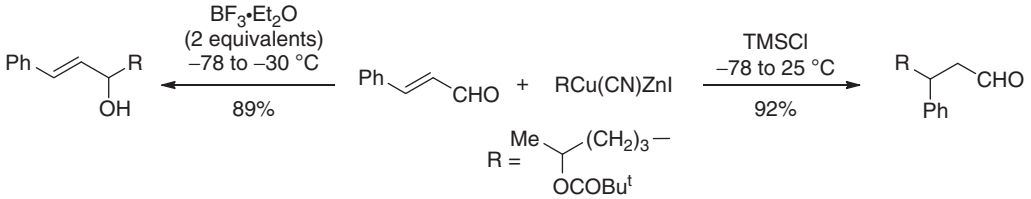
Scheme 3



R	Yield 1,4 (%)	Yield 1,2 (%)	1,4/1,2
H	–	86	0/100
Me	47	26	64/36
Bu^s	17	–	100/0
Bu^t	45	43	51/49

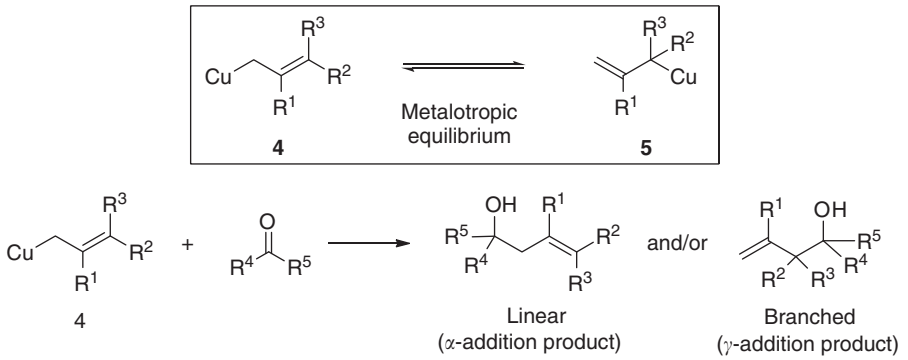
(3)

This drawback can be bypassed by the use of additives. Among them, $BF_3{\cdot}Et_2O$ and TMSCl are known to often change the regio- and stereoselectivity of the reaction.[1] An example of their influence on the regioselectivity of the addition to enals was reported by Knochel and coworkers.[9] In the presence of $BF_3{\cdot}Et_2O$, functionalized cyanocuprates obtained by transmetalation of the corresponding zinc reagents add to cinnamaldehyde to give the 1,2 adducts. In contrast, the 1,4 adduct is selectively obtained in the presence of TMSCl (Scheme 4). Of note, the nature of the electrophile used is crucial for the regioselectivity of the addition as both of these additives are known to accelerate the conjugate addition of various organocuprate reagents to α,β-unsaturated ketones, acids, or esters.[1]

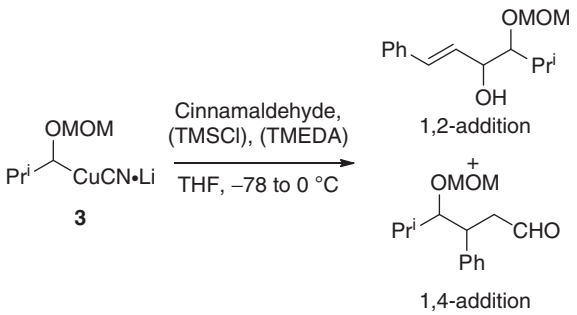


Scheme 4

Another example has been provided by Linderman who has shown that the cyanocuprate **3** derived from an α-alkoxyorganostannane adds onto cinnamaldehyde in the presence of TMSCl to give mainly the 1,4 adduct (Scheme 5). Interestingly, an inverse selectivity was observed when tetramethylethylendiamine (TMEDA) was added in the reaction mixture, giving rise to the formation of the 1,2 adduct (equation 4).[10]



Scheme 5



TMSCl	TMEDA	1,2/1,4[a]
–	–	–
5 equivalents	–	19/81
5 equivalents	2 equivalents	97/3

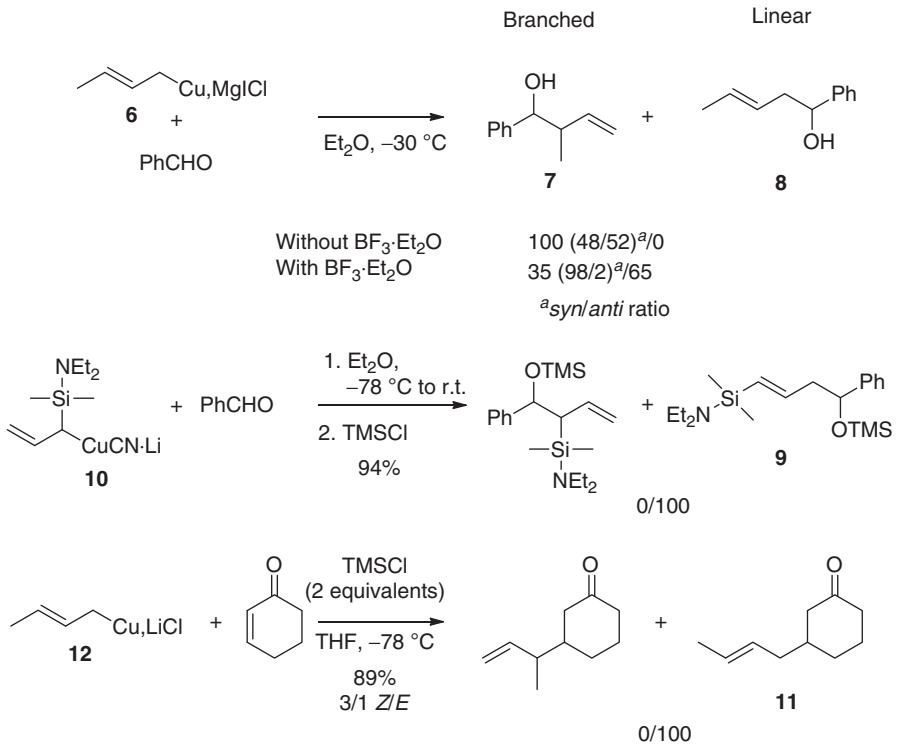
[a]GC analysis of crude reaction mixture.

(4)

Further studies are needed to rationalize the exact role of these additives on the regioselectivity. Nevertheless, in the last case, TMEDA is known to be an efficient ligand for the lithium cation, which suggests a crucial role of Li^+ on the mechanistic pathways of this particular transformation.

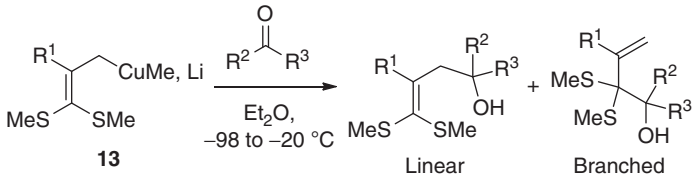
The regioselectivity issue may also involve the nucleophile. Indeed, organocopper reagents owning an unsaturated bond conjugated to the C–Cu bond may exist as a mixture of two distinct organometallic species **4** and **5** (Scheme 5). Depending on the nature of the substituents, these two forms can be under metallotropic equilibrium and are able to react with electrophiles through an S_E2 or an S_E2' mode. This is, for example, the case for allylic reagents which on addition onto aldehydes or ketones may yield an isomeric mixture of 'α- and γ-addition adducts.' Readers have to be aware that the terminology 'α- and γ-addition' (which products would respectively result from an S_E2 and S_E2' reaction) is ambiguous as the exact structure of the reactive organometallic species is usually unknown. The terms linear and branched products will thus be used instead as often as possible in the ensuing discussion.

The regioisomeric ratio is not easily predictable and, similar to the above discussion, is greatly dependent on the nature of the electrophile, the steric constraints, and the presence of additives in the reaction mixture. In a seminal publication, Yamamoto and Maruyama showed that the crotylcopper reagent **6** obtained *in situ* by addition of one equivalent of crotyl Grignard to CuI reacts with benzaldehyde to yield quantitatively the branched isomer **7** in a ratio of approximately 50/50 *anti*/*syn*.[11] In strong contrast, the linear product **8** is mainly formed when the $PhCHO{\cdot}BF_3$ complex is used instead of PhCHO under the same reaction conditions. Of note, the Lewis acid has a dramatic influence on the *anti*/*syn* ratio of the branched adduct **7**, which is enhanced to 98/2 (for a discussion about the diastereosectivity, see Section 1.04.2.2). Under Lewis acid-free conditions, linear product **9** is exclusively formed for the use of an allylic copper reagent **10** bearing a silylated group in the allylic position.[12] If the structures drawn for organocopper reagents **6** and **10** in Scheme 6 are the reactive ones, it could suggest that allylic copper adds preferentially onto carbonyls through a cyclic transition state (TS), in an S_E2' mode. Incidentally, the addition of the crotylcopper to enones yields linear 1,4-adducts.[13] As the conjugate addition is described to occur through a first oxidative addition step of the Cu(I) to the double bond followed by a reductive elimination of the transient Cu(III) intermediate,[1] the formation of linear adduct **11** is consistent with structure **12** (Scheme 6). In the case of the Cu(I) mechanism, it could be envisioned that the presence of additives such as $BF_3{\cdot}Et_2O$ would disfavor the cyclic TS due to precomplexation of the Lewis acid to the oxygen of the carbonyl. This would thus open the way to the direct addition of the metal center to the C–O bond via the Cu(III) mechanism, to give the linear adduct (Scheme 6).



Scheme 6

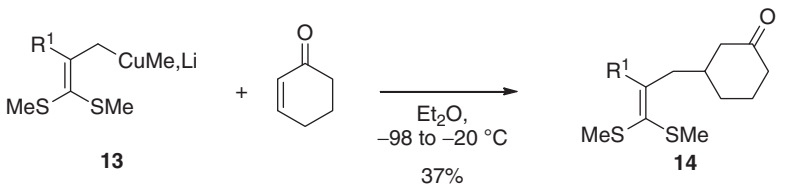
Whatever the mechanism, the most important factor for the control of the regioselectivity appears to be steric constraints. As a representative example, Hosomi and coworkers showed that the linear/branched ratio of products stemming from the addition of allylic methylcuprate **13** to carbonyls is strongly dependent on the steric hindrance of the electrophiles.[14] Indeed, the use of pentanone or pivalaldehyde gives mainly or exclusively linear adducts whereas the branched one is mainly formed with *iso*-butyraldehyde (equation 5).



R^1	$R^2(CO)R^3$	Yield (%)	Linear/ branched
Et	Pr^iCHO	77	31/69
Bu^n	Bu^tCHO	47	83/17
Ph	Et_2CO	66	100/0

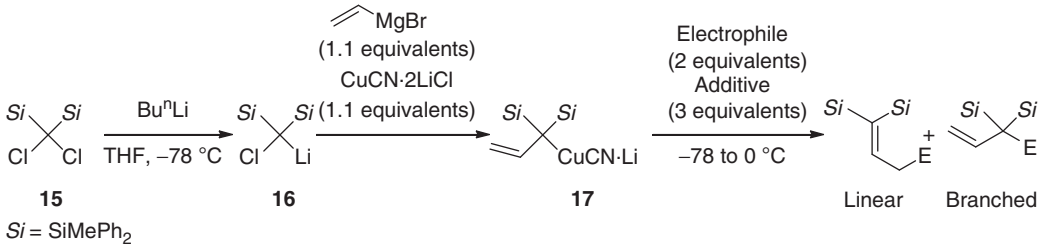
(5)

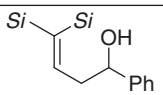
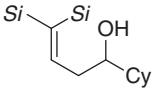
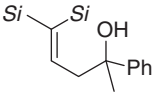
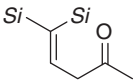
Surprisingly, **14** is formed when this organometallic reagent is subjected to cyclohexenone, which suggests structure **13** as the reactive species (equation 6).



(6)

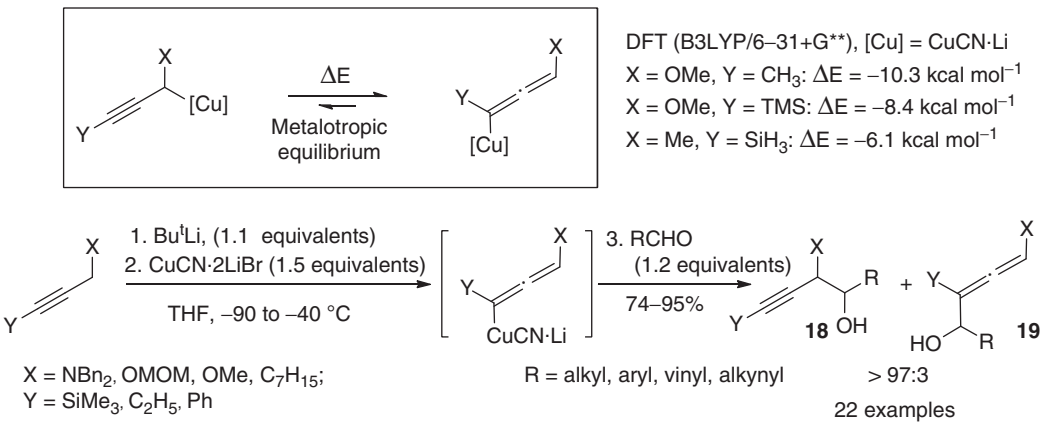
More recently, another interesting example was reported by Oshima and coworkers.[15] The dichlorobis(methyldiphenylsilyl) methane **15** is subjected to Bu^{n}Li in THF to yield carbenoid intermediate **16**. This transient species is then trapped by the vinyl cyanocuprate obtained from the corresponding Grignard reagent and CuCN·2LiCl to give allylic cyanocuprate **17** that can be seen as a silylated analog of **13** (equation 6). Its addition to various carbonyl derivatives gives exclusively the corresponding linear products, which could be the result of the steric hindrance of the geminal silyl substituents (equation 7).



Electrophile	Additive	Yield (%)	Linear/Branched	Product
PhCHO	TMSCl	69	100/0	
CyCHO	TMSCl	59	100/0	
		52	100/0	
CH_3COCl		57	100/0	

(7)

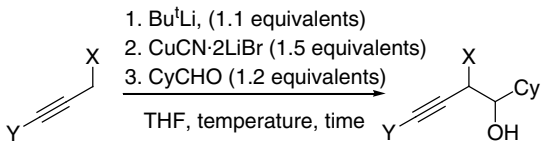
Organocopper reagents stemming from propargylic derivatives are also capable of metallotropic equilibrium, between an allenic and a propargylic form (Scheme 7). Those reagents, bearing the metal center in both vinylic and allylic position in the allenic form, are of particular interest as their addition onto aldehydes gives a straightforward access to synthetically valuable homopropargylic alcohols. Although an extensive amount of work has been devoted to the addition of allenyl metals onto aldehydes,[16] the case of copper derivatives has been totally omitted until recently, probably because a lack of regioselectivity was often observed with these reagents in cross-coupling or carbocupration reactions. The first general study was undertaken by Vrancken, Mangeney, and coworkers.[17] Cyanocuprates reagents were easily prepared by subjecting the corresponding propargylic reactant to ^{s}BuLi or ^{t}BuLi in THF at low temperatures and by a subsequent transmetalation step with the soluble CuCN·2LiBr complex. The addition of a variety of aliphatic, aromatic, vinylic, and acetylenic aldehydes to the reaction mixture gives the corresponding homopropargylic alcohols **18** with total regioselectivity (Scheme 7). The diastereoselectivity of these transformations will be discussed in Section 1.04.2.2.1.



Scheme 7

A complementary density functional theory (DFT) study predicted an allenic structure for the reactive species, with a ΔE between the allenic and the propargylic forms up to 10.3 kcal mol^{-1}. As no trace of allenic products **19** can be detected in the crude mixture, the reaction is supposed to occur through an overall S_E2' process. Additionally, the use of enals yields exclusively 1,2-addition products, which shows that these allenylcopper species behave more like allylic copper reagents than vinylic ones (Scheme 7).

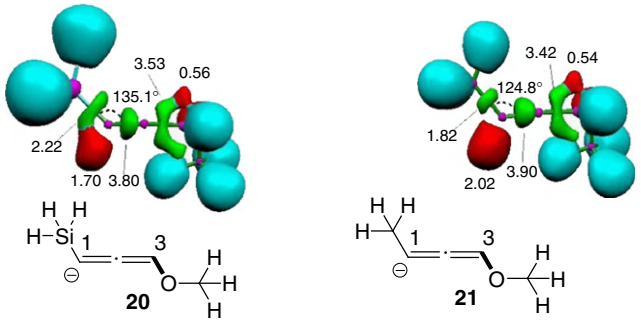
It was observed that the rate of the reaction strongly depends on the nature of the acetylenic substituent of the starting propargylic derivative, the reactivity scale being: $SiMe_3$ > Ph > Alkyl (Scheme 8).[17c] DFT calculations and a topological analysis of the electron localization function[18] of the free anions **20** and **21** have shown that these differences of reactivity are not the result of a displacement of the metallotropic equilibrium (Scheme 7), but of a variation of the electron distribution induced by the substituents. Indeed, a decrease of the electron population on C^1 is observed with silylated substituents (1.70 electrons) compared with alkyl ones (2.02 electrons) due to a partial electron transfer into the C–Si bond (Scheme 8). It has then been postulated that coordination of the Cu(I) cation will be enhanced in the more electron-rich case, leading to a stronger C-metal bond and consequently a less reactive species.



X	Y	Temperature (°C)	Time	Yield (%)
OBu^t	TMS	−90	< 5 min	81
OMOM	Ph	−80[a]	1 h	65
OMOM	Et	−60	16 h	78
NBn_2	TMS	−90	< 5 min	81
NBn_2	Ph	−40[b]	10 min	91

[a]10 min at −60 °C, 93% yield. [b]no reaction at −90 °C.

ELF isocontours (isosurface = 0.84) for **20** and **21**. The basin population are in electrons. The blue color stands for the H electrons, the green for bonding electrons and the red for the lone pairs:



Scheme 8

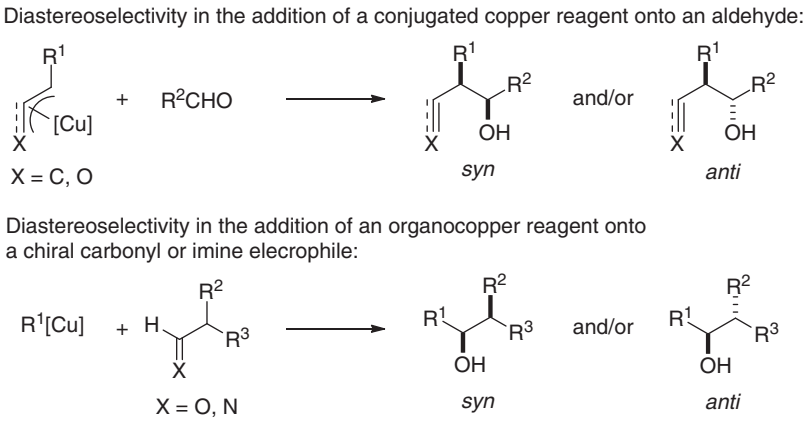
1.04.2.2 Diastereoselectivity

The ease of addition of copper reagents to aldehydes opens the way to the control of the stereoselectivity (diastereo- or enantio-) of the reaction and this is indeed the main objective of the published studies. Most of the enantioselective reactions are catalytic versions and will be described in the section (see Section 1.04.4). Two main kinds of diastereocontrol have been studied: (1) the *anti/syn* relationship between the two adjacent stereogenic centers resulting from the addition of a substituted conjugated copper reagent, namely an allyl copper, an allenylcopper, or a copper enolate onto a carbonyl (as, e.g., an aldehyde in Scheme 9) and (2) the facial selectivity during the addition to a carbonyl or an imine featuring a stereogenic center (Scheme 9).

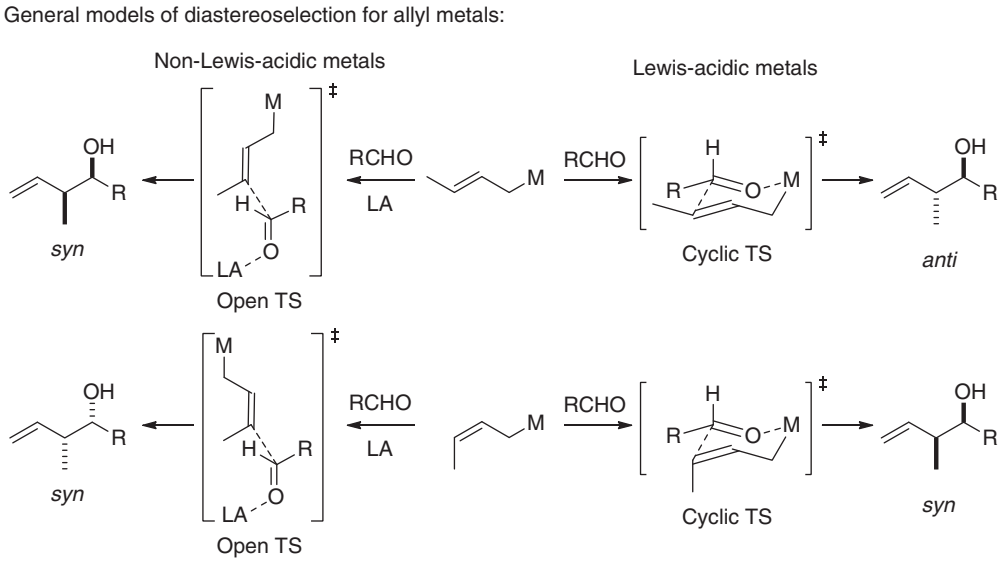
1.04.2.2.1 Prostereogenic organocopper reagents

The stereochemistry of the addition of a conjugated organometallic species to a C–O or a C–N double bond is usually explained using two types of TSs, the existence of which depends on the Lewis acidity of the metal center. When an oxophilic (or azaphilic) metal is involved, its complexation to the oxygen (or nitrogen) of the electrophile double bond induces a cyclic TS, whereas an open TS is expected to take place when a non-Lewis acidic species is employed in the presence of a strong external Lewis acid.[19] In the case of allyl metals, the open TS leads mainly to the *syn* adduct independently of the stereochemistry of the allyl moiety (Scheme 10), whereas, in the case of a cyclic TS, the *anti* or *syn* preference will result from the *E* or *Z* configuration of the double bond (Scheme 10).

Very few works have been devoted to this topic. The previously discussed example reported by Yamamoto and Maruyama (Scheme 6), that is, the addition of a crotylcopper reagent to the benzaldehyde in the presence or in the absence of $BF_3{\cdot}Et_2O$, represents a rare study involving such organometallic species. In this case, the increase of the *syn*-selectivity observed in the presence of the Lewis acid could be rationalized using an open TS as depicted in Scheme 10. However, the increase of the diastereoselectivity is followed by a dramatic drop of regioselectivity. One can imagine that this drawback has hampered the development of this approach compared with other very efficient metal-catalyzed allylation reactions.[19]

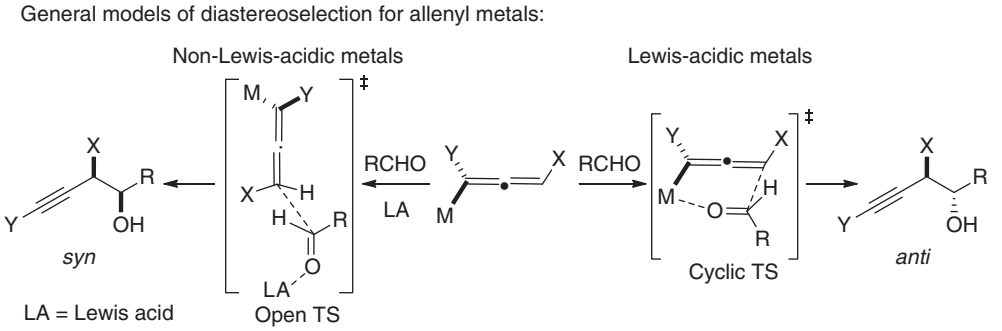


Scheme 9



Scheme 10

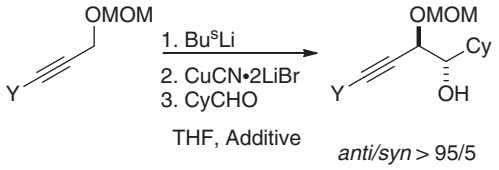
In the case of allenyl metals, an open TS, in which the aldehyde reacts at the opposite side of the metal center, is proposed to explain the *syn*-selectivity (**Scheme 11**), and the Yamamoto–Chodkiewicz[16] six-membered TS to explain the *anti* one (**Scheme 11**).



Scheme 11

More recently the case of the allenylcopper reagents has been studied in more detail by Gerard, Vrancken, Mangeney, and coworkers.[17] The addition of allenyl cyanocuprates onto various aldehydes yields the corresponding homopropargylic alcohols with an unexpected high level of *anti*-selectivity, regardless to the nature of the allenic substituents.[17] This behavior is particularly

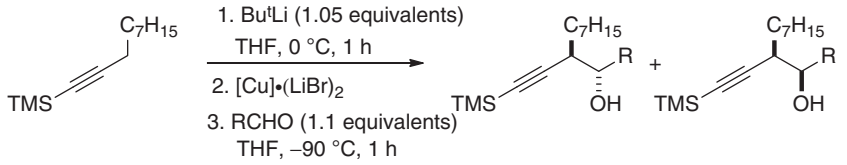
surprising as cyanocuprates are described as metal-centered nucleophiles and thus owing poor Lewis acidity properties,[20] which should inhibit a six-membered cyclic TS. It was also observed that the presence of additives in the reaction mixture has an influence on the rate of these transformations: they are generally dramatically slowed, or even stopped, in the presence of strong Li^+ chelating agents such as hexamethylphosphoramide (HMPA) or 12-crown-4 (equation 8).



Y	Additive	Temperature (°C)	Time	Yield (%)
Ph	–	–90	10 min	93
	HMPA	–60	4 h	90
Et	–	–50	16 h	78
	HMPA	–50	5 days	<5
TMS	–	–90	10 min	75
	12-C-4	–80	1 h	<5

(8)

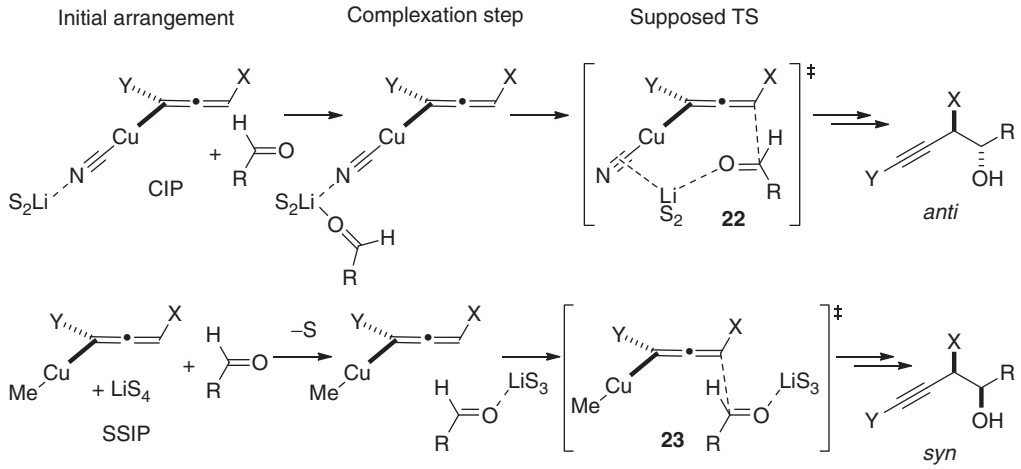
These results do not fit with the classical model in which the activation of the aldehyde is ensured by the metal itself, and further studies were thus required. Previous theoretical and experimental work has highlighted the crucial role played by the Li^+ counterion in the organization of the TS and the activation of various reactions involving organocuprate reagents.[1] In the particular case of cyanocuprates, a contact ion pair (CIP) is known to be formed in THF between the Li^+ and the cyano-ligand of the copper center, as shown by X-ray diffraction studies. In contrast, cuprates are known to exist in solution in equilibrium between CIPs and solvent separated ion pair (SSIP) species. In a Lewis-basic solvent such as THF, this equilibrium is in favor of SSIPs.[1] On the basis of these results, the researchers have undertaken an intertwined experimental and theoretical study which showed that the copper nontransferrable 'dummy ligand' controls the localization of Li^+ with respect to the allenyl moiety (equation 9), and two original reaction pathways have been consequently proposed. In the case of allenyl cyanocuprates, the strong association of Li^+ with the cyano-ligand induces the formation of a cyclic nine-membered TS **22** leading to the *anti*-adduct. In contrast, SSIPs species are formed with allenyl alkylcuprates, and the process goes through an open TS **23** in which the copper center and the aldehyde stand *cis* to each other, furnishing mainly *syn* products (Scheme 12).[21]



R	[Cu]	*anti/syn*	Yield (%)
Pr^n	CuCN	90/10	82
"	CuMe	20/80	78
Pr^i	CuCN	92/8	65
"	CuMe	10/90	76

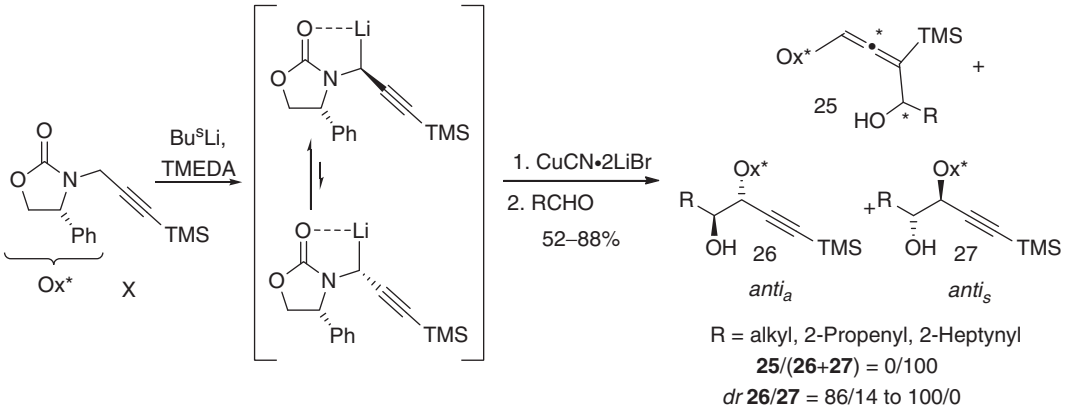
R	[Cu]	*anti/syn*	Yield (%)
Bu^t	CuCN	nd	–
"	CuMe	<5/>95	80
Ph	CuCN	80/20	68
"	CuMe	20/80	77

(9)



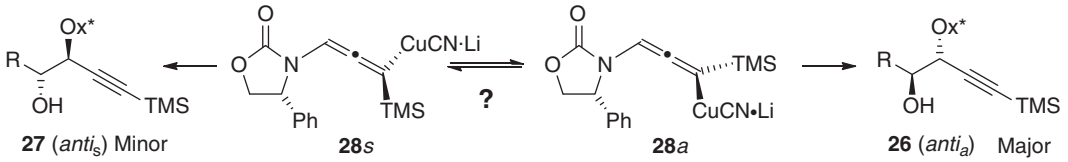
Scheme 12

An asymmetric version of this reaction has been provided based on a center-to-axis chirality transfer strategy. The optically pure oxazolidinone **24** was metalated in THF to yield a diastereomerically defined organolithium intermediate.[22] The addition of *iso*-butyraldehyde to the reaction mixture gave only the corresponding allenyl alcohol (*dr*=72/28). A transmetalation by $ZnBr_2$ furnished the zinc analog that led to a mixture of allenic **25** and homopropargylic alcohols **26** and **27** when reacted with the same aldehyde (*dr*=95/5 and 69/31, respectively). In contrast, the cyanocuprate reagent obtained by the addition of the soluble CuCN·2LiBr complex in the reaction media afforded regioselectively the corresponding homopropargylic amino alcohols as a mixture of two *anti*-diastereoisomers **26** and **27** with good to excellent diastereomeric ratios (Scheme 13).[23] It is reasonable to assume that the regioselectivity is dependent on the Lewis acidity of the metal: the more oxophilic ones remain in propargylic position and react in an S_E' mode to give the allene products. Thanks to its low Lewis acidity, the cyanocuprate would reside in the more stable allenic position, which explains its unique behavior. Of note, this copper methodology is nicely complementary to the tin-based reactions that provide the *syn* isomers as initially reported by Hegedus and coworkers.[24]



Scheme 13

Supposing that the transformation proceeds through cyclic TSs, the major *anti*$_a$-isomer **26** would arise from an allenyl cyanocuprate intermediate **28**$_a$ where the metal center stands *anti* to the phenyl group, and the minor *anti*$_s$-isomer **27** from the epimeric allene **28***s* (Scheme 14). Interestingly, the *anti*$_a$/*anti*$_s$ ratio varies with the nature of the aldehyde, which suggests that the formation of the minor *anti*$_s$-isomer do not result from a diastereodivergent transmetalation process but rather would be the sign of the configurational instability of the allenyl cyanocuprate reagent. Little is known on the configurational stability of copper reagents, but the rare studies devoted to such species show a clear tendency to configurational stability on the time scale of transmetallations, halogenations, conjugate additions, or nucleophilic substitution reactions. This behavior is thus surprising and further studies are needed to clarify this point (see Scheme 27, Section 1.04.3.1).



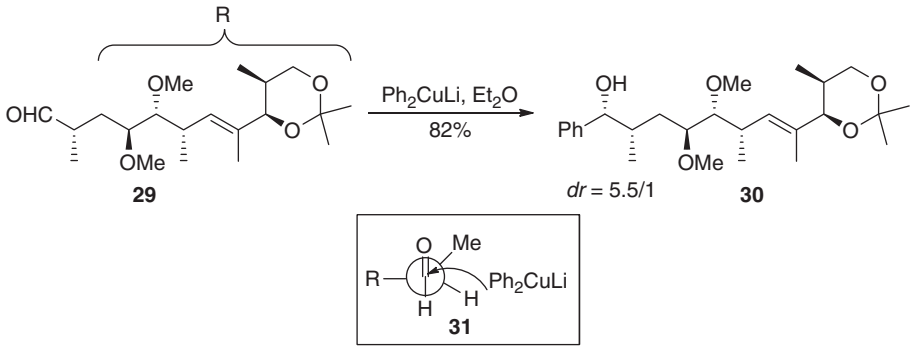
Scheme 14

In conclusion to this section, the key role of the copper counterion in the organization of the TSs, and thus the stereoselectivity outcome of the reaction, has been shown. The control of the facial selectivity during the addition organocopper reagents to chiral carbonyl or imine derivatives will furnish further illustrations of this concept. In this field, the diastereoselectivity is the result of chelation- or (and) of nonchelation controls.[25]

1.04.2.2.2 Addition of organocopper reagents to chiral aldehydes and ketones

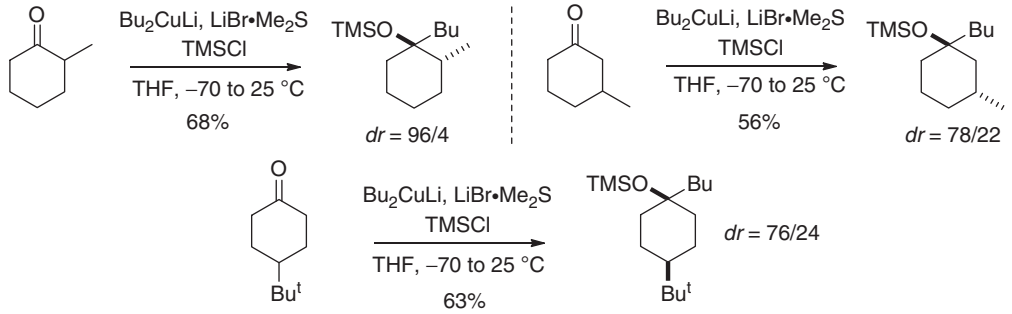
1.04.2.2.2.1 Nonchelate control

The nonchelation control has been first described by Yamamoto and Maruyama in the addition of R_2CuLi onto 2-phenylpropionaldehyde. The Felkin–Ahn products are generally obtained with moderate levels of selectivities (i.e., *syn*/*anti* ratio 3/1=for Bu^n_2CuLi), but interestingly the presence of one equivalent of 18-crown-6 in the reaction medium completely reverses the stereochemical course of the reaction, the *anti*-Felkin–Ahn adduct being mainly obtained (i.e., *syn*/*anti* ratio 1/4.2=for Bu^n_2CuLi).[2] This methodology has been exemplified by Marshall's synthesis of a subunit of the Macbecin. Indeed, the addition of Ph_2CuLi to aldehyde **29** yielded the Felkhin–Ahn adduct **30** in a 5.5/1 *anti*/*syn* ratio according to model **31** (equation 10).[26]



(10)

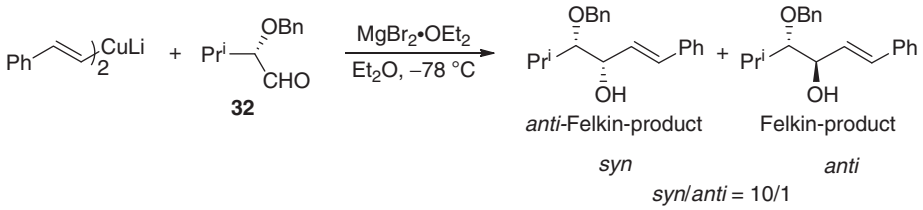
Examples of diastereoselective addition of organocopper reagents onto chiral ketones are rare[2] due to their inherent lack of reactivity on these electrophiles (*vide supra*). An interesting example was furnished by Nakamura, Kuwajima, and coworkers, who mentioned that the diastereoselectivities observed in the reaction of Gilman cuprates with substituted cyclohexanones in the presence of TMSCl (**Scheme 15**) were slightly higher than those obtained with BuLi.[4]



Scheme 15

1.04.2.2.2.2 1,2 Chelate control

An α-chelate model is usually proposed to rationalize the stereochemical course of the addition of copper reagents to α-alkoxy aldehydes. Accordingly, the *anti*-Felkin *syn* adduct is selectively obtained as shown in equation 11 where an $MgBr_2$-modified Gilman vinylcuprate is added to aldehyde **32**.[2,27]

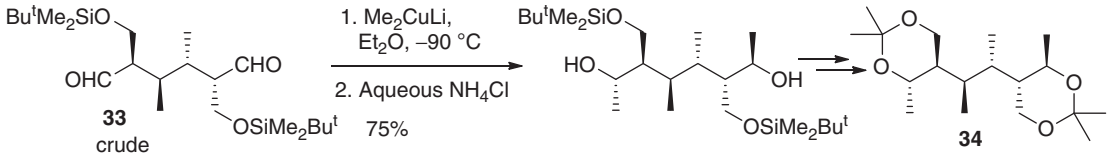


(11)

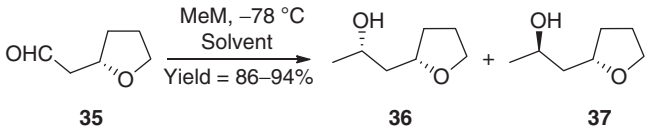
Similar results have been reported more recently by Hoffmann and coworkers, who realized the stereoselective double methylation of the dialdehyde **33** by Me_2CuLi, the key step in the synthesis of Bis(1,3-dioxan-5-yl)ethane derivative **34** (**Scheme 16**).[28]

1.04.2.2.2.3 1,3 Chelate control

The possibility of a chelate control by a β-alkoxy substituent has been studied by Baldwin for the addition of a series of methyl metallic derivatives to the β-alkoxy aldehyde **35** (equation 12). Almost no selectivity was observed with organolithium, magnesium, or aluminum derivatives. Organocoppers led to a modest but significant selectivity (**36**/**37** up to 85/15), although the best result was achieved with $MeTiCl_3$.[29]



Scheme 16

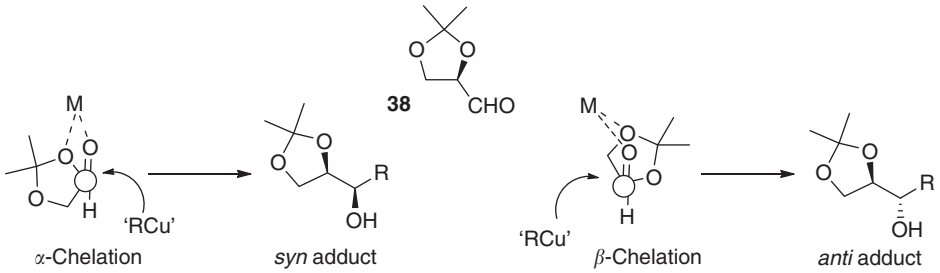


MeM	Solvent	36/37
Me_2CuLi	Et_2O	80/20
Me_2CuLi, Et_3B	Et_2O	85/15
Me_2CuLi, $BF_3{\cdot}Et_2O$	CH_2Cl_2	75/25
$MeTiCl_3$	CH_2Cl_2	140/1

(12)

1.04.2.2.2.4 1,2 versus 1,3 chelate control

Among the aldehydes leading to useful synthetic intermediates, one of the most popular is the 2,3-*O*-isopropylideneglyceraldehyde **38**. Using such reactant, the selectivity might be altered by the presence of two possible competitive chelations with α- and/or β-oxygens, the α-chelate affording the *syn* adduct (*anti*-Felkin product) and the β-chelate the *anti* one (Felkin product, Scheme 17).



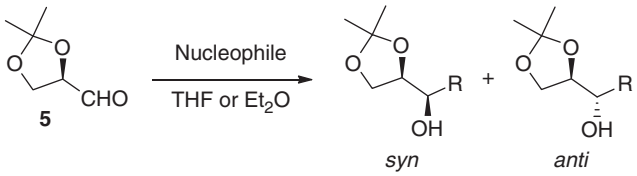
Scheme 17

Diastereomeric mixtures are thus frequently obtained with many organometallic reagents, which makes this transformation particularly challenging (Table 2, entries i and ii). Regarding alkyl-metal reagents, high *syn*-selectivity can be reached using alkyl copper reagents, which is complementary to the titanium-based methodology 2 (Table 2, entries iii and iv). Interestingly, the corresponding $PhTi(O\text{-}iPr)_3$ furnishes the *syn* (*anti*-Felkin) product, but with lower selectivity. Moreover, the scope of the reaction is broad, and the use of various alkyl, phenyl, or vinyl-copper reagent gives constantly the corresponding *syn* isomers with diastereomeric ratios up to >99/1 (Table 2, entries v–vii). The nature of the solvent has a dramatic impact on the selectivity for both titanium and copper reagents, as illustrated in entries iv and vi. It is not clear if the solvent plays a role on the formation of a potential chelate or on the aggregation state of the organometallic reagents, or both.

The synthetic value of this methodology can be illustrated by the concise asymmetric total synthesis of (+)-goniopypyrone performed in eight steps with an overall yield of 20% by Zhou and coworkers[30] (Scheme 18) and the efficient preparation of D-lyxo-phytosphingosine[31] by Bonini and coworkers (Scheme 18).

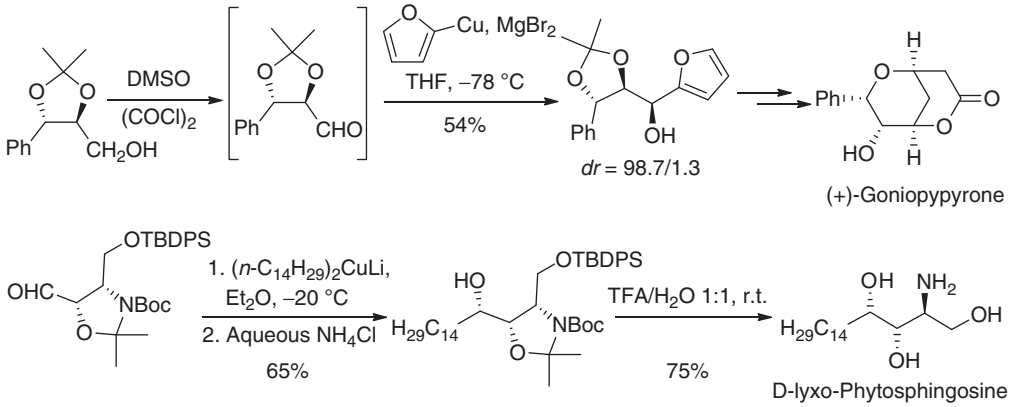
A more bulky relative of **38** in the form of bis(ketal) **39** has been proposed by Ley, and the addition of various methyl-metal reagents systematically studied.[32] As previously seen, organocopper reagents represent an interesting alternative to classical organometallics as Grignard or titanium species in terms of selectivity. As illustrated in Scheme 19, an *anti*-Felkin product is obtained using Me_2CuLi whereas the reverse selectivity is observed with $MeCu{\cdot}MgBr_2$. Although no simple explanation can be found to explain this result, it highlights the crucial importance of the nature of the organocopper reagent used and its counterion on the stereochemical outcome of the reaction.

Table 2 Addition of organometallic reagents to **38**

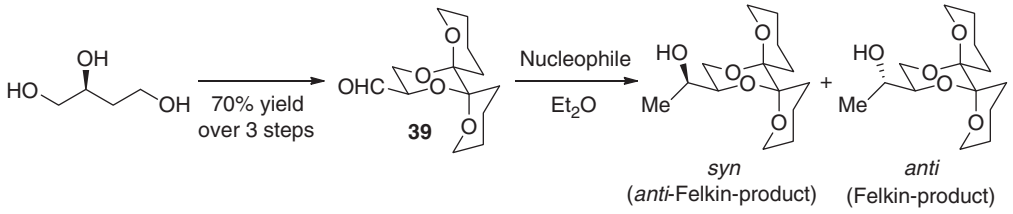


No.	*Nucleophile*	*Conditions*	*Yield (%)* (syn + anti)	syn/anti
i	$BuLi^n$	Et_2O, –78 °C	83	31/69
ii	Bu^nMgBr	Et_2O, –78 °C	86	25/75
iii	$Bu^nTi(Oi\text{-}Pr)_3$	Et_2O, r.t.	40	10/90
iv	$PhTi(Oi\text{-}Pr)_3$	THF, –78 °C	79	91/9[a]
v	$Bu^nCu{\cdot}MgBrI$	THF, –78 to 25 °C	75	94/6
vi	$PhCu{\cdot}MgBrI$	THF, –78 to 25 °C	91	>99/1[b]
vii	$CH_2CH(SiMe)_3Cu{\cdot}MgBrI$	THF, –78 to 25 °C	86	98/2

[a] *syn*/*anti* = 24/76 when the reaction is performed in Et_2O.
[b] *syn*/*anti* = 80/20 when the reaction is preformed in Et_2O/Me_2S.



Scheme 18



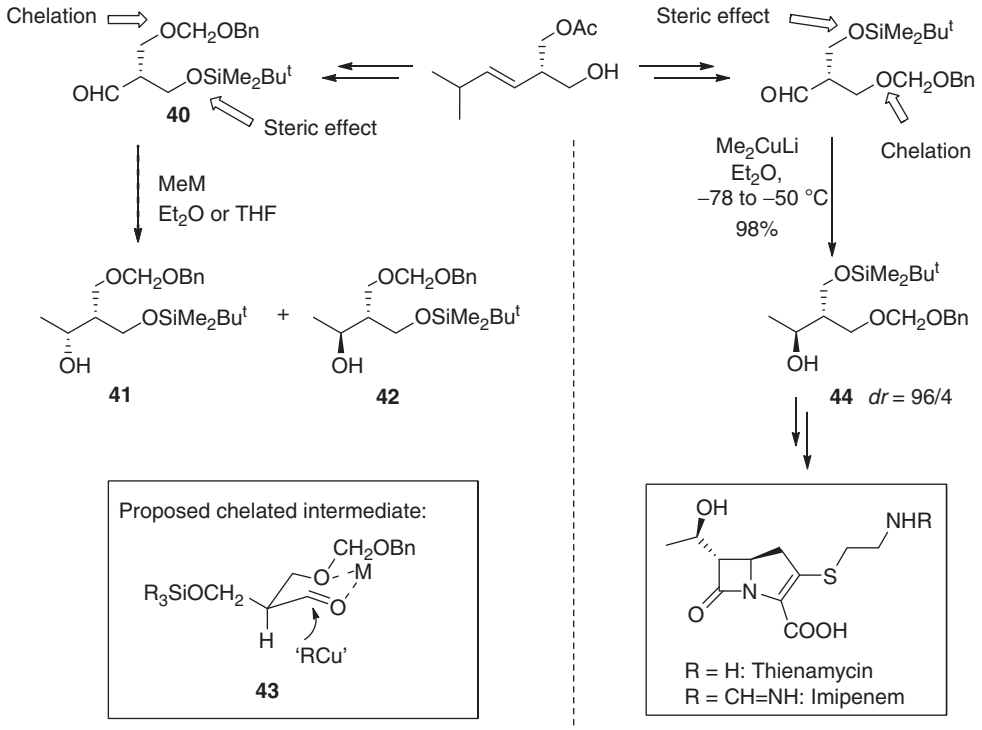
Nucleophile	Conditions	Yield (%) (*syn* + *anti*)	*syn*/*anti*
MeMgBr	THF, –78 °C	62	21/79
$MeTi(Oi\text{-}Pr)_3$	Et_2O, –40 °C	87	7/93
Me_2CuLi	Et_2O/Me_2S, –78 °C	69	88/12
$MeCu{\cdot}MgBr_2$	Et_2O/Me_2S, –78 °C	85	18/82

Scheme 19

1.04.2.2.2.5 Competitive 1,3 chelate controls

The stereochemical course of the addition of methyl-metal derivatives to aldehyde **40**, bearing two potential chelating oxygen atoms in β position, was examined by Guanti and coworkers (Scheme 20). To discriminate these two positions a judicious choice of chelating (OCH_2OBn) or nonchelating (SiR_3) protective groups was made. As shown in Table 3 methyllithium and

methyl-Grignard reagents were not selective. In contrast, a good control was observed with copper reagents, the more effective being Me_2CuLi, affording alcohols **41** and **42** in a 95/5 ratio.[33] A TS (**43**) involving a β-chelation was invoked to rationalize the observed selectivity. In contrast with the previous example, MeCu•MgBr and Me_2CuLi lead to the same stereoisomer (Felkin product) probably because here no competitive α-chelation can take place. An inversion of the two protecting groups allows the preparation of diastereomer **44**, which has been used as a key intermediate for the formal synthesis of thienamicyn and imipenem, two renowned members of the class of carbapenems, the third generation of β-lactam antibiotics (Scheme 20).[34]



Scheme 20

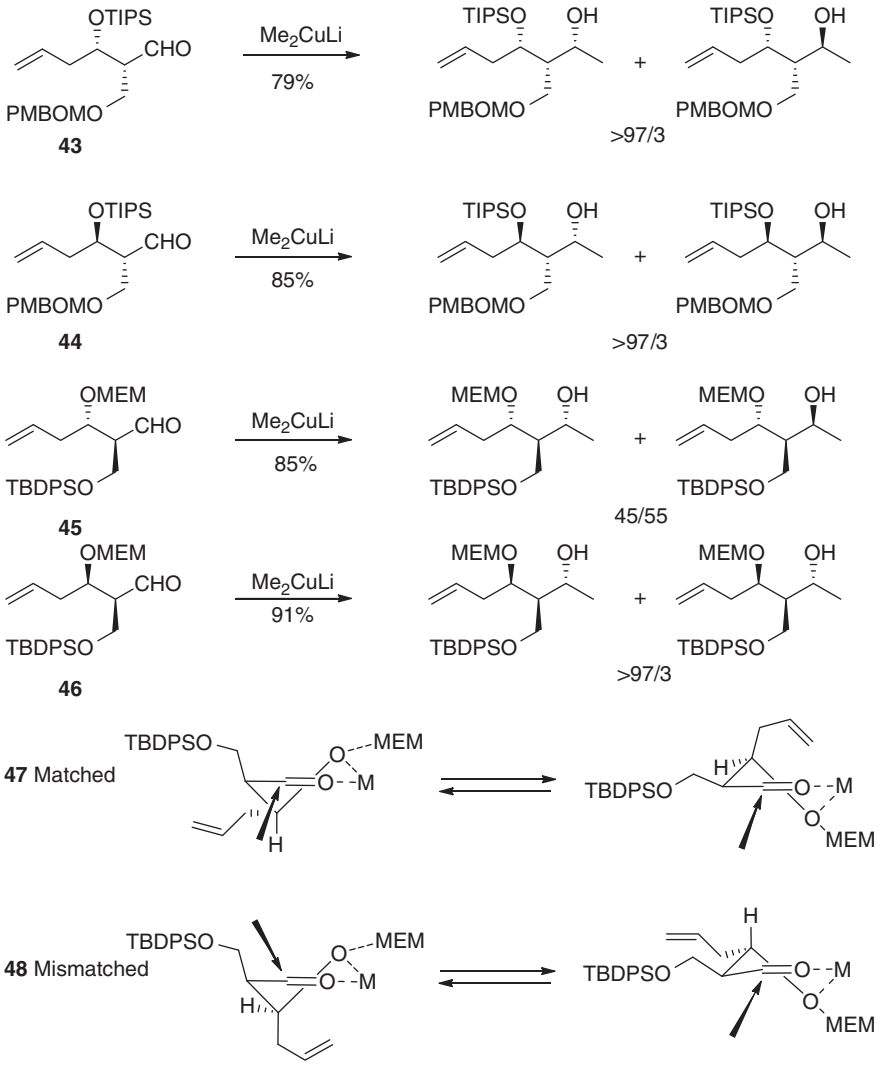
Table 3 Addition of organometallic reagents onto aldehyde **40** (Scheme 20)

No.	*MeM*	*Solvent*	*Temperature (°C)*	*Yield (%)*	***41/42***
i	MeLi	THF	–78	77	54/46
ii	MeLi	Et_2O	–78	79	52/48
iii	MeMgBr	Et_2O	–78 to –20	55	58/42
iv	MeMgI	Et_2O	–78 to –20	69	59/41
v	MeMgCl	THF	–78 to –20	61	57/43
vi	MeCu·$MgBr_2$	Et_2O/Me_2S	–78 to –25	53	82/18
vii	Me_2CuLi	Et_2O	–78 to –30	74	95/5

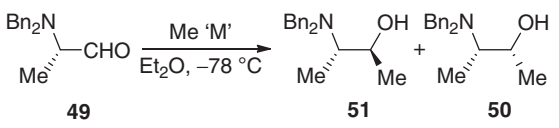
In a similar work, the addition of Me_2CuLi to diastereomeric aldehydes **43**, **44**, **45**, **46** (Scheme 21) was studied. Again a high stereoselectivity (>97/3) was obtained by tuning chelate and steric effects of protecting groups, except with aldehyde **45** (45/55). In the presence of a chelating protecting group on the primary alcohol, the addition is fully chelate controlled by the α-stereocenter without influence of the additional center in β-position. When the chelating group is on the secondary alcohol, the possibility of matched **47** (from **46**) or mismatched **48** (from **45**) chelate-transition states were postulated in order to explain the difference of diastereoselectivities observed with these aldehydes (Scheme 21).[35]

1.04.2.2.2.6 Aminoaldehydes

One of the main obstacles to the selective addition of organometallic reagents to aldehydes bearing an α-amino group is their possible racemization before reaction. This difficulty was overcome by Reetz with *N*,*N*-dibenzylamino aldehydes such as **49**. The addition of organocopper reagents to these aldehydes give mainly the nonchelate adduct **50** (equation 13) but the most effective was the titanium derivative (**51**/**50**=3/97).[36]



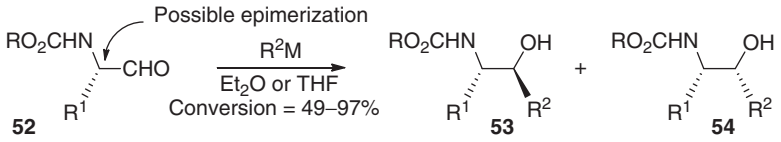
Scheme 21



Me 'M'	Yield (%)	**51/50**
MeMgI	87	5/95
$MeTi(OPr^i)_3$	78	3/97
Me_2CuLi	80	27/75

(13)

A change of the *N*-amino protecting group from *N*-dibenzyl in **49** to *N*-Boc or *N*-Cbz in **52** dramatically changes the stereochemical course of the reaction, affording the chelate adducts **53** without any epimerization in ether (equation 14). An excellent selectivity is generally achieved except for phenyl- (**53**/**54** = 69/31) or vinyl- (**53**/**54** = 80/20) copper reagents. Similar results were obtained with manganese reagents. In contrast, the selectivity with RLi or RMgX addition was poor.



R = Bu^t, $PhCH_2$
R^1 = Me, $PhCH_2$, Pr^iCH_2
R^2 = Me, Bu^n, Bu^t, CH_2=CH, CH_2=C(CH_3), Ph

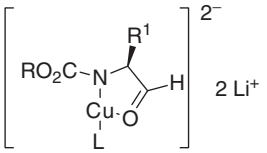
R^2M in Et_2O = $R^2{}_2CuLi$, $R^2{}_2CuCN{\cdot}Li$, 2LiCl
R^2M in THF = (R^2Li or R^2MgX)/MnX_2

'R^2Cu' in Et_2O :
53/**54** = from 69/31 to 96/4

(R^2Li or R^2MgX)/MnX_2 in THF:
53/**54** = from 66/34 to 96/4

(14)

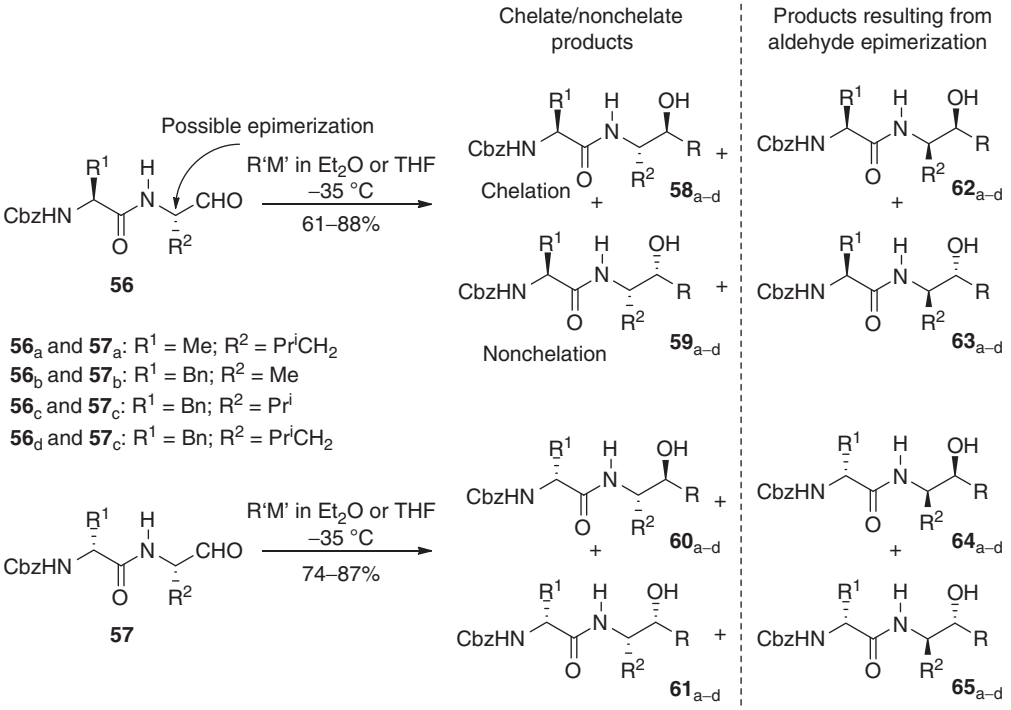
A mechanism involving a deprotonation of the NH-acidic position and the formation of a chelate complex **55** was postulated to account for the observed course of the addition of copper reagents.[37]



55

1.04.2.2.2.7 *Cooperative 1,2 plus 1,5 chelate controls*

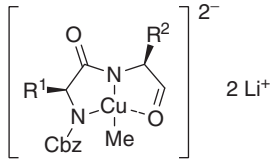
Such chelation control is also effective for the peptide aldehydes $\mathbf{56}_{a-d}$ and $\mathbf{57}_{a-d}$ irrespective of the relative configuration of the other stereogenic centers. Four diastereoisomers can theoretically be formed from each starting aldehydes. Two of them, $\mathbf{58}_{a-d}$, $\mathbf{59}_{a-d}$, and $\mathbf{60}_{a-d}$, $\mathbf{61}_{a-d}$ (from $\mathbf{56}_{a-d}$ and $\mathbf{57}_{a-d}$, respectively), would result from a nucleophilic addition onto double chelate such as **56**–2Li$^+$ and **57**–2Li$^+$, (Scheme 22) or nonchelate intermediates. The two other ones ($\mathbf{62}_{a-d}$, $\mathbf{63}_{a-d}$ and $\mathbf{64}_{a-d}$, $\mathbf{65}_{a-d}$) would be



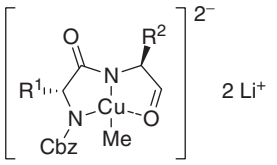
Aldehyde **56**	R'M'	**58/59/62/63**
a	MeMgI (Et_2O)	39/61/0/0
a	Me_2CuLi (THF)	>95/0/0/<5
b	"	93/3/0/4
c	"	99/1/0/0
d	"	89/2/0/9

Aldehyde **57**	R'M'	**60/61/64/65**
a	MeMgI (Et_2O)	42/30/17/11
a	Me_2CuLi (THF)	96/0/0/4
b	"	92/2/0/6
c	"	97/2/0/1
d	"	92/2/0/6

Proposed double chelate complexes:



Double chelate from **56**–2Li$^+$

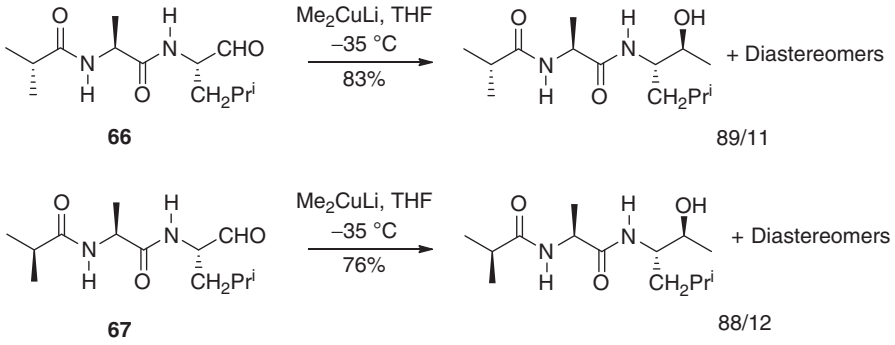


Double chelate from **57**–2Li$^+$

Scheme 22

obtained via the α-epimerization of the corresponding aldehyde in the reaction mixture before the addition of the organometallic reagent (Scheme 22). Using Me_2CuLi, the chelation-controlled products $\mathbf{58_{a-d}}$ and $\mathbf{60_{a-d}}$ were always the major ones (Scheme 22). Again the addition of the Grignard MeMgI was not selective.[38]

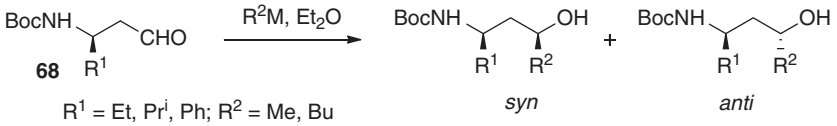
As expected, almost the same results were observed with the diastereomeric aldehydes **66** and **67** (Scheme 23).



Scheme 23

1.04.2.2.2.8 β-Aminoaldehydes

A chelation-controlled addition of Gilman reagents R_2CuLi,LiI to β-aminoaldehydes **68** in ether was described by Vaultier and coworkers[39] (equation 15, Table 4). The hypothesis of a chelated transition state was supported by the poor selectivity observed in THF (Table 4 entries i and ii). Remarkably, no selectivity was obtained with other organocopper derivatives (entries v–vii).



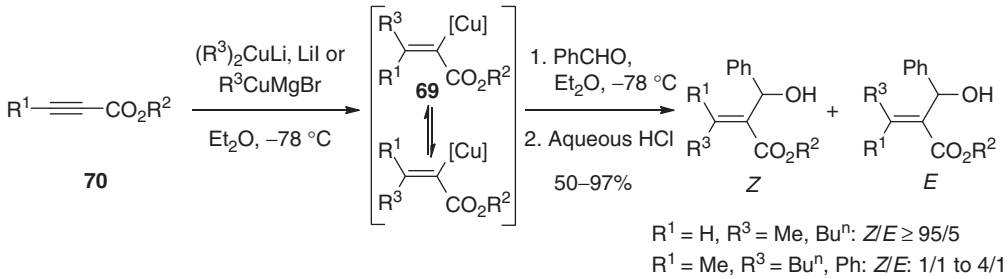
(15)

Table 4 Addition of organometallic reagents onto aldehyde **68** (equation **15**)

No.	*R^1*	*R^2M*	*Solvent*	*Temperature (°C)*	anti/syn	*Yield (%)*
i	Et	Me_2CuLi, LiI	Et_2O	–90	85/15	74
ii	Et	Me_2CuLi, LiI	THF	–85 to 0	53/47	–
iii	Et	Bu_2CuLi, LiI	Et_2O	–90	75/25	59
iv	Pr^i	Me_2CuLi, LiI	Et_2O	–90	82/18	76
v	Pr^i	Bu_2CuLi, LiI	Et_2O	–90	61/39	68
vi	Et	MeCu(CN), LiI	THF	–80	53/47	44
vii	Et	MeCu, MgBrI, SMe_2	Et_2O/SMe_2	–80	51/49	74

1.04.2.2.3 Copper enolates

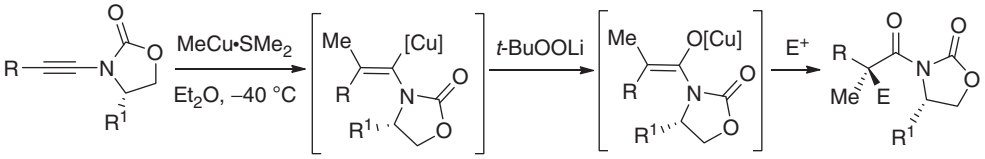
The organocopper reagents are commonly formed *in situ* by transmetalation of various organometallics such as organo-lithium, -magnesium, -zinc, -titanium, etc. or can result from a first copper-mediated transformation. This has been, for example, illustrated by Willis and coworkers, who showed that the vinylic copper enolate intermediate **69** stemming from the carbocupration of propiolates **70** add to aromatic aldehydes to give the allylic alcohols with good to excellent Z/E selectivity (Scheme 24).[40] In this



Scheme 24

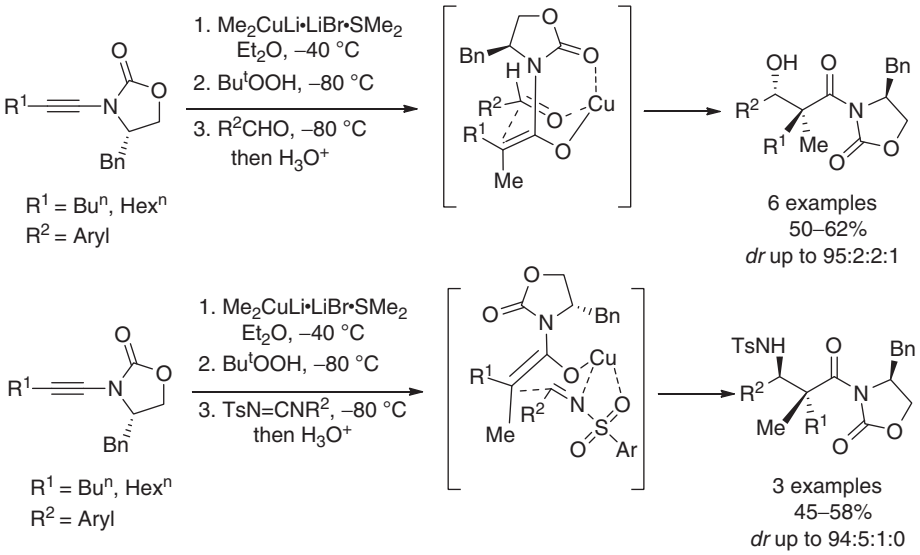
case, the excellent Z selectivity can be explained by a possible *cis*/*trans* equilibration, probably through a O-Cu enolate intermediate, before the addition. Enolate **69** is supposed to be the more reactive one for steric and kinetic reasons.

The carbocupration approach of alkyne derivatives has also recently been used for the stereoselective construction of copper enolates through an oxidation step (Scheme 25). The stereospecific oxidation, through a 1,2-metallate rearrangement, of the vinylcopper derivatives allows the access to a stereodefined copper enolate which is mandatory for a selective addition of an electrophile.[41]



Scheme 25

Starting from a chiral ynamide, Marek, and collaborators have described the enantioselective one-pot construction of all-carbon quaternary centers in aldol-type reactions. Thanks to highly the organized six-membered transition states, aldol and Mannich products are obtained from the corresponding aryl aldehydes and imines in good yields and excellent *dr* (Scheme 26).



Scheme 26

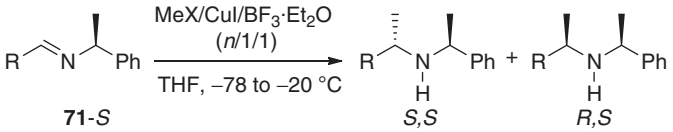
1.04.3 1,2 Addition to Imines and Derivatives

1.04.3.1 Imines

The addition of organometallic reagents to imines bearing hydrogen in β-position is challenging since the deprotonation leading to the corresponding metalloenamine might be competitive toward the addition. Thus, the low basicity of organocopper species makes them the reagents of choice for such transformations. However, imines are much less reactive than the carbonyl analogs, and the presence of a strong Lewis acid in the reaction mixture is often required. The use of $BF_3{\cdot}Et_2O$ as additive was first introduced by Akiba and coworkers. They showed that aliphatic copper reagents prepared *in situ* from RMgX, CuI, and $BF_3{\cdot}Et_2O$ (1/1/1 equivalent) and commonly described as copper–boron trifluoride complexes $RCu{\cdot}BF_3$[42] added cleanly on linear aldimines. Of note, a slightly lower yield was observed with RLi, RMgX, and RCu employed in the absence of $BF_3{\cdot}Et_2O$ failed to yield the desired products.[2] Owing to steric constraints, the case of branched aldimines is more challenging and it is crucial to switch to the Gilman complex R_2CuLi or R_2CuMgX in the presence of one equivalent of $BF_3{\cdot}Et_2O$. Unfortunately, ketimines proved to be unreactive whatever be the reaction conditions tried.[2]

A diastereoselective addition of methyl copper reagents to aldimines **71** carrying a stereogenic center on the nitrogen substituent (1,3-asymmetric induction) in the presence of $BF_3{\cdot}Et_2O$ was described by Savoia and Umani-Ronchi. In the case of aryl-derived aldimines, the methyl copper reagent was found to be somewhat more reactive and selective than its cuprate analog, and the nature of the counteranion, Li^+ versus $ClMg^+$, proved to be important. Indeed, the copper reagents prepared from MeLi are less reactive but more selective than those prepared from MeMgCl, despite the presence of $BF_3{\cdot}Et_2O$. The best balance between

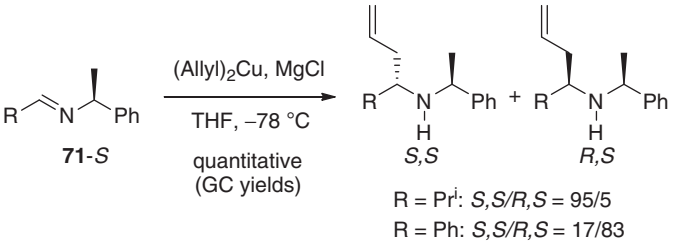
reactivity and selectivity was obtained using a 1/1/1 mixture of MeMgCl, CuI, and $BF_3{\cdot}Et_2O$. Interestingly, a reversed selectivity was observed for the imine in which R=Pent^n, and no reaction occurred for R=Bu^t (equation 16).[43]



R	MeX	(*n* equivalents)	Yield (%)	*SS/RS*
Ph	MeLi	1	43	94/6
"	MeMgCl	1	87	90/10
"	"	2	70	86/14
o-MeOPh	"	1	80	73/27
n-C_5H_{11}	"	2	80	15/85
Bu^t	"	2	0	–

(16)

This transformation has been successfully extended to allyl copper reagents. As for their aliphatic analogs, a reverse selectivity was observed when switching from aliphatic to aromatic. It is noteworthy that in this case no additive is required to reach high product yields due to the higher reactivity of this class of reagents (equation 17).[44]



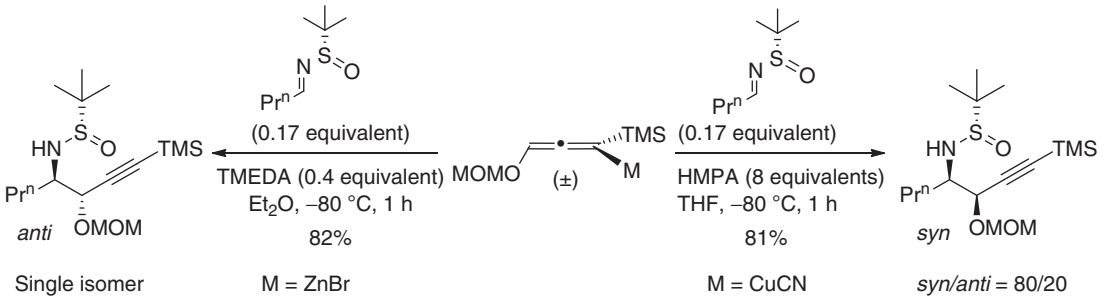
(17)

More recently Chemla, Ferreira, Pérez-Luna, and coworkers disclosed the stereoselective addition of racemic heteroallenyl metals onto enantiopure sulfinylimines through a kinetic resolution process.[45] The allenyl zinc and the allenyl cyano- or mesitylcuprates proved to be complementary, giving access respectively to the corresponding *anti*- and *syn*-1,2-amino alcohols with generally high diastereomeric ratios (Scheme 27). An optimization of the reaction conditions showed that higher levels of selectivities are observed in Et_2O for the use of the allenyl zinc reagent whereas a mixture of THF-HMPA is required with the allenyl cuprates. The allenyl metal/imine ratio is also crucial, and the best results are obtained for the use of 4–6 equivalents of the organometallic reagent. Indeed, the Hoffman test performed upon the allenyl cyanocuprate reagent demonstrated its configurational stability toward this electrophile under these reaction conditions, which ruled out the development of a kinetic dynamic resolution procedure. A fully chelated model was proposed in the case of the allenyl zinc reagent to rationalize the *anti*-selectivity. In contrast, a synclinal approach is proposed to explain the *syn*-selectivity in the case of allenyl cyanocuprates as the presence of HMPA and the low Lewis acidity of the metalate center should prevent the formation of any chelated intermediates (Figure 1).[45a] This methodology has been successfully applied to the synthesis of the (−)-swainsonine and the (−)-8-*epi*-swainsonine in which the key steps are, respectively, the addition of allenyl zinc or allenyl cyanocuprates reagents onto enantiopure functionalized α,β-dialkoxy *N-tert*-butanesulfinimines (Scheme 26).[45b]

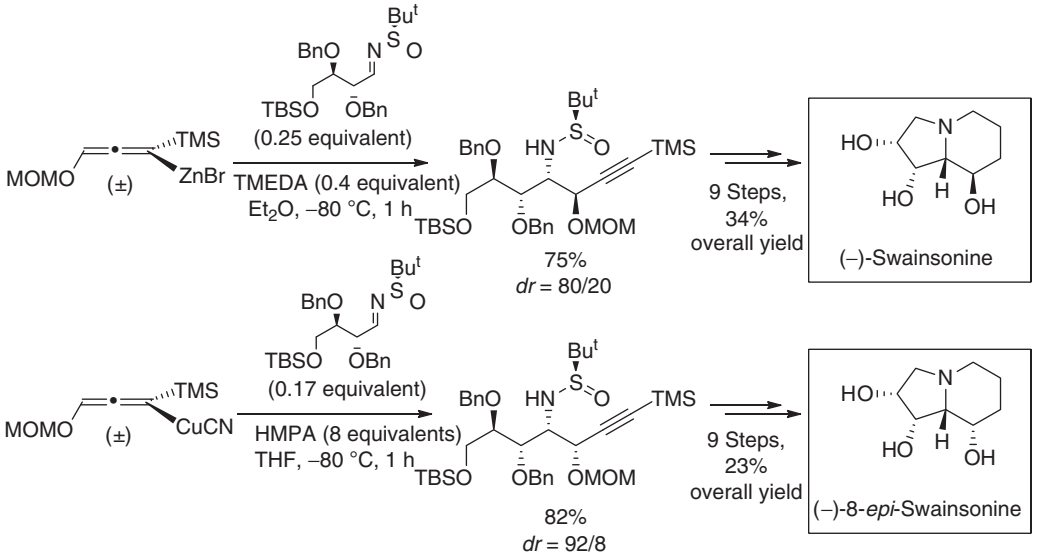
Akiba and coworkers studied the addition of various organometallic reagents to a α-silyloxyaldimine **72**. Several 1/1 complexes between organocopper RCuLi or organocuprate $R_2CuLi{\cdot}LiI$ and $BF_3{\bullet}Et_2O$ were tested (Scheme 28). For all of them a good to excellent *anti*-selectivity was observed to give amino alcohols **73**. In comparison the *syn* isomer **74** was mainly obtained with organolithium derivatives through a chelate TS, whereas a Felkin–Ahn model was proposed for the addition of the copper reagents.[46]

1.04.3.2 *N*-acyliminium

To overcome the poor reactivity of imines, it is possible to use iminium salts. One of the most popular ways to introduce a substituent in α-position of an amine is the nucleophilic addition to *N*-acyliminiums ions. Since the pionering work of Wistrand,[47] these species have received considerable attention.[48] Hemiaminal **75**, precursor of *N*-acyliminium ion **76** (Scheme 29), is quantitatively obtained from the corresponding lactam **77** by a two-step procedure (reduction and methylation) and is used without any purification. The presence of a Lewis acid such as BF_3 is needed when copper reagents obtained from either the corresponding organolithiums or magnesiums and $CuX{\cdot}Me_2S$ are used.



Example of application: concise synthesis of the (–)-swainsonine and the (–)-8-epi-swainsonine:



Scheme 27

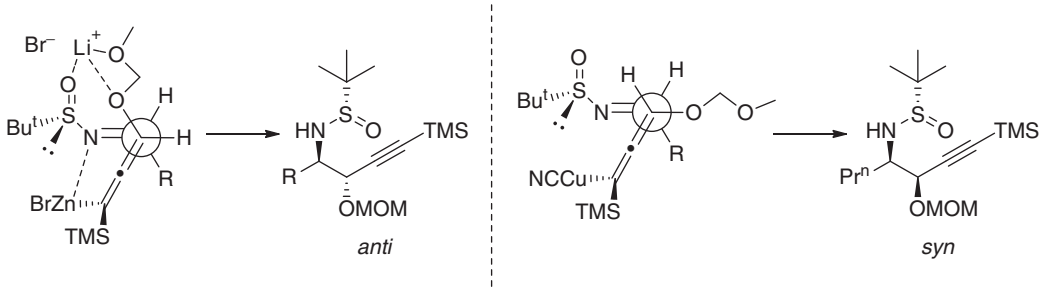
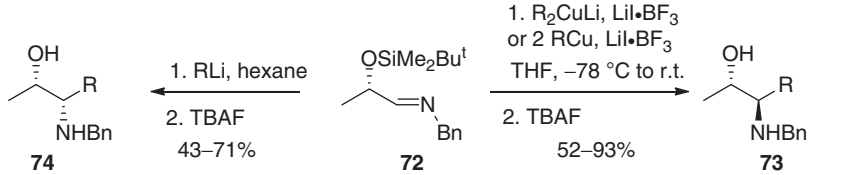
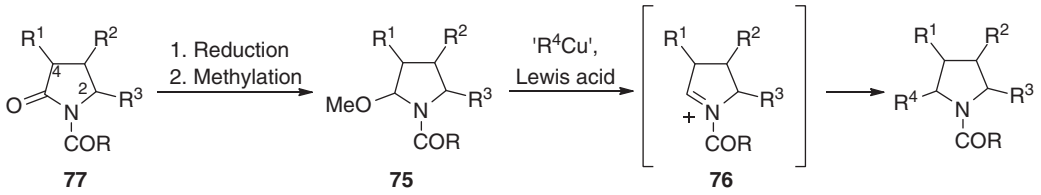


Figure 1 Chelated and synclinal models in asymmetric zinc vs. copper-mediated propargylation.

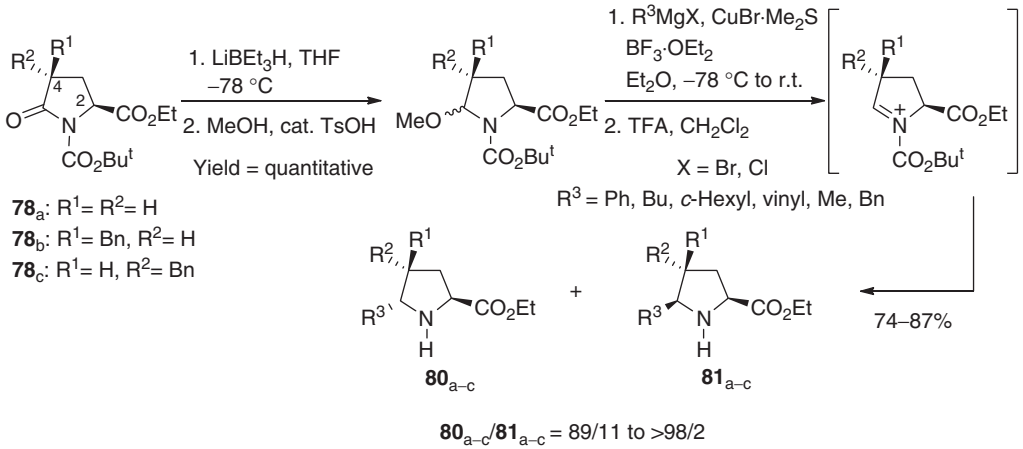


Scheme 28



Scheme 29

The stereochemical outcome of the reaction is mainly influenced by the substituent in the 2-position. In the presence of an ester group at the C_2 position (iminiums derived from $\mathbf{78}_{a-c}$, Scheme 30) the organocopper attacks the postulated copper complexes $\mathbf{79}_{a-c}$ at the opposite side of the ester group whatever be the relative configuration of the C_4 substituent (*cis* in $\mathbf{79}_b$ and *trans* in $\mathbf{79}_c$). Indeed, the same sense of selectivity ($\mathbf{80}_{a-c}/\mathbf{81}_{a-c}$ up to >98/2) is achieved for all three iminiums despite the possibility of matched or mismatched cases (Figure 2).[49]



Scheme 30

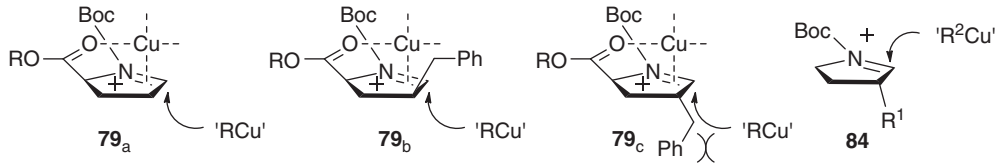


Figure 2 Diastereoselectivity models in organocopper addition onto iminiums.

In contrast, in the absence of an ester group at C_2, as in **82** (Scheme 31), the stereoselectivity is purely sterically controlled by the substituents at C_3, affording mainly the *trans* isomer **83** according to model **84** (Scheme 31 and Figure 2).[50]

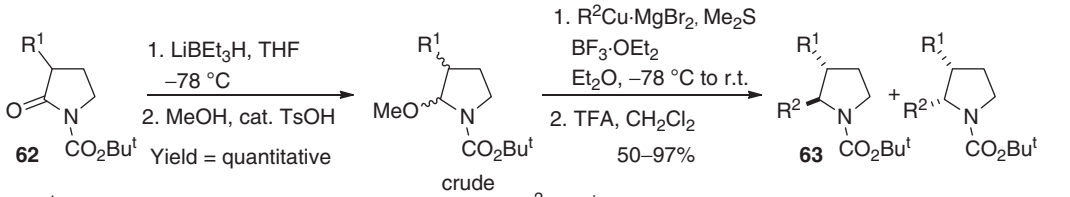
Owing to its efficiency, this methodology has been applied to the synthesis of valuable scaffolds or drugs such as functionalized indolizidinones **85**.[51] For more complex structures, such as precursors of substituted kainic acids **86**, the steric constraints are dominating and the *cis*-isomer is mainly formed[52] (Scheme 32).

1.04.4 Catalytic and Asymmetric Copper-Mediated Reactions

1.04.4.1 Catalytic and Asymmetric Addition of sp^3 Nucleophiles to C═O and C═N Bonds

1.04.4.1.1 Aliphatic nucleophiles

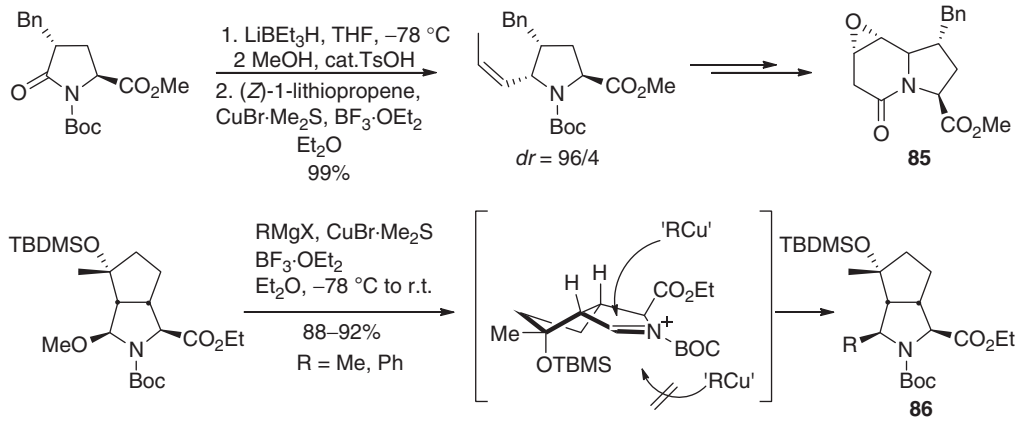
Organocopper reagents are especially used with aldehydes and ketones for conjugate addition. The catalytic asymmetric version of this reaction has been the subject of intense work. The catalyzed enantioselective 1,2-addition has also been extensively studied particularly with the use of organozinc reagents. In contrast, catalytic enantioselective 1,2-additions of inexpensive, readily accessible and reactive Grignard reagents are rare. This copper-catalyzed possibility was studied by Harutyunyan in 2012 as a route to synthetically useful enantiomerically enriched allylic alcohols starting from α-substituted α,β-unsaturated ketones. It was observed that regio- and enantioselectivities were dependent on several factors including the presence of an α-substituent, the



R^1	R^2	*trans*/*cis*
Me	Bu^i	60/40
Me	Ph	88/12
Me	*p*-F-C_6H_5	87/13
Me	*p*-tolyl	88/12

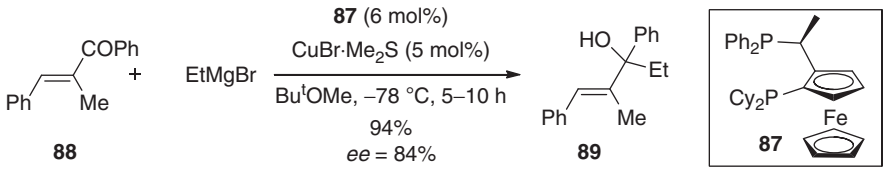
R^1	R^2	*trans*/*cis*
Ph	Bu^i	74/26
Ph	Ph	91/9
Ph	*p*-F-C_6H_5	88/12

Scheme 31



Scheme 32

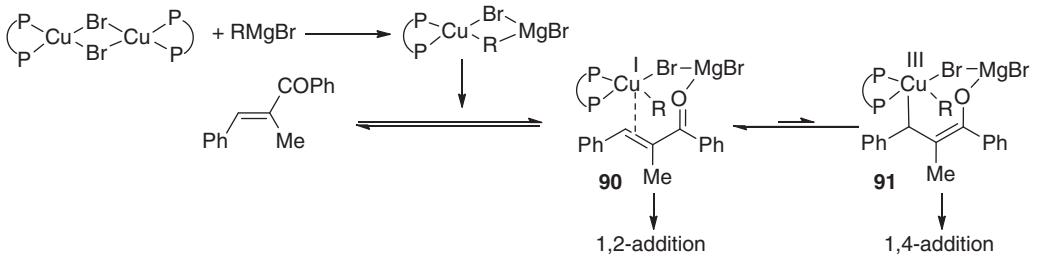
necessary presence of the ligand, the nature of the copper salt, and the nature of the solvent. The best results were obtained with CuBr·Me_2S and ligand **87** in Bu^tOMe as solvent (equation 18). An illustrative example of the addition of EtMgBr to ketone **88** is shown: in the presence of a ferrocenyl-based diphosphine ligand, an *ee* = 84% is achieved for the allylic alcohol **89**. It is noteworthy that the use of Me- or PhMgBr did not give satisfactory results.[53]



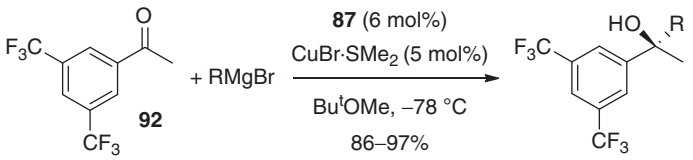
(18)

Interestingly, the unsaturation is also important for enantioselectivity. Indeed, the use of aliphatic ketones afforded the corresponding alcohols in low yield and no selectivity. These observations support the hypothesis that the reaction follows the classical preliminary steps of the conjugate addition until the formation of the π-Cu^I-complex **90**. At this stage, the presence of the α-substituent would disfavor the formation of the σ-Cu^{III}-complex **91**, thus favoring 1,2-addition (**Scheme 33**).

The same procedure has been extended to variously substituted aryl–alkyl ketones (among the 20 ketones tested, only **92** is shown in equation 19). The influence of the substituents on enantioselectivity was not clear, but generally good results were reached (*ee* from 54 to 98% using 2-ethylbutylmagnesium bromide). The nature of the Grignard reagents was found to be crucial as only bulky reagents led to high selectivity (*ee* = 22% with EtMgBr and 98% with *c*-hexyl$(CH_2)_2$MgBr).[54]



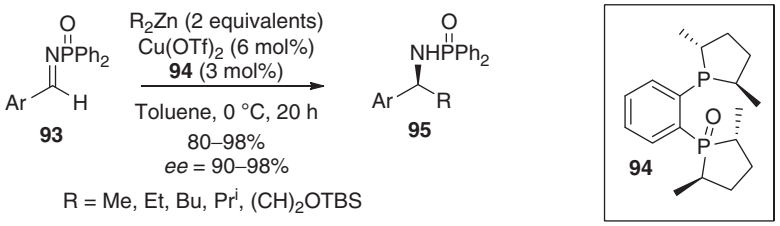
Scheme 33



R	*ee* (%)
Et	22
CH_2=$CH(CH_2)_2$	44
$Ph(CH_2)_2$	68
Pr^iCH_2	95
c-hexyl$(CH_2)_2$	98
Me_3SiCH_2	74

(19)

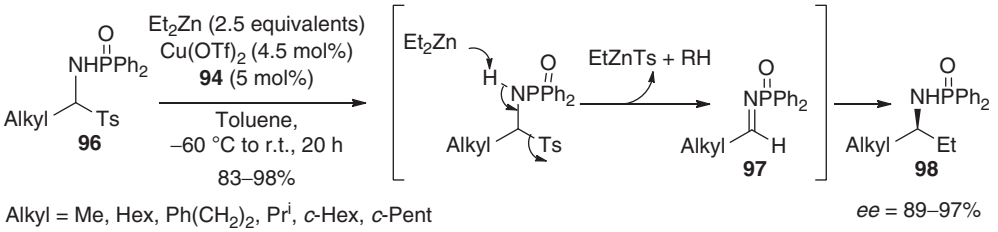
Some attempts to develop asymmetric and catalytic additions of aliphatic nucleophiles onto imines derivatives have been developed by Charette in a copper-catalyzed addition of diethyl zinc to the poorly reactive *N*-phosphinoylaldimines **93** (equation 20). The advantage of such *N*-protected imines is the easy cleavage of the protecting group. The success of this method depends on the use of the strongly donating bidentate ligand **94**, which contains a hemilabile group and increases the nucleophilicity of the organometallic reagent. A total of 14 aryl imines were tested and excellent selectivities were observed (*ee* up to 98% for **95**).[55]



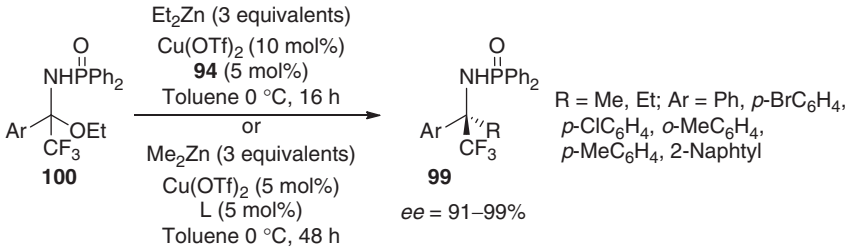
(20)

Alkyl-substituted phosphinoylimines are compatible with this reaction but are not easy to handle due to their moisture sensitivity. Furthermore, they are in equilibrium with the corresponding enamine. These difficulties were overcome using easily available sulfinic acid precursors **96** (Scheme 34) which gave, in the presence of the zinc reagent, the intermediate imine **97**. After addition of the copper reagent, the corresponding amines **98** were obtained in good yields and enantioselectivities (Scheme 34).[56]

A similar procedure has been used for the enantioselective preparation of α,α',α''-trisubstituted trifluoromethyl amines **99** (*ee* up to 99%, equation 21). In this case, the ketimine precursor is a stable, isolable, and easily prepared hemiaminal **100**.[57]



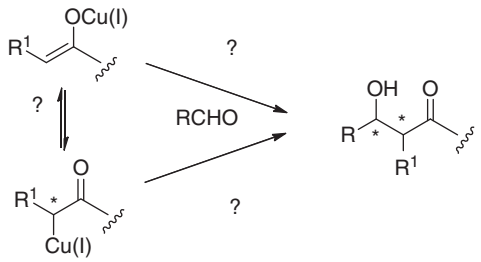
Scheme 34



(21)

1.04.4.1.2 Enolate nucleophiles

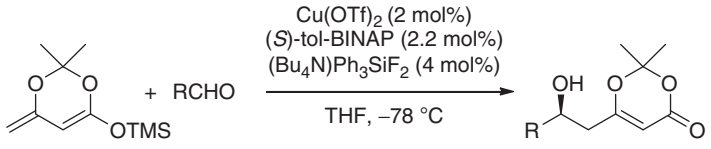
The use of copper enolates has emerged at the outset of this century as an efficient tool for the catalytic and enantioselective construction of aldol (Mannich)-type moieties (*see* Chapter 2.10 for an overview on metal enolate chemistry). At this stage, it should be emphasized that little is known about the structure of these soft metal enolates. Indeed, these species can either exist as O- and/or C-enolates, or in tautomeric equilibrium between these two forms (**Scheme 35**).[58] Moreover, if relevant, the presence of a C-bonded enolate would possess a stereogenic center, which could conceivably impact the organization of the transition state. Finally, in the presence of other metal salts sources, the transmetallation of the copper enolate could also occur, as observed, for example, in the copper-catalyzed 1,4-addition of organometallic species to enones.[59] In Section 1.04.4.1.2, examples in which copper enolates are believed to be the key catalytic species will be described. Various strategies have been employed to catalytically generate these copper enolates using either Mukaiyama (and vinylogous Mukaiyama) aldol, reductive aldol, alkylative aldol, and more recently decarboxylative and direct aldol strategies. Reactions involving Cu(II) species as Lewis acids in aldol reactions (i.e., a copper–carbon bond is not created) are beyond the scope of this chapter and will not be thus covered.



Scheme 35

1.04.4.1.3 Mukaiyama and vinylogous Mukaiyama-type reactions

The use of copper enolates in Mukaiyama-aldol reactions was first investigated in 1998 by Carreira in the vinylogous aldol reaction of 1,3-dioxin-4-one derived silyl dienolate **101** with aldehydes, in the presence of copper triflate and of a fluoride source.[60,61] The formation of a copper(I) dienolate intermediate could be confirmed by *in situ* IR experimental studies.[62] High yields and enantioselectivities have been observed for aromatic, heteroaromatic, and olefinic aldehydes whereas lower yields are obtained with aliphatic ones (equation 22).[62]

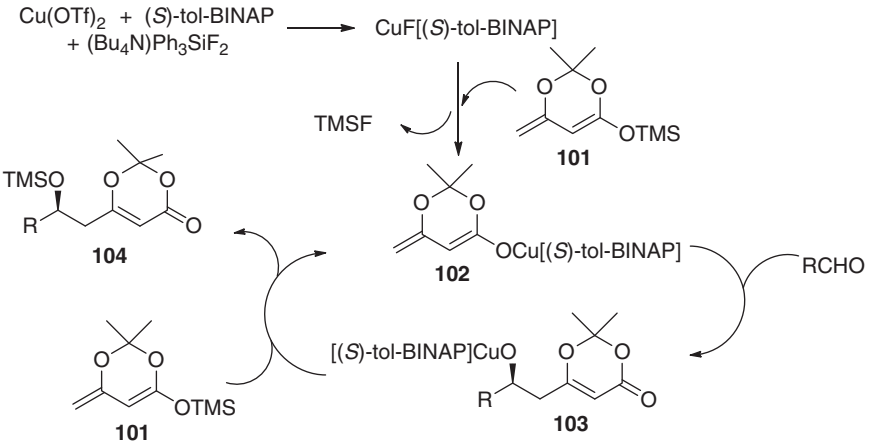


R	Yield (%)	*ee* (%)
Ph	92	94
β-Napthyl	86	93
2-Thienyl	98	95
Cinnamyl	83	85
Crotyl	48	91

(22)

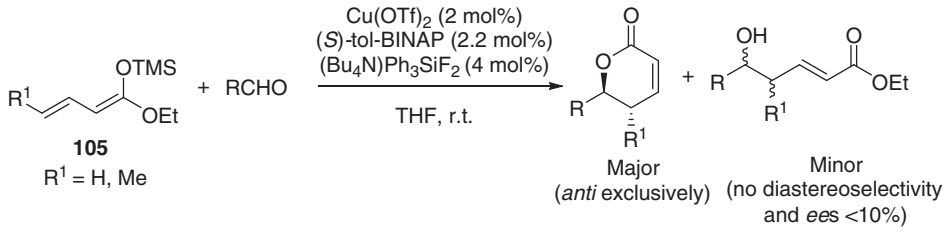
These reactions have met with great success in the total syntheses (and approaches to) of various natural products such as leucascandrolide A, salicylihalamide A, amphotericin, and a subunit of streptogramin.[63–66] The mechanism is believed to proceed first through the formation of a CuF(tol-BINAP) precatalyst that is then able to react with the silyl dienolate **101** to form a copper dienolate **102** (observed by IR), which is actually the catalytic species. The copper dienolate is then trapped by the aldehyde to

form a copper alkoxide **103** (also observed by IR). The last step of the catalytic cycle is the regeneration of the copper dienolate from the σ-bond metathesis of the copper alkoxide with silyl dienolate **101** and the concomitant formation of the TMS-protected vinylogous aldol product **104** (Scheme 36).



Scheme 36

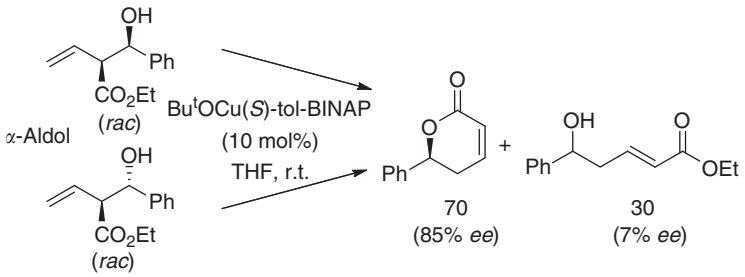
When these catalytic conditions were applied to noncyclic, and less nucleophilic, silyl dienolates of type **105**, a mixture of lactones and 'linear' vinylogous aldol products was obtained. Although lactones are usually obtained in high diastereo- and good enantioselectivities, the linear products are obtained with no diastereoselectivity nor enantioselectivity (equation 23).[67–69]



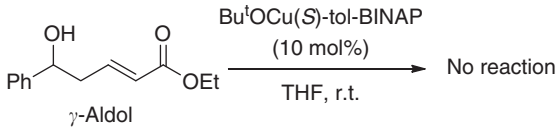
(23)

R^1	RCHO	Yield δ-Lactone (%)	δ-Lactone /linear	*ee* δ-Lactone (%)
Me	Benzaldehyde	73	86/14	87
Me	2-Naphthaldehyde	76	80/20	85
Me	Isobutyraldehyde	61	64/36	91
H	Benzaldehyde	72	90/10	85
H	2-Naphthaldehyde	8	90/10	75
H	Isobutyraldehyde	65	75/25	85

Interestingly, it has been found that the *anti*-stereochemical outcome of the reaction is independent of the dienolate (**105**) double-bond geometries.[69] Moreover, it has also been shown that both racemic *syn* and *anti* α-aldol products could, in the presence of the catalyst, rearrange to give the same mixture of enantioenriched lactone and nearly racemic linear γ-aldol product (equation 24). In the same reaction conditions, the linear γ-aldol product remained unchanged (equation 25). These reactions might thus proceed through a reversible non selective α-aldolization followed by an irreversible γ-aldolization.[69] This methodology has been applied to the syntheses of the Prelog-Djerassi lactone,[68] disorazole,[70] the three main fragments of discodermolide,[71] and C1–C12 fragment[72] of iriometeolide.

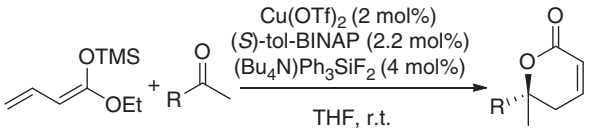


(24)



(25)

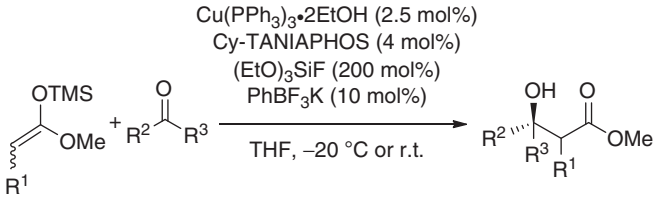
These catalytic conditions have then successfully been extended to methyl ketones (equation 26) and further applied to a formal synthesis of taurospongin A.[73]

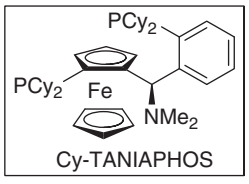


R	Yield δ–Lactone (%)	*ee* (%)
Ph	71	80
p-BrPh	58	81
$PhCH_2CH_2$-	70	87
CH_2=CH-CH_2CH_2-	81	90
Pr^iCH_2-	40	93

(26)

Nonvinylogous Mukaiyama-aldol reactions involving a copper enolate have been investigated by the Shibasaki group.[74–77] Simple silyl ketene acetals react with ketones to give aldol products in very good yields, diastereo- and enantioselectivities (equation 27). The best catalytic system was found to be $CuF(PPh_3)_3{\cdot}2EtOH$/Cy-taniaphos, in the presence of $(EtO)_3SiF$ (200 mol%) and $PhBF_3K$ (10 mol%). It should be emphasized that the diastereoselectivty outcome is independent of the *E*/*Z* ratio of the starting silyl enolate.



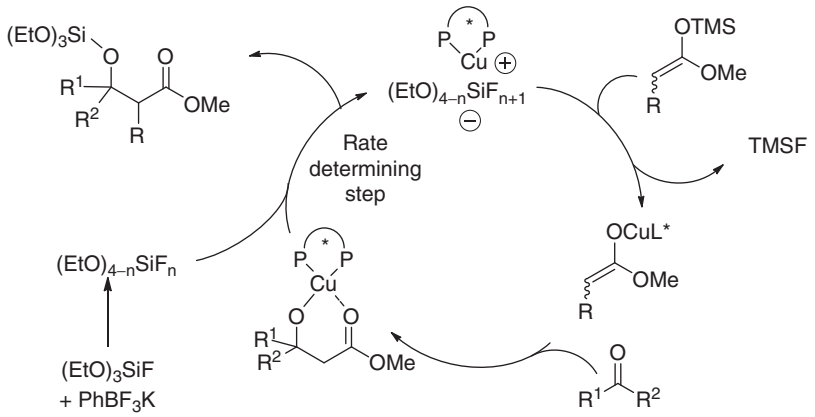


R^1	R^2	R^3	Yield (%)	*dr*	*ee* (%)
H	Ph	Me	93	–	92
H	*p*-MeOPh	Me	95	–	91
H	2-furyl	Me	88	–	83
H	Pr^iCH_2-	Me	73	–	84
H	Ph	Et	89	–	78
Me	Ph	Me	96	80/20	91
Bu^n	Ph	Me	97	86/14	91

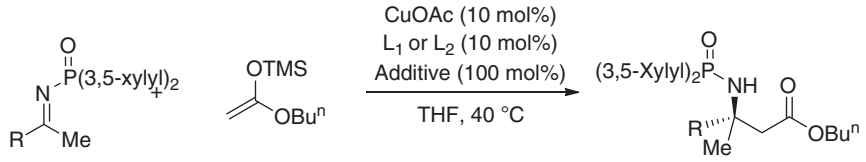
(27)

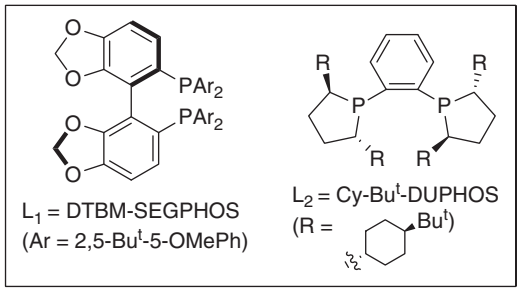
According to the researchers, as illustrated in **Scheme 37**, the rate-determining step is the regeneration of the copper(I) catalyst from the copper aldolate. In the presence of $PhBF_3K$, more electrophilic species ($EtO_{4-n}SiF_n$) are produced maximizing the catalytic cycle efficiency. Indeed in the absence of $PhBF_3K$, enantioselectivty remains unchanged whereas lower yields are observed.

Catalytic enantioselective Mannich-type reactions of ketene silyl acetals with ketoimines were next successfully achieved. Once again, the key to success was the choice of an efficient silylating group transfer. With aromatic ketimines, easily accessible $(EtO)_2Si(OAc)_2$ proved to be a very efficient trapping agent, whereas with more sensitive aliphatic ketoimines the use of the more electrophilic $(EtO)_3SiF$ species is required to obtain useful yields (equation 28).



Scheme 37



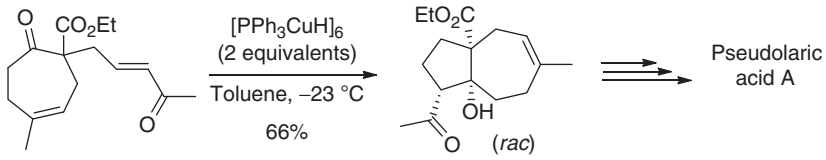


R	Additive	L	Yield (%)	*ee* (%)
Ph	$(EtO)_2Si(OAc)_2$	L_1	81	95
p-MeOPh	"	L_1	87	97
2-Furyl	"	L_1	87	97
Cy	$(EtO)_3SiF$	L_2	81	75
Pr^n-CH=CH-	"	L_2	65	77
	"	L_2	99	81

(28)

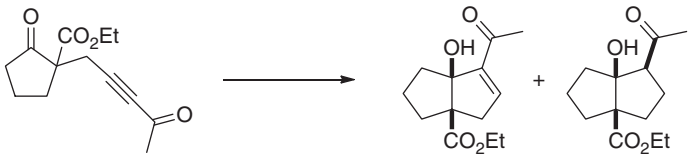
1.04.4.1.4 Reductive aldol strategies

Reductive aldol strategies have seminally been explored by Chiu in an approach to the synthesis of pseudolaric acid A,[78] using the Stryker reagent $[PPh_3CuH]_6$.[79] The bicyclic core of the natural product was obtained in good diastereoselectivity and 66% yield using two equivalents of Stryker's reagent at −23 °C (Scheme 38).[80] Intramolecular reductive nitroaldol reactions have then been developed.[81]



Scheme 38

A catalytic-in-copper version of this reaction was next reported by Chiu where Stryker's reagent (10 mol%) was used in the presence of a stoichiometric amount of the polymeric hydrosiloxane polymethylhydrosiloxane (PMHS), as the hydride source. With alkynones, good diastereoselectivities and comparable yields are usually reached but byproducts resulting from over-reduction and/or dehydration are frequently observed (equation 29).

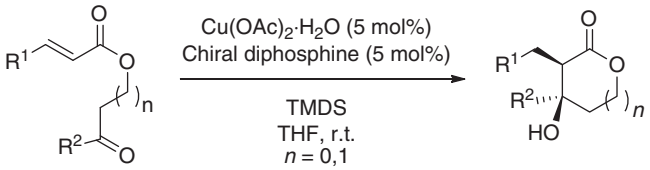


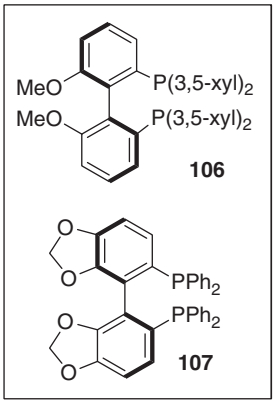
$[PPh_3CuH]_6$ (10 mol%) PMHS (2 equivalents) 58% 39%

$[PPh_3CuH]_6$ (1.5 equivalents) 54% 13%

(29)

In 2005, Lam has reexplored these intramolecular reductive aldol reactions by screening various copper sources in the presence of biphosphine ligands and 1,1,3,3-tetramethylsiloxane (TMDS) as the stoichiometric hydride source, ultimately leading to catalytic and enantioselective intramolecular reactions (equation 30) in the presence of diphosphine ligands such as biphenyl phosphine or 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole (SEGPHOS) derivatives **106** and **107**.[82]

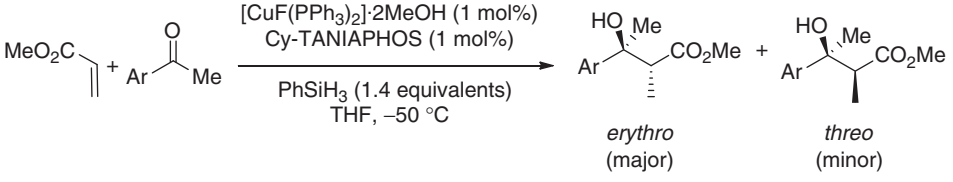


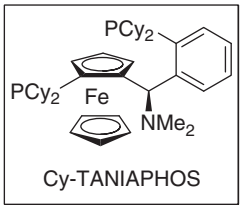


L	*n*	R^1	R^2	Yield (%)	*ee* (%)
106	1	Ph	Me	69	70
106	1	*p*-ClPh	Me	71	80
106	1	$PhCH_2CH_2$	Me	61	83
106	0	$PhCH_2CH_2$	Ph	51	49
107	1	Ph	Me	62	74
107	1	*p*-ClPh	Me	73	82
107	1	$PhCH_2CH_2$	Me	68	80

(30)

In 2006, Riant reported the first copper-catalyzed enantioselective intermolecular aldol reactions between methyl acrylate and aromatic ketones in the presence of [CuF(PPh3)2•2MeOH]/Cy-TANIAPHOS (1 mol% loading) and $PhSiH_3$ as the hydride source (equation 31). Excellent yields, diastereo- and enantioselectivities could be observed using low catalyst loadings (1 mol%).[83]

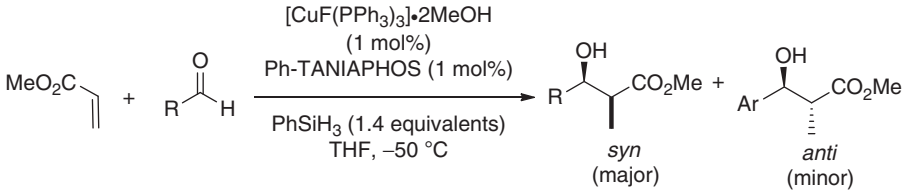




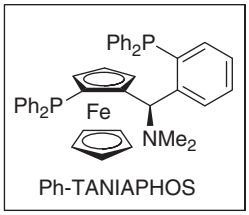
Ar	Yield (%)	*dr*	*ee erythro* (%)
Ph	98	92/8	95
p-$CF_3C_6H_4$	89	80/20	83
p-$MeOC_6H_4$	31	92/8	90
2-Thienyl	94	69/4	90
3-Thienyl	95	95/5	95

(31)

The use of aldehydes as electrophiles was next studied by Riant and in this case, Ph-Taniaphos proved to be the best ligand, but moderate *syn*/*anti* diastereoselectivities are usually observed.[84] The reaction could be extended to nonaromatic aldehydes as illustrated in equation 32.

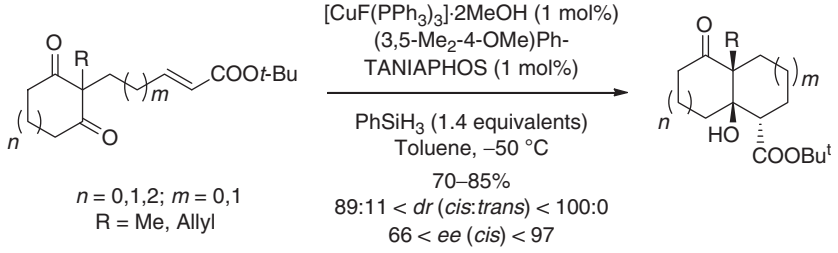


Ar	Yield (%)	*dr*	*ee syn* (%)
Pr^i	99	64/36	73
Cy	99	57/43	86
Bu^t	77	76/24	0
Ph	95	41/58	nd
p-CF_3Ph	74	47/53	84
p-MeOPh	95	60/40	68
2-Thienyl	95	67/33	83
2-Pyridyl	82	67/33	34

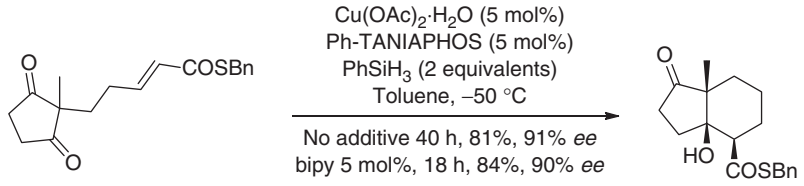


(32)

In parallel to Riant's work, Shibasaki and Kanai have developed an alternative catalytic system using tol-BINAP as ligand and $(EtO)_3SiH$ as the hydride source. If low *ee*s were usually observed with aromatic ketones (30% *ee* with acetophenone), the catalytic system proved efficient with symmetric ones leading to aldol products in good enantioselectivities.[85] This strategy has thus been used in desymmetrizing reductive aldol cyclizations where various five- and six-membered bicyclic compounds have been obtained in very good diastereo- and enantioselectivities (equation 33).[86,87] Related studies have then been described by Chiu, unveiling the beneficial role of a cocatalyst such as bipy to accelerate the reaction (equation 34).[88]



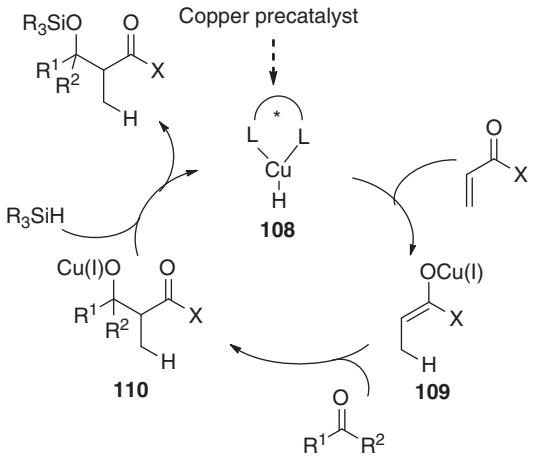
(33)



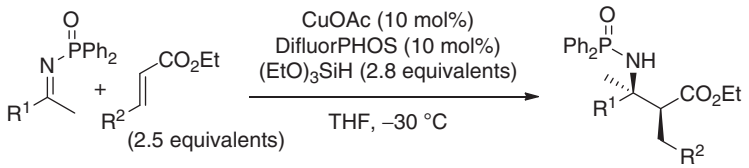
(34)

The catalytic cycle of the reactions is believed to proceed through the initial formation of a copper(I) hydride species **108**,[89,90] which is then able to react with the Michael acceptor to form copper enolate **109**. This copper enolate is in turn trapped by the electrophile to form copper alcoholate **110** that finally reacts with the silane source to regenerate the copper hydride species and furnish the silylated aldol product (**Scheme 39**).

Finally, catalytic and enantioselective reductive Mannich reactions on ketimines have been described by the Shibasaki group (equation 35).[91]



Scheme 39

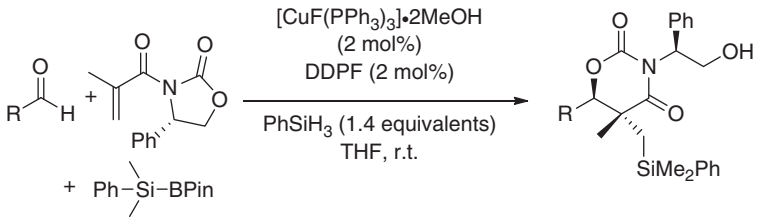


(35)

R^1	R^2	Yield (%)	*dr*	*ee* (%)
Ph	H	95	9/1	85
2-Naphthyl	H	88	3/1	86
1-Cyclohexenyl	H	90	9/1	91
p-Cl-Ph	Me	96	5/1	82
p-Cl-Ph	CO_2Et	65	17/1	82

1.04.4.1.5 Extension to alkylative, silylative, and borylative aldol strategies

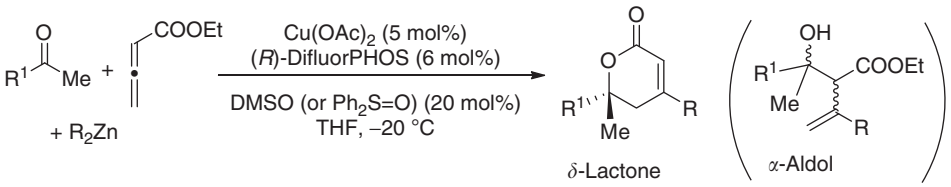
These reductive aldol processes have then been extended to alternative nucleophile species by the groups of Shibasaki and Riant. The use of borosilanes in silylative aldol reactions between chiral enoyloxazolidinones and aldehydes led to good yields and high diastereoselectivities. When extended to methacryloyloxazolidinones, the corresponding aldol product bearing a quaternary carbon was created in good yields and selectivities but the expected aldol product has undergone a rearrangement through an intramolecular oxazolidone ring opening (equation 36).[92] Finally starting from bis-(pinacolato)-diboron (pinB-Bpin), borylated aldol products have been obtained with moderate selectivities.[93]



(36)

R	Yield (%)	*dr*
Ph	90	>95/5
p-CNC_6H_4	59	87/13
p-$MeOC_6H_4$	69	88/12
2-Thienyl	74	78/22
2-Furyl	75	86/14

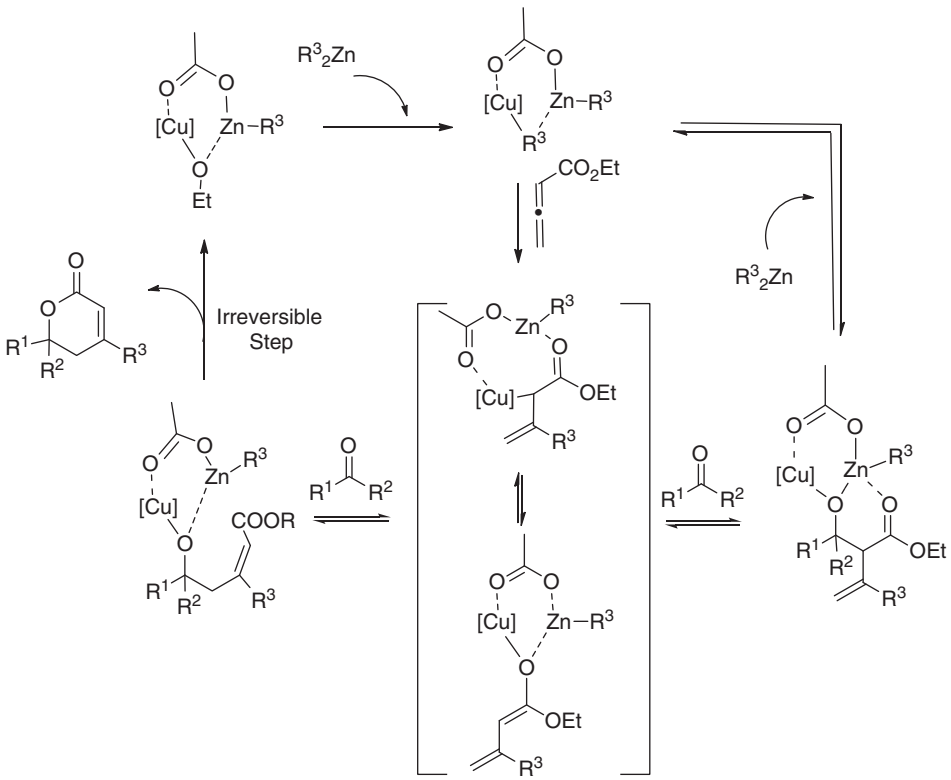
Shibasaki and Kanai have independently developed a catalytic and enantioselective alkylative aldol process based on the addition of Et_2Zn to allenic esters in the presence of arylketones.[94] In these reactions, both α-aldolization products and δ-lactones can be formed. The researchers found that a catalytic amount of a Lewis base ($Ph_2S=O$, dimethyl sulfoxide (DMSO) or HMPA) was essential to promote the retro-aldolization of α-products to give the irreversible formation of the δ-lactone. As illustrated in equation 37, the δ-lactones are obtained in good yields and high enantioselectivities.



R^1	R	Yield (%) d-Lactone	*ee* (%)
Ph	Et	92	96
p-$MeOC_6H_4$	Et	73	95
Bu^i	Et	76	96
Cy	Et	67	94
Ph	Pr^i	89	94
Ph	Bu^n	73	92

(37)

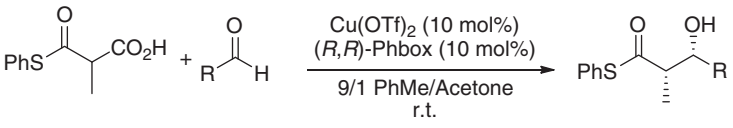
A mechanistic rationale involving two parallel catalytic cycles (Scheme 40), a reversible one leading to the α-aldol product and an irreversible one ultimately providing the lactone has been proposed by the researchers (see also equations 25 and 26). In the left-handed cycle, the irreversible lactonization step drives the equilibrium to the formation of the δ-lactone, whereas the α-aldolization product is in equilibrium through a retro-aldol and/or a copper/zinc transmetalation.

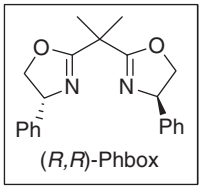


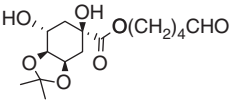
Scheme 40

1.04.4.1.6 Decarboxylative and direct aldol strategies

In the past few years, decarboxylative and direct aldol and Mannich reactions involving copper enolates have blossomed. Mimicking fatty acid and polyketide biosynthesis, the copper-catalyzed decarboxylative Claisen condensation of malonic acid half thioesters (MAHTS) with aldehydes has been first investigated.[95] In 2005, Shair finally described an efficient $Cu(OTf)_2$/(R,R)-Phbox catalytic system that leads to the aldol products in good *syn* diasteroeselectivities and excellent *ee*s (equation 38).[96] Very interestingly, Shair and coworkers have shown in further studies that, contrary to the biosynthetic pathway, the decarboxylation occurs after the aldolization step.[96] Although a Cu(I) mechanistic pathway has been advocated by the researchers, a mechanism involving copper(II) as a Lewis acid cannot be ruled out.

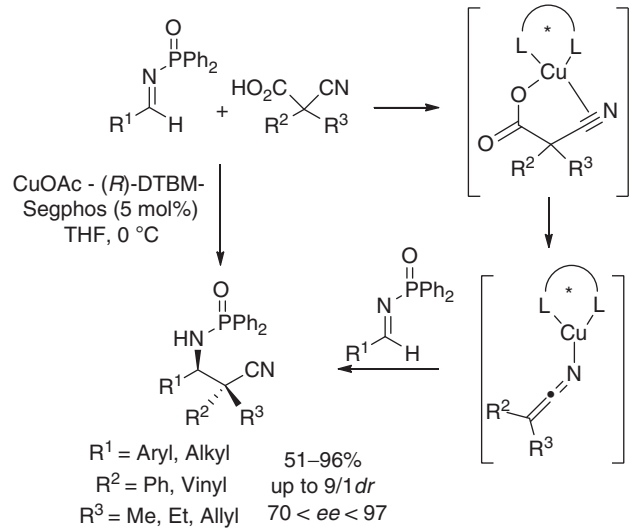




RCHO	Yield (%)	*dr syn/anti*	*ee* (%)
$Me(CH_2)_6CHO$	80	9/1	92
$MeO_2C(CH_2)_4CHO$	80	9/1	92
$Me(CH_2)_5$-≡-CHO	59	2.2/1	96
Pr^iCH_2CHO	73	7.5/1	89
CyCHO	48	36/1	93
	70	5.5/1	92
	70	5.5/1	92

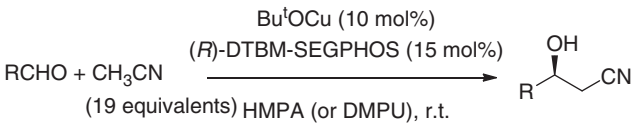
(38)

In somewhat related studies, catalytic enantioselective decarboxylative Mannich reactions between cyanocarboxylic acids and aldimines have been described by Kanai and Shibasaki. In the presence of CuOAc–(*R*)-DTBM-SEGPHOS as catalyst, the reaction leads to quaternary centers in moderate diastereo- and enantioselectivities with aliphatic and aromatic imines. A mechanism involving a Cu(I)-catalyzed decarboxylative reaction followed by the addition of the resulting chiral Cu ketenimide to the imine is invoked by the researchers (Scheme 41).[97]



Scheme 41

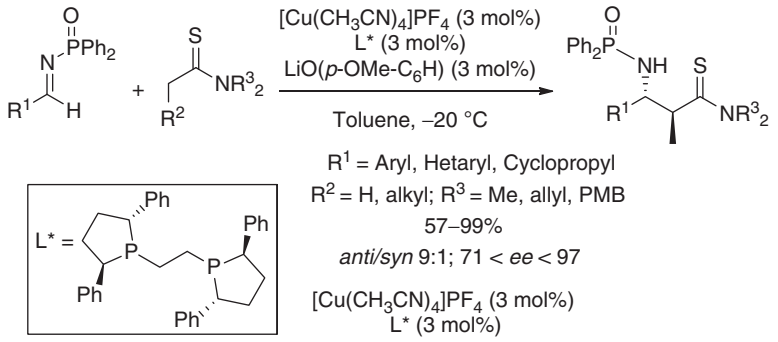
In 2005, Kanai and Shibasaki have also described the direct enantioselective reaction of acetonitrile with various aldehydes in good yields and enantioselectivities.[98] The use of HMPA or DMPU as solvent, the slow addition of the aldehyde, and an excess of acetonitrile (19 equivalents) are essential in good yields, to minimize the aldehyde self-condensation. In these conditions, the aldol products are obtained in good yields and moderate enantioselectivities (equation 39).



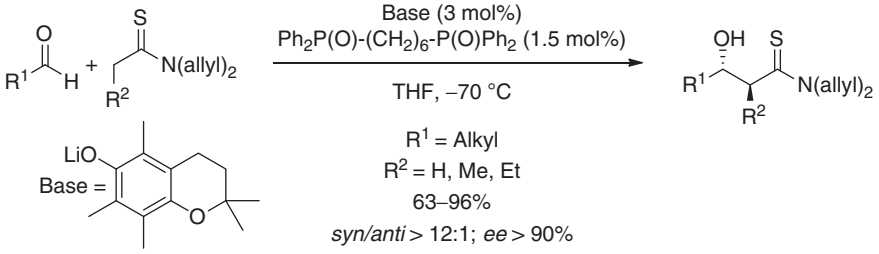
RCHO	Yield (%)	*ee* (%)
$Me(CH_2)_5CHO$	72	74
$Ph(CH_2)_2CHO$	62	73
$CyCH_2CHO$	88	76
CyCHO	91	75
PhCHO	85	51

(39)

Starting from this seminal result, copper-catalyzed direct aldol[99] and Mannich reactions have then been investigated by the Kanai and Shibasaki groups using thioamides as the nucleophile partner.[100–102] Despite their synthetic utility and atom economy, these reactions are usually very difficult due to the low acidity of the α-proton of the aldol donor, the propensity of the aldehyde to self-dimerize, and the difficulty to regenerate the catalytic species from the metal–aldol complex. Shibasaki anticipated that soft–soft interaction between thioamide and a copper salt would, in the presence of a strong base such as an alcoholate, selectively deprotonate the thioamide. The generated thioamide enolate will then be able to add to the electrophile (aldehyde or imine) to form a hard (phenoxide)–soft (copper) ionic pair which in turn could play the role of base in order to regenerate the thioamide enolate. The use of imines as electrophiles has been first investigated leading to the Mannich-type products in good yields, high diastereoselectivities, and moderate to high enantioselectivities (equation 40).[100] Moving to aldehydes, the previously described optimized conditions proved inefficient (<5% yield). After further optimization, it was found that a stronger base such as the lithium salt of 2,2,5,7,8-pentamethylchromanol and a cocatalytic amount of a Lewis base such as 1,6-bis(diphenylphosphino) hexane dioxide were necessary to efficiently promote this reaction. The presence of this Lewis base is crucial to reduce the rate of the retro-aldol process. These conditions, combining a soft Lewis acid (Cu salt), a hard Brønsted base and a hard Lewis base, were successful in promoting the catalytic and enantioselective direct aldol reaction of thioamides with aliphatic (branched and linear) aldehydes. The aldol products have been obtained in good yields, high *syn* diastereoselectivities and *ee*'s (equation 41). In the presence of aromatic aldehydes, the process is not efficient due to retro-aldol and β-elimination reactions.

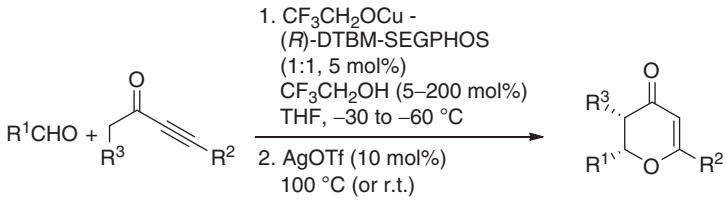


(40)



(41)

The use of thiolactams as aldol donors has been described by the same researchers, leading to the *anti*-aldol products in good to high diastereoselectivities.[103] In the search of alternative aldol donors, ynones have been next investigated in the asymmetric synthesis of enantiomerically enriched substituted dihydropyranones (equation 42).[104] The products are obtained in two steps by a copper(I)-catalyzed direct aldol reaction of ynones followed by a silver-catalyzed oxy-Michael reaction. This method is compatible with both aromatic and aliphatic substrates, and provides excellent chemoselectivity under mild reaction conditions. The success might be attributed to the presence of the alkyne moiety which is able by coordination to the soft copper salt to promote a selective enolization at the α-position of the ynone, and also to stabilize the copper aldolate (and prevent retro-aldol).

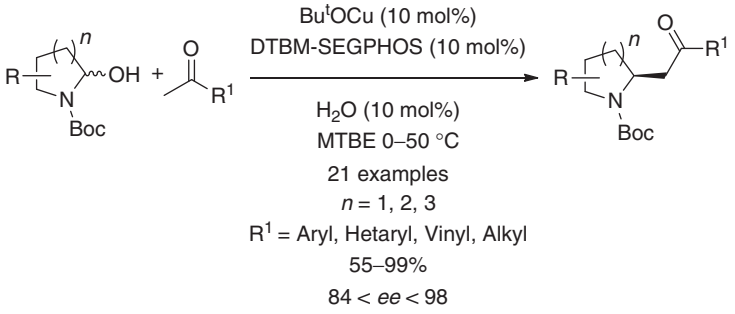


(42)

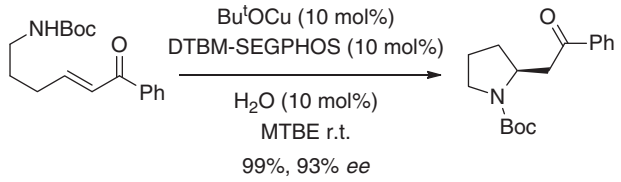
R^3 = H 13 examples
R^1 = aryl, alkyl
R^2 = Me, Et, Ph
56–99%
75 < *ee* > 90%

R^3 = Me 1 example
R^1 = Bu^t, R^2 = Ph
cis/trans 6.5:1
63%, 85% *ee*

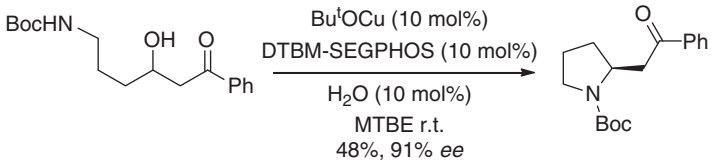
Kanai has also described the enantioselective copper-catalyzed addition of ketones to hemiaminals (equation 43).[105] As illustrated by control experiments (equations 44 and 45), the overall process involves three copper-catalyzed consecutive steps in the same pot: (i) aldol reaction, (ii) dehydration, and (iii) enantioselective intramolecular 1,4-addition of the nitrogen nucleophile. This sequence highlights the unique properties of the catalyst formed by the combination of a soft metal (Cu) and a hard anion (alkoxide).



(43)



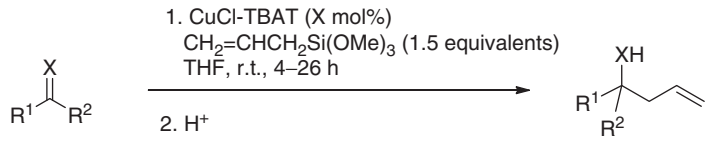
(44)

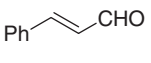
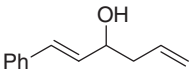
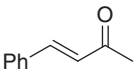
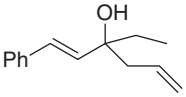
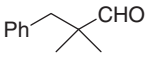
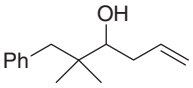
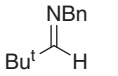
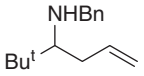
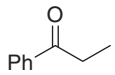
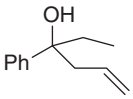
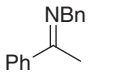
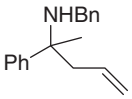


(45)

1.04.4.1.7 Allylic nucleophiles

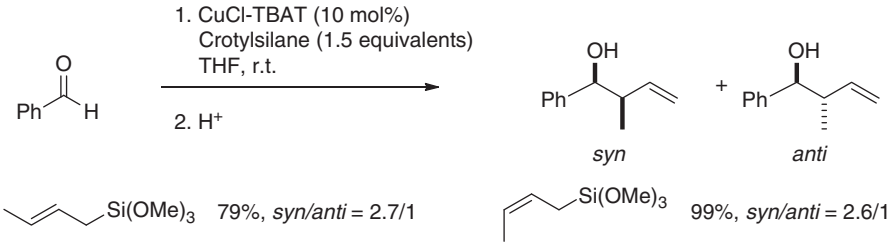
The asymmetric allylation of C–O or C–N double bonds, which leads to highly valuable enantiomerically enriched homoallylic alcohols or amines, is one of the most useful transformations in organic synthesis. This is an intensive field of research, and great efforts have been directed toward the development of efficient catalytic methodologies (*see* Chapters 2.01 and 2.02 for an overview on allylic organometallic reagents).[106] Among them, copper-catalyzed allylation reactions emerge as an interesting alternative. The high reactivity of the allyl copper intermediate indeed permits mild reaction conditions, low catalyst loading, and offers the possibility to create functionalized quaternary centers when the electrophile is an imine or a ketone.[107] The first examples were reported by Shibasaki, Kanai, and coworkers, using allyltrimethoxysilane or allylboronates as environmentally friendly allyl sources. Alone they are poorly reactive toward carbonyl derivatives (so there is minimal background rate) and easily transmetalated by copper salts, which yields an efficient catalytic process. A first racemic and catalytic version was developed by this group in 2002, using a combination of allyltrimethoxysilane (1.5 equivalents), tetrabutylammonium difluorotriphenyl silicate (TBAT, 1–10 mol%), and CuCl (1–10 mol%) in THF at room temperature.[108] Various aldehydes, ketones, aldimines, and ketoimines were subjected to these reaction conditions to furnish the desired homoallylic alcohol or amine in high isolated yields and with a catalyst loading as low as 1 mol%. The 1,2-addition products are exclusively obtained from α,β-unsaturated aldehydes or ketones. Notably, the presence of a sterically hindered quaternary center adjacent to the carbonyl or imine group is well tolerated and even very challenging ketimines can be employed successfully as electrophiles, which demonstrates the high efficiency of this catalytic system (equation 46).



Electrophile	Cat. (X mol%)	Product	Yield (%)	Electrophile	Cat. (X mol%)	Product	Yield (%)
	1		92		2		92
	1		91		10		92
	2		94		5		68

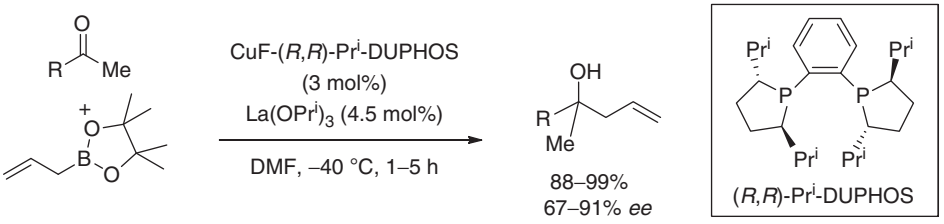
(46)

Homoallylic alcohols bearing two contiguous stereogenic centers can be obtained via this methodology by crotylation of benzaldehyde. Mainly the *syn* isomer is obtained irrespective of the *Z*/*E* geometry of the starting silane reagent (equation 47).



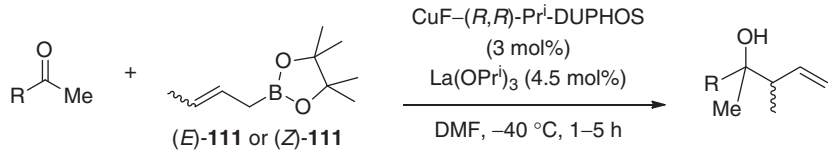
(47)

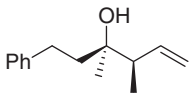
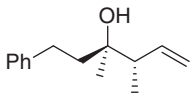
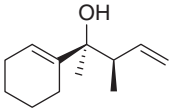
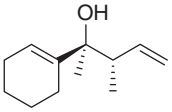
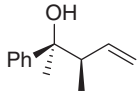
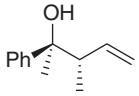
The attempts of this group to extend these seminal results to an asymmetric version were partially unsuccessful due to the deceleration effects induced by the presence of the chiral ligands: the enantioselectivities were moderate and 15 mol% of catalyst was necessary to ensure good conversions. This difficulty was circumvented by switching to a combination of allylborane reagents in the presence of catalytic amount of the CuF·Pr^i-DUPHOS complex, generated *in situ* by reduction of $CuF_2{\cdot}2H_2O$ by one equivalent of the diphosphine ligand. Importantly, the use of La(OPr^i)$_3$ as a cocatalyst dramatically enhanced the reactivity, allowing the allylation of ketones at a low temperature (CH_2Cl_2, −40 °C) with only 3 mol% of catalyst. Under these optimized reaction conditions, both aromatic, heteroaromatic, cyclic, and aliphatic ketones react smoothly to give the corresponding allylation products in excellent yields and moderate to good enantioselectivities (67–91% *ee*). Although the enantioselectivity is slightly substrate dependent, the efficiency of this catalytic system is remarkable. Even sterically hindered ketones such as methyl-*tert*-butylketone are converted within 1 h in excellent yields (equation 48).[109]



(48)

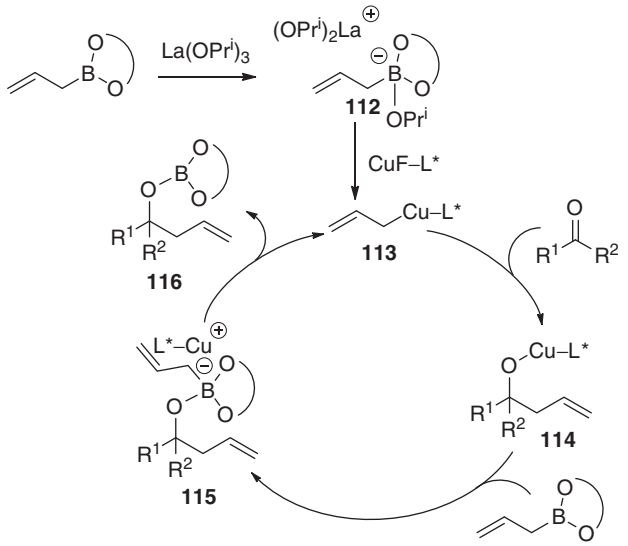
The high activity of the CuF–(*R*,*R*)-Pr^i-DUPHOS/La(OPr^i)$_3$ catalytic system allowed for the first time asymmetric catalytic crotylation of ketones, giving a simple access to products bearing two contiguous tetrasubstituted–trisubstituted centers with a good enantioselectivity, although the diastereoselectivity remains modest. As with their previous catalytic system (equation 47), a diastereoconvergence was observed when the *α*,*β*-unsaturated or aliphatic ketones were reacted with *E*- and *Z*-crotylboronates (*E*)-**111** and (*Z*)-**111**. The corresponding *anti*-isomers were indeed obtained as the major products in all cases. Intriguingly, the use of an aromatic ketone dramatically change the diastereoselective outcome of the reaction as, in this case, the geometry of the starting crotylboronate reflects the final *anti*/*syn* ratio, (*E*)-**111** leading mainly to the *anti*-product and its isomer, (*Z*)-**111**, to the *syn* (equation 49).[107,109]



Products		Reagent	Time (h)	Yield (%)	*syn/anti*	*ee* (%)
syn	*anti*					
		(*E*)-**111**	–	100	34/**66**	16/85
		(*Z*)-**111**	–	100	36/**64**	21/85
		(*E*)-**111**	3	80	27/**73**	90/93
		(*Z*)-**111**	4	90	38/**62**	90/92
		(*E*)-**111**	1	73	30/**70**	75/90
		(*Z*)-**111**	5	94	**84**/16	87/74

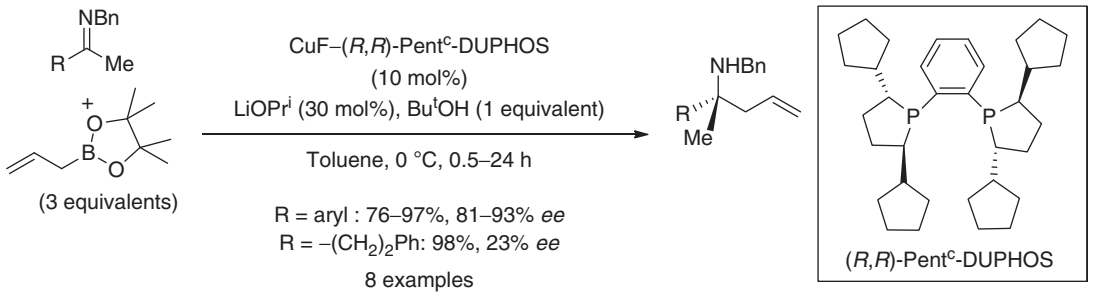
(49)

Important mechanism details were clarified on the basis of nuclear magnetic resonance (NMR) and kinetic studies. An allyl copper species, generated through a B-to-Cu transmetallation, was proposed as the reactive species. The La(OPr^i)$_3$ would facilitate the transmetallation step by transferring an *iso*-propoxide onto the boron atom. The resulting alkoxy-boronate intermediate **112** would more efficiently deliver its allyl substituent to the soft Cu center than the fluoroborate analog, obtained in the absence of cocatalyst by direct transfer of fluoride from CuF. This would increase the concentration of reactive allyl copper species **113** in the reaction mixture and thus to enhance the reactivity. The addition of **113** to the electrophile (a ketone in Scheme 42) would furnish a copper–alkoxide intermediate **114** that would undergo a Cu-to-B transmetalation. The resulting ate complex **115** would then collapse to yield the desired product as a borane derivative (**116**) and regenerate the reactive allyl copper reagent **113** (Scheme 42).[110]



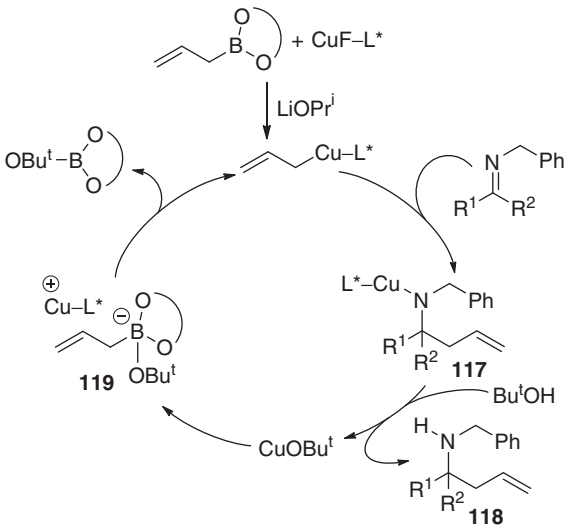
Scheme 42

The reaction was then extended to the first successful catalytic and enantioselective allylation of ketimines. The reaction conditions were slightly modified: (1) cyclopentyl-DUPHOS was used instead of *iso*-propyl-DUPHOS as a chiral inductor, (2) a slow addition over 1 h of one equivalent of Bu^{t}OH, and (3) LiOPr^i was employed instead of La(OPr^i)$_3$ as the cocatalyst. Using this optimized catalytic system, various nonactivated aromatic ketimines were converted into their allylation products in high yields and with enantiomeric excesses in the range of 81–93%. The aliphatic ketimines were efficiently converted, but with a disappointing 23% *ee* (equation 50).[111]



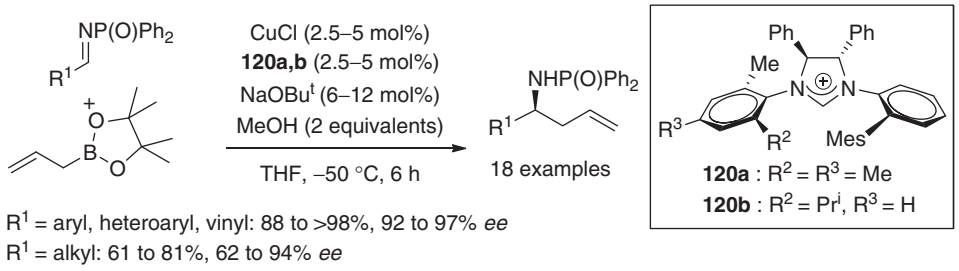
(50)

Further NMR studies were undertaken by the researchers to get insights into the accelerating effect of $LiOPr^i$ and Bu^tOH on the rate of this transformation. The results allowed assignment of precise roles for each of these additives. At the very beginning of the reaction, the $LiOPr^i$ would promote more efficiently the B-to-Cu transmetalation than its lanthanum analog. The allyl copper thus generated would add to the ketimine to furnish a copper–amide intermediate **117** that would dissociate by protonolysis under the action of Bu^tOH to give the homoallyl amine product **118** and $CuOBu^t$. This copper-alkoxide intermediate would thus add onto allylborane to regenerate the active allyl copper reagent through the formation of a transient boronate species **119** (Scheme 43).



Scheme 43

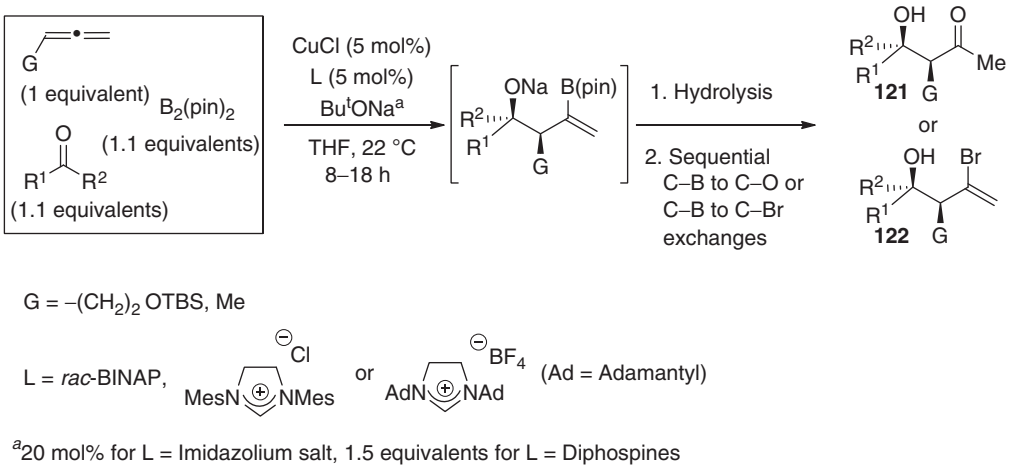
From this seminal work, useful extensions employing similar catalytic systems have been reported by this group and others. For example, Snapper, Hoveyda, and coworkers described in 2011 the catalytic and asymmetric addition of an allyl boron reagent onto *N*-phosphinoylaldimines promoted by an *N*-heterocyclic carbenes (NHC)−Cu complex.[112] This catalyst proved to be particularly efficient for a large scope of substrates. Indeed, various aryl-, heteroaryl-, alkenyl-, and alkyl-substituted aldimines readily react with derivatives in high yields and enantioselectivities (equation 51). Interestingly, the reaction can be conducted on a 1 g scale with only 1 mol% of catalyst without significant loss of reactivity and selectivity.



R^1 = aryl, heteroaryl, vinyl: 88 to >98%, 92 to 97% *ee*
R^1 = alkyl: 61 to 81%, 62 to 94% *ee*

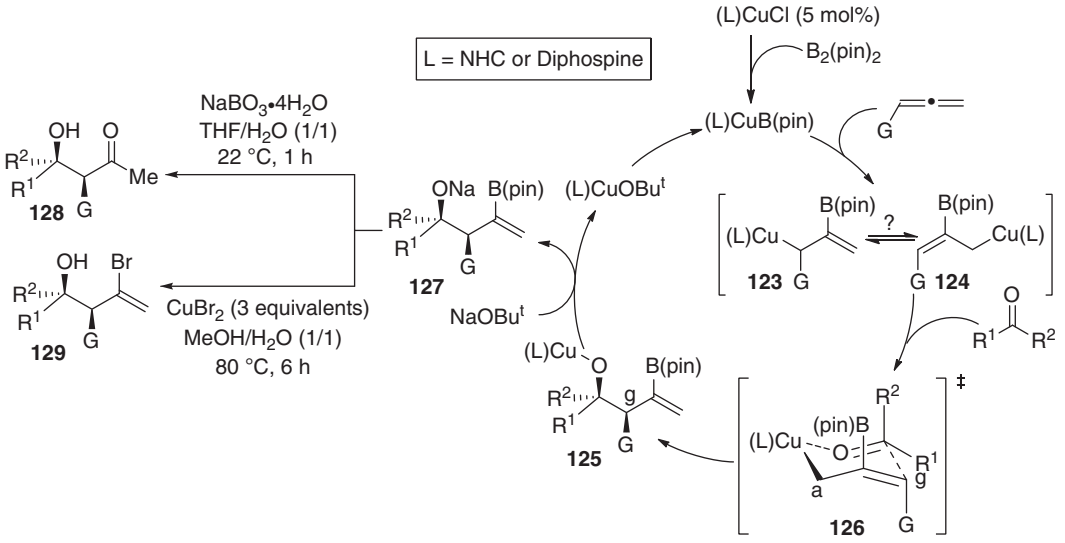
(51)

Very recently, Hoveyda and coworkers integrated this catalytic system in the design of a three-component catalytic domino transformation for the one-pot asymmetric preparation of various *β*-hydroxy ketones **121** or vinyl bromides **122** bearing two contiguous stereogenic centers from simple allenes with high regio- (*γ*), diastereo-, and, in selected examples, enantioselectivities (Scheme 44).[113]



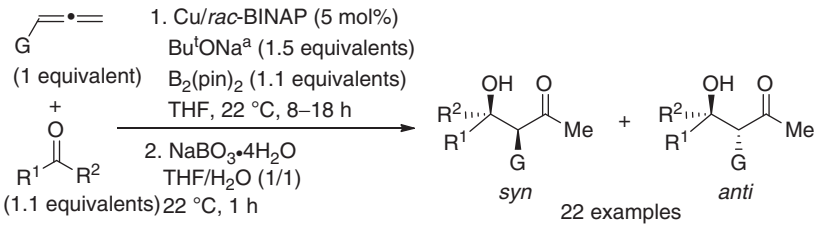
Scheme 44

During this transformation, the copper catalyst is involved in two consecutive steps: it promotes the chemoselective addition of bis(pinacolato)diboron ($B_2(pin)_2$) to monosubstituted allenes to give, in the presence of aldehydes or ketones in the reaction mixture, B(pin)-substituted allyl copper intermediates. These organometallic reagents can exist in solution as two distinct allylic forms **123** and **124** that may be in equilibrium through a metallotropic shift. In a subsequent step, their addition onto carbonyl compounds give the corresponding B(pin)-substituted copper alkoxides **125** via a postulated cyclic six-membered TS **126** involving the less sterically constrained allylic copper reagent **124**. Reaction with $NaOBu^t$ releases the copper catalyst in the reaction mixture and provides intermediate **127** that can undergo a further *in situ* C–B to C–O or C–B to C–Br exchange to yield the corresponding products **128** and **129** (Scheme 45).



Scheme 45

Both aldehydes and ketones are suitable electrophiles, allowing the preparation of products bearing a quaternary center with good to high diastereoselectivities (equation 52). Notably, due to competitive NHC/Cu-catalyzed Cu–B addition to aromatic aldehydes, best yields are reached using less Lewis basic *rac*-BINAP instead of NHC as ligand, whereas similar results are obtained with aliphatic aldehydes or aromatic ketones. Only results employing the *rac*-BINAP/Cu complexes as catalyst are reported herein. Addition onto α,β-unsaturated carbonyls yields mainly the 1,2-addition products, which support an overall S_E' process.



(52)

G = -$(CH_2)_2$OTBS, Me

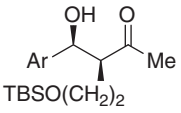
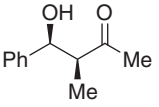
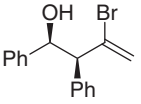
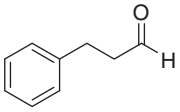
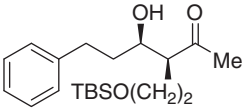
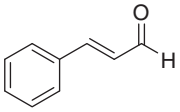
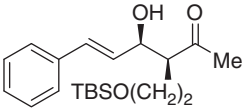
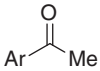
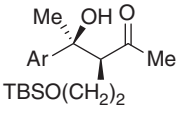
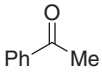
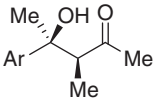
>98 γ-Selectivity in all cases

R^1 = aryl, alkyl, R^2 = H: 71 to 86%, *dr* (*syn/anti*): 93/7 to >98/2

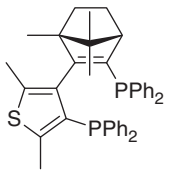
R^1 = aryl, heteroaryl, vinyl, alkyl, R^2 = alkyl: 68 to 92%, *dr* (*syn/anti*): 87/13 to >98/2

NHC are not effective catalysts for the asymmetric version of this transformation (up to 20% *ee*), but high enantiomeric excesses can be reached when using commercially available diphosphine **130** as a ligand with various aldehydes in the experimental conditions depicted in equation 52 (Table 5, entries i–vi). In the case of ketones, the best results are obtained using commercially available diphosphine **131**, and compounds bearing two contiguous tertiary/quaternary centers can be formed in high yields, with excellent γ- and diastereoselectivities and enantiomeric excesses up to 90% (Table 5, entries vii–ix).

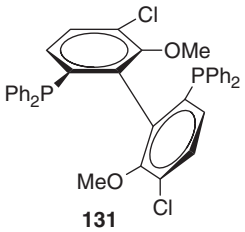
Table 5 Site-, diastereo- and enantioselective Cu-catalyzed coupling of allene with aldehydes or ketones followed by an oxidation or a boron/bromine exchange step

No.	*Carbonyl substrate*	*Ligand*	*Product*	syn/anti	ee *(%)*	*Yield (%)*
		130				
i			Ar = Ph	96/4	90	81
ii			Ar = *p*-OMeC$_6$H$_4$	98/2	90	86
iii		**130**		95/5	86	79
iv		**130**		90/10	94	81
v		**130**		94/6	92	77
vi		**130**		96/4	94	84
		**131**				
vii			Ar = Ph	94/6	78	84
viii			Ar = *p*-$CF_3C_6H_4$	>98/2	90	92
ix		**131**		>98/2	70	88

Experimental conditions: see Scheme 44 and equation 52.



130

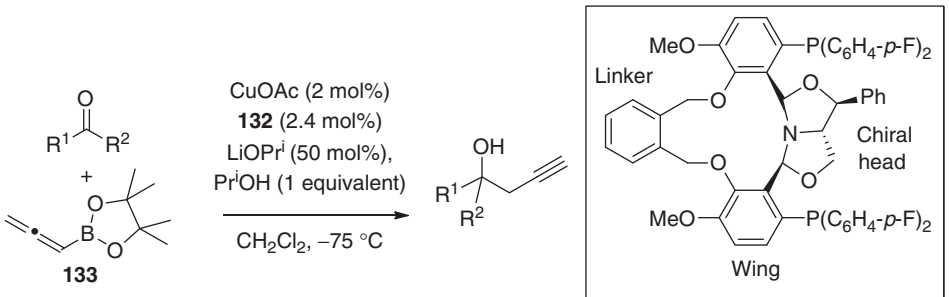


131

1.04.4.2 Catalytic and Asymmetric Addition of sp^2 Nucleophiles to C═O and C═N Bonds

1.04.4.2.1 Allenic nucleophiles

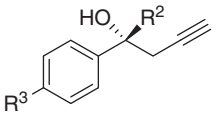
The use of a combination of copper–ligand complexes, alkoxides, and borolane derivatives for the development of catalytic and asymmetric propargylation of ketones was first reported in 2010 by the group of Kanai, Shibazaki, and coworkers as an extension of a work that aimed to develop improved chiral phosphine ligands for the asymmetric allylation of ketones (*see* Chapter 2.05 for an overview on propargyl and allenyl organometallic reagents). A careful experimental study led to the development of diphosphine **132** made of a rigid macrocyclic structure defined by an aromatic linker and two wing modules. The phosphorus atoms bear aromatic cores substituted by electron withdrawing at the para position. The use of a combination of this designed ligand (2.4 mol%), CuOAc (2 mol %), $LiOPr^i$ (0.5 equivalent), and Pr^iOH (1 equivalent) allowed the clean addition of allenic borolanes onto a large variety of ketones in CH_2Cl_2 at −75 °C with improved enantioselectivities and catalytic activities compared with the above CuX–Pr^i-DuPHOS-based catalytic system.[114] Notably, the presence of Pr^iOH was found to be beneficial to the reactivity as the temperature of the reaction needs to be increased to −40 °C in the absence of this additive. Under the same experimental conditions, various aromatic, heteroaromatic, aliphatic, and conjugated ketones undergo propargylation reactions by allenyl borolane **133** in generally good yields, regio- and enantioselectivities (equation 53).

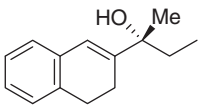
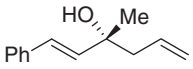
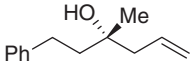


133

132

Selected examples:

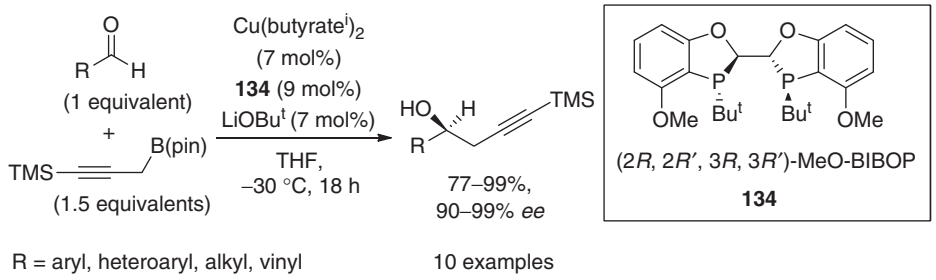
Product	Yield (%)	*ee* (%)
		
R^2 = Me, R^3 = H	93	95
R^2 = Me, R^3 = Br	85	90
R^2 = Me, R^3 = Me	94	93
R^2 = Me, R^3 = OMe	82	93
R^2 = Et, R^3 = H	94	42

Product	Yield (%)	*ee* (%)
	88	93
	90	86
	72	72

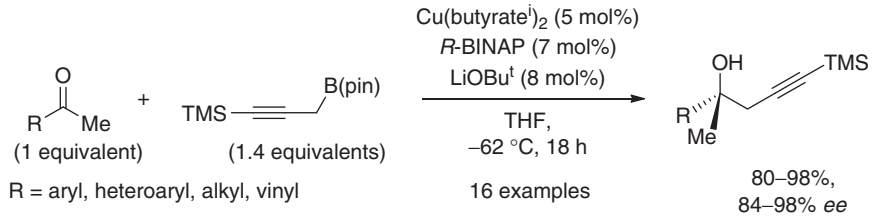
(53)

Almost at the same time, Fandrick and coworkers reported the first copper-catalyzed asymmetric propargylation of aldehydes. Inspired by the work of Kanai and Shibasazki, the catalytic system consists of a copper–diphosphine complex and a catalytic amount of $LiOBu^t$ as additive. It promotes the clean addition of a propargyl borolane reagent mainly on aromatic and heteroaromatic aldehydes in THF at −10 °C and allows the preparation of homopropargylic alcohols with enantiomeric excesses in the range of 90–99% (equation 54).[115] Interestingly, the propargylic versus allenic products ratio was found to be highly dependent on the nature of the diphosphine ligand used, from 2/1 for the use of BINAP to 93/1 with MeO-BIBOP **134**. A simple

change of the copper ligand allows the development of a catalytic and asymmetric protocol for the propargylation of ketones in nearly the same reaction conditions. On the contrary to the observations made when aldehydes were used as electrophiles, the best results in terms of both site- and enantioselectivities were obtained in this case for the use of BINAP as chiral inductor (equation 55).[116]

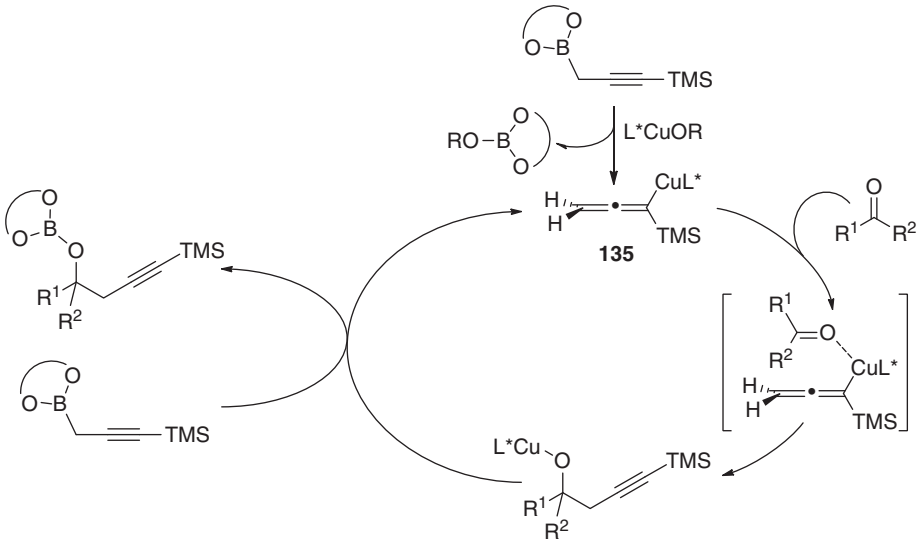


(54)



(55)

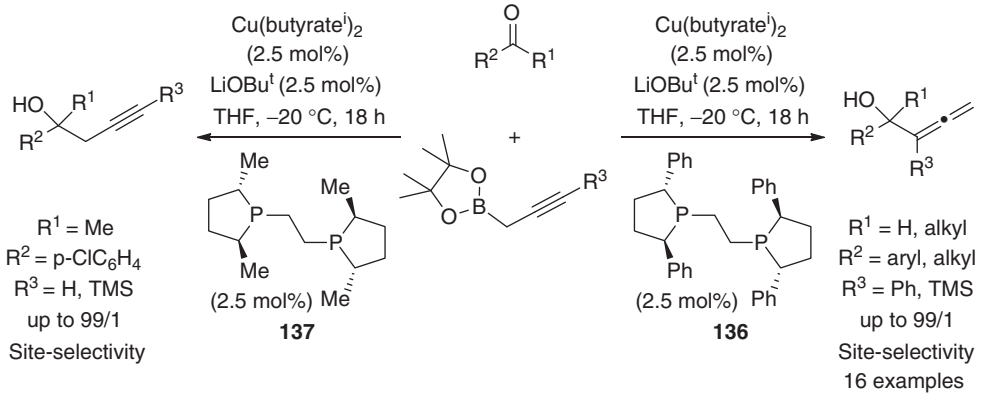
Similar to the copper-catalyzed allylation case, the reaction is supposed to proceed through an allenylcopper species **135** that result from an alcoholate-promoted C–B to C–Cu transmetalation process according to the catalytic cycle depicted Scheme 46.



Scheme 46

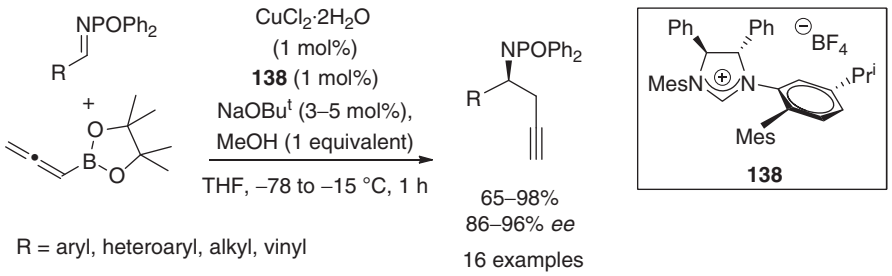
Further experimental studies from these researchers on the site selectivity of the copper-catalyzed addition of propargyl boronates onto ketones not only confirmed the role of the phosphine ligand, but also highlighted the crucial effect on the nature of the acetylenic substituent of the boronate reagent. It was postulated on the basis of molecular modeling (Spartan calculation) that the ligand/acetylenic substituent combination could have an influence on the nature of the reactive organocopper species that could exist either in its allenic or propargylic form in the TS, leading respectively, to the corresponding propargylic or allenic

product through an S_E' process. Nevertheless, a fine tuning of the nature of the ligand and of the boronate reagent allows a remarkable site-selectivity control, up to 99/1 for both the synthesis of allenic or propargylic products using ligands **136** and **137**, respectively (Scheme 47).[117]



Scheme 47

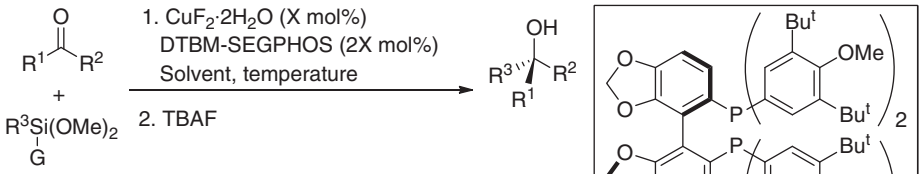
Hoveyda and coworkers recently reported a site- and enantioselective protocol for the preparation of homopropargyl amines using a chiral NHC copper complex .[118] In a typical experimental procedure, *N*-phosphinoyl aldimines are subjected to the action of allenyl borolane **133** in the presence of an equimolar mixture of the air-stable $CuCl_2{\cdot}2H_2O$ copper salt and the readily available imidazolinium salt **138** (1 mol%), NaOBu^t (5 mol%), and two equivalents of MeOH in THF, from −78 to −15 °C for 1 h. Interestingly, the reaction is highly site selective with less than 2% of allenic products formed, easy to operate, scalable to 1 g, and the free amine products are easily obtained by a simple aqueous HCl workup. Both aliphatic, vinylic, hateroaromatic, and variously substituted aromatic *N*-phosphinoyl aldimines are suitable substrates for this transformation and the corresponding homopropargylic products are isolated in 65–98% yield and 86–96% *ee* (equation 56).



(56)

1.04.4.2.2 Vinylic nucleophiles

Chiral allylic alcohols are among the most important building block in organic synthesis, and the development of catalytic and enantioselective access to this compounds is highly desirable. On the basis of this observation, Kanai, Shibasaki, and coworkers decided to extend the methodologies they developed for the allylation reaction to the catalytic and asymmetric vinylation reaction. A first protocol using a copper–diphosphine complex as catalyst and vinylsilanes derivatives as nucleophile was first developed.[119] The main difficulty that the researchers faced was the intrinsic low reactivity of the vinyl-copper intermediate, and the presence of a diphosphine ligand on the metal center was found to be crucial to accelerate the reaction. After a careful optimization of the ligand and of the experimental conditions, the researchers showed that a combination of the air-stable $CuF{\cdot}2H_2O$ copper salt and the DTBM–SEGPHOS diphosphine efficiently catalyzed the addition of variously substituted alkenysilanes derivatives **139a** and **139b** to aromatic, heteroaromatic, and aliphatic aldehydes as well as activated ketones under mild reaction conditions, with high yield and generally excellent enantioselectivities. Interestingly, arylsilanes **140** are also effective nucleophiles in these reaction conditions, providing an interesting catalytic and asymmetric arylation procedure (equation 57).



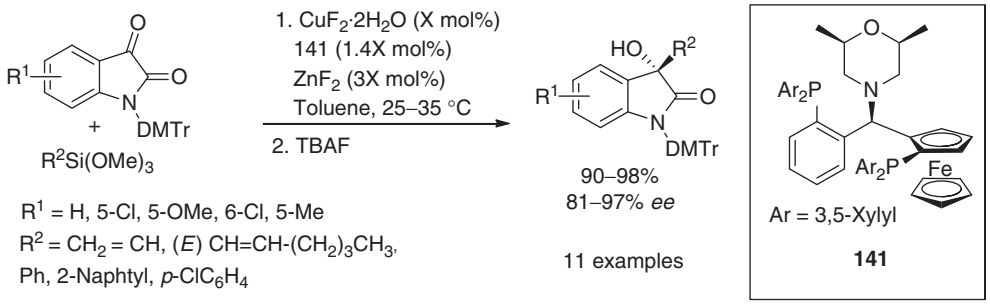
139a: $R^3 = CH_2{=}CH$, G = OMe
139b: $R^3 = CH_2{=}CH$, G = Me
140: R^3 = G = Ph

Selected examples:

Substrate R^1	Substrate R^2	Reagent	Catalyst (X mol%)	Solvent, Temperature (°C)	Time (h)	Yield (%)	*ee* (%)
Ph	H	**139a**	3	DMF, 40 °C	0.5	99	94
p-Cl-C_6H_4	H	**139a**	3	"	2	99	97
p-Me-C_6H_4	H	**139a**	3	"	8	99	99
2-Thienyl	H	**139a**	10	"	0.5	99	91
(*E*)-PhCH=CH	H	**139b**	10	"	1	73	83
Hex[c]	H	**140**	10	Toluene, r.t.	16	84	98
p-Cl-C_6H_4	H	**140**	3	DMF, 40 °C	1	81	92
p-Me-C_6H_4	H	**139a**	5	"	3	83	90
Ph	CF_3	**139b**	5	Toluene, 70 °C	39	100	84
p-Me-C_6H_4	CF_3	**139b**	10	"	18	100	83
p-Cl-C_6H_4	CF_3	**139b**	10	"	43	77	84

(57)

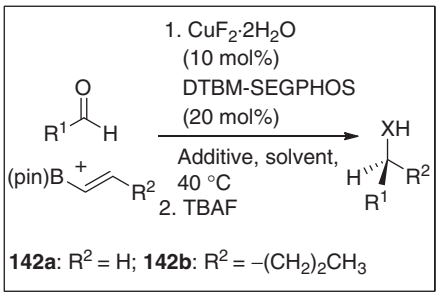
An intertwined experimental, kinetic, and ^{19}F NMR study assigned the alkenyl or aryl copper reagent as reactive species. Similar to the allylation parent reaction, their formation would result from a fluoride- or an alkoxide-promoted silicon-to-copper transmetalation step. The role of the diphosphine ligand would be to facilitate the regeneration of the alkenyl- or aryl copper reactive species from a copper-alkoxide intermediate, thus increasing the reactivity. The researchers also found that the presence of a catalytic amount of a fluoride additive accelerated the reaction without affecting the enantioselectivity, which allowed them to develop an efficient Cu-catalyzed enantioselective alkenylation and arylation of isatins using **141** as the chiral inductor (equation 58).[120]



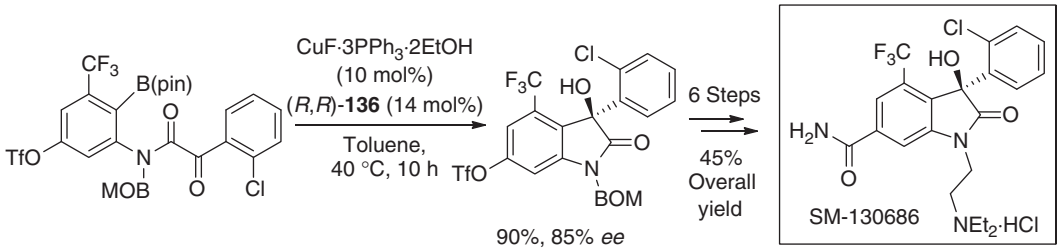
R^1 = H, 5-Cl, 5-OMe, 6-Cl, 5-Me
$R^2 = CH_2{=}CH$, (*E*) CH=CH-$(CH_2)_3CH_3$, Ph, 2-Naphtyl, *p*-ClC_6H_4

(58)

The possibility to use alkenyl- and aryl-boronates as nucleophiles was also explored.[121] The previously developed CuF-DTBM−SEGPHOS catalyst was found to convert nonenolizable aldehydes into their corresponding allylic alcohol products. The same level of enantioselectivity as when using alkenylsilanes as nucleophiles was achieved, which suggests that the same alkenylcopper intermediate is the reactive species. However, the yield was lower and an optimization of the reaction conditions showed that the reactivity can be significantly improved by using toluene as the solvent and by adding substoichiometric amounts of TBAT into the reaction mixture. The use of an equimolar combination of TBAT and $BF_3{\cdot}Et_2O$ as coadditives prevents the formation of homoaldol byproducts that were obtained when aliphatic aldehydes were employed as electrophiles. To explain this result, the researchers hypothesized that this combination could produce small amounts of free BF_3 that would trap the copper-alkoxide intermediate before it deprotonates the aldehyde. Under these optimized reaction conditions, various aliphatic, conjugated aromatic and heteroaromatic aldehydes can be converted into the corresponding allylic alcohol products using **142a,b** with high yields and excellent enantioselectivities. Unfortunately, the reaction failed when ketones were used as electrophiles (Scheme 48). This protocol has been used, after optimization of the chiral ligands, to achieve the first catalytic enantioselective synthesis of SM-130686, an important growth hormone secretagogue, using a CuF-catalyzed intramolecular asymmetric arylation as the key step (Scheme 48, down).[120]



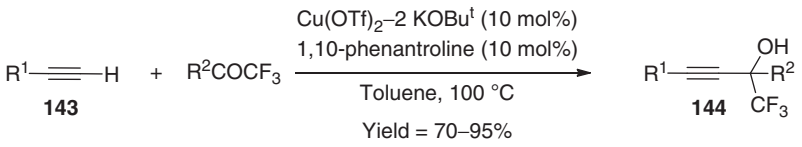
Substrate (R^1)	Reagent	Additives (mol%)	Solvent	Time (h)	Yield (%)	*ee* (%)
Ph	**142a**	none	DMF	24	67	90
Ph	**142a**	TBAT (15)	"	0.5	90	90
Ph	**142b**	"	"	8	88	88
p-Me-C_6H_4	**142a**	"	"	1	99	93
p-Cl-C_6H_4	**142a**	"	"	1	99	93
2-Thienyl	**142a**	"	Toluene	6	95	96
(*E*)-PhCH=CH	**142a**	"	"	1	98	90
Hex[c]	**142a**	"	"	12	42	98
Hex[c]	**142a**	TBAT (15)+ $BF_3·Et_2O$ (30)	"	14	94	98



Scheme 48

1.04.4.3 Catalytic and Asymmetric Addition of *sp* Nucleophiles to C═O Bonds

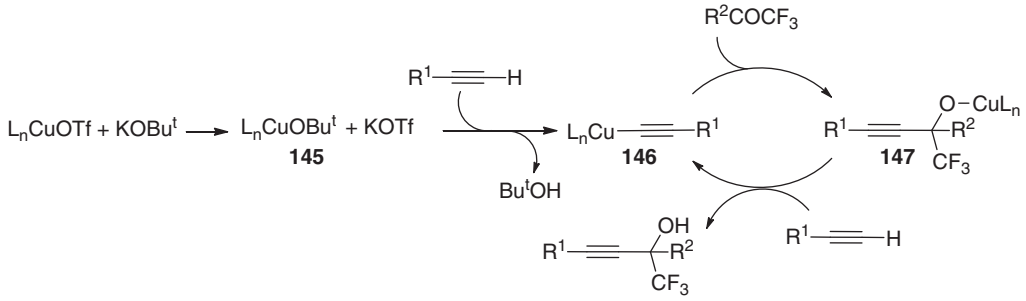
The great interest of propargylic alcohols prompted several groups to develop catalytic additions of alkynes to ketones.[122] A direct copper alkoxide-catalyzed alkynylation of trifluoromethyl ketones **143** has been described by Shibasaki (equation 12). The catalytic copper-alkoxide $CuOBu^t$, generated from a $Cu(OTf)·(toluene)_{0.5}$ complex or $Cu^{II}(OTf)_2$ (reduced *in situ* by alkynes) and two equivalents of $KOBu^t$, was complexed with xantphos or 1,10-phenanthroline. For practical reasons, the use of Cu^{II} is much easier due to its air stability. As shown in equation 59, good yields of propargylic alcohols **144** were obtained even with enolizable ketones.[123]



(59)

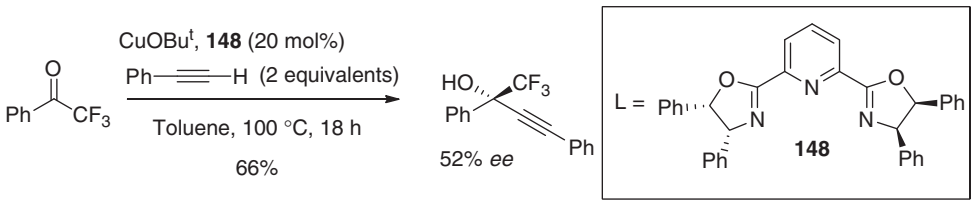
R^1 = Ph, $Ph(CH_2)_2$, Et_3Si
R^2 = Ph, *p*-Me-C_6H_4, *p*-Br(Cl)-C_6H_4, *o*-Me-C_6H_4, *m*-Me-C_6H_4, 3-Thiophene, $Ph(CH_2)_2$, $CH_3(CH_2)_9$, c-Hexyl

A mechanism involving a copper alkynide was proposed (Scheme 49). Selective interaction between soft Cu and alkyne allows deprotonation by the copper alkoxyde **145** to give a copper alkynide **146** which reacts with the ketone. By this way, a new copper alkoxyde **147** is formed to initiate a second cycle.



Scheme 49

An enantioselective approach of this reaction was attempted. A moderate but promising result was obtained using pybox **148** as ligand (equation 60).



(60)

1.04.5 Miscellaneous

1.04.5.1 Pyridinium Salts and Related Electrophiles

Addition of organometallic reagents to pyridines, activated via the formation of pyridinium salts, is a common method in the preparation of 1,2- or 1,4-dihydropyridines. The regioselectivity of the addition (1,2- or 1,6- versus 1,4-) is dependent upon both the activating reagent and the organometallic species, as well as the nature and position of the pyridinium substituents. Soft nucleophiles such as copper reagents lead generally almost exclusively to the formation of 1,4-dihydropyridines. This tendency is not completely general. It has been observed by Bosch[124] on *N*-alkylpyridinium salts **149** that if the addition of an alkyl copper is mainly 1,4-selective, that of alkynyl, allyl, and vinyl various copper species is 1,2- or 1,6-selective. Curiously, on an *N*-acylpyridinium salt **150** the same 1,2-regioselectivity is obtained with alkynyl and allyl copper reagents but not with vinyl-Cu which was fully 1,4-selective (Figure 3).[125,126]

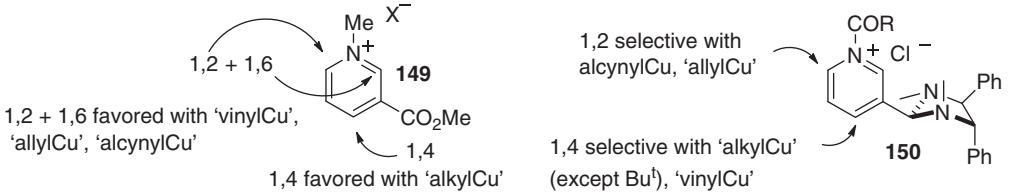
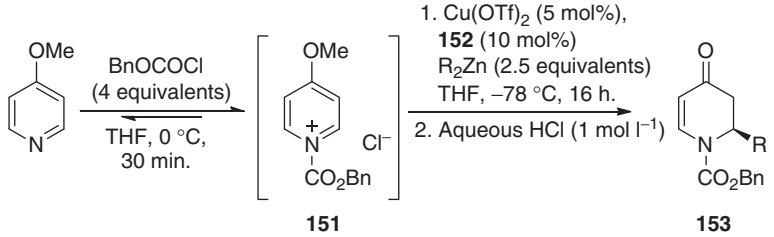
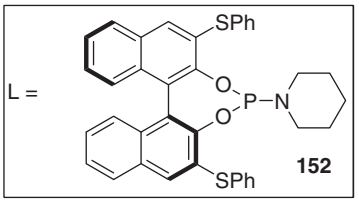


Figure 3 Regioselectivity trends in organocopper addition to pyridinium salts.

A copper-catalyzed 1,2 addition of dialkyl zinc reagents to *N*-acyl-4-methoxypyridinium **151** was described by Feringa. Cu(II) triflate was found to be the best copper source but the reactive species is a Cu(I) derivative, probably as a bimetallic cluster[1,127] resulting from a reduction of the Cu(II) salt by the dialkyl zinc. Among the three phosphoramidite ligands used in this chapter, the more effective was ligand **152** (equation 61). The success of this reaction is strongly dependent on the conditions. The pyridinium salt has to be preformed at 0 °C with an excess of benzylchloroformate before the the dropwise addition of the catalyst and R_2Zn at −78 °C. Accordingly, good yields and excellent enantioselectivities (except for R=Pr^i) were obtained, after acidic hydrolysis, for adducts **153**.[128]

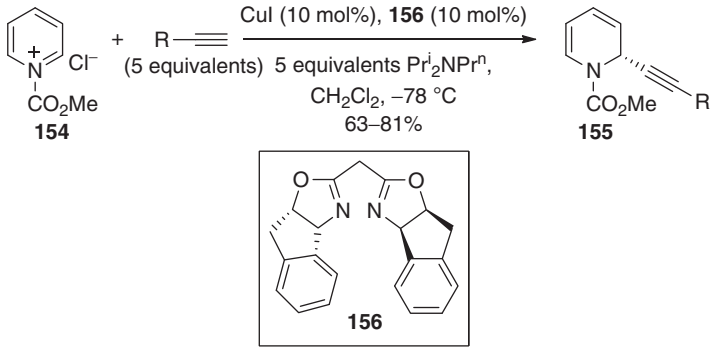


(61)



R	Yield (%)	*ee* (%)
Et	69	95
Bu	63	93
$Ph(CH_2)_2$	50	97
Pr^i	65	56

The preference for terminal alkynes to undergo a 1,2-addition to pyridinium salts **154** was exploited by Ma into a catalytic and enantioselective version using a bidentate bisoxazoline **155** as ligand (equation 62). Again this reaction is dependent on the reaction conditions. An excess of chloroformate and alkyne was needed to achieve good results (*ee* from 77% to 95% for dihydropyridines **156** using activated alkynes). Inactivated alkynes were found to be reactive but without enantioselectivity.[129] Similar catalytic procedures have been extended to several azaaromatic rings.[130]

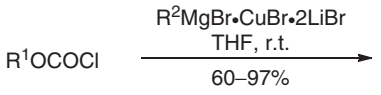


R	*ee* (%)
CO_2Me	95
CO_2Bn	86
COMe	93
COEt	99
COBu	91
$CO(CH_2)_2OBn$	77
Ph	1
Bu^n	11
CH_2OAc	3

(62)

1.04.5.2 Acyl Chlorides and Related Electrophiles

Ketones and esters are easily obtained by the addition of Grignard reagents, at room temperature, to chloroformates (equation 63) or acyl chlorides (equation 64) in the presence of CuBr·2LiBr. No racemization was observed from **157** which gave the corresponding ketones **158** with a total conservation of the enantiomeric excess (equation 64).[131]



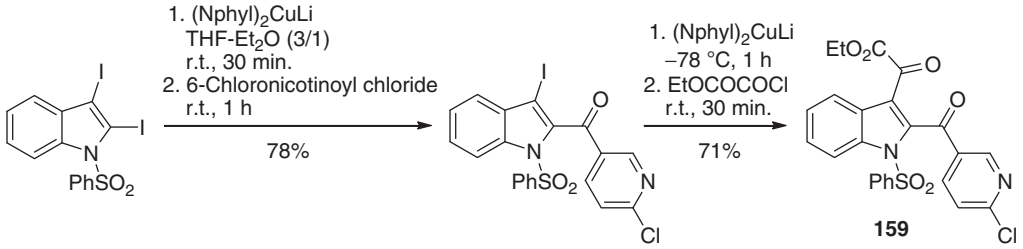
(63)

R^1 = Et, Ph R^2 = Octyl^n, c-hexyl, 9-Decenyl, 2-(1,3-Dioxan-2-yl)ethyl, Phenyl *p*-Methoxyphenyl, 2,6-Dimethylphenyl, *p*-Fluorophenyl, 2-Thienyl

(64)

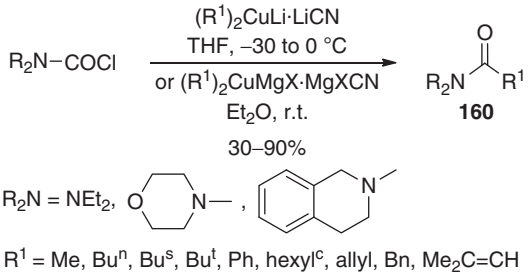
R^1 = Me, Bn, Ph R^2 = Ph, *p*-MeoPh, thienyl, decyl^n, 2-(1,3-dioxan-2-yl)ethyl

Highly functionalized keto-esters were prepared by Knochel and coworkers by the addition of unsaturated organocopper reagents, obtained by iterative iodine–copper exchange reactions, to acyl chlorides. One illustrative example for the preparation of **159** is given in Scheme 50.[132]



Scheme 50

An efficient method for the preparation of tertiary amides **160** (equation 65) from carbamoyl chlorides was described by Lasne and coworkers. Lithio- or magnesiocuprates were found to be effective, but the best results were obtained with Et_2O as solvent using cyano-Gilman magnesiocuprates $R_2CuMgX{\cdot}MgXCN$ obtained by mixing one equivalent of copper cyanide with 2 equivalents of Grignard reagent at −30 °C.[133]



(65)

1.04.6 Conclusion

Organocopper reagents are long known, popular, and versatile organometallics. They have historically been developed in cross-coupling and carbocupration of unsaturated bonds (including 1,4-addition reactions). In comparison, the direct additions onto carbonyl or imine derivatives have been less explored, probably due to the intrinsic soft nucleophilic character of these reagents and organic chemist's perception that harder organometallics would be more suitable for this kind of transformations. In the last 15 years, this soft character clearly appeared as an advantage, allowing the conception of catalytic and asymmetric reactions using increasingly complex and highly functionalized substrates. The spectacular successes obtained by the groups of Carreira, Shibasaki, and others induced a regain of interest in this field that is now blossoming. One of the most promising areas of research is probably the development of multicomponent reactions in which the versatile properties of copper could be advantageously exploited to design efficient domino and one-pot processes, combining, for example, carbocupration and nucleophilic addition reactions, as recently illustrated by the groups of Hoveyda and Marek. However, the success of such approaches is intimately linked to a better comprehension of the mechanisms implied, and the use of intertwined analytical, physical organic chemistry, and theoretical studies will certainly be a key to success.

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1.05 Organotitanium and Organozirconium Reagents

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Glossary

Carbometallation The addition of organometallic compounds to a multiple bond leading to other organometallic compounds.

Carbonyl A molecular fragment consisting of a carbon and an oxygen atom linked by a double bond.

Hydrometallation The addition of a metal hydride to a multiple bond leading to organometallic compounds.

Metallacyclopropanes The nucleophilic organometallic reagents sharing alkene metal complexes-like properties due to a significant electron backbonding from the metal atom.

Organotitanium reagents The organometallic compounds containing carbon-to-titanium chemical bonds.

Organozirconium reagents The organometallic compounds containing carbon-to-zirconium chemical bonds.

Transmetallation The organometallic reaction that involves transfer of organic ligand from one metal to another.

1.05.1 Introduction

Titanium and zirconium are among the most abundant elements available in the earth's crust and some of their derivatives are relatively inexpensive and widely applicable to many areas of human life. In particular, intensive study of organotitanium and organozirconium compounds during the past half century resulted in finding their utility in organic synthesis, specifically as reagents in the formation of carbon–carbon bonds. Lower nucleophilicity of such reagents relative to the corresponding organomagnesium or organolithium derivatives assists in performing many synthetically useful alkylation reactions in a highly chemo-, regio-, and stereoselective manner. The methylated titanium and zirconium derivatives were studied in carbonyl addition reactions more extensively than most other monoanionic derivatives, perhaps due to their greater stability and synthetic importance of the methyl carbinols. For example, methylation of easily enolized carbonyl compounds by using methylzirconium reagents can be achieved owing to low basicity of the zirconium alkoxides. Direct geminal dimethylation of ketones using dimethyl titanium derivatives also found a wide application in organic synthesis. Another useful feature of organotitanium reagents bearing alkoxide or *N*,*N*-dialkylamine ligands lies in their ability to transform active carbonyl groups (typically aldehydes) to the corresponding alkoxy- or dialkylaminotitanates, and in this way protect the carbonyl group from interacting with carbon nucleophiles. The addition of organotitanium and organozirconium reagents to conformationally labile aldehydes and ketones usually proceeds in accordance with general stereochemical rules, but is often characterized by increased influence of both steric hindrance and electronic effects of substituents. Sometimes, this is due to an existence of

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organotitanium compounds in solution as five- or six-coordinated complexes. Stereochemical features of allyl and crotyl addition to carbonyl with titanium or zirconium reagents were studied in most detail. In particular, cyclopentadienyl η^1-allytitanium(IV) and zirconium(IV) reagents as well as η^3-allyltitanium(III) species often exhibit a high stereoselectivity in the carbonyl allylation reactions.

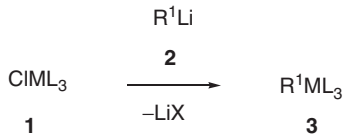
These and other aspects of the transformation of carbonyl compounds under treatment with organotitanium and zirconium derivatives were covered extensively in the previous edition of this monograph series[1] and several previous reviews.[2] The recent development of synthetic methodologies based on the carbonyl addition reactions of the organotitanium or organozirconium compounds, where they act as monoanionic equivalents, could be found in detailed reviews.[3] Important synthetic applications have been also found in the reactions of carbonyl compounds with titanium–carbene complexes[4] and metallacyclopropane derivatives,[5] leading to the products of the formal transformations of 1,1- or 1,2-dicarbanionic organometallic reagents. These reactions were not addressed in the previous edition of this book and will be examined in greater detail in this chapter. The transformations of carbonyl compounds with organometallic reagents generated by transmetallation of organotitanium or organozirconium precursors has also been of considerable use in organic synthesis, but is outside the scope of this section.

1.05.2 Preparation of Principal Organotitanium and Organozirconium Reagents

The main approaches to the preparation of organotitanium and organozirconium compounds are based on the reactions of *trans*-, hydro-, and carbometallation of alkenes or alkynes, as well as a disproportionation of the dialkyl derivatives of these transition metals.

1.05.2.1 Transmetallation Reactions

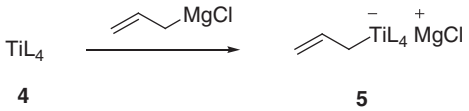
Transmetallation reactions of titanium and zirconium chlorides **1** with organolithium compounds **2** represent the most widely applicable method in the synthesis of monoalkylated and monoarylated derivatives **3** (Scheme 1). This way is effectively used in the preparation of transition organometallics which do not contain considerable impurities of the corresponding lithium salts due to their poor solubility in ether or hydrocarbon solvents.



R^1 = alkyl, aryl
M = Ti or Zr
L = OR, NR_2, Cp

Scheme 1

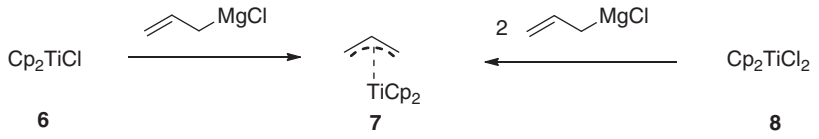
The high oxophilicity of titanium and zirconium atoms, coupled with the tendency of these elements to form penta- or hexacoordinated complexes, creates difficulties in obtaining their monomeric organometallic derivatives. In addition, the reagents used for the transmetallation can be involved in the formation of the corresponding titanium and zirconium ate complexes. For example, the allylation of titanium(IV) dialkylamides or alkoxides **4** with the Grignard reagents leads to the formation of the corresponding ate complexes **5** (Scheme 2), and their reactivity toward carbonyl derivatives differs significantly from the allyltitanium compounds obtained by substitution of the halogen atom at the transition metal.[2i,6]



L = OR or NR_2

Scheme 2

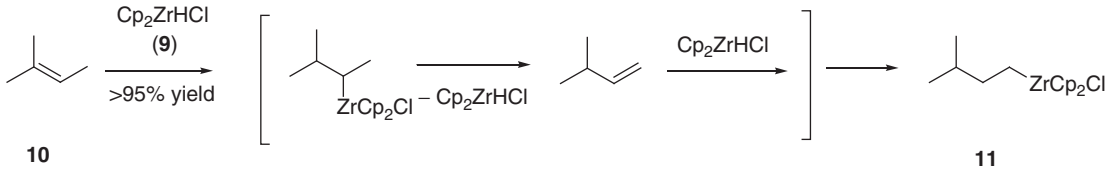
The reaction of allylmagnesium chloride with titanocene(III) chloride **6** leads to the deeply colored η^3-allyltitanocene **7**, which is formed also under the reaction of titanocene(IV) chloride **8** with 2 equivalents of allylmagnesium chloride (Scheme 3).[7]



Scheme 3

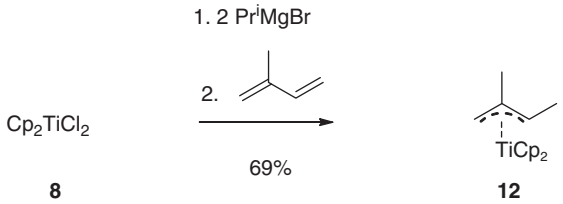
1.05.2.2 Hydrometallation Reactions

Hydrozirconation of alkenes is an effective method for the preparation of the zirconocenes bearing primary alkyl or alkenyl groups. The regiospecific addition of zirconium hydride to a terminal double bond, or the rearrangement of products' hydrozirconation of alkenes with an internal double bond via Zr–H elimination and readdition, lead to alkylzirconocenes with the metal at the less-hindered terminal position of the alkyl group. For example, hydrozirconation of trimethylethylene **10** with zirconocene hydrochloride[8] (Schwartz's reagent) **9** leads to the formation of isoamylzirconocene derivative **11** (Scheme 4).[3e,o]



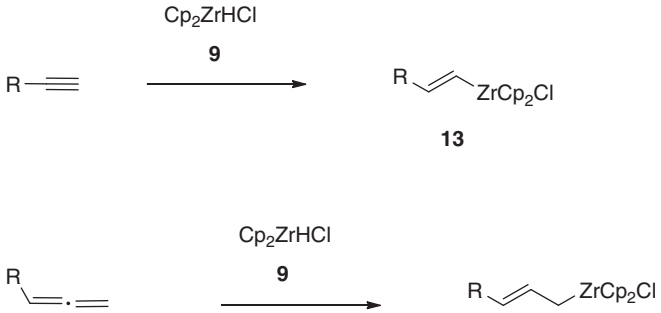
Scheme 4

The addition of the titanium(III) hydrides to dienes is a convenient alternative approach to the η^3-allyltitanium(III) complexes. This way leads to a highly selective formation of the thermodynamically more stable reagents. In particular, hydrotitanation of 2-substituted-1,4 dienes with titanocene hydride leads exclusively to sterically less-hindered 2,3-disubstituted allyltitanium reagents. However, better yields of the products are usually obtained at the hydrometallation of the conjugated dienes. For example, treatment of titanocene dichloride **8** with 2 equivalents of isopropylmagnesium bromide in the presence of more isoprene leads to the formation η^3-dimethylallyltitanium(III) reagent **12** (Scheme 5).[9]



Scheme 5

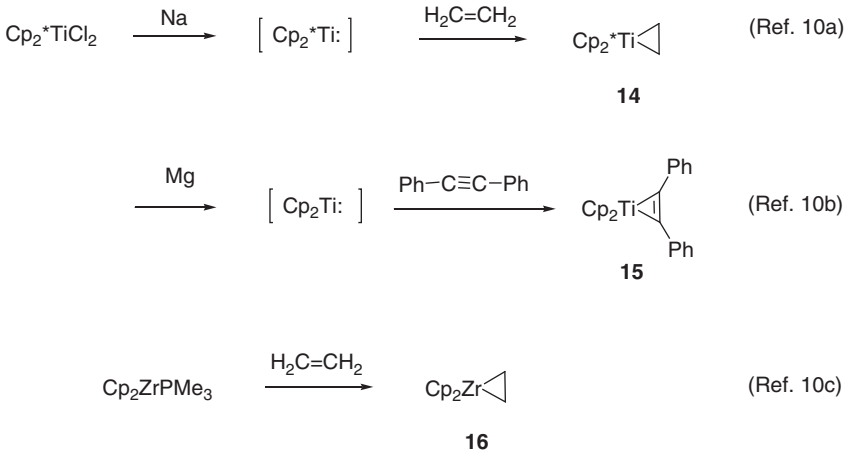
Hydrometallation reactions are frequently used for the preparation of alkenyl zirconocene derivatives.[10] Hydrozirconation of acetylenes with zirconocene hydrochloride **9** proceeds with high *cis*-stereoselectivity to give the corresponding *trans*-alkenylzirconium derivatives. The terminal alkynes in high regioselectivity afford sterically less-hindered terminal organometallic derivatives **13**, whereas the hydrozirconation of allenes leads to the corresponding allylzirconium compounds (Scheme 6).



Scheme 6

1.05.2.3 Cycloaddition of Ti(II) and Zr(II) Species to Alkenes and Alkynes

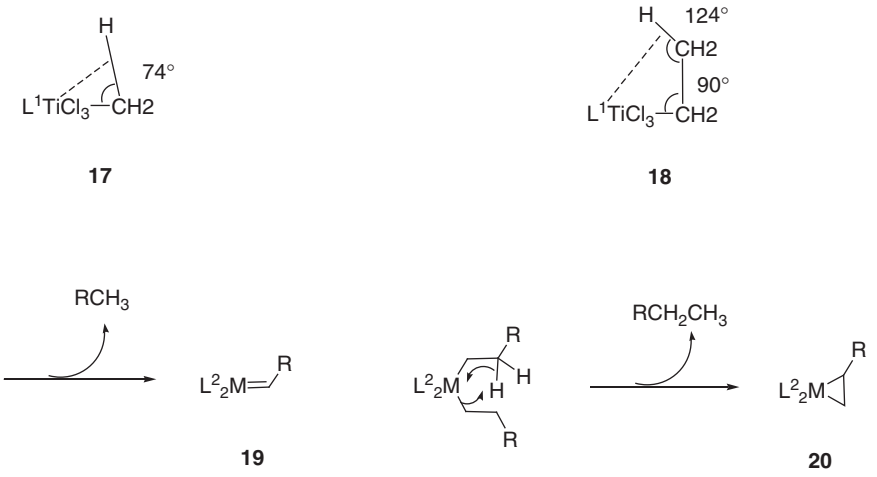
Titanium(II) and zirconium(II) compounds are isoelectronic to carbenes and could be involved in the cycloaddition reactions with alkenes and alkynes[5n] to afford a highly reactive metallacyclopropane and metallacyclopropene derivatives. Some representatives of the latter (e.g., metallacyclopropanes **14**,[10a] **16**,[10c] and titanacyclopropene **15**[10b]) were isolated in crystalline state and their geometric characteristics were determined with X-ray analysis (Scheme 7).



Scheme 7

1.05.2.4 Disproportionation of Dialkyltitanium and Dialkylzirconium Precursors

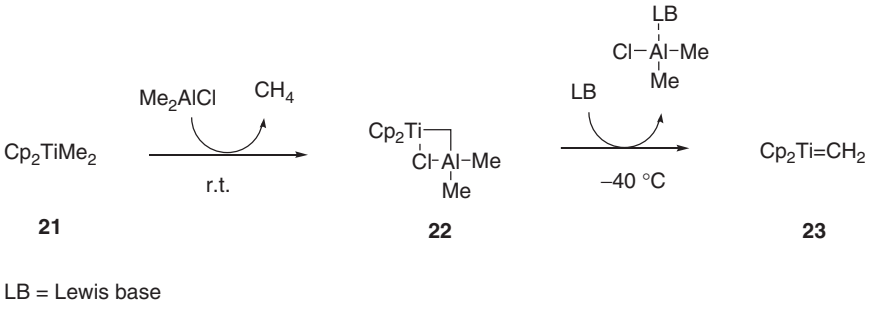
Dialkylated Ti(IV) and Zr(IV) compounds are thermally unstable and are capable of undergoing disproportionation with an elimination of the alkane molecules in many cases taking place even at lowered temperatures. The reaction proceeds by means of the abstraction of a hydrogen atom in α- or β-position to the metal atom of one of the alkyl groups by the second alkyl group.[2l,e,f,4,5] It is believed that the driving force for these transformations is the electronic interactions of the C–H bonds of alkyl groups with low-lying empty d-orbitals of the metal. The situations in which a hydrogen atom is covalently bonded simultaneously to both a carbon atom and a transition metal atom are named as agostic interactions.[11] In particular, significant deviations from the tetrahedral values of dihedral angles adjacent to the titanium atom and C–H or C–C bonds in the phosphine complexes of methyltitanium trichloride **17** and ethyltitanium trichloride **18** could be explained by operation of the agostic interactions (Scheme 8) that were experimentally detected.[12] Elimination of the alkane molecules from dialkylated Ti(IV) and Zr(IV) derivatives leads to an unstable and highly reactive alkylidene **19** or metallacyclopropane derivatives **20**.



M = Ti, Zr
$L^1 = PMe_2CH_2CH_2PMe_2$
L = Cp, alkoxy, halogen, or other ligands

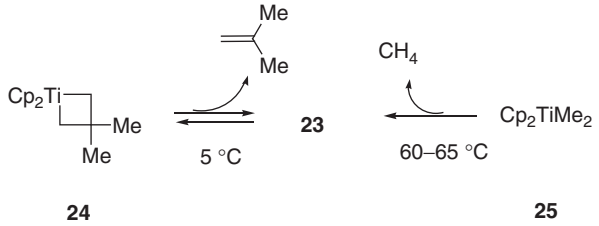
Scheme 8

An especially valuable crystalline complex **22** (the Tebbe reagent) arises from the reaction of dimethyltitanocene **21** with dimethylaluminium chloride, proceeding through the formation of titanocene methylene intermediate **23** (Scheme 9).[13] In turn, the latter is generated at lowered temperatures as reactive species by binding of the aluminum component of the bimetallic complex **22** with a Lewis base, such as pyridine.



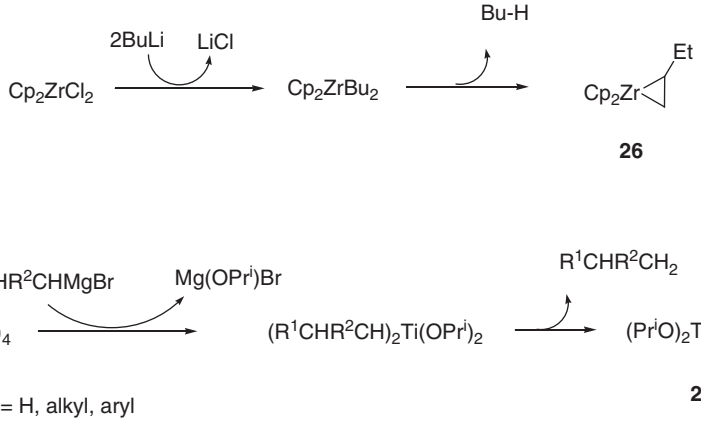
Scheme 9

One of the drawbacks of the Tebbe reagent **22** is the fact that a highly reactive organoaluminum component may initiate side reactions of sensitive carbonyl compounds. It was found that its reaction with isobutylene leads to crystalline titanacyclobutane derivative **24**, which can serve as a source for the generation of an aluminum-free methylene complex **23** under neutral conditions.[14] A more convenient method for the generation of methylene complex **23**, avoiding the difficulties associated with the handling of organoaluminum compounds and allowing the reactions to be performed at moderate temperatures, is based on the thermolysis of dimethyltitanocene **25** (the Petasis reagent, Scheme 10).[15]



Scheme 10

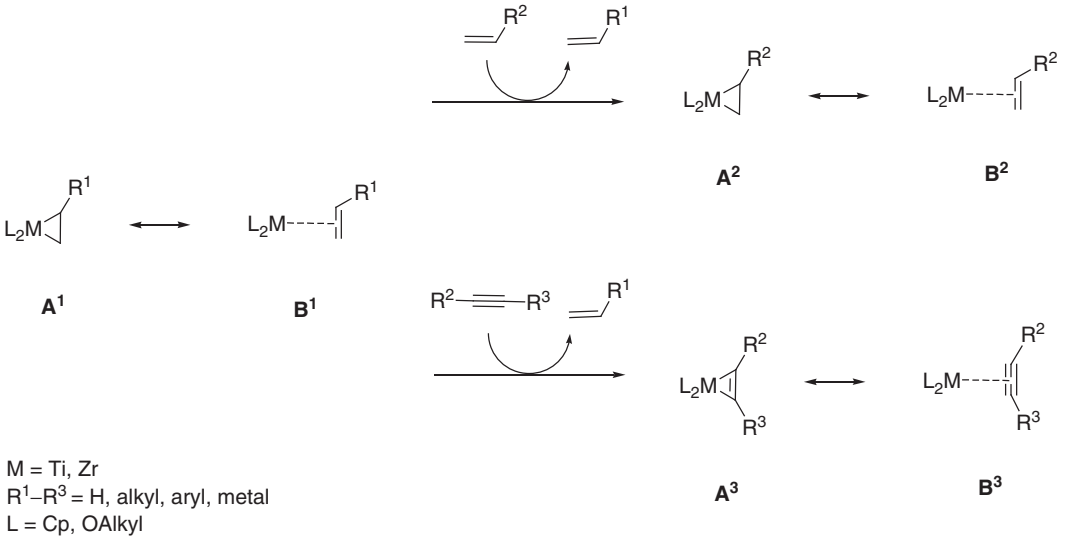
Disproportionation of dialkyltitanium and dialkylzirconium compounds having hydrogen atoms in β-position to the transition metal, usually proceeds at lowered temperatures to afford the corresponding metallacyclopropane species.[5] Generated by this way, ethyl-substituted zirconacyclopropane compound (the Negishi reagent) **26**[16] and alkoxytitanacyclopropane compounds (the Kulinkovich reagents) **27**[17] found wide synthetic applications (Scheme 11).



Scheme 11

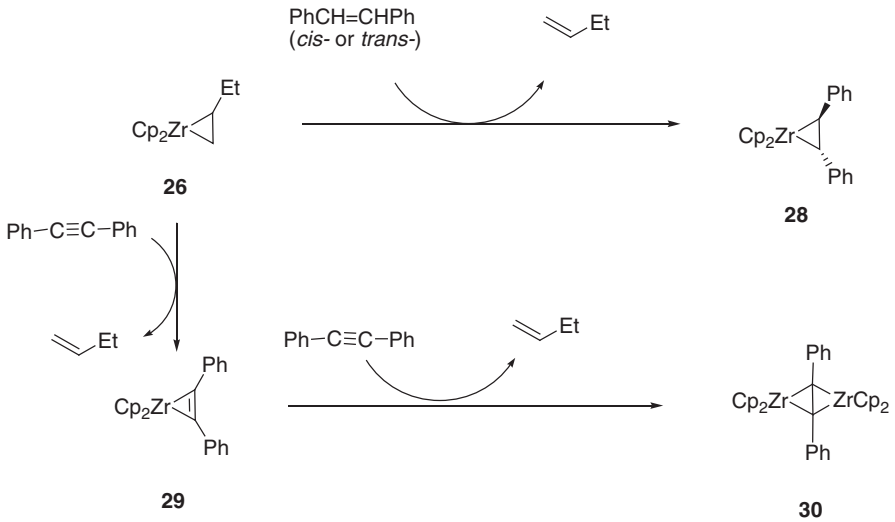
1.05.2.5 Ligand Exchange Reactions in Metallacyclopropane Species

The data on the structure of metallacyclopropane derivatives of early transition metals show that the geometry of the metallacycles corresponds to almost equivalent superposition of the classical metallacyclopropane A1 and metal-olefin B1 resonance structures (Scheme 12). As a consequence of this feature, the exchange of the organic ligand by other ligands, such as terminal olefins or disubstituted acetylenes, can be considered. The exchange leads to the formation of new metallacyclopropane A2 ↔ B2 or metallacyclopropene A3 ↔ B3 derivatives. This approach is particularly useful for generation of the metallacyclopropane and metallacyclopropene reagents bearing functional groups.[2a,f–h,5]



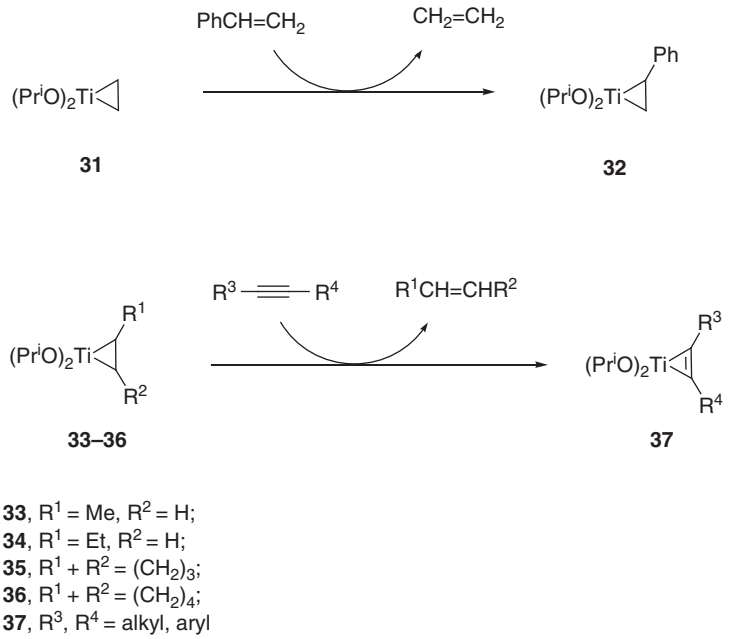
Scheme 12

A wide variety of metallacyclopropropane species bearing one alkyl or aryl substituent at the metallacycle were generated by the ligand exchange reactions, whereas data on the generation of their more substituted analogs in this way are relatively rare. As an example of an exception, crystalline *trans*-diphenylzirconacyclopropane **28** was obtained in good yield by displacement of 1-butene in zirconacyclopropane **26** with *cis*- or *trans*-stilbene (Scheme 13).[18] At the same time the preparation of disubstituted metallacyclopropene derivatives by the ligand exchange reactions usually occurs without complications. Remarkably, the interaction of metallacyclopropane **26** generated *in situ* by disproportionation of dibutylzirconocene in the presence of equimolecular amounts of diphenylacetylene led quantitatively, after deuterolysis of the resulting reaction mixture, to dibenzyl with fully deuterated methylene groups, presumably through metallacyclopropene intermediate (**29**), which under the reaction conditions are also involved in the exchange of olefin ligands giving the corresponding dimetallabicyclobutane species **30**.[19]



Scheme 13

Alkoxytitanacyclopropane species are also involved in the ligand exchange reactions. Thus, alkoxytitanacyclopropane reagent **31**, generated *in situ* by treatment of titanium isopropoxide(IV) with ethylmagnesium bromide in the presence of styrene, converts into the corresponding phenyl-substituted derivative **32** (Scheme 14).[20] Alkoxytitanacyclopropane species bearing alkyl substituents in the three-membered metallacycle (e.g., **33–36**) are usually involved in ligand exchange reactions with a better efficiency,[21] and their applications are especially useful for the generation of the titanacyclopropene species **37**.[22]



33, R^1 = Me, R^2 = H;
34, R^1 = Et, R^2 = H;
35, $R^1 + R^2 = (CH_2)_3$;
36, $R^1 + R^2 = (CH_2)_4$;
37, R^3, R^4 = alkyl, aryl

Scheme 14

1.05.2.6 Rearrangements of the Metallacyclopropane Precursors

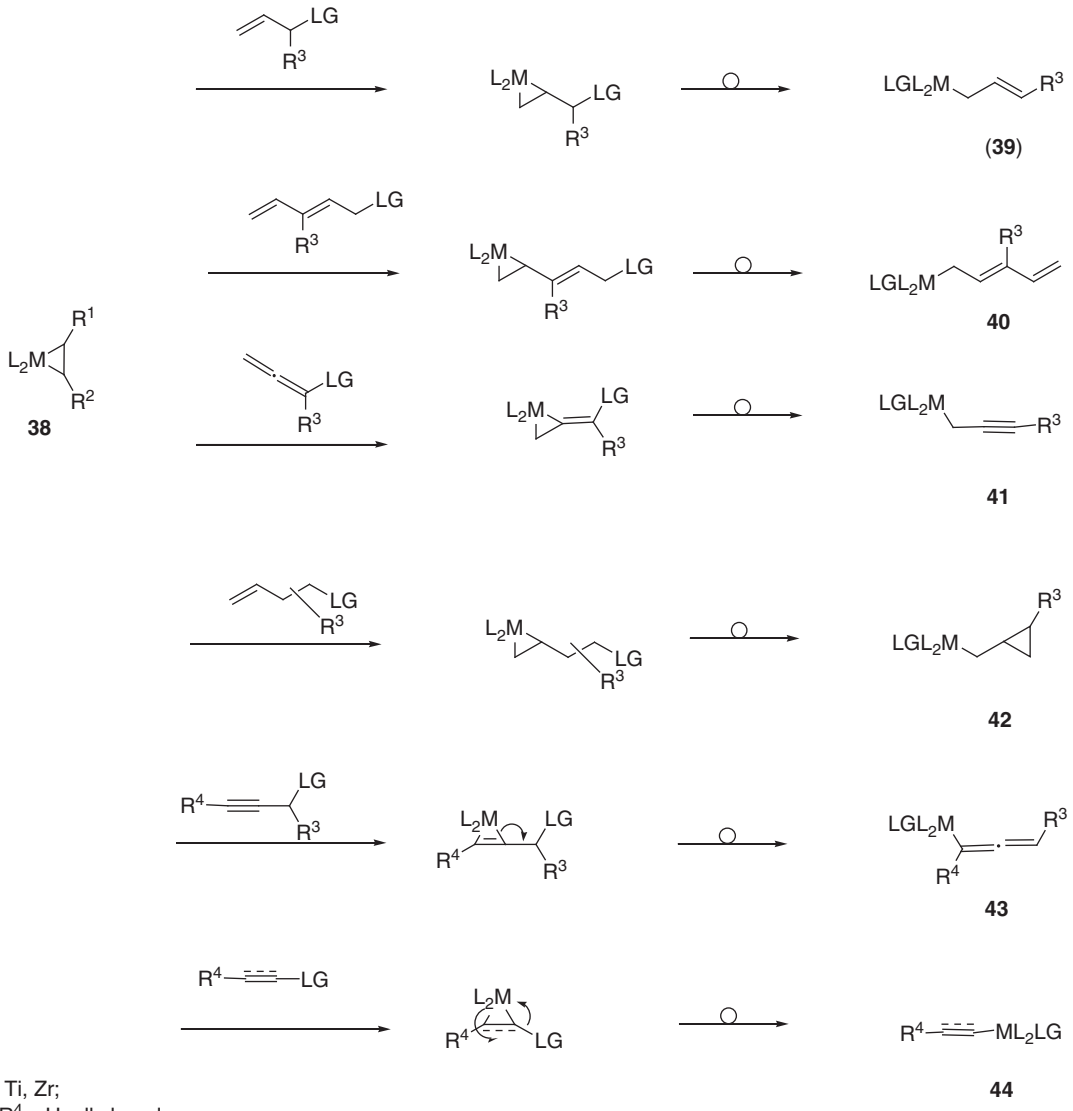
A convenient way for the generation of allyl-**39**, dienyl-**40**, propargyl **41**, cyclopropylmethyl **42**, allenyl-**43**, or alkenyl and alkynyl-**44** titanium(IV) and zirconium(IV) reagents involves ligand exchange reactions of metallacyclopropane species **38** with olefins or acetylenes bearing an appropriately positioned leaving group (LG), often a halogen atom or oxygen-containing substituent[5] or, in some cases, a hydrogen atom[23] (Scheme 15).

1.05.2.7 Carbometallation

The carbometallation of alkenes and alkynes with the corresponding metallacyclopropane or metallacyclopropene reagents, leading to the formation of metallacyclopentane, metallacyclopentene, or metallacyclopentadiene derivatives **45**, achieves the generation of 1,4-dicarbanionic intermediates (Scheme 16).[2a,d–h,5c–e,m–v] Carbometallation compete with the corresponding ligand exchange reactions and are more common for metallacyclopropene and unsubstituted metallacyclopropane reagents (metal–ethylene complexes), as well as for the intramolecular cyclizations.

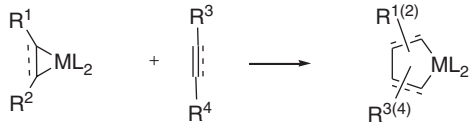
1.05.3 Carbonyl Addition Reactions

The development of flexible methods for the generation of organotitanium and organozirconium compounds allows the scope of synthetic applications of these reagents with carbonyl derivatives to be considerably expanded. Alkyl and aryl derivatives of titanium and zirconium are usually less reactive in nucleophilic addition to polar multiple bonds in comparison to organolithium or organomagnesium compounds. They react with ketones usually much slower than with aldehydes and are inert toward ester or dialkylcarboxamide carbonyl groups. In addition to the greater electronegativity and greater steric bulk surrounding the transition metals, the difference can also be associated with specific electronic interactions of C–H and C–C bonds of alkyl groups with low-lying empty d-orbitals. Polyalkylated titanium and zirconium compounds exhibit enhanced activity in comparison with the monoalkylated analogs in nucleophilic additions to the carbonyl group, but it seems that they have not yet found wide synthetic applications (in contrast to the products that are formed as a result of their disproportonation – the carbene complexes and metallacyclopropane reagents).



M = Ti, Zr;
R^1–R^4 = H, alkyl, aryl;
LG = heteroatom leaving group.

Scheme 15



M = Ti, Zr;
L = ligand

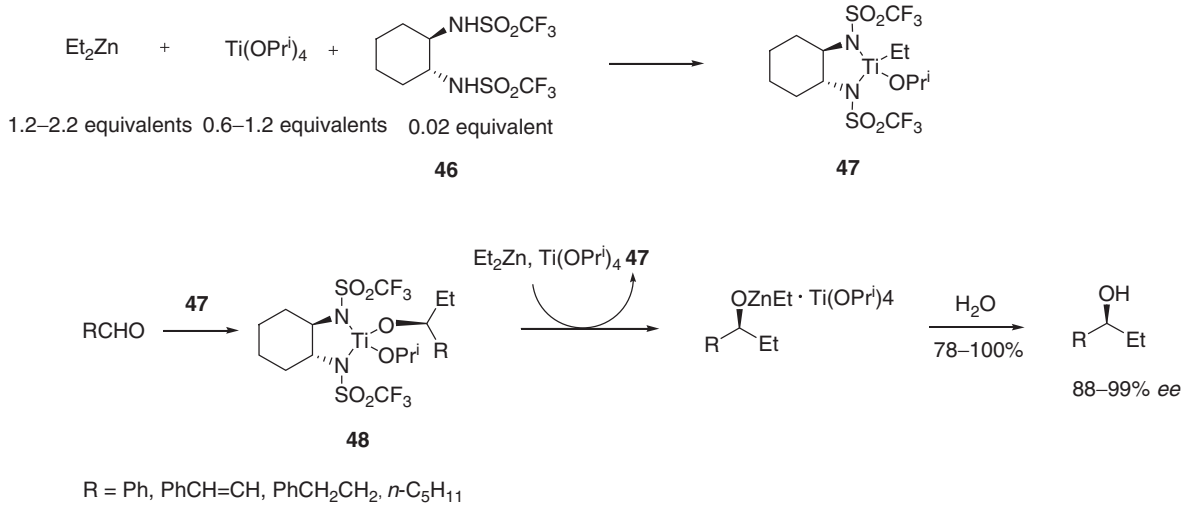
45

Scheme 16

1.05.3.1 Alkyl and Aryl Titanium and Zirconium Reagents

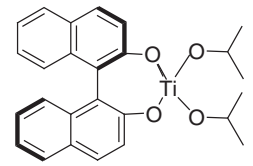
The lowered activity of the alkyl and aryl titanium and zirconium compounds toward the carbonyl addition is accompanied by higher chemo-, regio-, and stereoselectivity.[2i–k] A rational choice or design of the ligands at the metal is important for the elaboration of highly selective reagents and catalysts, due to a tendency of these metals to form sterically hindered five- or six-coordinated complexes and pronounced influence of the ligands on the reactivity of organometallic species.[2b,i–k,3a,f,g,j–n,r] An illustrative example of a highly enantioselective catalytic alkylation system presents the reaction of diethylzinc with aromatic and

aliphatic aldehydes in the presence of titanium tetraisopropoxide and sulfamide catalyst **46**.[24] It was found that various aggregates are formed between Et_2Zn and titanium complexes in the reaction mixture. Among them, ethyltitanium derivative **47** is likely the most active due to a higher electrophilicity of titanium atom connected with electron-withdrawing sulfonamide groups. After electrophilic activation of the carbonyl group and their insertion into the titanium–carbon bond, the key reagent **47** is regenerated by transmetallation of alkoxide derivative **48** with the diethylzinc-derived organometallics (Scheme 17).

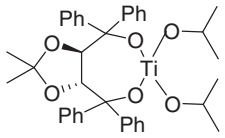


Scheme 17

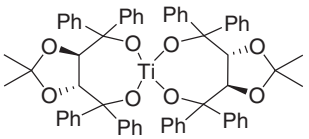
Among the numerous chiral ligands that were tested in enantioselective addition of alkyl and aryl titanium derivatives to aldehydes, good properties were shown by titanium BINOLates (e.g., (*S*)-**49**)[25] and TADDOLates (e.g. (3*R*, 4*R*)-**50**).[26] Such compounds are able to provide high enantioselectivity in stoichiometric reactions of the organotitanium derivatives with aromatic and aliphatic aldehydes. For example, 'ate' complexes resulting from the treatment of the spirocyclic titanate **51** with MeLi or MeMgBr react with benzaldehyde with good enantioselectivity and MeLi to give better results than the Grignard reagents (Scheme 18).[27]



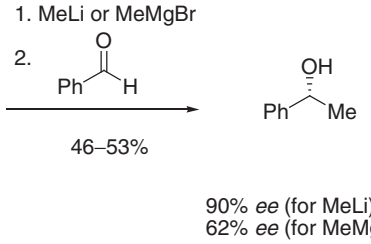
(*R*)-**49**



(3*R*, 4*R*)-**50**



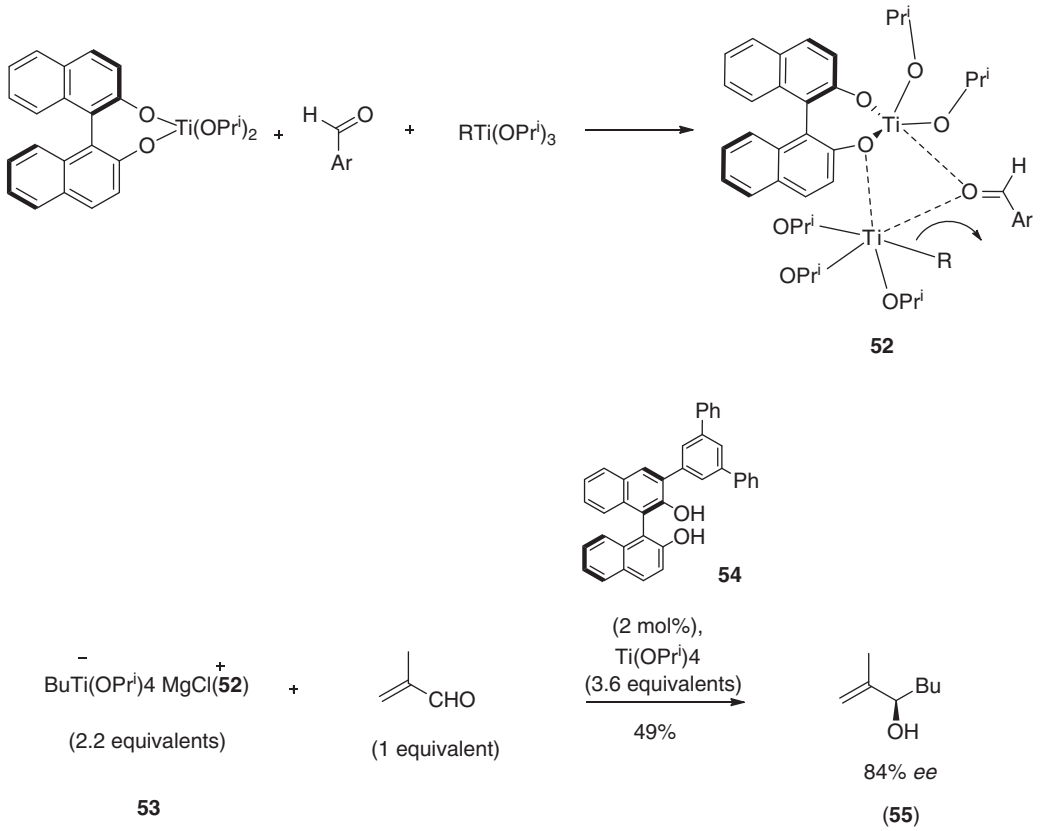
51



Scheme 18

Enantioselective addition of the alkyl and aryl titanium ate complexes to carbonyl compounds could be carried out also under treatment of catalytic amounts of chiral Ti-BINOLates in the presence of a large amount of titanium tetraisopropoxide. The data on solution structures, reactivity, and solid-state structures provide evidence that the most reactive reagent **52** involves two

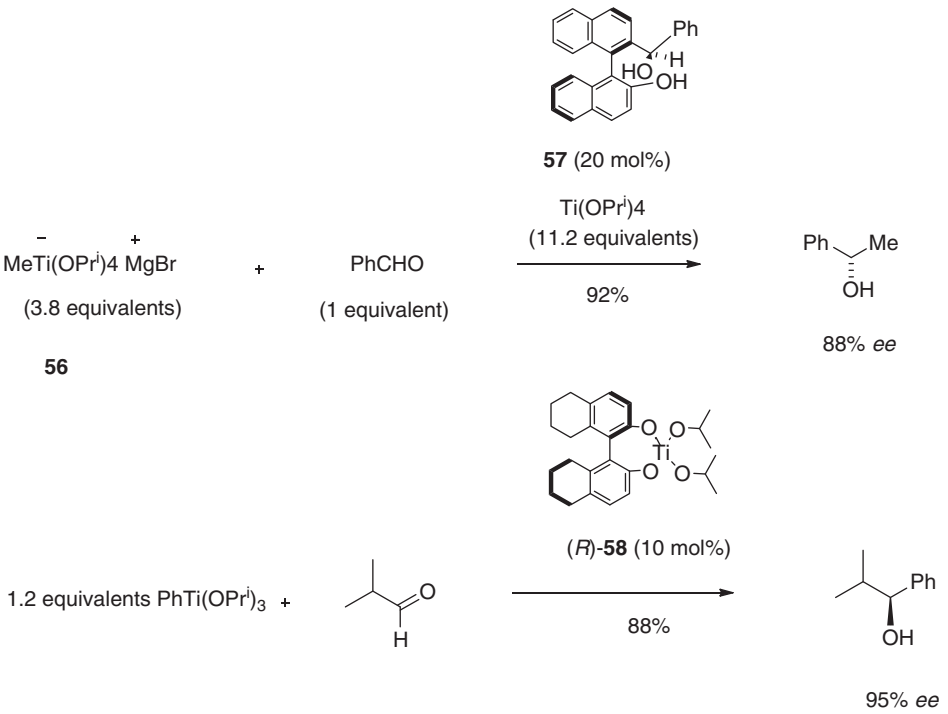
titanium centers, one of them bears a BINOLate ligand and another one is alkylated titanium isopropoxide (Scheme 19).[28] The authors suggest that the titanium atom, which is covalently bonded with chiral ligand, to be more active toward coordination of aldehyde and provides the activation of the carbonyl group to addition of the organometallic reagent. Thus, the treatment of methacrolein with excess ate complex **53** and titanium(IV) isopropoxide in the presence of small amounts of aryl-substituted BINOL catalyst **54** afforded enantiomerically enriched alcohol (*R*)-(**55**).[29]



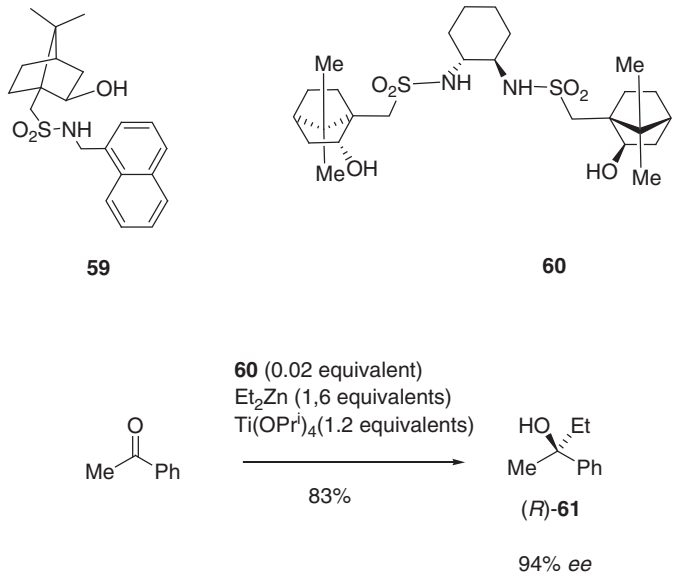
Scheme 19

An excess amount of titanium tetraisopropoxide was found to be crucial for achieving high enantioselectivity in the addition of alkyl Grignard ate complexes (e.g., **56**) to aromatic aldehydes in the presence of readily available BINOL derivative **57** (Scheme 20).[30] At the same time, the enantioselective addition of alkyl and aryl Grignard reagents to aldehydes in the presence of (*S*)-**49** and titanium tetraisopropoxide with no excess of the latter was successfully achieved when the reaction was performed in the presence of *bis*-[2-(*N*,*N*-dimethylamino)ethyl] ether as chelating additive.[31] It was assumed that the latter inhibits the racemic background reaction promoted by Lewis acidic salt MgBr(OPr^i). Remarkably, the direct addition of ArTi(OPr^i)$_3$ to aromatic and aliphatic aldehydes catalyzed by (*R*)-H8-BINOL-derived titanium catalyst **57** efficiently proceeds without excess of titanium tetraisopropoxide at ambient temperature with very good enantioselectivity. For example, PhTi(OPr^i)$_3$ reacts with isobutyraldehyde to afford phenylcarbinol **58** with 88% *ee* (Scheme 20).[32]

A high enantioselective addition of organometallics to ketones provides access to synthetically valuable enantioenriched tertiary alcohols and remains a challenging task in asymmetric catalysis. Good progress was achieved by using titanium ate complexes of zinc,[33] aluminum,[34] and lithium[35] in combination with chiral camphorsulfonamide ligands. For example, titanium catalyst prepared from sulfonamide **59** promotes the addition of dimethyl or diethyl zinc-derived titanium ate complexes to aromatic ketones leading to the tertiary alcohols with up to 89% *ee* (Scheme 21).[33a] The reaction proceeds slowly and its completion takes several days with 20 mol% catalyst. More efficient addition of aryl and ethylzinc-derived titanium reagents to ketones with enantioselectivity often exceeding 90% have been achieved by using *bis*-(sulfonamido)Ti(OPr^i)$_2$ ligands.[33c,d] For example, 2–10 mol% of the catalysts bearing C_2-symmetric sulfonamide-derived ligand **60** promotes the addition of the diethylzinc ate complex to acetophenone to afford, after 1 or 2 days at room temperature, alcohol (*S*)-**61** with 96% *ee*. The addition of the corresponding dimethylzinc reagent to propiophenone gave the (*R*)-enantiomer of the same alcohol **61** in 83% yield and 94% *ee* (Scheme 16).[33c]



Scheme 20

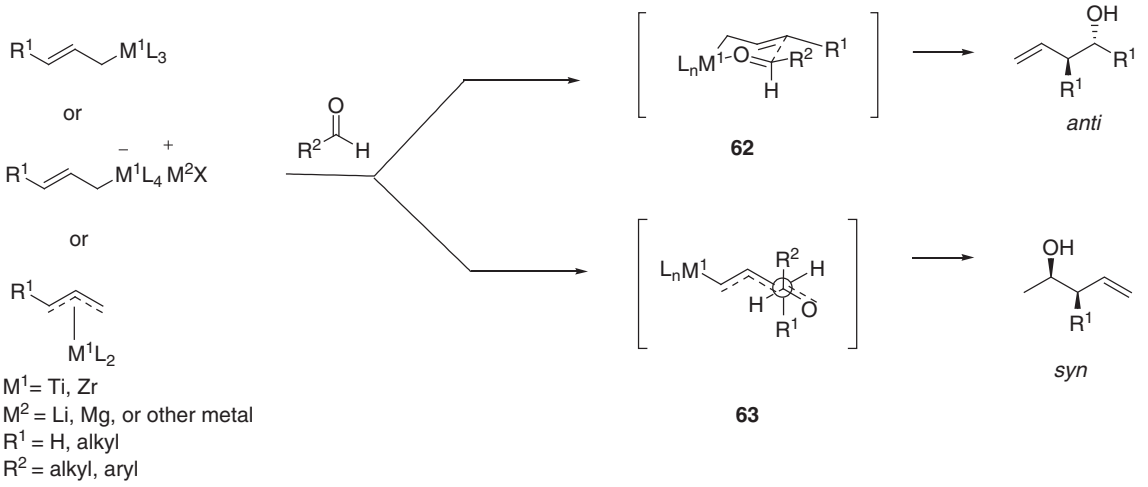


Scheme 21

1.05.3.2 Allyl and Dienyl Reagents

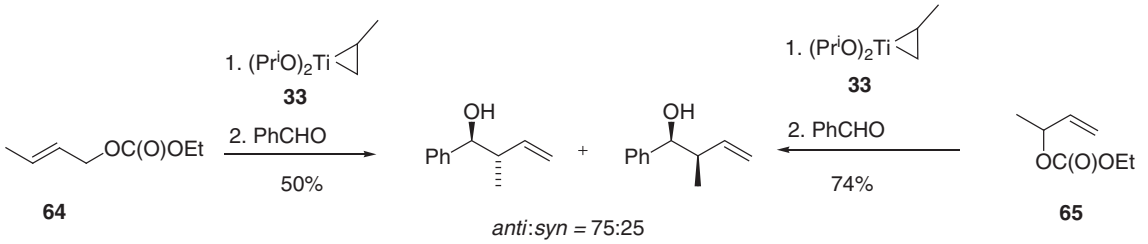
Allylation of the carbonyl group of aldehydes and ketones are frequently used in the practice of organic synthesis due to the possibility of further conversion of the double bond in the resulting homoallylic carbinols to various functional groups. Allyltitanium and allylzirconium derivatives exhibit enhanced reactivity to the carbonyl addition reactions in comparison with the corresponding aliphatic and aromatic derivatives.[2b,i,l,3a,c,f–h,j–n,r] Allyltitanium compounds react easily with aldehydes than with ketones, but the chemoselectivity can be turned out by using the reagents with dialkylamine ligands. The latter are able to add quickly to a carbon atom of aldehyde to afford the corresponding hemiamonals and provide by this way the protection of the carbonyl group from addition of the organometallic reagent. η^1- and η^3-allyltitanium and zirconium compounds bearing substituents at C-3 react with the carbonyl group of the aldehyde in regioselective manner to afford the corresponding α-branched

homoallylic alcohols. Addition of the *trans*-3-substituted allyltitanium reagents with aldehydes proceeds with high *anti*-diastereoselectivity. The latter arises from a pseudoequatorial orientation of the substituent at C-3 carbon and the aldehyde R group in the cyclic transition state **62**. Location of the alkyl substituent at C-3 in *trans*-position of the transition state is especially favorable in η^3-allyltitanium complexes with cyclopentadienyl ligands (Scheme 22).[2b] At the same time, in the presence of strong Lewis acids ($BF_3{\cdot}OEt_2$) or highly coordinating solvents (tetrahydrofuran (THF) and hexamethylphosphoramide) the allylation proceeds via open transition state **63** giving the *syn*-adducts.[3l]



Scheme 22

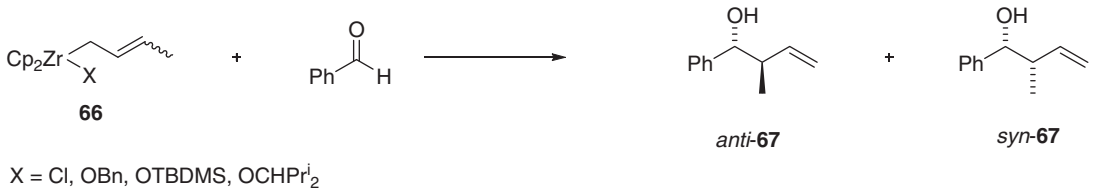
An efficient synthetic approach to the preparation of allyltitanium compounds is based on the reactions of allyl halides or allyl alcohol derivatives with suitable alkoxytitanacyclopropane reagents. The reactions proceed via olefin ligand exchange followed by formation of the allylic carbon–carbon double bond by means of an intramolecular β-elimination of the corresponding metal halide or metal oxide (Scheme 9, the transformation **38** to **39**). This approach to allylic derivatives of titanium and zirconium can be formally regarded as oxidative addition of the allylic compounds to a titanium(II) species. The allylic titanium compounds prepared by this way show reactivity similar to those obtained in the reaction of $ClTi(OPr^i)_3$ with allyllithium or magnesium compounds and were applied for allylation of a wide range of aldehydes and ketones.[5c,i,k,o] When regioisomeric allylic derivatives were used as starting compounds, the same allyltitanium compounds were generated; however, better yields of the allylation products were obtained from the regioisomers with less-substituted carbon–carbon double bond. Thus, in reaction of benzaldehyde with the allyl titanium compound derived from either 2-buten-1-yl ethyl carbonate (**64**) or 1-buten-3-yl ethyl carbonate (**65**) the better yield was obtained by using the latter substrate, whereas the formation of the corresponding methylhomoallyl alcohols with a *anti*:*syn* ratio of 75:25 was observed irrespective of the starting carbonate (Scheme 23).[36]



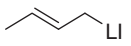
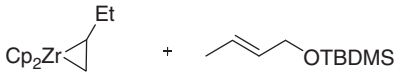
Scheme 23

The *anti*-alcohols are formed also predominantly in the reaction of aldehydes with substituted at C-3 η^1-allylzirconium derivatives generated by transmetallation of allylmetal with Cp_2ZrCl_2, hydrozirconation of allenes, or rearrangement of zirconacyclopropane intermediates.[5k,u]

For example, addition of η^1-crotylzirconium reagents **66**, generated from lithium precursors by transmetallation or oxidative addition reactions, to benzaldehyde afforded α-methylated alcohols **67** with a similar diastereoselectivity (Scheme 24),[37,38] which is slightly lower in comparison with the corresponding reactions of the crotyltitanium reagents.[2b]

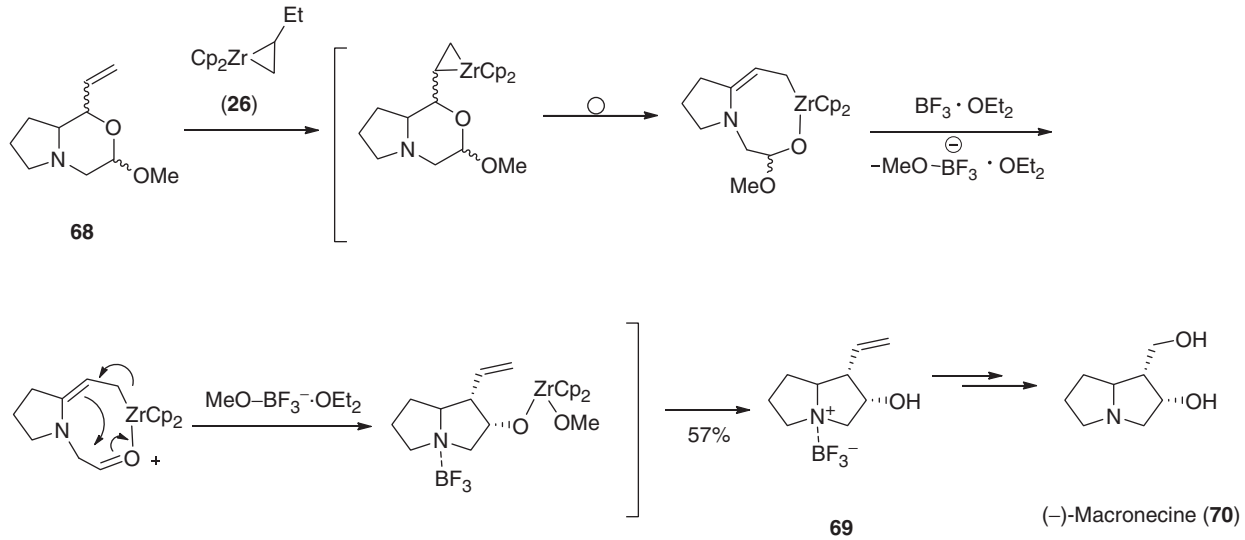


X = Cl, OBn, OTBDMS, $OCHPr^i_2$

X	Method for generation	Temp. (°C)	Yield	Diastereoselectivity *anti*-**67** : *syn*-**67** *anti*-/*syn*-ratio	References
Cl	Cp_2ZrCl_2 + 	–78	95	85:15	37
OBn		r.t.	76	63:37	38
OBn		r.t.	67	66:34	38
OTBDMS		r.t.	77	67:33	38

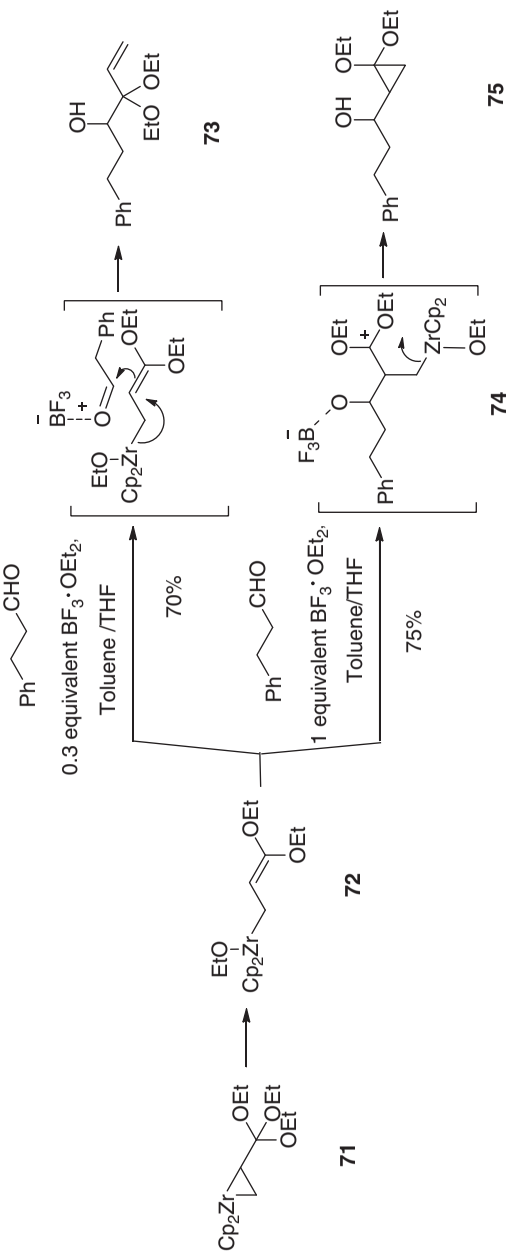
Scheme 24

The use of α-oxysubstituted zirconacyclopropane precursors are especially convenient for the generation of highly functionalized allylzirconium intermediates, which is illustrated by the synthesis of the pyrrolizidine alkaloid (–)-macronecine **70** (Scheme 25).[39] Involving of the diastereomeric mixture of morpholine derivative **68** in the olefin ligand exchange reaction with zirconacyclopropane intermediate **26** in the presence of $BF_3 \cdot OEt_2$ gave a reasonable yield of pyrrolizidine-derived BF_3 complex **69** as a single isomer via intramolecular addition of allylzirconium intermediate **68** to the aldehyde carbonyl group.



Scheme 25

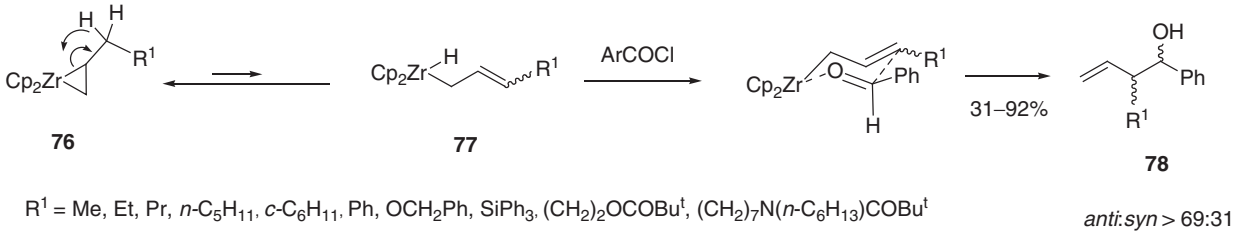
γ,γ-Dialkoxyallylic zirconium species **72**, generated by the olefin ligand exchange in zirconacyclopropane precursor **71**, react smoothly with aromatic and α,β-unsaturated aldehydes providing the corresponding α-hydroxy acetal derivatives **72** (Scheme 26).[40] It is noteworthy that in the reaction of **72** with β-phenyl propionic aldehyde leading to α-hydroxy acetal **73**,


Cp2Zr
OEt
OEt
OEt
71
EtO
Cp2Zr
OEt
OEt
72
Ph
CHO
0.3 equivalent BF3·OEt2,
Toluene /THF
70%
EtO
Cp2Zr
BF3
O
Ph
OEt
OEt
OH
Ph
EtO
OEt
73
Ph
CHO
1 equivalent BF3·OEt2,
Toluene/THF
75%
F3B
O
OEt
OEt
ZrCp2
OEt
Ph
OH
OEt
OEt
Ph
74
75

Scheme 26

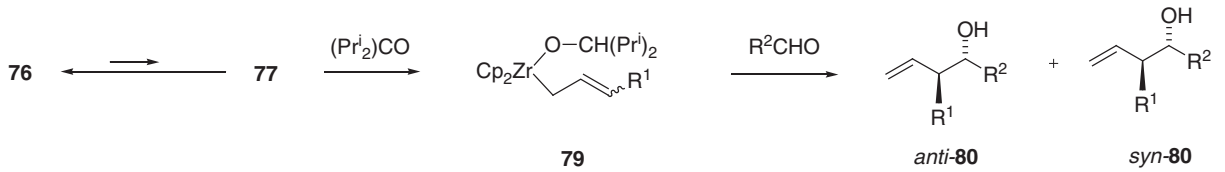
addition of 0.2–0.3 equivalent of $BF_3 \cdot OEt_2$ is necessary to activate the carbonyl group, whereas in the presence of more than 1 equivalent of Lewis acid an electrophilic addition of the carbonyl proceeds at *β*-position of the reagent **72** due to nucleophilic activation of the double bond by *π*-electron-donating alkoxide groups. The *in situ* generated oxocarbenium intermediate **74** quenches intramolecularly with cleavage of the alkyl zirconium bond to give the *gem*-diethoxycyclopropane derivatives **75**.

The formation of homoallylic alcohols **78** in the reaction of zirconacyclopropane **76** with aryl chlorides has been explained by existence of an equilibrium between the zirconacyclopropanes **76** and the zirconocene allyl hydrides **77**, which is shifted toward **76** (Scheme 27).[23,41] The authors supposed that hydride attack of the minor component **77** on aryl chlorides should result in formation of the corresponding aldehydes, which further undergoes allylation to form the homoallylic alcohols **78** with moderate *anti*-diastereoselectivity.



Scheme 27

By using diisopropyl ketone for an acceptance of an hydride ion in the zirconocene allyl hydride complexes **77** allows to generate the corresponding allylzirconium intermediates **79** bearing sterically hindered alkoxide ligand (Scheme 28).[28c] The reaction of aldehydes with threefold excess of allylzirconium reagents **79** generated in this way proceeds in high yields with

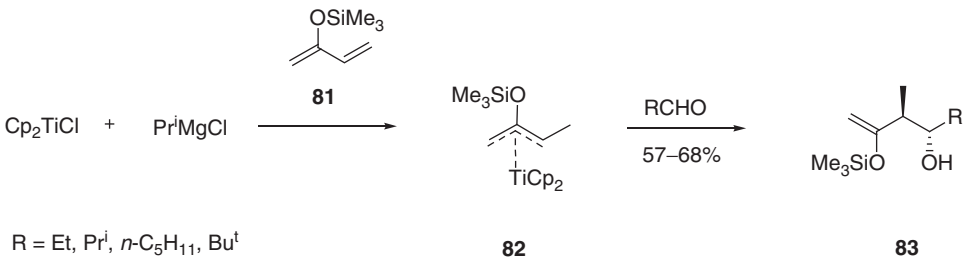


Diastereoselectivity *anti*-(**80**)/*syn*-(**80**)					
Method	R^1	R^2	Temp. (°C)	Yield	*anti*-/*syn*- Ratio
A	Me	*n*-C_9H_{19}	–78	85	86:14
A	Me	Ph	–78	98	68:32
A	Me	PhCH=CH	–78	80	77:23
A	*n*-Pr	*c*-C_6H_{11}	–78	99	94:6
A	Me	*n*-C_9H_{19}	25	91	43:57
A	Me	Ph	25	99	35:65
A	Me	PhCH=CH	25	95	14:86
A	*n*-Pr	*c*-C_6H_{11}	25	95	17:83
B	Et	Ph	–78	83	81:19
B	*n*-C_5H_{11}	PhCH=CH	–78	64	89:11
B	Et	Ph	25	93	26:74
B	*n*-C_5H_{11}	PhCH=CH	25	72	28:72

Scheme 28

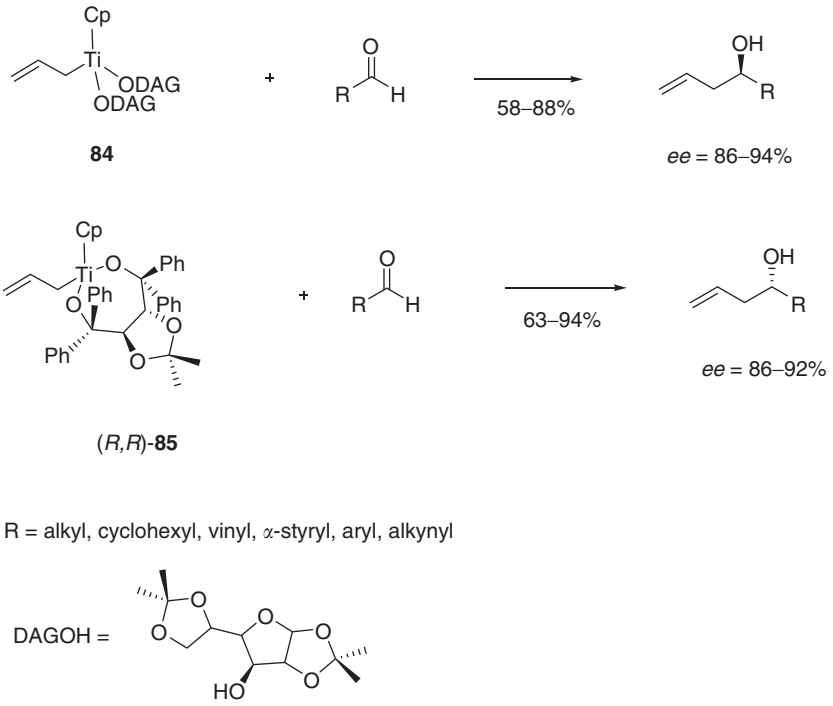
standard *anti*-diastereoselectivity at −78 °C, but at 25 °C *syn*-alcohols are formed as the major products. The effect of temperature on stereoselectivity was attributed to isomerization of the homoallylic alcohols **80** at ambient temperature via a retro-allylation process.

Heteroatom-substituted allyltitanium reagents also react with the carbonyl group in a stereoselective manner, creating a rich opportunity for their synthetic applications. For example, the reaction of aliphatic aldehydes with η^3-allyltitanium reagent **82**, obtained by hydrotitanation of 2-trimethylsilyloxydiene **81**, proceeds in a highly regio- and diastereoselective fashion to afford exclusively *anti*-adducts **83**, presumably via transition states with boat-like structures (Scheme 29).[42]



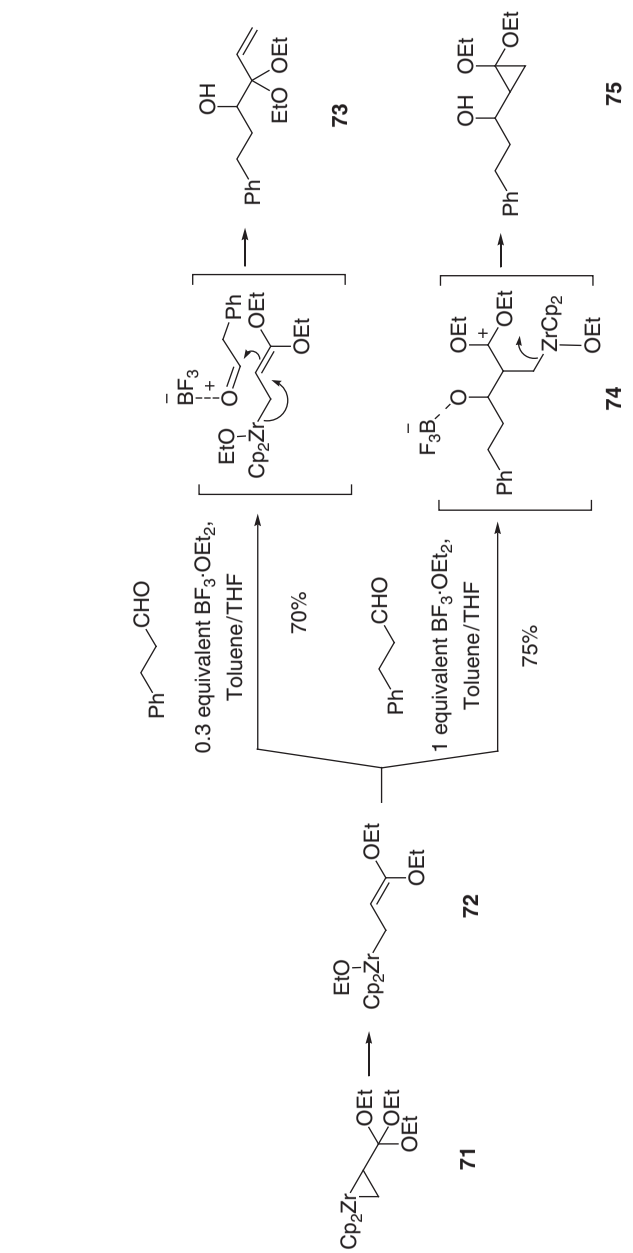
Scheme 29

Successful asymmetric allylation of the aldehydes with organotitanium compounds was accomplished at first by using allyl monocyclopentadienyltitanium reagent **84** with diacetoneglucose (DAGOH)-derived ligands.[2b] Later, it was found that (*R,R*)-complex **85** with a tartrate-derived ligand obtained from natural tartaric acid is the complementary reagent for the transfer of allyl groups to aldehydes with the opposite enantioselectivity (Scheme 30).[43]



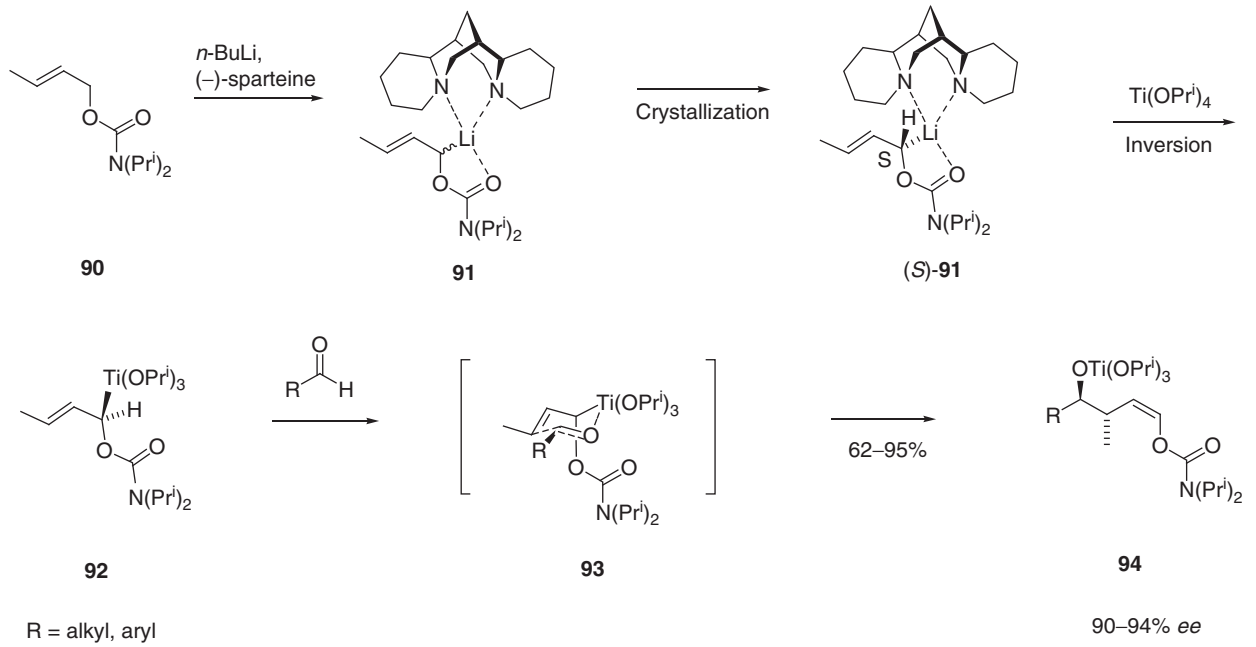
Scheme 30

When chiral allyltitanium reagent has a substituent at C-3 of the allyl group, the double *syn*-/*anti*- and (*R*)-/(*S*)-stereocontrol in the addition reactions to aldehydes is observed. Methodology for the asymmetric synthesis of 1,2-, 1,3-, and 1,5-diols and polypropionate units employing addition of chiral allyltitanium complexes such as **85** and **87** to suitable aldehydes and its application to syntheses of natural products was described.[3h] Thus, the key intermediate **88** in asymmetric total synthesis of the immunosuppressant (–)-pironetin **89** was prepared from (*S*)-aldehyde **86** by the construction of the stereogenic centers at C-8 and C-9 with the help of the crotyltitanium reagent (*R,R*)-(**87**), whereas at C-7 by using the allyltitanium complex (*S,S*)-**85** (Scheme 31).[44]


Cp2Zr
OEt
OEt
OEt
71
EtO
Cp2Zr
OEt
OEt
72
Ph
CHO
0.3 equivalent BF3·OEt2,
Toluene/THF
70%
BF3
O
EtO
Cp2Zr
Ph
OEt
OEt
OH
Ph
EtO OEt
73
Ph
CHO
1 equivalent BF3·OEt2,
Toluene/THF
75%
F3B
O
OEt
OEt
ZrCp2
OEt
Ph
74
OH OEt
OEt
Ph
75

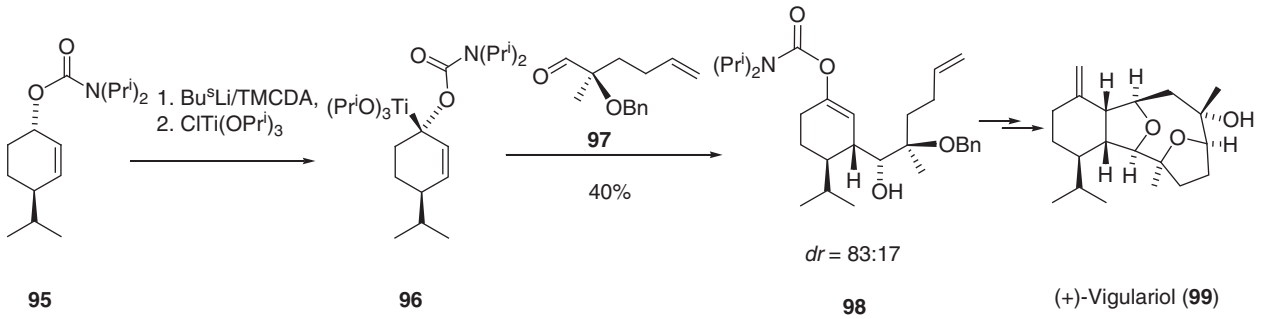
Scheme 31

Allyltitanium reagents in which the titanium atom is directly bonded to the chiral carbon atom have also significant synthetic potential. The preparation of such reagents is a difficult task, which was achieved by Hoppe.[3b] The chiral allyltitanium reagent (*R*)-**92** was generated by deprotonation of *N*,*N*-diisopropylcarbamate **90** by butyllithium in hydrocarbon solvents in the presence of (–)-sparteine at low temperature leading to the configurationally unstable allyltitanium derivative **91** (Scheme 32). Fortunately, in cyclohexane, dynamic resolution induced by crystallization of (*S*)-**91** is observed, allowing isolation of this reagent for further operations. The transmetallation of the crystalline lithium compound (*S*)-**91** with titanium tetraisopropoxide proceeds with inversion and essentially completes chiral transmission to form configurationally stable titanium intermediate (*R*)-**92**. The addition of the latter to aldehydes proceeds in high enantioselectivity via cyclic transition state **93** to form latent homoaldol products **94**.[45]



Scheme 32

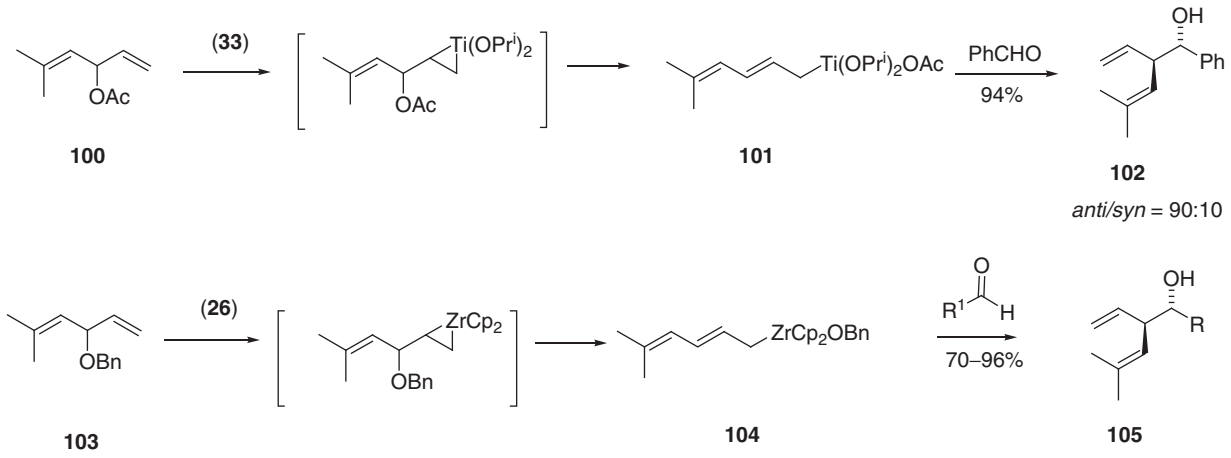
A synthetic route for cytotoxic diterpene (+)-vigulariol **99** was elaborated by using diasteroselective allylation of aldehyde (**97**) with chiral allyltitanium reagent **96** (Scheme 33).[45] The latter was obtained from natural (*R*)-(–)-cryptone by transformation to carbamate **95**, followed by diastereoselective deprotonation with *s*-BuLi in the presence of racemic tetralkyldiamine complexing agent and lithium–titanium exchange. The addition of the allyltitanium reagent **96** to aldehyde **97** afforded in moderate stereoselectivity the α-diol derivative **98**, which was transformed in the target product **99** by standard synthetic manipulations. Flexible synthetic opportunities for stereoselective synthesis also provide an addition reaction to the carbonyl group of the allyltitanium reagents bearing heteroatoms such as Si, N, P, and S.[2j,k,3r]



TMCDA = *rac-trans-N,N,N′,N′*-tetramethyl-1,2-diaminocyclohexane

Scheme 33

A convenient and practical route for the preparation of 2,4-pentadienyltitanium and zirconium reagents is based on olefin ligand exchange reaction of suitable metallacyclopropane species with the easily available pentadienol derivatives. These organometallic species react with aldehydes and ketones also in the γ-regioselective manner to produce *bis*-(homoallylic) alcohols with predominant *anti*-stereoselectivity. For example, dienyl acetate **100**[46] and benzyl derivative **103**[47] are transformed into *bis*-(homoallylic) alcohols **102** and **105**, respectively, via 2,4-pentadienyltitanium **101** and zirconium intermediates **104** with comparable yields in a highly γ-regioselective manner (Scheme 34).



Scheme 34

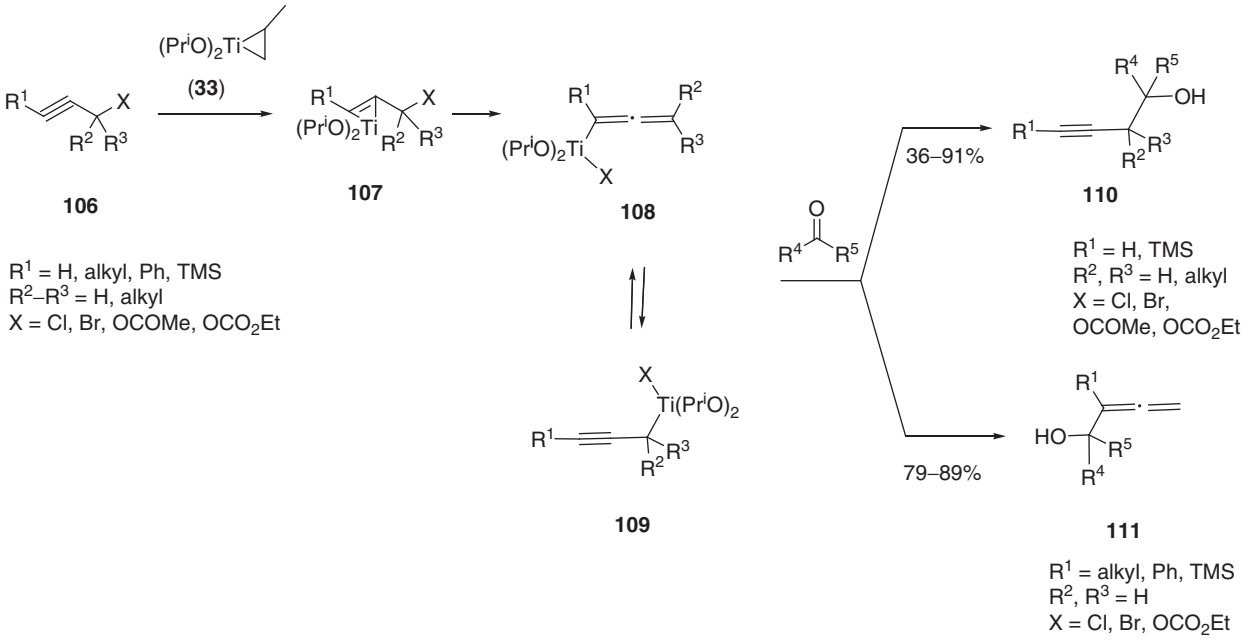
1.05.3.3 Allenyl and Propargyl Reagents

Allenyltitanium derivatives **108**, generated from propargyl halides (R^1 = H and TMS) or propargylic alcohol derivatives **106** via titanacyclopropane intermediate **107**, smoothly react with aldehydes and ketones to give the corresponding homopropargyl alcohols **124** (Scheme 35).[48] At the same time, the titanium reagents prepared from 1-substituted 3-halo-2-propynes **106** ($R^1 \neq$ H, X = Cl and Br) lead to allenyl alcohols **111**. These data evidence that in the latter case metallotropic rearrangement of allenyltytanium **108** to propargyltitanium species **109** takes place. Allenyl and propargyl titanium reagents are generated by this way to provide highly predominant *anti*-addition products that were used in the preparation of synthetically useful optically active allenic and homopropargylic 1,2-aminoalcohol derivatives **112** from available aldehyde **113** (Scheme 36).[49]

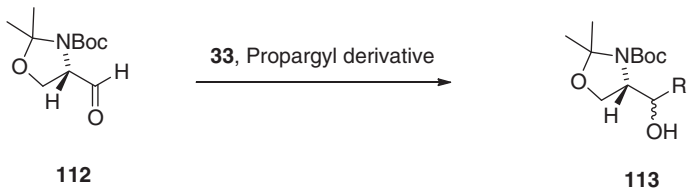
1.05.3.4 Alkenyl and Alkynyl Reagents

Interaction of carbonates from easily available alka-1,3-dien-1-ols with alkoxytitanacyclopropane reagents represents a convenient way for the generation of 1,3-dienyltitanium reagents that smoothly react with aldehydes to afford the corresponding allylic and allenylic alcohols. In the case of secondary allenylcarbonates (e.g., **114**), the reaction proceeds with highly *trans*-diastereoselectivity for the formation of diene alcohol **115** and *anti*-diastereoselectivity for the formation of α-ethyl-branched alcohol **116** (Scheme 37).[50]

Alkoxytitanacyclopropane reagents can also effectively induce intramolecular cyclization reaction of dienes, enynes, and diynes to form corresponding five-membered metallacycles, which by reactions with electrophiles could be transformed into various cyclic or acyclic derivatives. The reduced reactivity of alkyl and alkenyltitanium compounds toward the carbonyl compounds allows these transformations to be performed with unsaturated carbonyl compounds, for example, alkenoic and alkynoic esters. At the same time, the carbonyl groups are active enough to be involved in intramolecular insertion into titanium–carbon bonds, which is favorable for the implementation of cascade transformations. For example, the titanium-mediated intramolecular cyclization of (*Z*)-enol ester of acetylene aldehyde **117** leads to the stereoselective formation of functionalized bicyclo[3.3.0]octene **123** (Scheme 38). The reaction proceeds via the alkene–alkyne ligand exchange initiated with titanacyclopropane reagent **33**, leading to formation of titanacyclopropene intermediate **118**. The latter engages in carbometallation of the double bond with retention of the olefin geometry to give sterically less-hindered titanacycle **119**. Nucleophilic addition of the sp^3 carbanionic center of **119** to the nearby ester carbonyl group leads to the formation of ketone **121** via oxirane intermediate **120**. The geometric arrangement of the carbonyl group in the intermediate **121** facilitates a nucleophilic attack to the carbonyl by the remaining sp^2 carbanionic center. As a result, stereochemically homogenous bicyclic diol **123** was formed after hydrolysis of titanate **122**.[51]

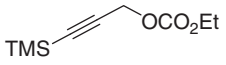
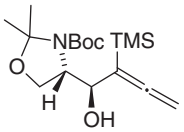
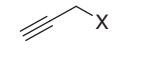
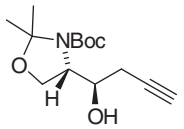
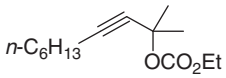
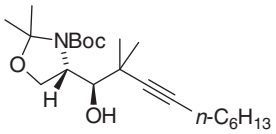

(PriO)2Ti
(33)
R1
X
R2
R3
106
107
108
109
R1 = H, alkyl, Ph, TMS
R2–R3 = H, alkyl
X = Cl, Br, OCOMe, OCO2Et
O
R4
R5
36–91%
79–89%
OH
HO
110
111
R1 = H, TMS
R2, R3 = H, alkyl
X = Cl, Br,
OCOMe, OCO2Et
R1 = alkyl, Ph, TMS
R2, R3 = H
X = Cl, Br, OCO2Et

Scheme 35

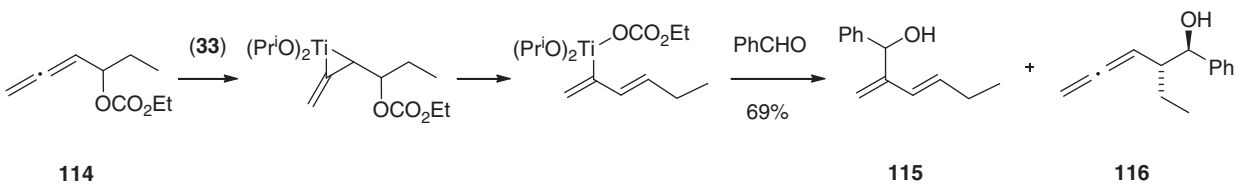


112 **113**

Diastereoselectivity of the formation of *anti*-(**113**)

Propargyl derivative	Major diastereomer	Yield (%)	*ds* (%)
		96	77
		83–88	86–87
		98	72

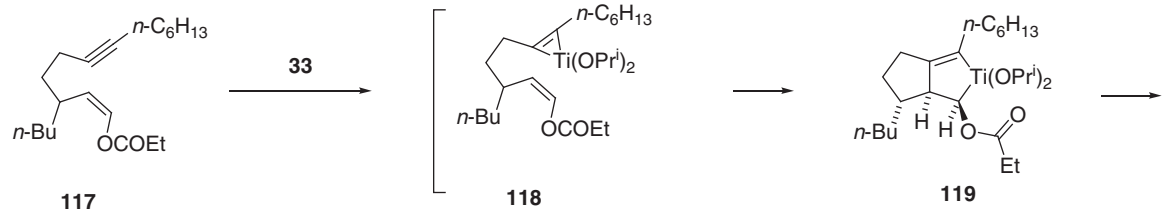
Scheme 36



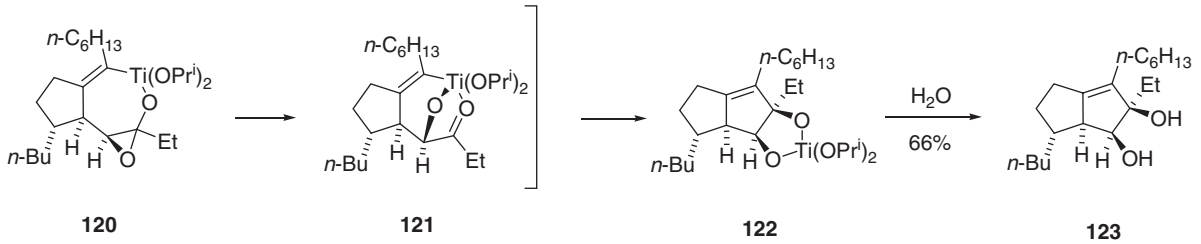
114 **115** **116**

115:**116** = 85:15

Scheme 37



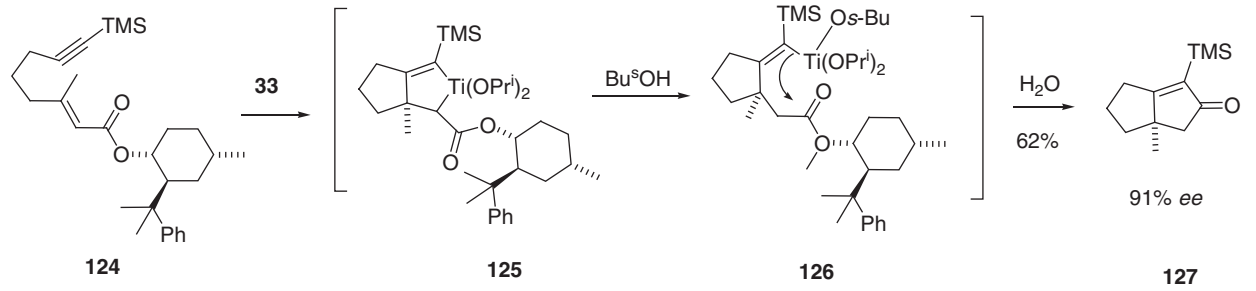
117 **118** **119**



120 **121** **122** **123**

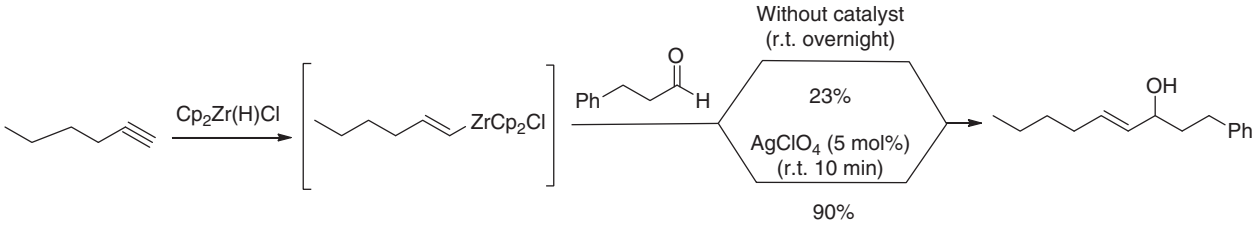
Scheme 38

A similar method was exploited for the elaboration of an efficient approach to angularly substituted optically active bicyclic ketones from the alkenyne esters with trisubstituted double bond and menthol-based auxiliary. For example, carbometallation of enynoate **124** initiated by alkoxytitanacyclopropane reagent **33** leads to the formation of titanacycle **125** which, after site-selective protonation with *s*-BuOH of the more reactive sp^3 carbanionic center, affords alkenyltitanium intermediate **126** (Scheme 39).[52] The latter undergoes intramolecular addition of the sp^2 carbanionic center to the ester carbonyl group to afford bicyclic ketone (–)-**127** isolated in good yield and with high enantiopurity. The presence of the *β*-alkyl group to the ester in monocyclic intermediates is critical for the final intramolecular addition of alkenyltitanium segment to ester carbonyl group.



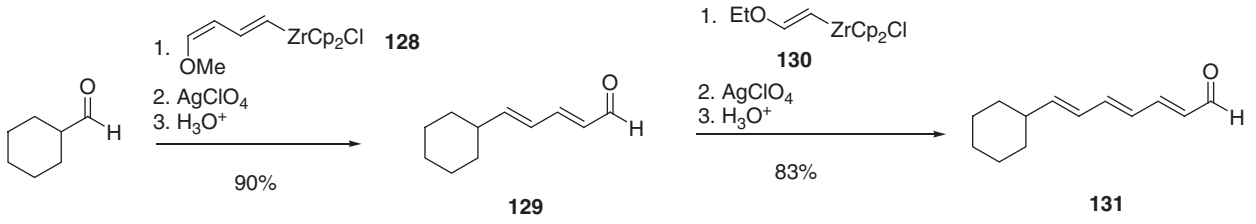
Scheme 39

Alkenylzirconium species exhibit lower reactivity toward carbonyl compounds than the corresponding alkyl derivatives and these reactions are too slow for direct synthetic applications. However, the Grignard-type addition of alkenylzirconocene chlorides to aldehydes is considerably accelerated in the presence of a catalytic amount of $AgClO_4$ as, for example, in the case of hexenylation of *β*-phenylpropionic aldehyde (Scheme 40).[31l,53] The catalytic action of silver ions on the reaction is explained by elimination of chloride anion from zirconocene chloride intermediates leading to the corresponding cationic zirconocene species, which enhances the electrophilicity of the carbonyl group on binding.



Scheme 40

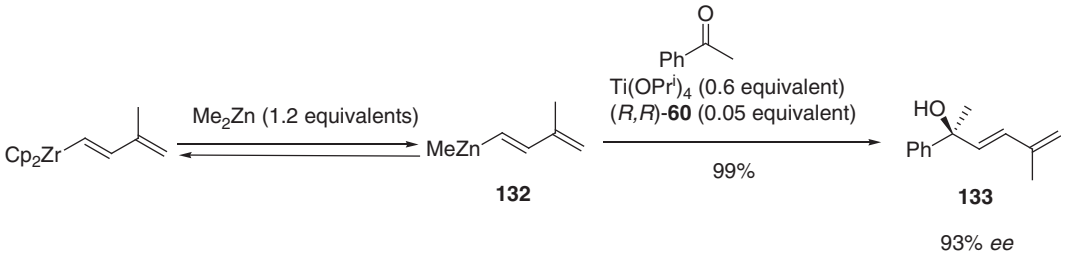
Alkoxyacetylenes may also serve as substrates for the preparation of synthetically useful functionalized alkenylzirconium compounds. Vinylzirconium reagents, prepared by this method, were used for two- and four-carbon vinylogation of aldehydes and such an approach is well suited for iterative applications. Thus, treatment of (*Z*)-1-methoxy-1-buten-3-yne and 1-ethoxyacetylene with $Cp_2Zr(H)Cl$ leads to the generation of alkenylzirconium reagents **128** and **130**, respectively. Ag^+-catalyzed consecutive reactions with cyclohexanecarbaldehyde result in the product of the five-carbon vinylogation **131** via dienal **129** (Scheme 41).[54]



Scheme 41

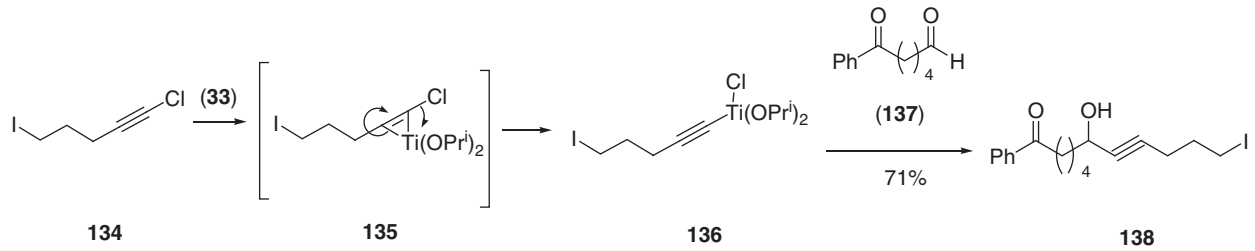
Alkenyl titanium reagents derived from the *bis*-(sulfonamide) diol ligand **60** are involved in the catalytic asymmetric addition to ketones with formation of (*E*)-disubstituted tertiary allylic alcohols in high enantioselectivity. The titanium reagents were generated from the corresponding alkenyl zinc precursors which, in turn, were prepared from the corresponding alkynes using

the hydrozirconation–transmetallation protocol. The hydrozirconation, followed by double transmetallation, and asymmetric addition of the resulted titanium reagents to ketones afford the chiral diene alcohols as exemplified in obtaining compound **133** by using dienylzirconium reagent **132** (Scheme 42).[55] A variety of vinylzirconium species can be also obtained by interaction of zirconacyclopropane reagents with vinyl halides, enol derivatives, vinyl sulfides, sulfoxides, and sulfones through olefin ligand exchange and followed by rearrangement of the heterosubstituted zirconacyclopropane intermediates[5g] (Scheme 15, the rearrangement of **38**–**44**).



Scheme 42

The reactivity of alkynyl titanium reagents toward aldehydes and ketones is sufficiently different that effective differentiation between these two functional groups can be achieved.[3d] A flexible route to the preparation of functionalized alkynyl titanium derivatives represents their generation from halogenoalkynes via appropriate titanacyclopropene precursors. Bromide, iodide, tosylate, carbonate, and ester groups are compatible with the formation of the organotitanium intermediates. For example, the reaction of ketoaldehyde **137** with iodo-substituted alkynyltitanium reagent **136**, prepared from acetylene dihalide **134** via rearrangement of chloro-substituted titanacyclopropene intermediate **135**, leading to secondary alcohol **138** is a good example of the alkynylation with high chemoselectivity between aldehyde and ketone carbonyls (Scheme 43).[56] A highly enantioselective addition of triisopropoxytitanium phenylacetylenide to aromatic ketones (up to 90% *ee*), promoted by (*R*,*R*)-BINOL, was also described.[57]

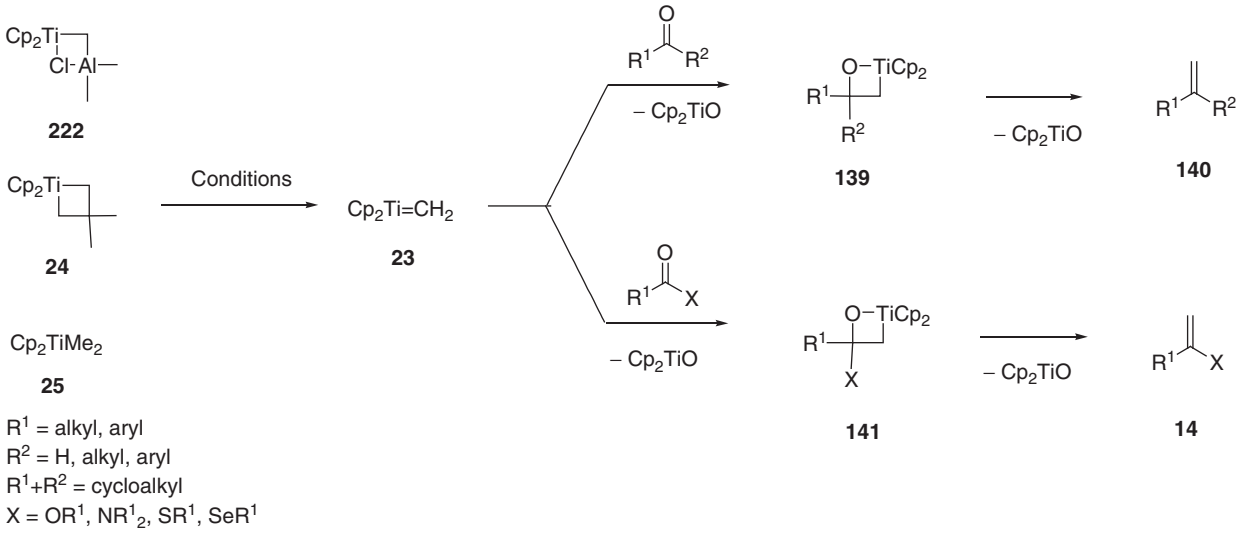


Scheme 43

1.05.3.5 Alkylidene Reagents

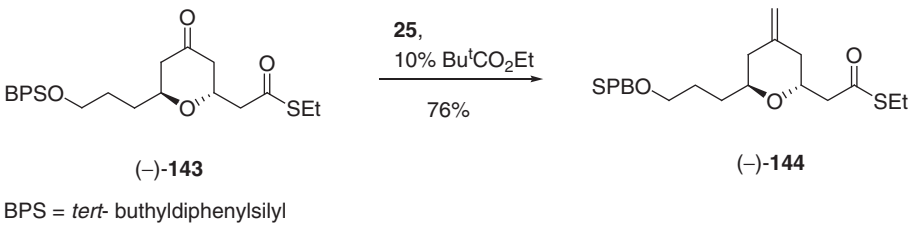
Highly reactive titanocene methylidene **23** is usually generated *in situ* by disproportionation of dimethyltitanocene **25**, as well as its thermally more stable complexes with methylaluminium dichloride **22** or isobutylene **24**. The advantage of the Tebbe reagent **22** is that the reactive titanium methylidene **23** is generated and reacts at low temperature. The main advantage of the Grubbs (**2**) and Petasis reagent **25** is in the generation of titanocene methylidene **23** in neutral conditions without using the additives. A procedure for the preparation of titanocene methylidene **23** based on the reactions of titanocenedichloride **8** or titanium tetrachloride with a zinc carbenoid was also developed. In the reactions with aldehydes, ketones, and carboxylic acid derivatives, titanocene methylidene **23** usually acts as an agent, leading to the methylenation of the carbonyl group **140** (Scheme 44).[4] Methylenation of the carboxylic acid derivatives, including esters, lactones, lactams, amides, thioesters, and selenoesters give the corresponding acid-sensitive heterosubstituted alkenes **142**, and these reactions are often used in synthetic practice. The methylenation reactions proceed at room temperature and below presumably via a nucleophilic addition of carbenoid carbon to carbonyl carbon with formation of oxatitanacyclobutane intermediates **139** and **141**. The driving force for irreversible fragmentation of the latter is presumably the formation of a strong titanium oxygen double bond.

Reactive species **23** is not basic, which is important for the methylenation of chiral aldehydes and ketones to avoid their epimerization or other undesired base-induced transformations.[4] For example, chemoselective olefination of functionalized pyranone **143** with the Petasis reagent **25** in the presence of minor amounts of ethyl pivalate furnished methylene pyran derivative



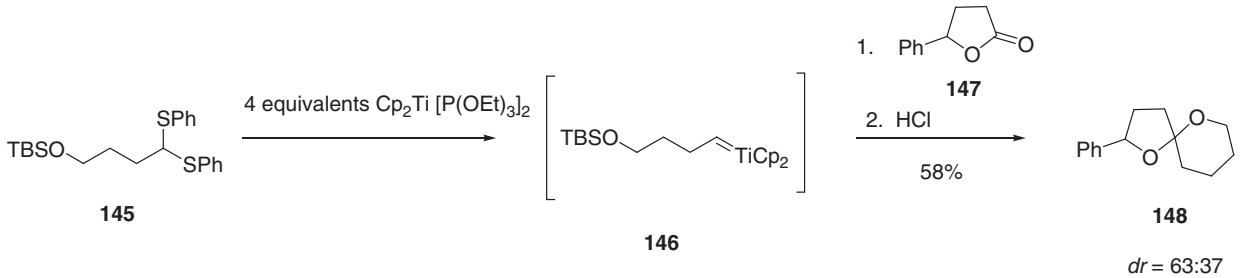
Scheme 44

144 in good yield. The ethyl pivalate was employed as sacrificed additive to prevent side reactions of **23** with the resultant *exo*-olefin **144** (Scheme 45).[58]



Scheme 45

Alkylidenetitanocenes generated by disproportionation of dibenzyltitanocene and some other dialkylated titanocenes are also able to alkenylate carbonyl compounds with moderate-to-good yields. An alternative approach to olefination of carbonyl compounds by using organotitanium compounds consists in the generation of putative alkylidene intermediates by the desulfurizative titanation of thioacetals with the low-valent titanium species.[4] For example, alkylidenation of lactone **147** with functionalized titanium carbenoid reagents **146** generated from thioacetal **145** leads to the corresponding enol ethers, which after acid-induced cyclization yield spiroacetal **148** (Scheme 46).[59]

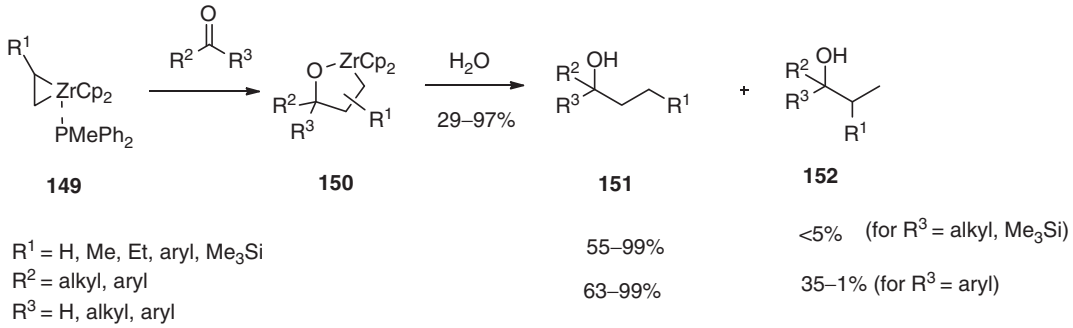


Scheme 46

1.05.3.6 Metallacyclopropane Reagents

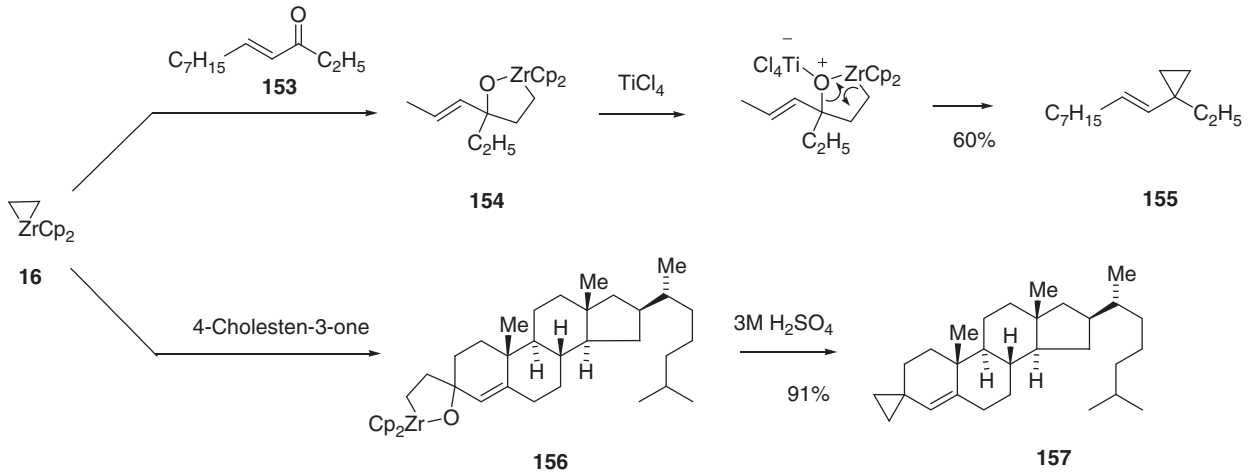
Metallacyclopropane species **20**, such as alkylidene complexes **19**, exhibit an increased reactivity toward the carbonyl compounds. Titanacyclopropane and zirconacyclopropane reagents are easily involved in coupling with aldehydes or ketones and most of the features for these transformations were established at first for zirconacyclopropane reagents.[5e,r,w–x] Thus,

zirconacyclopropane–phosphine complexes **149** react with aldehydes preferably at less-substituted carbons to give the corresponding alcohols **151** and **152** after hydrolysis of the oxazirconacyclopentane intermediates **150**. The reaction proceeds with high regioselectivity, which decreases in the order R^1 = alkyl > silyl > aryl and is somewhat smaller in the case of the ketones (Scheme 47).[60]



Scheme 47

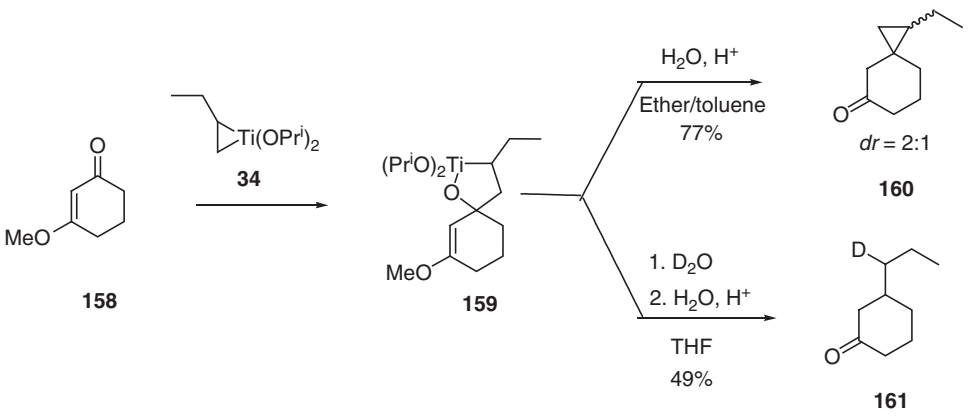
Oxametallacyclopentane intermediates, formed in the first step of the addition reaction of the zirconacyclopropane reagents to the carbonyl group, are capable of undergoing 1,3-elimination of the zirconocene oxide under treatment of proton or Lewis acids with formation of the cyclopropane derivatives. Various cyclopropanes were obtained from saturated, unsaturated, and aromatic aldehydes and ketones in moderate-to-good yields by this two-step sequence. Thus, the addition of the zirconacyclopropane reagent **16** to the unsaturated ketone **153** and followed by treatment of the resulting oxazirconacyclopentane **154** with titanium tetrachloride leads to the alkenylcyclopropane **155** (Scheme 48).[61] In the case of the reaction of the zirconacyclopropane reagent **16** with cholestenone, high yield of the cyclopropane derivative **157** was obtained under treatment of the oxyzirconacyclopentane precursor **156** with sulfuric acid.



Scheme 48

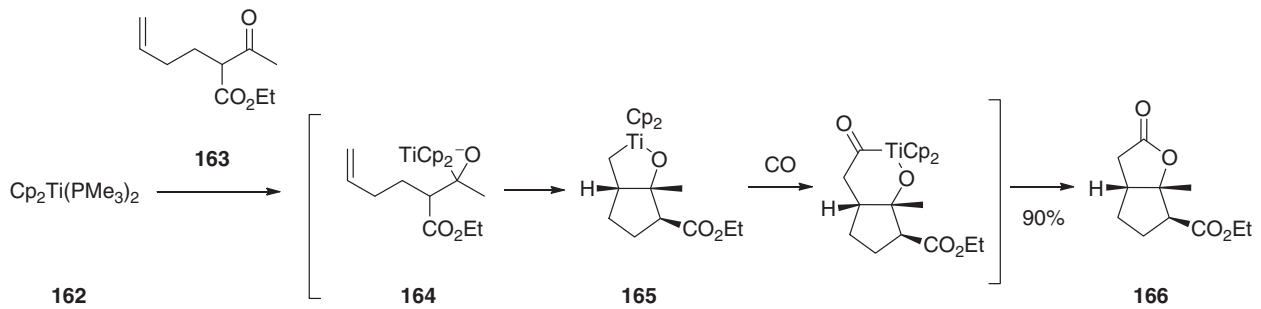
Methoxycyclohexenone **158** reacts with *in situ* generated alkoxytitanacyclopropane **34** in toluene at room temperature to form cyclopropanation product **160** after acidic treatment of the oxatitanacyclopentane adduct **159** (Scheme 49). The cyclopropane ring closure may be induced by protonation of the intermediate **159**, because the quenching with D_2O of the reaction mixture obtained in THF leads to deuterated 3-propylcyclohexanone **161**.[62]

Oxametallacyclopropane derivatives, which are usually generated by the cycloaddition of metal(II) species to the carbonyl group or by the rearrangement of the organylzirconocene carbonylation products, have some similarity with the corresponding metallacyclopropane species.[2e,m] Their carbometallation reactions with nonactivated alkenes or alkynes lead to the corresponding oxametallacyclopentane or oxametallacyclopentene intermediates, which involve in the formation of new carbon–carbon bonds in the reaction with carbon monoxide. An approach to the diastereoselective synthesis of γ-butyrolactones or γ-butenolides from



Scheme 49

suitable enones or ynones was elaborated on this base. Thus, treatment of the unsaturated ketoester **163** with titanocene complex **162** leads to the intramolecular cyclization with formation of fused butanolide **166** via oxatitanacyclopropane and oxatitanacyclopentane intermediates **164** and **169** (Scheme 50).[63] The carbonylation of the latter is followed by hydrolysis to give the bicyclic lactone **166**.

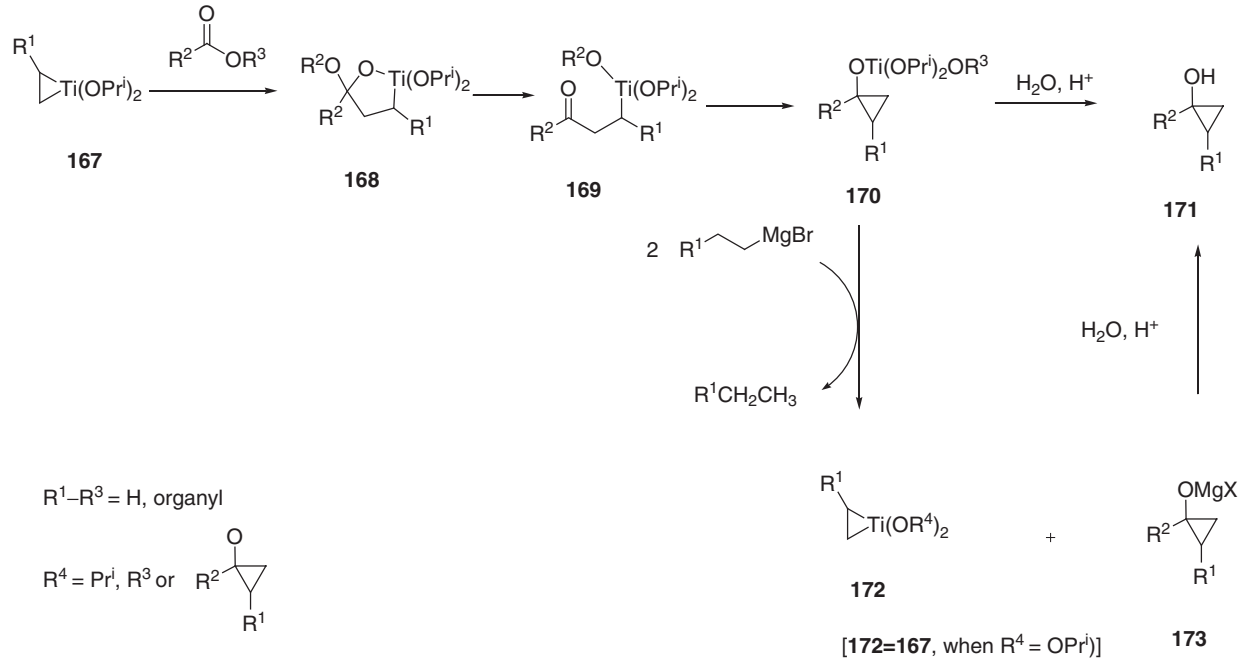


Scheme 50

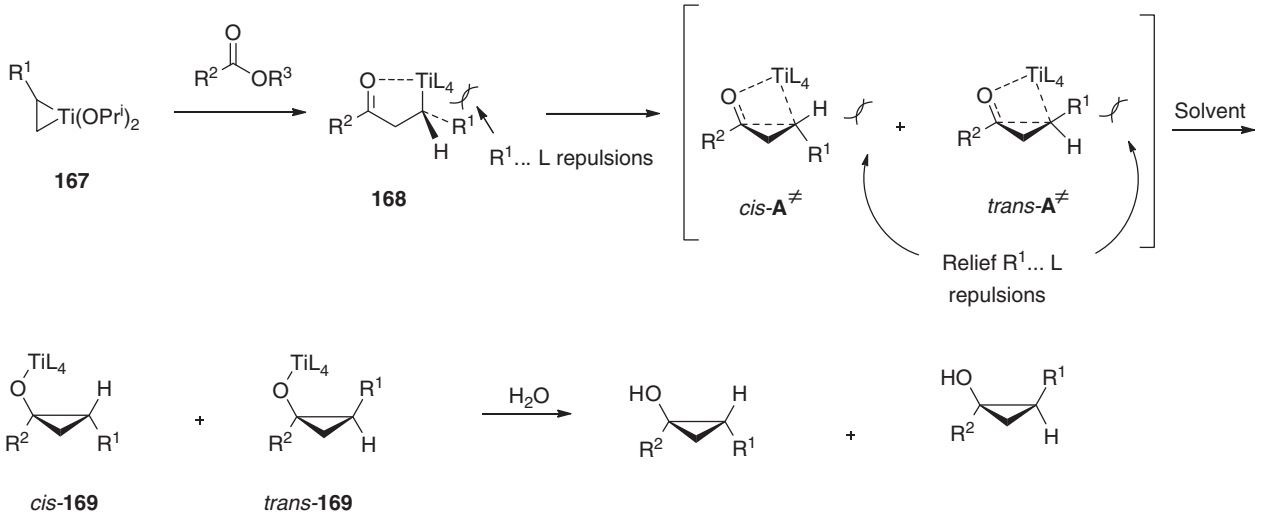
Interaction of the alkoxytitanacyclopropane species with carboxylic esters results in the formation of substituted cyclopropanols.[5a,b,d,f,j,m,n,17] Mechanistically, this reaction involves insertion of the ester carbonyl group into the titanium–carbon bond of the alkoxytitanacyclopropane species **167** with formation of oxatitanacyclopentane intermediate **168**, which is further transformed into titanium cyclopropanolate **170** via the *β*-oxotitanium derivatives **169**. Titanium cyclopropanolates **170** are the suitable precursors for the regeneration of the key titanacyclopropane **172** (**167** when R^4 = OPr^i) and it allows to perform the reaction in the catalytic version (Scheme 51). A more detailed mechanism of the cyclopropanation involving the formation of the corresponding highly coordinated ate complex intermediates was also presented.[64]

Interaction of unfunctionalized alkyl- and aryl-substituted alkoxytitanacyclopropanes with carboxylic esters preferably leads to 1,2-disubstituted cyclopropanols with *cis*-disposition of the hydrocarbon substituents.[20] This stereochemical feature of the reaction was attributed to more effective relief of repulsive interactions between ligands at the highly coordinated titanium in the transition state *cis*-**A**$^{\neq}$ for the transformation of *β*-titanoketones **168** into the cyclopropanolates *cis*-**169**,[65] proceeding with retention of configuration at the carbon bound to titanium[66] (Scheme 52, for six-coordinated titanium). In accordance with this model the energy barrier for the transition state *cis*-**A**$^{\neq}$ should decrease as R^1 becomes larger. Thus, a better *cis*-diastereoselectivity in this reaction for the formation of 1,2-disubstituted cyclopropanol *cis*-**171** in comparison with isomeric cyclopropanols **170** and **172** is in good agreement with this model. The theoretical calculations indicate that α-agostic interaction between hydrogen atom and the titanium atom in *β*-titanoketones **168** can also contribute to the *cis*-diastereoselectivity of the cyclopropanation.[67]

The cyclopropanation of the ester carbonyl group proceeds with a high *trans*-diastereoselectivity with alkoxytitanacyclopropane reagents generated by olefin ligand exchange with homoallylic alcohols.[68] The formation of a covalent bond between titanium atom and the oxygen atom at the side chain with formation of five- or six-membered oxatitanacyclic intermediates (e.g., **174**–**177**) is probably responsible for the predominant formation of *trans*-isomeric 1,2-dialkylsubstituted cyclopropanols in these cases (Scheme 53). In addition, moderate or good 1,3-diastereocontrol is also observed for these transformations. For example, the hydroxycyclopropanation of homoallylic titanate **173** with ethyl acetate leads to the *trans*-cyclopropanol **178** with good diastereoselectivity.[68b]

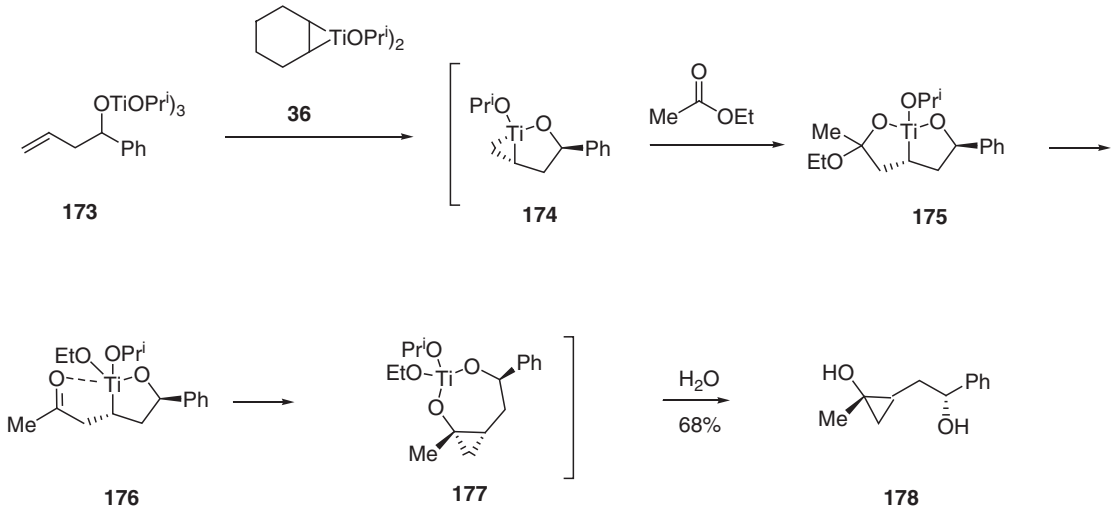


Scheme 51



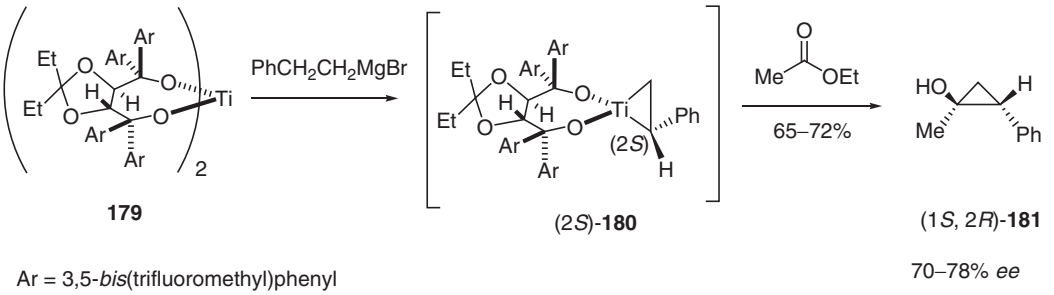
Diastereoselectivity of the formation of isomeric cycloproanols **171**–**173**			
Cyclopropanol			
	cis-**170**	*cis*-**171**	*cis*-**172**
cis/*trans dr*	20:1	23:1	1:1

Scheme 52



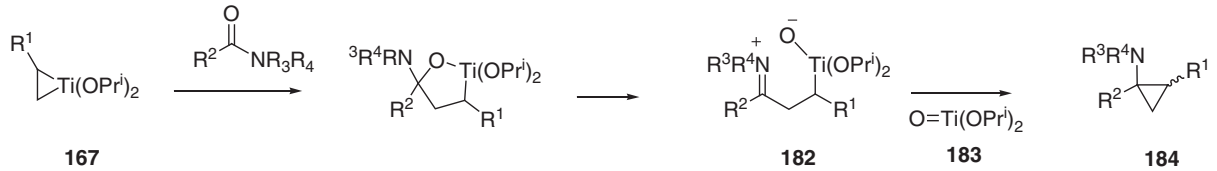
Scheme 53

(1*S*,2*R*)-Cyclopropanol **181** was obtained in 70–78% *ee* from the reaction of ethyl acetate with alkoxytitanacyclopropane reagent **180**, generated by treatment of *bis*-TADDOLate **179** with (2-phenetyl)magnesium bromide (Scheme 54).[69] Chiral titanium alkoxide analogs **179** with other aryl substituents were tested and led to the cyclopropanol **178** with lower enantioselectivity. For the explanation of the stereochemical outcome the mechanistical model was proposed in which TADDOLate **179** is preferably transformed to the key titanacyclopropane reagent (2*S*)-**180** with distant disposition of the phenyl group from the nearest pseudoaxial aryl group.



Scheme 54

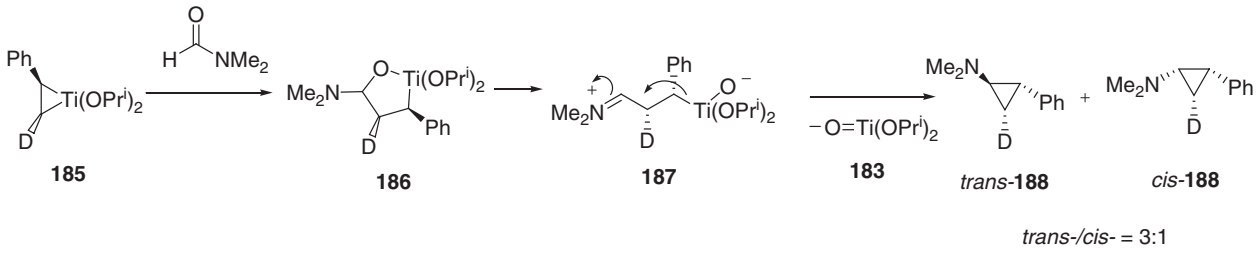
The interaction of alkoxytitanacyclopropanes **167** with carboxylic acid *N*,*N*-dialkylamides leads to the corresponding *N*,*N*-dialkylaminocyclopropanes **184**.[70] The latter are usually formed in lower yields and with lower *cis*-/*trans*-diastereoselectivity than the corresponding cyclopropanols. The reaction proceeds likely via cyclization of iminium intermediate **182** with the elimination of titanium oxide **183** (Scheme 55). The latter is probably not transformed in the reaction conditions into the corresponding titanacyclopropane species that explains the failure of the attempts to perform the catalytic version of the cyclopropanation of *N*,*N*-dialkylcarboxamides.



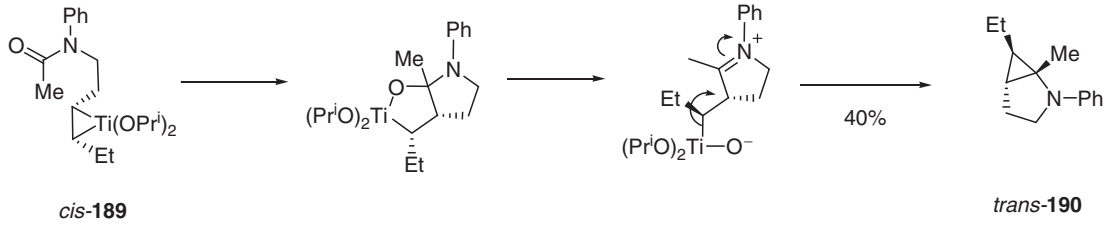
Scheme 55

The reaction of deuterated titanacyclopropane species **185** with dimethylformamide proceeds with inversion of configuration at the carbon bound to titanium probably via W-shaped transition structure **187**, giving a 3:1 mixture of 1,2-disubstituted *trans*-**188** and *cis*-cyclopropylamine **188** with relative *cis*-disposition of deuterium atom and phenyl group (Scheme 56).[66]

An inversion of stereochemistry at a titanium–carbon bond also occurs in the course of the intramolecular cyclization of titanacyclopropane intermediates *cis*-**189** and *trans*-**189** (not shown) leading, respectively, to the isomeric bicyclic amines *trans*-**190** and *cis*-**190** (not shown) (Scheme 57).[71] The preparation of enantiomerically pure 2-azabicyclo [3.1.0] hexane and 2-azabicyclo [4.1.0] heptane derivatives by a similar intramolecular cyclopropanation of suitable unsaturated carboxamide bearing of chiral N benzyl-type protecting group was also elaborated.[72]

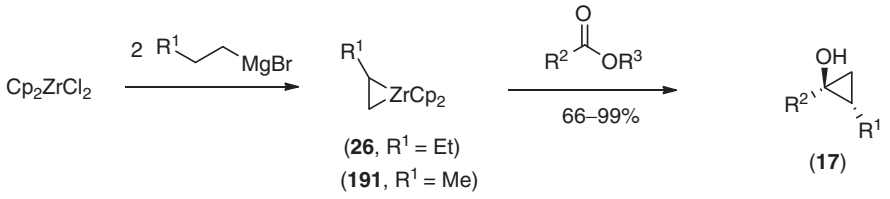


Scheme 56



Scheme 57

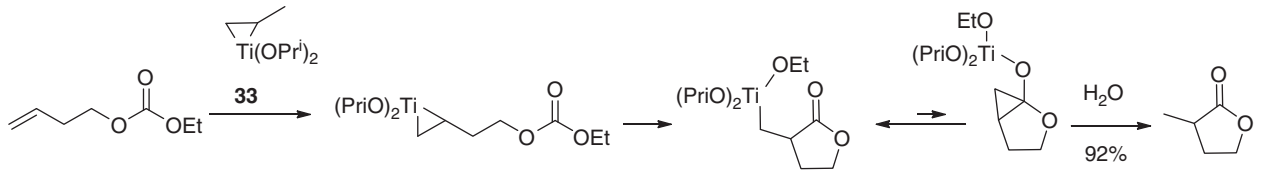
Zirconacyclopropane species react with carboxylic acid esters in the same fashion to give the corresponding cyclopropanols. Thus, treatment of aryl-, alkyl-, cycloalkyl-, and alkenylcarboxylates with more zirconacyclopropane reagents **26** and **191** at 0 °C furnished the corresponding 1,2-disubstituted cyclopropanols **171** in good yield and with high *cis*-diastereoselectivity (Scheme 58).[47b]



Scheme 58

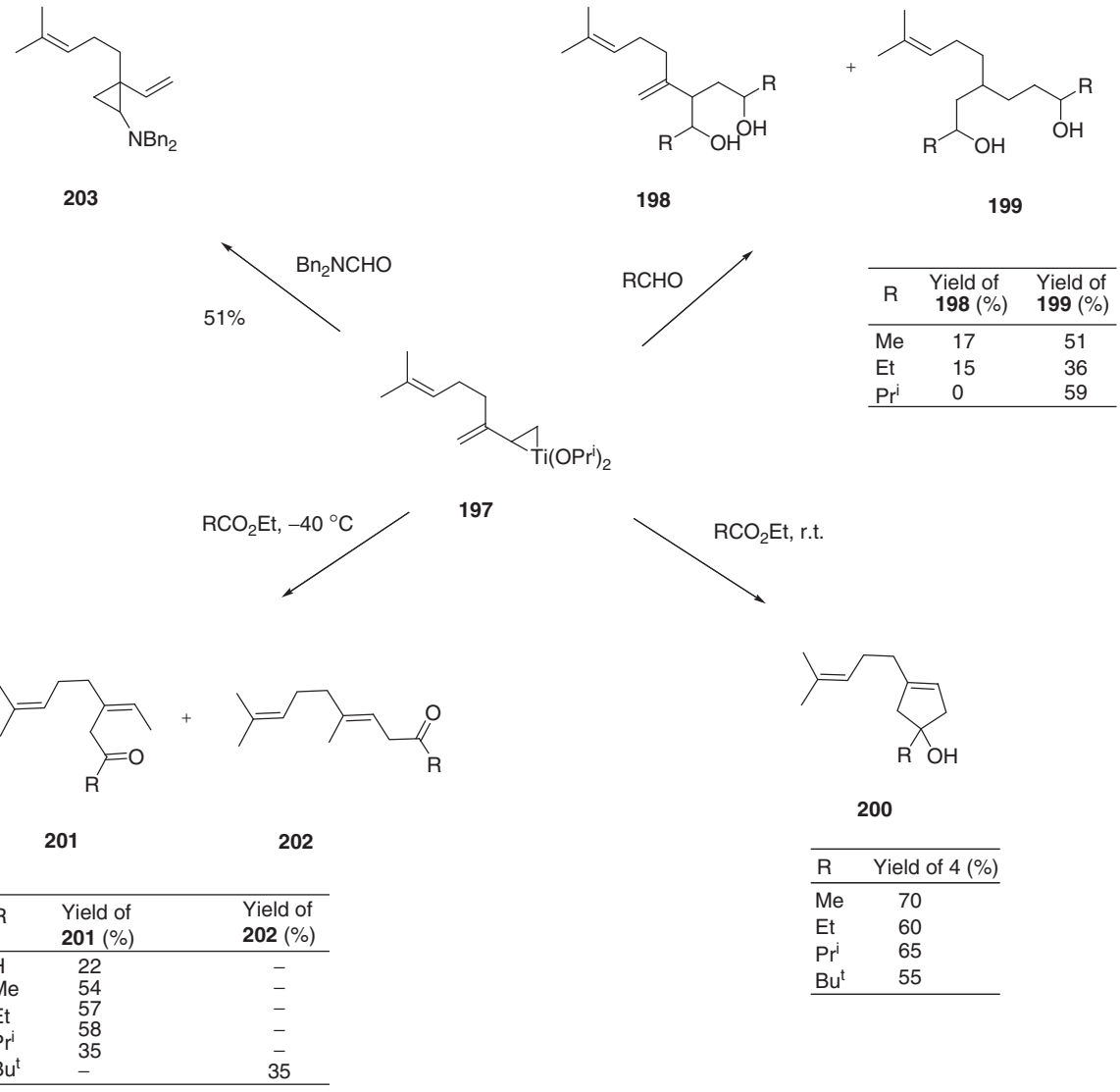
Although the intramolecular cyclopropanation of the ester groups proceeds smoothly for the formation of five- and six-membered carbon rings, as well as for the formation of seven- and eight-membered oxacyclic derivatives,[5a] a three-carbon ring closure step in some other cases is inhibited with the steric, entropic, or electronic effects. Thus, the reaction of carbonates of homoallylic alcohols (e.g., **192**) with the titanacyclopropane reagent **33** leads to the formation of *β*-titanolactone **194** from intramolecular monoalkylation of the carbonate carbonyl group in the titanacyclopropane intermediate **193** (Scheme 59). Further cyclization of the *β*-titanolactone **194** to the cyclopropane derivative **195** is prevented probably by internal strain of bicyclohexane system accompanied by activating effect of the oxygen substituents on the reverse three-carbon ring cleavage reaction. The titanium–carbon bond of the monoalkylation product **194** is nucleophilic enough to be involved in the insertion of benzaldehyde carbonyl and some other electrophiles, but to be not active to the carbonyl group of aliphatic aldehydes.[73]

An easily accessible vinyltitanacyclopropane reagent can exhibit similarities both with titanacyclopropane and allyltitanium species and operate in the reactions with carbonyl compounds as 1,2- or 1,4-dicarbanionic equivalents. Thus, the vinyltitanacyclopropane intermediates **197**, generated from myrcene by olefin ligand exchange reaction, adds to aliphatic aldehydes leading to the corresponding 1,4- (**198**) or 1,6-diols (**199**) (Scheme 60).[74] In the reaction with esters the cyclopentenols **200** are formed



192 193 194 195 196

Scheme 59



R	Yield of **198** (%)	Yield of **199** (%)
Me	17	51
Et	15	36
Pr^i	0	59

R	Yield of **201** (%)	Yield of **202** (%)
H	22	–
Me	54	–
Et	57	–
Pr^i	58	–
Bu^t	35	–
	–	35

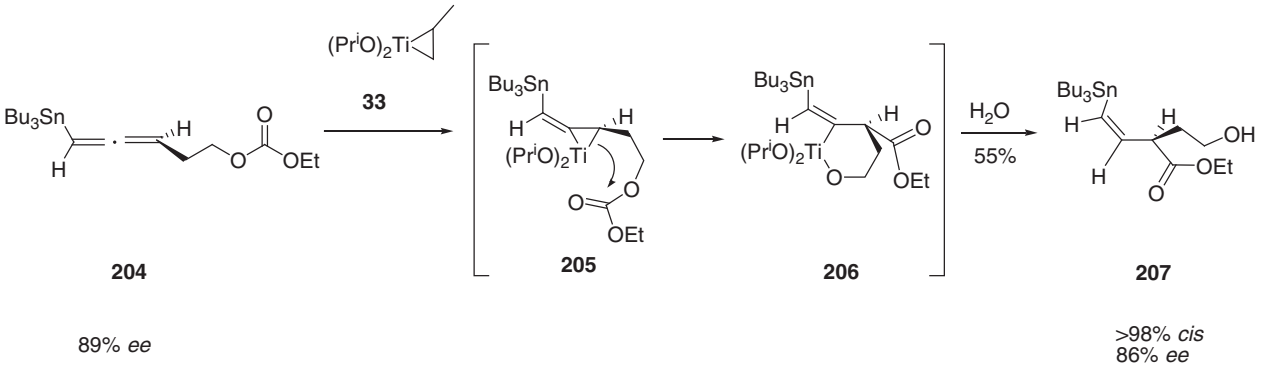
R	Yield of 4 (%)
Me	70
Et	60
Pr^i	65
Bu^t	55

Scheme 60

in moderate-to-good yields at room temperature, whereas at -40 °C allylic ketones **201** and **202** were obtained. The reaction of *N*,*N*-dibenzylformamide gave aminocyclopropane derivative **205** as the main product.[75] These data indicate that among three nucleophilic carbons in the vinyltitanacyclopropane intermediate **197**, the terminal olefinic carbon is most active toward addition to the carbonyl carbon.

A high activity in the intramolecular nucleophilic addition to the carbonyl group is exhibited by alkylidenecyclopropane species. Thus, the interaction of titanacyclopropane reagent **33** with 3,4-alkadienyl carbonates bearing substituents at C-5 (e.g., **204**) provides the formation of α-substituted β,γ-unsaturated esters (e.g., **205**) (Scheme 61).[76] A stereochemistry of the olefin

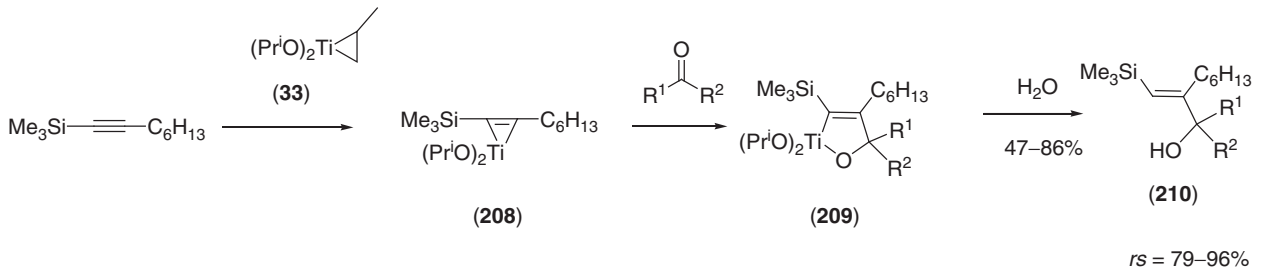
moiety in the products is highly dependent on the bulkiness of the allenic substituent, and the substrate **204** having a sterically demanding tributylstannyl group provides *cis*-isomer exclusively. An optically active allene derivative (*R*)-**204** with high selectivity converts to ester (*R*)-**207**. This stereochemical outcome agrees with the preferable formation of a sterically less-hindered titanacyclopropane intermediate **205**, whose incorporation into the ester carbonyl proceeds with retention of the configuration of Ti–C bond leading to the formation of oxatitanacyclohexane precursor **206** of the final product **207**.



Scheme 61

1.05.3.7 Metallacyclopropene Reagents

Titanacyclopropene intermediates add to aldehydes and ketones giving 1:1 adducts. The formation of the corresponding allylic diols, as a result of double addition of the carbonyl compounds at both carbanionic centers of titanacyclopropene reagents, is not observed. In the case of nonsymmetrical alkoxycyclopropenes, the regioselectivity of the addition is largely dependent on the substituents in the metallacycle. The best regioselectivity for the reaction was observed in the case of silyl-substituted titanacyclopropenes. For example, titanacyclopropene intermediate **208**, generated by treatment of 1-trimethylsilyloctyne with titanacyclopropane reagent **33**, reacts with aldehydes and ketones with good regioselectivity to give, after hydrolysis of the oxatitanacyclopentene intermediate **209**, the *β*-silylated allylic alcohols **210** (Scheme 62).[22]

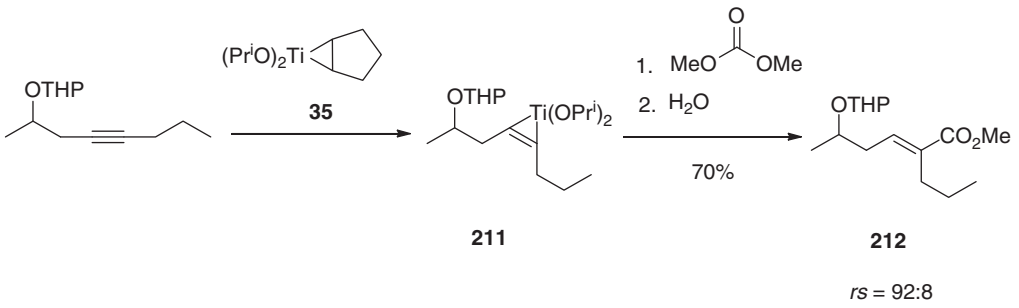


R^1 = C_5H_{11}, $CH_3CH_2CHCH_3$, *c*-C_6H_{11}, Ph, *trans*-PhCH=CH, $CH_2CH_2CO_2Me$
R^2 = H, Me
R^1+R^2 = $(CH_2)_5$

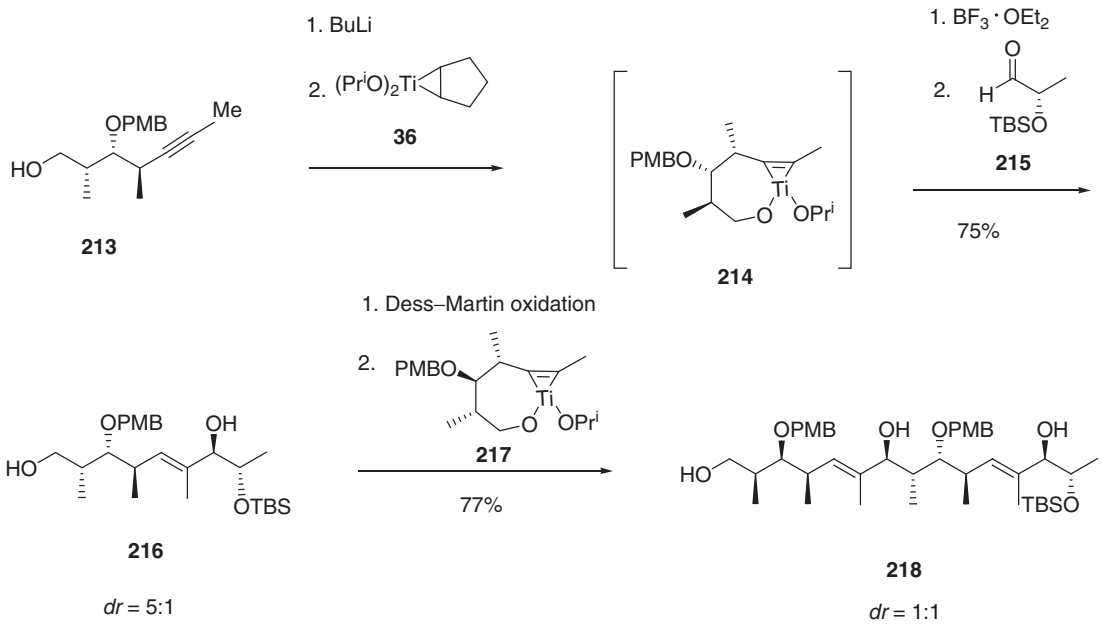
Scheme 62

The alkoxytitanacyclopropene species exhibits high activity even in the intermolecular addition reactions to carbon dioxide and dialkyl carbonates leading with high *cis*-/*trans*-diastereoselectivity to the corresponding *α*,*β*-unsaturated carboxylic acids or esters, although in many cases the regioselectivity of the Ti–C bond cleavage was low. The best result was obtained in the reaction of the titanacyclopropene **211** with dimethyl carbonate, leading to *α*,*β*-unsaturated carboxylic ester **212** with regioselective cleavage of the Ti–C bond which was far away from complexing THP group (Scheme 63).[77] The same reactions of the titanacyclopropene species having methoxymethyl or benzyl groups proceed with much poor regioselectivity.

Another example of the control of regioselectivity C–C bond formation with alkoxytitanacyclopropene intermediates are provided by tethered complexing groups representing the titanacyclopropane-mediated addition of tris-homopropargylic alkoxides that exhibit to the aldehydes with formation of *α*-methyl branched *cis*-allylicalcohols. The authors used this finding for a convergent synthesis of a functionalized C1–C15 diene **218**, the precursor of erythromycin-based macrolide antibiotics (Scheme 64). Prepared from the alcohol **213**, bicyclic titanacyclopropene **214** reacted with the carbonyl group of the



Scheme 63



Scheme 64

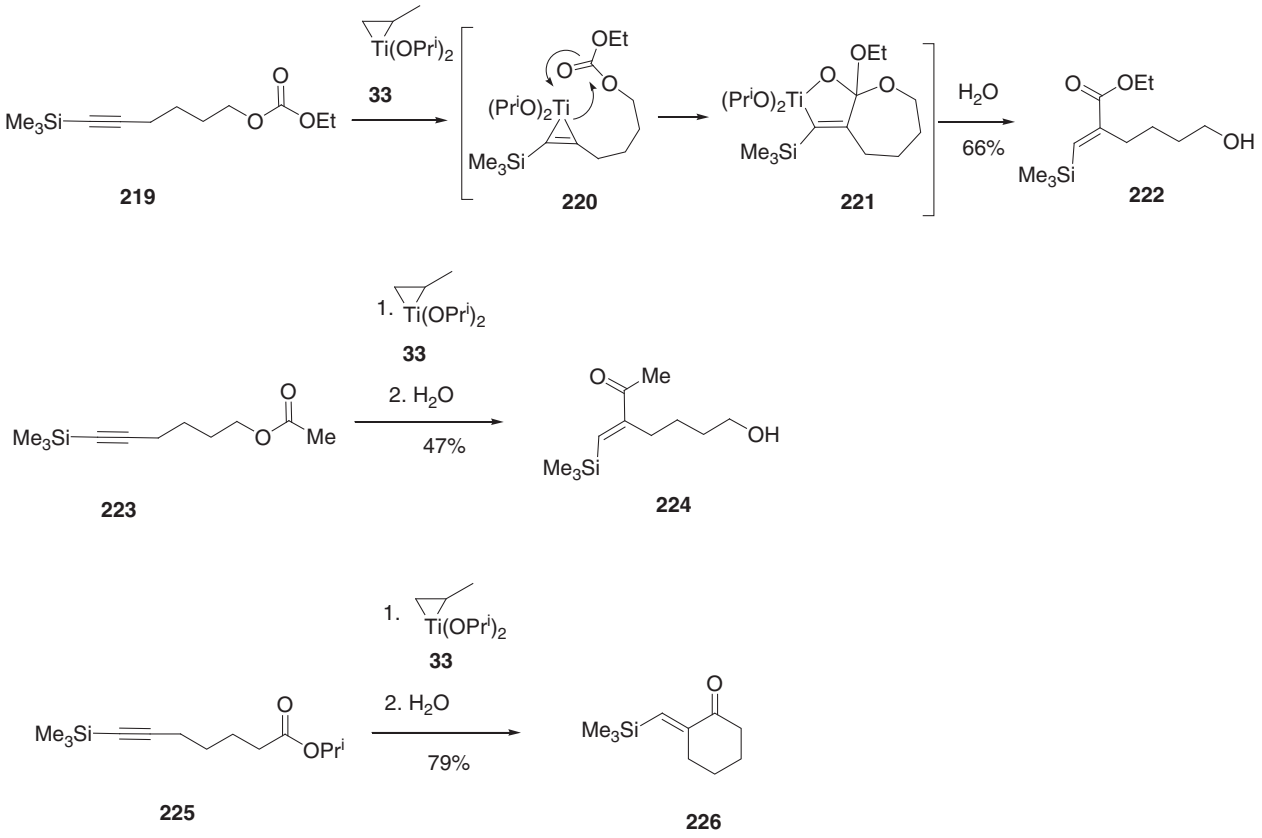
TBS-protected lactaldehyde **215** providing with ≥20:1 regioselectivity and with good diastereoselectivity the allylic alcohol **216**. At the same time the addition of the titanacyclopropene intermediate **216** to the aldehyde derived from the primary alcohol **216** was not diastereoselective, although regioselectivity cleavage of the C–Ti remained high.[78]

The intramolecular addition of the titanacyclopropene intermediates to the carbonyl compounds proceeds with high regioselectivity at the proximal Ti–C bond via the corresponding functionalized bicyclic intermediates. For example, intramolecular cyclization of the carbonate **219** proceeds through formation of the titanacyclopropene **220** and bicyclic dioxatitanium derivative **221** giving, after hydrolysis of the latter, the unsaturated ester **222**. Analogously, after the cyclization of acetate the same alcohol **223** gives the unsaturated ketone **224**, whereas alkynoic ester **225** transfers in similar conditions to silylated cyclohexenone **226** (Scheme 65).[73]

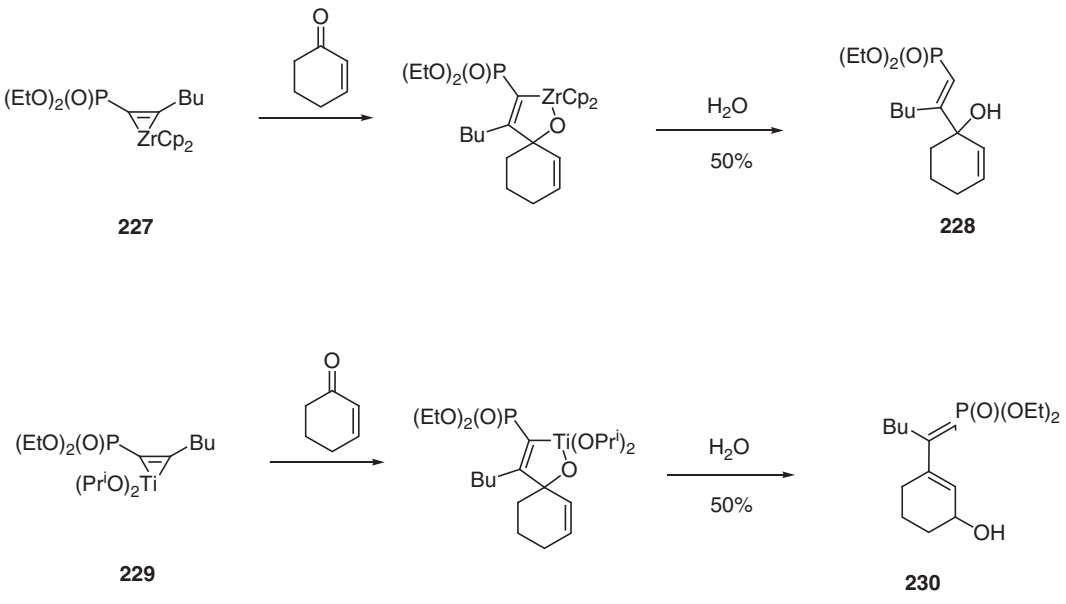
Zirconacyclopropene reagents add to the carbonyl group of aldehydes, ketones, and some carboxylic acid derivatives at room temperature or lower. Lowered acidity of the zirconium intermediates compared to the corresponding titanium derivatives can have some impact on the structure of the resulting products. For example, the interaction of 2-cyclohexenone with zirconacyclopropene reagent **227** leads to a nonconjugated dienol **228**, whereas in the reaction with titanacyclopropene reagent **229** the same ketone gave the conjugated diene alcohol **230** as a result of an allylic rearrangement (Scheme 66).[79]

Titanacyclopropene reagents with sulfonamide substituents **231** react with aldehydes with complete regio- and olefinic stereoselectivity, as well as with the high level of the remote 1,5-diastereocontrol to give, after hydrolysis of the oxatitanacyclopentene intermediate **232**, the corresponding unsaturated alcohols **233** (Scheme 67).[80] When the reaction of chiral titanacyclopropene (*S*)-**231** ($R^1 = C_6H_{13}$, $R^2 = Bu^t$, 96% *ee*) was performed with aldehydes ($R^3 = Pr^i$, Bu^t) the corresponding optically active products **233** were obtained without loss of the enantiopurity.

In conclusion, the development of new approaches for the generation of diverse mono- and dicarbanionic organotitanium and organozirconium compounds has enabled their application in highly selective reactions with carbonyl derivatives, as well as with



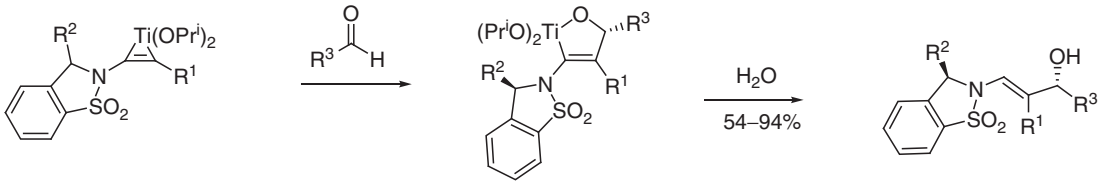
Scheme 65



Scheme 66

other unsaturated or electrophilic compounds also considered in this book, creating a good basis for the further elaboration of new general and efficient methodologies for modern organic synthesis.

For related chapters in this Comprehensive, you can refer to – Chapters 4.15, 5.34, 2.04, 8.32, 8.25, 1.10, 1.11, 1.03, 1.07, 8.18, and 5.24.



231 **232** **233**

1,5-*dr* > 88:12

R^1 = C_6H_{13}, $SiMe_3$
R^2 = Me, Bu^t
R^3 = Pr^i, Bu^t, *c*-C_6H_{11}, C_8H_{17}, *trans*-MeCH=CH, *trans*-$C_5H_{11}CH$=CH, Ph, *p*-ClC_6H_4

Scheme 67

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1.06 Organochromium Reagents

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1.06.1 Introduction

Organochromium compounds can be prepared by two methods: (1) transmetalation from the corresponding organolithium, magnesium, or zinc compounds with chromium(III) halides and (2) reduction of organic substrates, such as organic halides and unsaturated compounds, with chromium(II) salts.[1–4] Preparation of organochromium reagents is usually performed by the second method because the first method suffers from both low solubility of chromium(III) salts in ethereal solvents, and difficulty in preparing organolithium and -magnesium compounds, especially those with highly oxygenated substituents. The reducing ability of chromium(II) is weaker than low-valent metals such as magnesium(0) and samarium(II), thus carbonyl compounds, even aldehydes, can survive in the presence of chromium(II) ion. Therefore, the reduction can be conducted either by (1) adding an electrophile to a solution of chromium(II) before addition of the organic halide, or (2) adding the chromium(II) salt to the mixture of electrophile and organic halide. The latter procedure is suitable for microscale reactions and intramolecular cyclizations. Chromium(II) cannot reduce alkenyl (or aryl) and primary alkyl halides under aprotic conditions;[1] however, the reduction can be accomplished by the aid of nickel[5–7] or cobalt catalysts.[8] This method has expanded the kinds of organochromium reagents available. Since the catalytic use of chromium salts using a stoichiometric amount of manganese metal as a reductant was developed in 1996,[9] research on asymmetric synthesis with chromium reagents has made great progress.

The Pauling electronegativity of chromium is almost the same as titanium. Therefore, the nucleophilicity of organochromium reagents is not as great as for the corresponding organolithium or organomagnesium compounds. The steric effect of the ligands on chromium also affects the nucleophilicity. These features enable the reagent to discriminate between the carbonyl groups of aldehydes and those of ketones or esters under typical reaction conditions.[10] In addition, it is possible to prepare organochromium compounds that contain such functional groups as ketones, esters, or nitriles. Because of the weak basicity of organochromium compounds, epimerization of a stereocenter α to a carbonyl group is minimal. The covalent character of the carbon–chromium bond enables the generation of geminal dichromium compounds for (*E*)-selective olefination by reduction of geminal dihalides with chromium(II).[11,12]

Although organochromium compounds react with water to give the corresponding hydrolysis products, the hydrolysis of carbon–chromium bonds proceeds slower than that of carbon–magnesium or carbon–lithium bonds and is not very sensitive to small amounts of water due to the covalent character of the bonds. This feature derives from the slow exchange of ligands inside the coordination sphere of chromium(III).[13–16] Addition of a few equivalents of water does not disturb carbon–carbon bond formation with organochromium(III), allowing chromium-containing reactive species to be generated.[17,18] There are also cases for which chromium-mediated reactions can be performed without protecting free hydroxyl groups.[19]

The chromium(III) ion has moderate Lewis acidity, and so the carbonyl oxygen can coordinate to it. This feature affects the geometry of the transition state in reactions of allylchromium reagents[20,21] and also facilitates intramolecular cyclization by bringing the organochromium moiety and the carbonyl group into proximity.

The allyl-, alkenyl-, and alkylchromium, and even geminal dichromium reagents discussed in the following section (Sections 1.06.2.1, 1.06.2.3, and 1.06.2.5) have these advantages, and therefore, the reagents can also be used in the late stages of total syntheses.

To date, several reviews have dealt with organochromium reagents.[22–31]

1.06.2 C–C Single Bond Formation

1.06.2.1 Allylic Chromium Reagents

1.06.2.1.1 Preparation and mechanism of reduction

In 1977, Hiyama and Nozaki developed a preparation of chromium(II) species from chromium(III) chloride with lithium aluminum hydride (2:1 M ratio) in an aprotic solvent.[10] They reported the addition of allylic chromium reagents, derived by reduction of allylic halides with chromium(II) species, to carbonyl compounds in a chemoselective manner. The following year, Heathcock reported that coupling products between the crotylchromium reagent and aldehydes have mainly the *anti* configuration.[20] The commercial availability of anhydrous chromium(II) chloride led to the widespread application of these reagents for 1,2-diastereoselective construction of carbon skeletons. The reaction is called the Nozaki–Hiyama allylation.

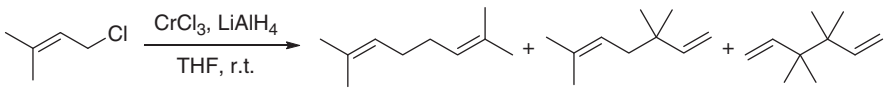
Allylic halides are reduced smoothly in aprotic solvents such as tetrahydrofuran (THF) or *N*,*N*-dimethylformamide (DMF) with two equivalents of chromium(II) salts ($CrCl_2$ or $CrCl_3$-$LiAlH_4$) to generate allylic chromium compounds.[32] Allylic tosylates,[10] mesylates,[33] diethylphosphates,[23,34] and sulfonylchloride[35] are also suitable precursors of the allylic chromium compounds. The chromium reagents add to carbonyl compounds such as aldehydes or ketones to furnish homoallylic alcohols (equation 1).[10,36] The amount of the chromium salts can be reduced using manganese metal and chlorotrimethylsilane (see Section 1.06.2.7).

$CrCl_2$ (4 equivalents) 6 h 81%

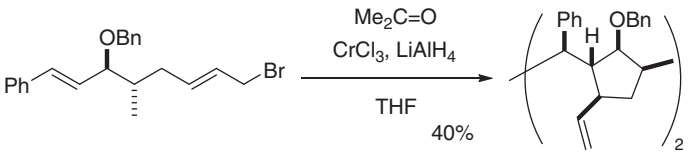
$CrCl_2$ (0.072 equivalent), Mn (1.7 equivalents), Me_3SiCl (2.4 equivalents) 6 h 78%[a] (1)

[a]Yield after desilylation

When the reduction is conducted in the absence of the carbonyl compound, dimerization to 1,5-dienes occurs (equation 2).[32] Moreover, when the carbonyl compound is bulky and a carbon–carbon double bond is present at a suitable position for the intramolecular reaction, radical cyclization occurs, and a dimer of the formed radical is produced (equation 3).[37] These results suggest that allylic radical species are generated as intermediates in the direct reduction of allylic halides with chromium(II). Allylic radicals can also be generated by (1) addition of radicals to 1,3-dienes (see Section 1.06.4.3),[38] or (2) homolytic cleavage of allylic cobalt(III) species (see Section 1.06.2.1.4),[17] and the corresponding allylic chromium compounds are prepared by these methods.



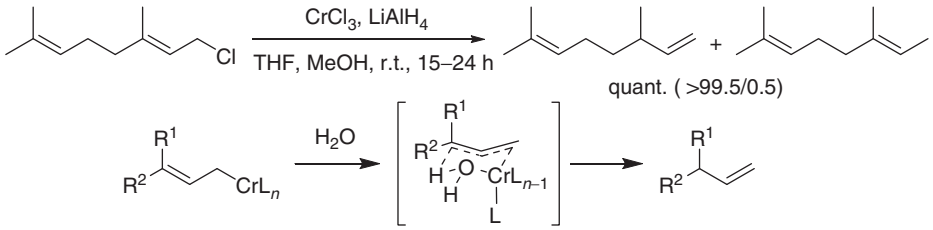
70% (77:22:6) (2)



(3)

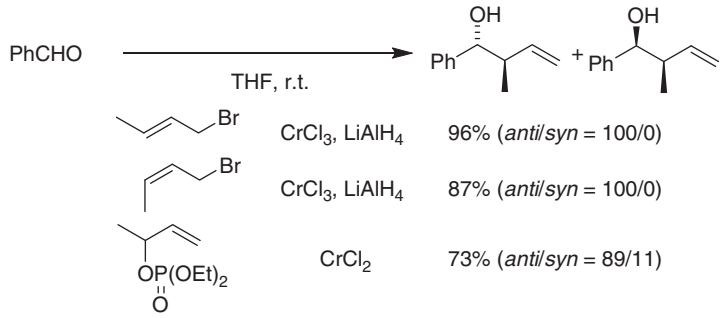
1.06.2.1.2 Allylchromium equilibration and 1,2-diastereoselectivity

Although the η^1 or η^3 structure of reagents derived from an allylic halide and chromium(II) chloride is not clear, it is likely to be η^1 at least in the transition state of the reaction with carbonyl compounds. Equilibration between three isomeric allylic chromium compounds is fast at room temperature, causing *E*/*Z* isomerization except in the case of γ,γ-disubstituted allylic chromium compounds.[34] Because of the steric interaction between ligands on chromium and the substituents on the allyl fragment, the equilibrium lies toward the allylic chromium species possessing less steric crowding of the carbon–chromium bond. The allylic chromium compounds react with water at the γ position of the allylmetal unit via a six-membered transition state. Therefore, the reduction of geranyl chloride with chromium(II) in the presence of a proton source gives the less substituted terminal olefin selectively (equation 4).[39]



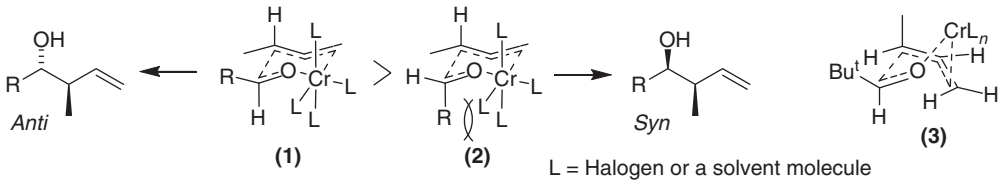
(4)

Similarly, allylic chromium compounds normally react with carbonyl compounds at the γ position. Thus, reactions between prenyl halides and aldehydes afford 3,3-dimethyl substituted homoallylic alcohols. The reaction of crotyl bromide and benzaldehyde mediated by chromium(II) chloride in tetrahydrofuran gives the *anti* adduct with high diastereocontrol regardless of the geometry of the crotyl bromide (equation 5).[20,21]

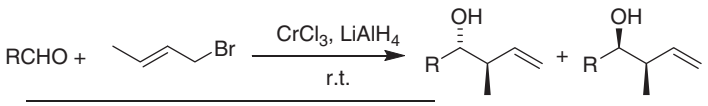


(5)

This observation suggests that the crotylchromium reagent prepared *in situ* equilibrates to the more stable and/or more reactive *E* isomer (Scheme 1). Chromium(III) complexes prefer an octahedral configuration in which the coordination sphere is often supplemented with solvent molecules such as tetrahydrofuran.[40–42] Ligand displacement at the octahedral (*E*)-crotylchromium with the aldehyde generates a cyclic six-membered transition state. In the absence of any additional stabilization, a chair-form cyclic transition state is more favorable than a boat form. Two idealized chair-form Zimmerman–Traxler six-membered transition states (**1**) and (**2**) for the reaction of (*E*)-crotylchromium are shown in Scheme 1.[20,21] The *anti* selectivity in the addition of crotylchromium reagents to aldehydes is explained by the transition state (**1**), in which both the methyl group and R occupy equatorial positions. The diastereoselectivity stems from different steric interactions between R and the aldehydic hydrogen with ligands on chromium(III). As the aldehyde substituent R becomes larger, higher diastereoselectivities are obtained (equation 6).[21,43] One exception, however, is 2,2-dimethylpropanal (R=Bu^t), where the *syn*-diastereomer is the main product. This result is explained by a preference for the skew-boat-like transition state because of the severe *gauche* interaction between the *tert*-butyl and methyl groups in (**3**).



Scheme 1



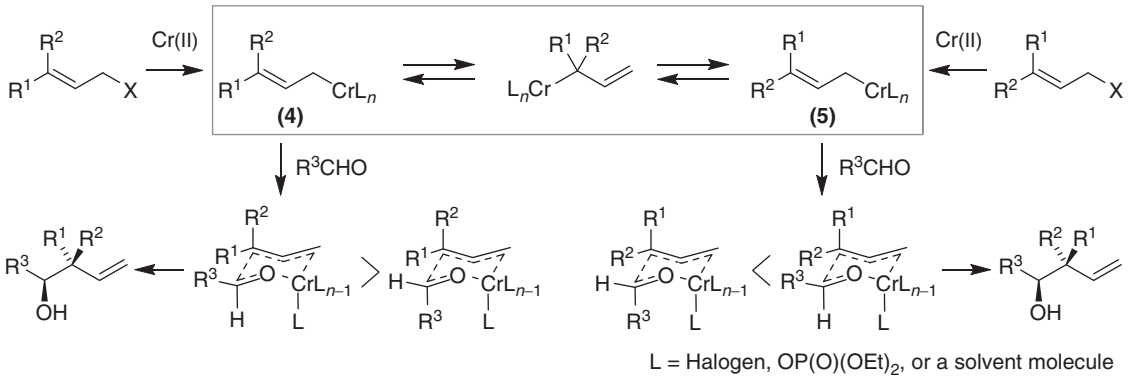
R	Solvent	*Anti*/*syn*
n-C_5H_{11}	THF	97/3
	THF	92/8[a]
	DMF	68/32
Pr^i	THF	95/5
Bu^t	THF	35/65

[a]$CrCl_2$ (7 mol%), Mn, Me_3SiCl

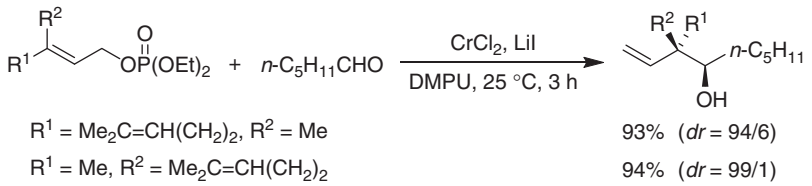
(6)

The diastereoselectivity depends on the solvent, with lower selectivity observed in dimethylformamide than in tetrahydrofuran. Strong coordination of dimethylformamide to chromium(III) could interfere with the formation of a tight six-membered transition state.

The presence of two substituents at the γ position of an allylic chromium retards the allylic equilibration of Scheme 2.[44] Therefore, the two stereoisomeric allylic chromium compounds (**4**) and (**5**), generated by the reduction of (*E*) and (*Z*)-γ,γ-disubstituted allylic phosphates with chromium(II) and lithium iodide in *N*,*N*-dimethylpropyleneurea (DMPU), react with aldehydes to give the corresponding homoallylic alcohols (equation 7).[34,45]



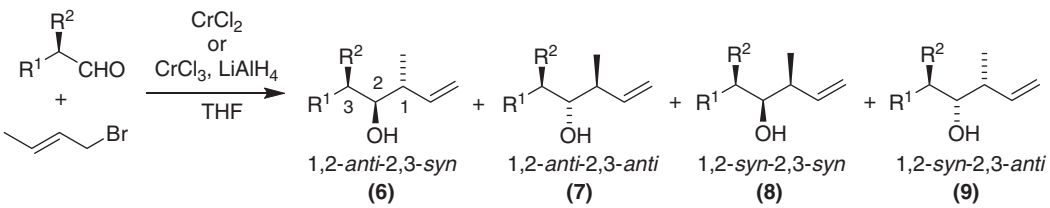
Scheme 2

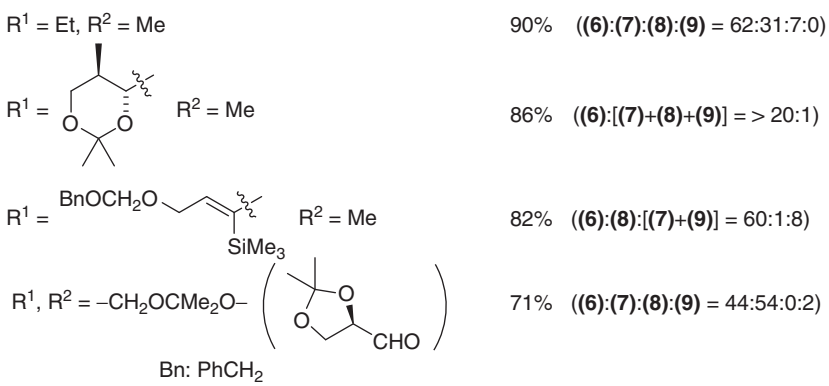


(7)

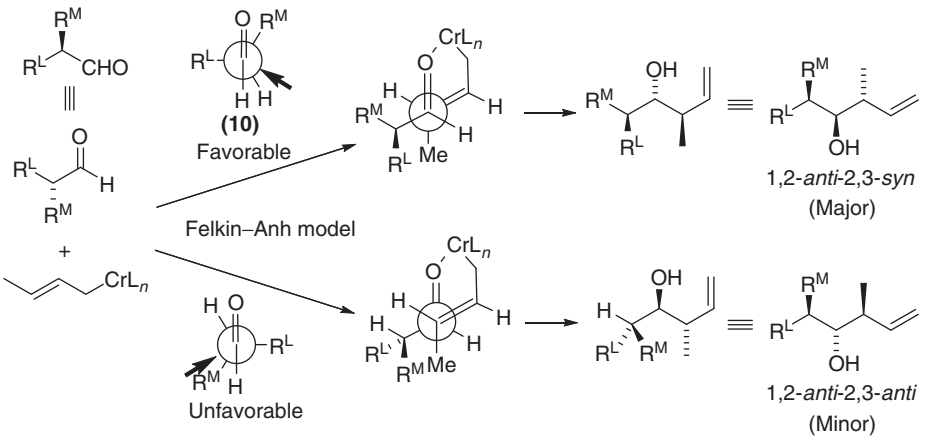
1.06.2.1.3 Effects of chiral centers of aldehydes or allylic halides on diastereoselectivity

Allylation of aldehydes with allylic chromium reagents usually proceeds without epimerization at the α position because of the low basicity of the reagent. Addition of crotylchromium to aldehydes bearing a stereogenic center α to the carbonyl group can generate four diastereomers. The problem of aldehyde diastereofacial selectivity (Cram and *anti*-Cram selectivity) arises in addition to the 1,2-*syn*-*anti* selectivity issue associated with the carbon–carbon bond-forming event. In contrast to the excellent *anti* selectivity at the 1,2 positions, selectivity at the 2,3 positions (the Cram/*anti*-Cram ratio) is only moderate in many cases (equation 8).[21,46] Large substituents at the α carbon predominantly lead to stereoisomer (**6**) with the 1,2-*anti*, 2,3-*syn* configuration. This orientation is consistent with the Felkin–Anh modification (**10**)[47,48] of Cram's rule (**Scheme 3**). Acyclic aldehydes with protected β-hydroxy groups tend to have ratios in the range 1.6:1 ~1:1, and the ratios are not sensitive to either solvent or the type of protecting group.[49] In contrast, high 2,3 diastereoselectivity is obtained with aldehydes having large substituents such as a cyclic acetal group on the β carbon.[50,51] The diastereomeric ratios at the 2,3-position vary and the controlling factors concerning the influence of the aldehyde structure on the diastereoselectivity are not clear.



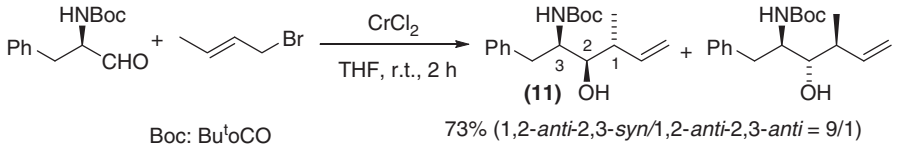


(8)



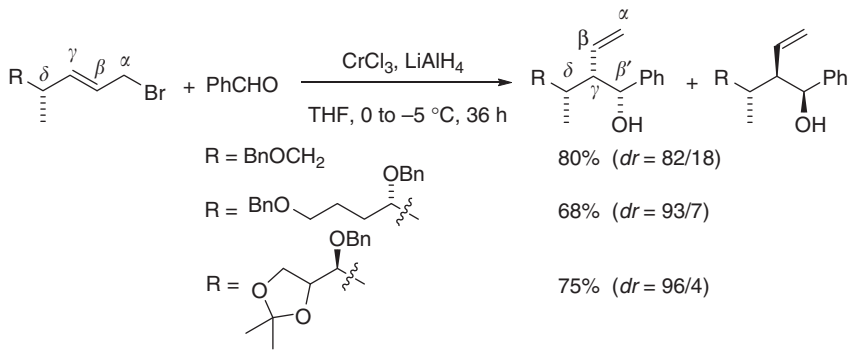
Scheme 3

When an amino group is present at the α-position of an aldehyde, the Cram- and *anti*-Cram selectivity varies with the amino protective group. Addition of a crotylchromium reagent to an aldehyde, however, results in high 2,3-*syn*-selectivity when one of the amino hydrogens is unprotected, and the 1,2-*anti*-2,3-*syn* adduct (**11**) is produced (equation 9).[52] In contrast, the addition of allylchromium reagents to an aldehyde is not stereoselective except when the amino group is protected with bulky groups, producing 2,3-*anti*-selectivity.[52,53]



(9)

Reaction of acyclic chiral allylic bromides with aldehydes gives two adducts with moderate to high diastereofacial control (equation 10).[54] The principal adducts have an all-*syn* arrangement of β′-hydroxy, γ-vinyl, and δ-methyl substituents. The stereogenic center at the δ carbon of the allylic halide determines the configuration of the stereocenters created at the γ and β′ positions of the products. The selectivity is also in accord with the transition state shown in **Scheme 3**. Additional stereocenters at ε and ζ carbons of the allylic bromides increase the diastereoselectivity because of the increase in the effective size of R^L (large group).

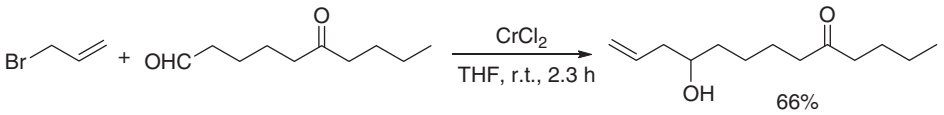


(10)

Double stereodifferentiation is observed in the reaction of chiral aldehydes with chiral allylic halides mediated by chromium(II) chloride.[54–56]

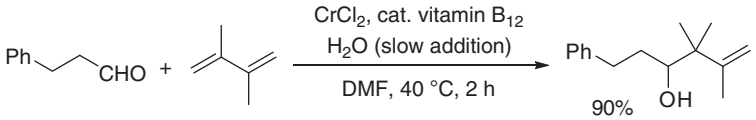
1.06.2.1.4 Functional group selectivity

Allylic chromium reagents also add to ketones to give homoallylic alcohols. Since ketones are less reactive than aldehydes due to steric and electronic factors, selective addition of an allyl group to aldehydes can be accomplished (equation 11).[10] In addition, the allylchromium reagent discriminates between the two ketone groups of 2- and 4-heptanone with a selectivity of 84–88%.[10]



(11)

The following functional groups are also tolerated under the usual reaction conditions: ester, lactone, amide, nitrile, acetylene, olefin, 1,3-diene, conjugated enyne, chloride, and acetal. A hydroxy group can be protected as OAc, OBn, OTBDMS, OTBDPS, OMOM, OCH_2OBn, or $OCH_2C_6H_4OMe$-*p* (OPMB). Because chromium–carbon bonds are not so sensitive to water (or a hydroxy group), chemoselective addition of an allyl group to a *β*-hydroxy ketone is accomplished by the chelation-accelerating effect.[57,58] In addition, allylic chromium compounds can be generated by slow addition of water to a mixture of a 1,3-diene and aldehyde in the presence of a cobalt catalyst (equation 12).[17]

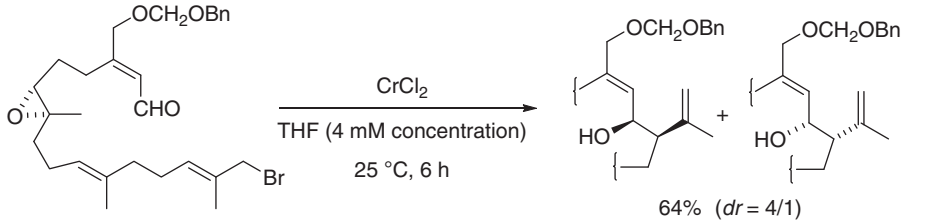


(12)

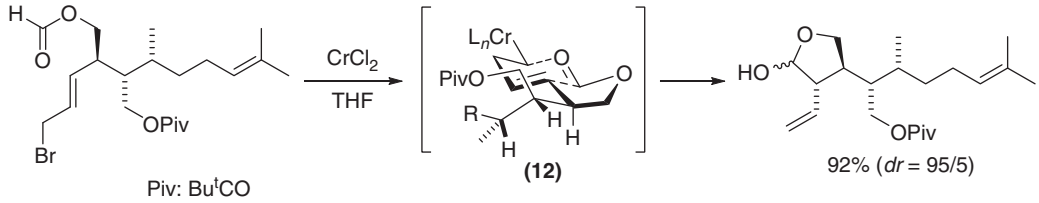
Allylic chromium compounds add to *α*,*β*-unsaturated aldehydes in a 1,2-fashion selectively.[36,59]

1.06.2.1.5 Intramolecular cyclization

Because the chromium-mediated coupling reaction of allylic halides and aldehydes is conducted under mild conditions by the Barbier-type procedure, the method is suitable for intramolecular cyclization. The cyclization proceeds to give medium-[33,60–62] and large-sized (equation 13) rings,[59,63–66] showing high 1,2-*anti* selectivity. Concerning the diastereocontrol of the cyclization, moderate selectivity is observed in the case of the macrocyclization owing to the influence of the remote asymmetric centers on the transition state. In contrast, high selectivity is observed in the case of a five-membered ring due to the restriction of the conformation and steric interaction in (**12**) (equation 14).[67]

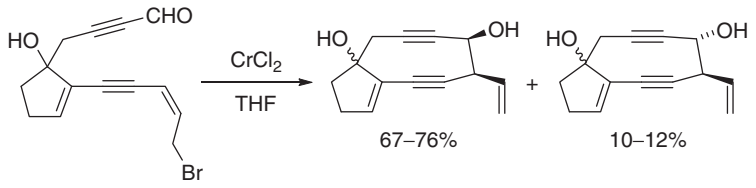


(13)



(14)

Because of the moderate Lewis acidity of chromium(III), labile hydroxy groups survive during the carbon–carbon bond formation (equation 15).[62,68]

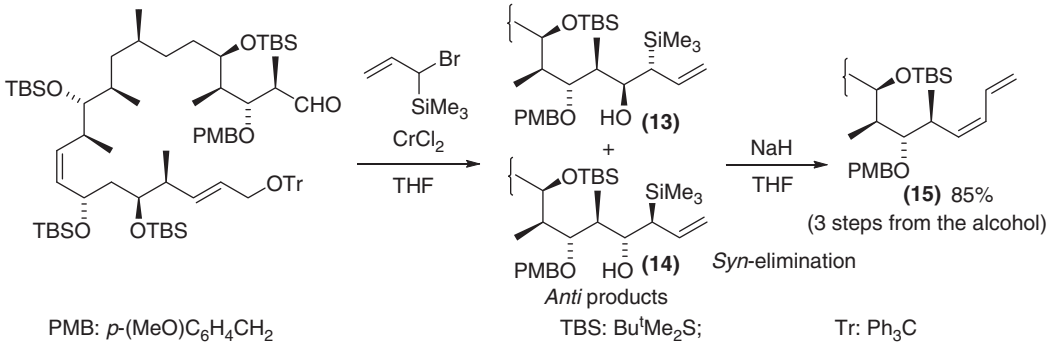


(15)

1.06.2.1.6 Functionalized and heterosubstituted allylic chromium reagents

When functionalized allylic halides are used as precursors of allylic chromium reagents, an acyclic molecule functionalized for further manipulation is produced. In addition, the internal coordination of heteroatoms sometimes fixes the conformation of the intermediate allylic chromium species and, consequently, high diastereoselectivity may arise.

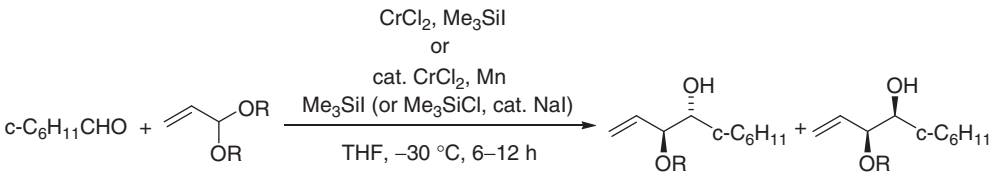
A trimethylsilyl-substituted allylchromium reagent can be prepared by treating either 1-trimethylsilyl-3-bromopropene or 3-trimethylsilyl-3-bromopropene with chromium(II) chloride. This reagent reacts with aldehydes at room temperature to yield exclusively *anti*-*β*-hydroxysilanes (**13**) and (**14**).[69] These *anti* adducts can be converted smoothly to *Z*-terminal diene (**15**) by a Peterson *syn*-elimination with potassium or sodium hydride (equation 16).[70–75]



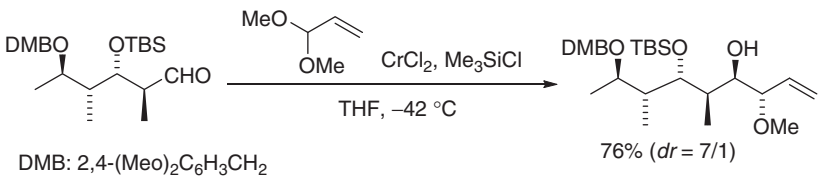
(16)

PMB: *p*-(MeO)$C_6H_4CH_2$ TBS: Bu^tMe_2S; Tr: Ph_3C

In situ reduction of acrolein dialkyl acetals with chromium(II) chloride in tetrahydrofuran provides *γ*-alkoxy-substituted allylic chromium reagents, which add to aldehydes to afford 3-buten-1,2-diol derivatives. The reaction rate and stereoselectivity are increased by adding iodotrimethylsilane (equation 17).[76] *In situ* formation of *α*- and *γ*-alkoxy-substituted allyl iodides with iodotrimethylsilane is postulated. Using manganese as a reductant, a catalytic version of this reaction using a chromium(II) salt can also be achieved.[77] The method is used for the total synthesis of bafilomycins (equation 18).[78–83]



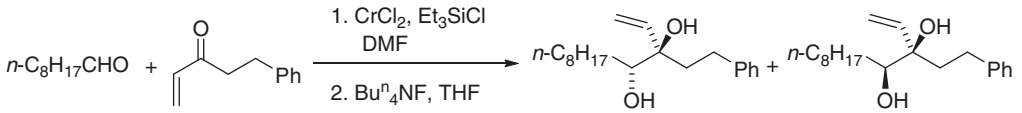
(17)



(18)

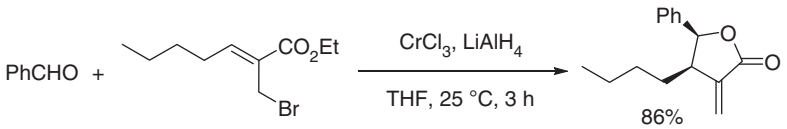
DMB: 2,4-$(Meo)_2C_6H_3CH_2$

γ-Siloxysubstituted allylic chromium reagents are generated by electron transfer to *α*,*β*-unsaturated ketones with chromium(II), successive trapping with chlorotrimethylsilane, and further one-electron reduction. The *anti*:*syn* ratio of the reaction depends markedly on the reaction temperature (equation 19).[84,85] Chromium-catalyzed reactions with manganese[86] and intramolecular cyclization have also been reported.[87]



(19)

The reduction of *α*-bromomethyl-*α*,*β*-unsaturated esters, 1,3-diene monoepoxides, and 3-alkyl-substituted 1,1-dichloro-2-propene (or 1,3-dichloro-1-propene) with chromium(II) proceeds to generate the corresponding functionalized allylic chromium compounds, which add to aldehydes to give *α*-methylene-*γ*-lactones (equation 20),[88,89] (*R**,*R**)-1,3-diols (equation 21),[90] and *anti*-(*Z*)-4-chloro-3-buten-1-ols (equation 22),[91] respectively, in a regio- and stereoselective manner.



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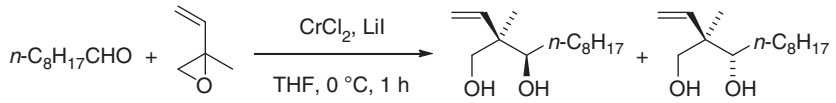

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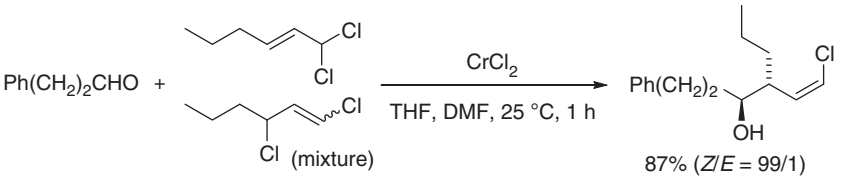
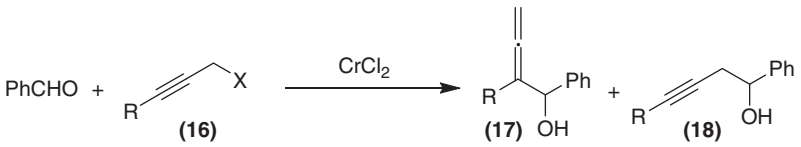


(22)

1.06.2.2 Propargylic Chromium Reagents

Propargylic halides react with carbonyl compounds in the presence of chromium(II) to give a mixture of allenic and homopropargylic alcohols.[92,93] The selectivity of the reaction depends on the substitution of the propargylic halide, the structure of the carbonyl compound and the presence of hexamethylphosphoric triamide in the mixture. For example, organochromium reagents, derived from primary propargylic halides (**16**) with a substituent on the acetylenic carbon, react with carbonyl compounds to afford allenic alcohols (**17**) accompanied by only small amounts of homopropargylic alcohols (**18**) (equation 23).[92–94] When secondary propargylic halides (**19**) are used, the product distribution depends on the carbonyl compound (equation 24).[93] Adding hexamethylphosphoric triamide as a cosolvent increases the amount of allenic products.



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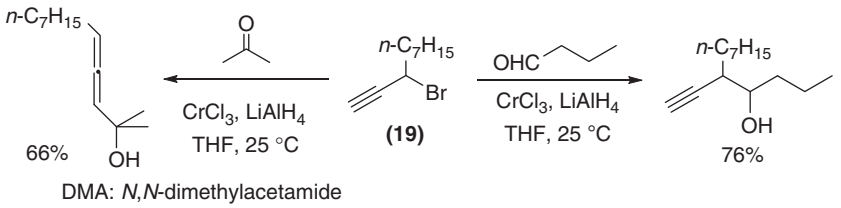
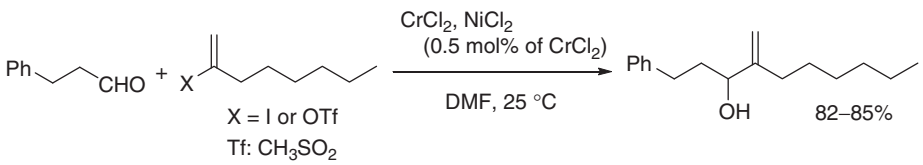


(24)

1.06.2.3 Alkenylchromium Reagents

1.06.2.3.1 Discovery of nickel catalysis

Reduction of alkenyl and aryl halides with chromium(II) chloride leading to the corresponding organochromium reagents and subsequent Barbier-type carbonyl addition was discovered in 1983 by Hiyama, Takai, and Nozaki.[5] The reaction was performed with only chromium(II) chloride. The result was not consistent with the observation that alkenyl and aryl halides are difficult to reduce with chromium(II), as reported by Castro and Kray.[1] Later, it was proved by Takai that the commercial chromium(II) chloride employed contained a catalytic amount of a nickel salt that was indispensable in promoting the coupling reaction.[6] At the same time, Kishi independently discovered the catalytic effect of nickel, and applied the protocol to the total synthesis of palytoxin.[7] By addition of a catalytic amount of nickel, the Barbier-type carbonyl addition of alkenyl halides (or triflates) to aldehydes proceeds with good reproducibility (equation 25).[95]

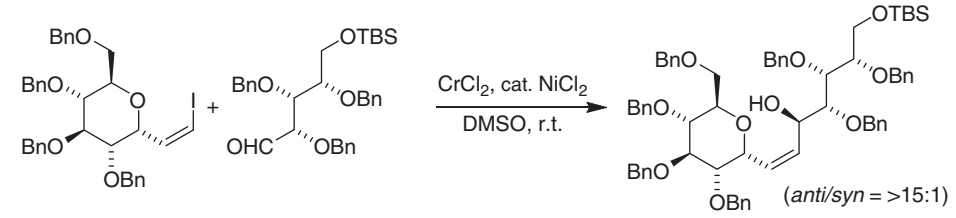


(25)

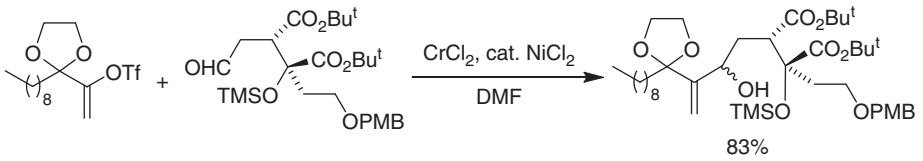
1.06.2.3.2 Comparison with other alkenylmetals

If suitable alkynes or ketones are easily accessible for preparation of alkenylmetal compounds, hydrometalation (or carbometalation) of the alkynes or Shapiro reaction[96] is the method of choice. However, the most popular method is the use of alkenyl halides as starting materials, especially for regio- and stereoselective preparations. Reduction of alkenyl halides with magnesium leading to alkenyl Grignard reagents,[97] and iodine–metal exchange from alkenyl iodides with butyllithium[98,99] are typical examples in this category. An easy preparation of alkenyllithium reagents from the corresponding alkenyl iodides with *n*-butyllithium at room temperature has also been reported.[100] One of the problems in employing these reagents is controlling the chemoselectivity of the reactions of alkenylmetal reagents.

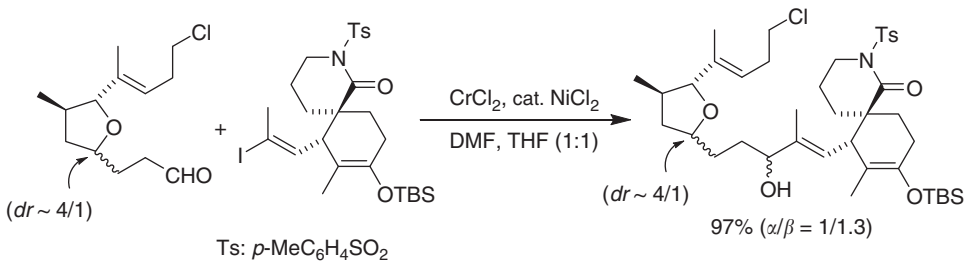
Compared to the above reagents, alkenylchromium reagents have the following advantages for preparation: (1) As shown in the first representative example, total synthesis of palytoxin,[7,101,102] the chromium method can be applied to highly oxygenated, multifunctional substrates, from which conventional organolithium or -magnesium reagents are sometimes difficult to generate (equations 26–28). Therefore, the chromium protocol offers a solution to anionic coupling at the alkenyl positions of substrates containing many oxygen functionalities such as halicondrin,[103–105] brevetoxin,[106] pinnatoxin A,[107] ulapualide A,[108] ciguatoxin,[109,110] aurisides,[111] amphidinol 3,[112] and goniodomin A.[113,114–117] (2) Preparation of alkenylchromium species does not require the use of strong bases, and the basicity of the generated alkenylchromium is weak. Therefore, functionalities that are labile to strong bases or nucleophiles can survive throughout the reaction, and the formation of undesired side products is suppressed. (3) Because the reducing power of chromium(II) is not strong compared to magnesium and zinc, excess amounts of chromium(II) salt do not affect the reaction, and thus, the method is suitable for small scale reactions. (4) The reaction is conducted under Barbier-type conditions, so the method is suitable for intramolecular cyclization (*vide infra*).



(26)



(27)



(28)

1.06.2.3.3 Generation of alkenylchromium reagents

In contrast to traditional reactions with alkenyllithium, -magnesium, and -cuprate reagents, the alkenylchromium reaction is experimentally simple. The reaction is conducted under Barbier-type conditions, i.e., in the presence of carbonyl compounds. The reaction can be accomplished by adding a mixture of an aldehyde and an alkenyl halide to a stirred mixture of chromium(II) chloride and a catalytic amount of nickel(II) chloride in dimethylformamide or dimethyl sulfoxide (or vice versa).

Iodoalkenes are more reactive than bromoalkenes, and product yields are generally better with the former. The Barbier-type reaction between alkenyl triflates (or mesylates) and aldehydes also proceeds under the same conditions.[6,118] A soluble form of chromium(II) chloride is essential to promote a smooth reaction, and thus, the following are used as the preferred solvents: dimethylformamide, dimethyl sulfoxide, dimethyl sulfoxide-dimethyl sulfide, and a mixture of dimethylformamide and tetrahydrofuran. These solvents should be dried and deoxygenated. Little or no reaction occurs in ether or tetrahydrofuran alone. Normally 0.1–1 wt.% of nickel(II) chloride is added to chromium(II) chloride. Nickel acetylacetonate[119,120] and $Ni(cod)_2$[121] are reportedly effective in some reactions. It is important to keep the content of nickel(II) chloride low (approximately 0.01–1 wt.%)

to avoid the formation of dienes by homocoupling of the haloalkenes.[122] Other potential catalysts, such as manganese(II) chloride, iron(III) chloride, cobalt(II) chloride, copper(I) chloride, and palladium(II) chloride are not as effective.

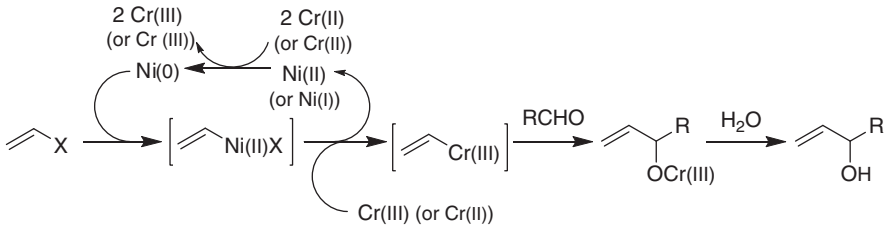
When an electron-withdrawing group, i.e., ketone, ester, or sulfonate group, is attached to the β-position of a haloalkene, the coupling reaction proceeds without addition of a nickel salt,[123] but the yields are generally lower.

Addition of pyridine ligands, especially 4-*tert*-butylpyridine, to a mixture of chromium(II) chloride and nickel(II) chloride in tetrahydrofuran (THF) gives a homogeneous solution.[124] The additive accelerates the reactions of alkenyl halides (or triflates) with aldehydes,[124,125] and also inhibits homocoupling of the alkenyl halides (or triflates), even when the amount of nickel is increased to 0.5 mol relative to the chromium(II) chloride.[126] When 2 equivalents of lithium chloride are added to a suspension of chromium(II) chloride in tetrahydrofuran, the chromium salt dissolves. This $CrCl_2 \cdot 2LiCl$ solution can also be used for the nickel-catalyzed coupling reaction. Ultrasonic irradiation is sometimes reported to accelerate the reaction.

Reaction workup is typically accomplished by addition of the reaction mixture to water and extraction with ether (or ethyl acetate). When separation of the organic and aqueous phases is difficult, addition of sodium (or potassium) serinate,[124] potassium sodium tartrate tetrahydrate (Rochelle salt), ethylenediamine,[124] or sodium (or potassium) fluoride to the reaction mixture sometimes improves the efficiency of the extractive workup.

1.06.2.3.4 Mechanism of the reaction

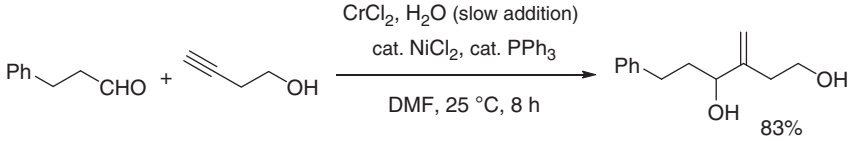
In contrast to allylic halides, reduction of alkenyl and aryl halides requires catalytic amounts of nickel salts (or complexes). The first proposed mechanism for the nickel-catalyzed Grignard-type addition of alkenylchromium reagents to aldehydes is shown in Scheme 4. Nickel(II) chloride is first reduced to nickel(0) with 2 equivalents of chromium(II) chloride. Oxidative addition of an alkenyl halide to the nickel(0) occurs, then the transmetalation reaction between the resulting alkenylnickel species and the chromium(III) salt affords an alkenylchromium reagent, which reacts with an aldehyde to produce the allylic alcohol.



Scheme 4

The following are observed about this process: (1) The reduction of alkenyl halides does not proceed without nickel catalysts. (2) When the amount of the nickel salts is increased, formation of the dimer of the alkenyl halides leading to 1,3-dienes increases. This observation suggests that the key to the reaction is the transmetalation from the alkenylnickel to the alkenylchromium species. However, because reduction potentials of metal complexes are affected by their ligands including solvent molecules, the following mechanistic details are still unclear: the valences of the nickel species in the cycle, and the valence of the chromium species that acts at the transmetalation step. The addition step of an alkenylchromium species to an aldehyde is proposed to proceed via a four-membered transition state, which is in sharp contrast to that of an allylic chromium species.[127,128] A catalytic cycle of chromium and development for asymmetric addition is discussed in Sections 1.06.2.7.2 and 1.06.2.8.3.

From the mechanism in Scheme 4, it is suggested that alkenylchromium compounds can be prepared from alkenylnickel species in the presence of chromium(III) (or chromium(II)). Because 1-substituted alkenylnickel compounds are generated regioselectively by addition of nickel hydride species to terminal alkynes, the corresponding alkenylchromium compounds can be prepared directly from terminal alkynes by slow addition of 1 equivalent of water (based on the alkyne) in the presence of a nickel complex and chromium(II) chloride (equation 29).[129]



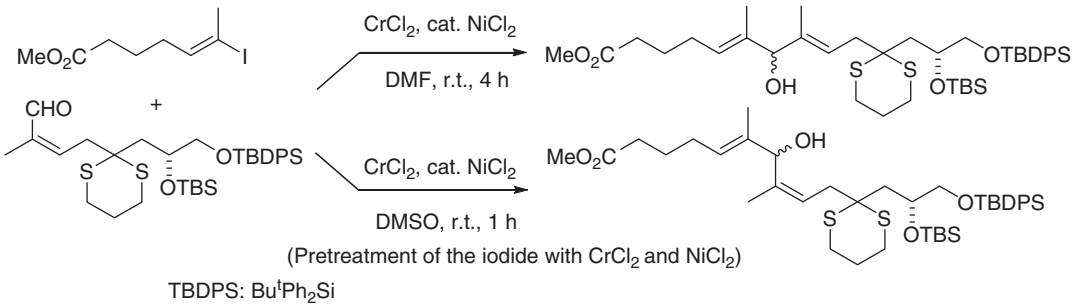
(29)

1.06.2.3.5 Typical features of alkenylchromium reagents

Because alkenylchromium reagents can be prepared securely even on a small scale and can add to an aldehyde with high functional group selectivity, the method is often employed in the last few steps of total syntheses. Typical features of alkenylchromium reagents are listed below:

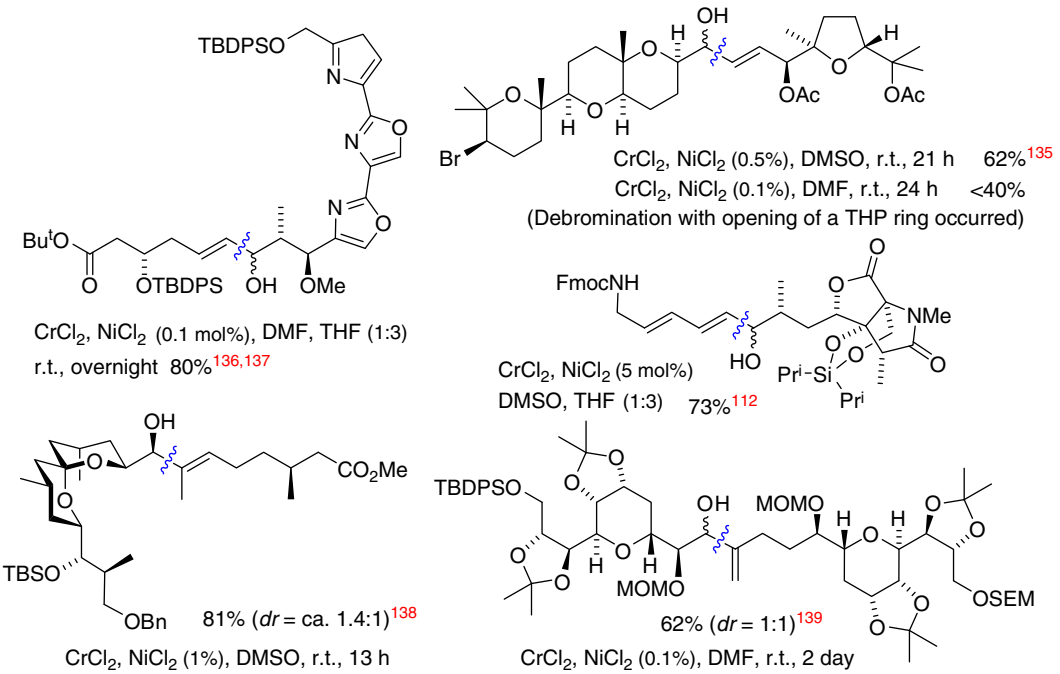
1. 1,2-Addition: Alkenylchromium reagents produce 1,2-addition products from reactions with α,β-unsaturated aldehydes as the corresponding lithium and magnesium reagents. The stereochemistry of the α,β-unsaturated aldehydes is usually maintained.

In some cases, however, the isomerization of the double bonds occurs. The isomerization can be prevented by changing the solvent from DMF to dimethyl sulfoxide (DMSO) and pretreating the alkenyliodide with chromium(II) chloride and a catalytic amount of nickel(II) chloride before addition of the α,β-unsaturated aldehyde (equation 30).[130]



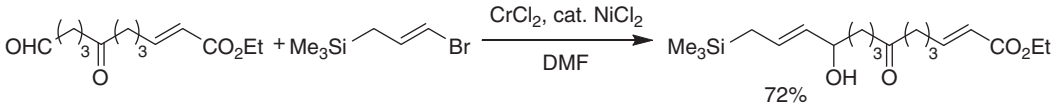
(30)

2. Functional group selectivity: Alkenylchromium reagents add to ketones. However, due to the low nucleophilicity of the reagents, the yields are relatively low except in intramolecular reactions leading to five-membered carbocycles.[131–133] Aldehyde-selective additions can be accomplished in good-to-excellent yields without affecting coexisting ketone, ester, amide, acetal, nitrile, and sulfinyl groups.[134] The following protecting groups for hydroxy groups are untouched during the reaction: ethers, silyl ethers (Me_3Si (TMS), Bu^tMe_2Si (TBS), Pr^i_3Si (TIPS), etc.), esters, and acetals (tetrahydropyranyl (THP), $MeOCH_2$ (MOM), $Me_3Si(CH_2)_2OCH_2$ (SEM), etc.). When the aldehyde has a secondary bromide at the 3-position of a tetrahydropyran ring, reduction of the bromide with ring opening occurs as a side reaction. The elimination can be minimized by increasing the amount of doped nickel (0.1–0.5%) and changing the solvent from DMF to DMSO.[135] The alkenylchromium reagent is not very basic; epimerization at the α-position of the aldehyde does not normally occur. See examples in **Scheme 5**.[136–139]



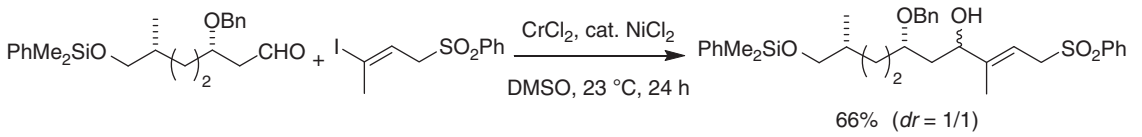
Scheme 5

As the Lewis acidity of chromium(III) in dimethylformamide is moderate, the allylsilane moiety survives the reaction (equation 31).[134]



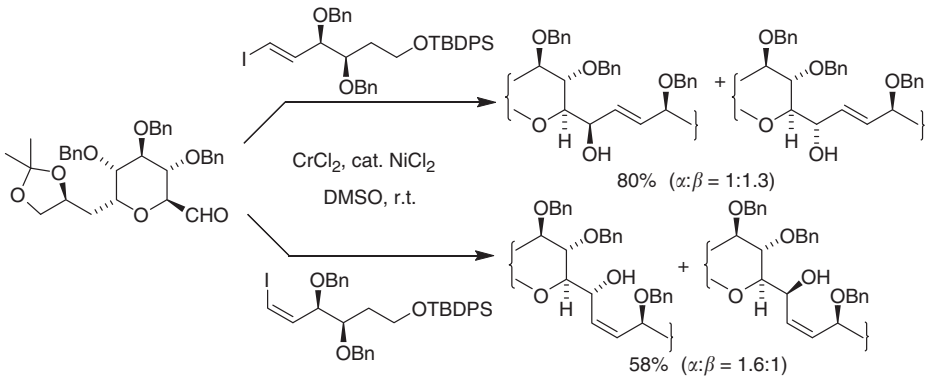
(31)

3. Regio- and stereoselectivity of double bonds: The regiochemistry of double bonds is maintained during the coupling reaction even when the compound has a highly acidic allylic proton (equation 32).[140]



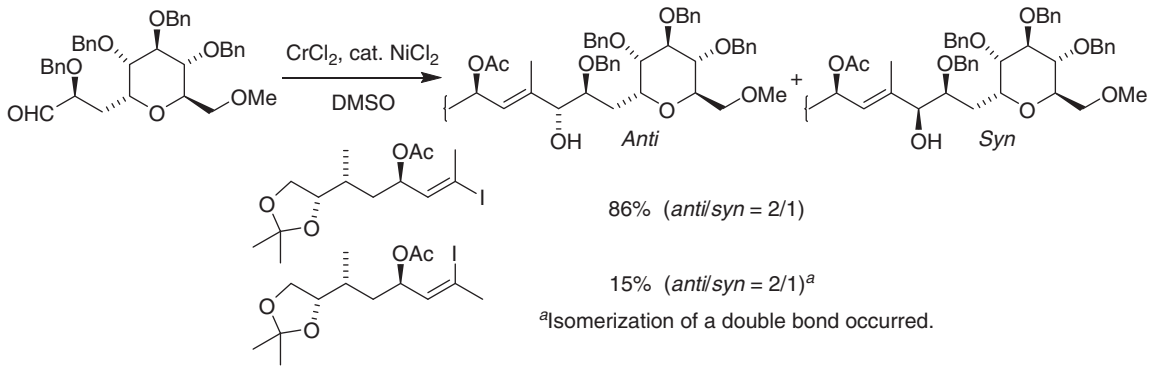
(32)

The stereochemistry of *trans*- and *cis*-disubstituted haloalkenes and trisubstituted *trans*-haloalkenes is retained in the reaction (equation 33).[6,7] Reactions of (*E*)- and (*Z*)-2-bromostyrene and benzaldehyde proceed stereospecifically.

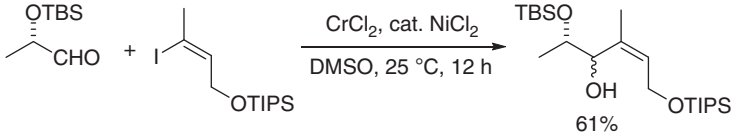


(33)

In the case of a trisubstituted *cis*-haloalkene (or an alkenyl triflate), *cis-trans* isomerization can occur with the desired coupling reaction with the chromium(II)-nickel(II) system, or occasionally in the recovery of the starting alkenyl halide because of steric interactions of substituents *cis* to the halogen. For example, both (*E*)- and (*Z*)-2-iodo-1-phenyl-1-propene react with benzaldehyde to give (*E*)-1,3-diphenyl-2-methyl-2-propen-1-ol as the sole product.[5,6] Coupling reactions with[7] and without[141] *cis-trans* isomerization of the double bonds are shown in equations 34 and 35, respectively.



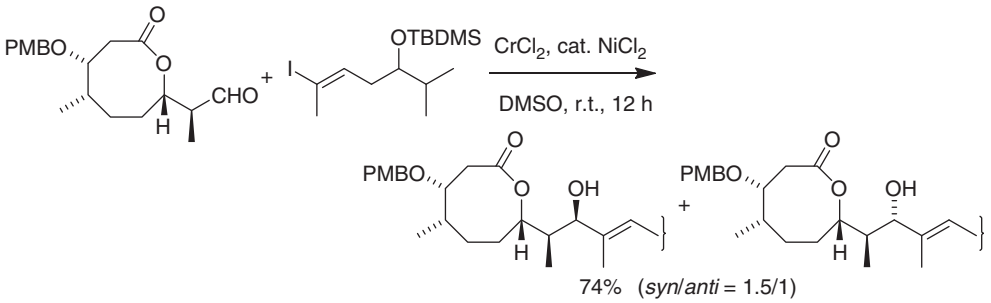
(34)



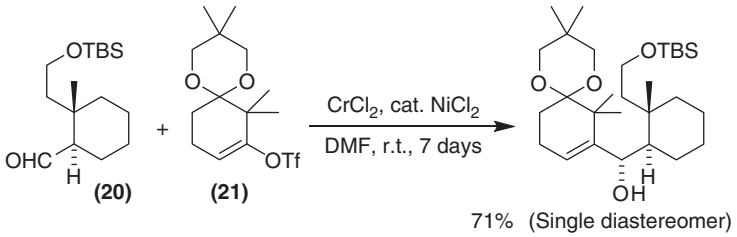
(35)

4. Diastereoselectivity of reactions with chiral aldehydes: The reaction of chiral aldehydes produces a mixture of two diastereomers with a moderate-to-good selectivity for the Felkin isomer. *Syn* adducts predominate from α-methyl-substituted

secondary aldehydes, but the diastereoselectivity is typically less than 2:1 (equation 36).[142] A reaction between the sterically congested aldehyde (**20**) and the hindered alkenyl triflate (**21**) produces a single diastereomer, probably because of the steric demands of the two substrates (equation 37).[143] Reactions between α-alkoxyaldehydes and alkenylchromium reagents normally produce *anti* adducts as the main products.[7,144,145] The diastereoselectivities are 1.3:1–15:1 and vary with the combination of the aldehyde and the alkenylchromium reagent.



(36)



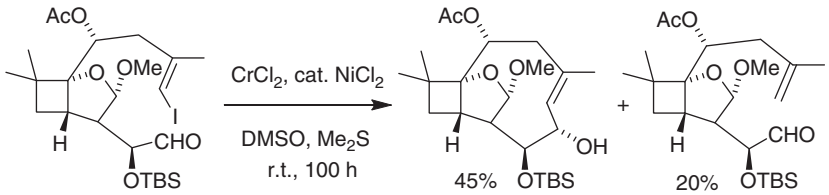
(37)

In order to converge the produced diastereomers, oxidation of the formed allylic alcohols sometimes follows the addition. The diastereomeric ratio of the desired product can be improved by reduction under the appropriate conditions. As the convergent method, chlorination of the allylic alcohol with thionyl chloride is also employed.[146]

1.06.2.3.6 Intramolecular cyclization

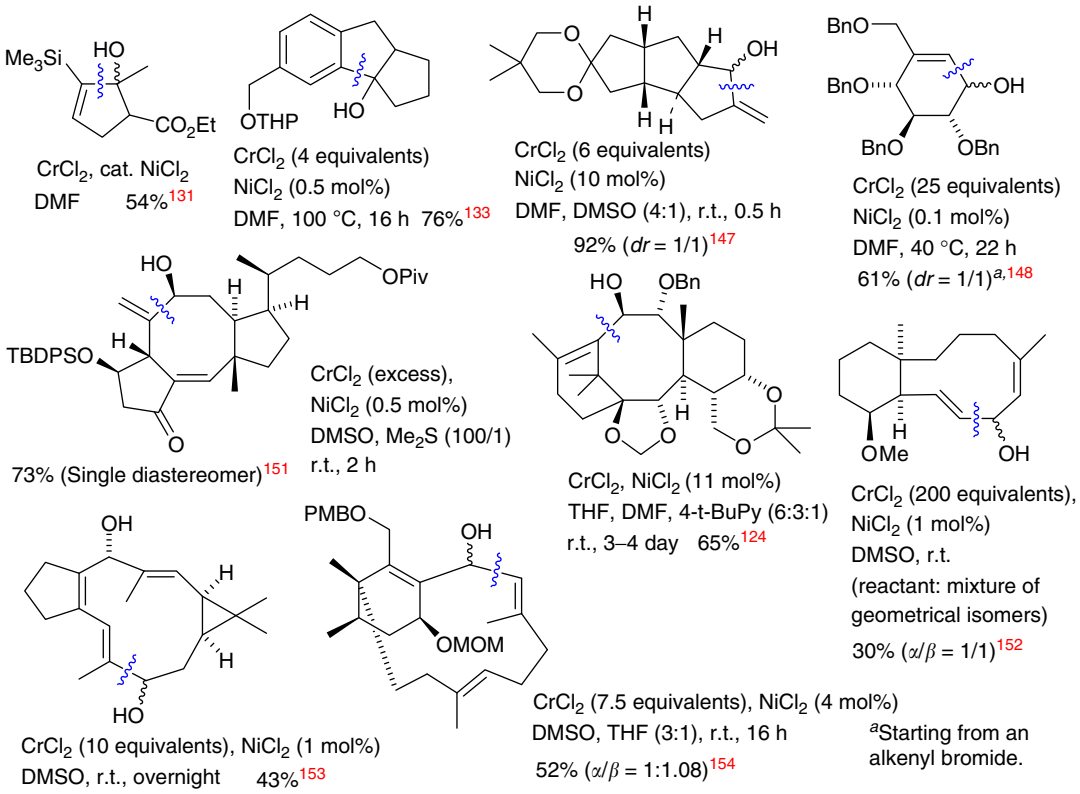
Because alkenylchromium reagents can be prepared in the presence of aldehydes, i.e., Barbier-type addition, the protocol is suitable for intramolecular cyclization. The 5-,[131,132,147] 6-,[148] 7-,[149] 8-,[150,151] 10-,[152] 11-,[153] 12-,[120,154,155] 16-,[156] and 22-membered[157] carbocycles are effectively constructed by intramolecular cyclization with chromium(II) chloride and nickel catalysts (Scheme 6). Large excesses (10–100 equivalents) of chromium are sometimes required. In the case of macrocycles, a high-dilution method is frequently employed; however, by choosing the catalytic conditions using appropriate bipyridyl complexes of chromium(III) and nickel(II), the high-dilution method is not required (see Section 1.06.2.7.2).[158] Stereoselectivity of the newly formed stereogenic centers depends on several factors such as the stability of the cyclic compounds, and in some cases, only one diastereomer is produced. In the case of a five-membered ring, an alkenylchromium formed *in situ* adds to the ketone group in good yield, although heating is necessary in some cases.[133,159,160]

Oxygen-containing 9-,[127,161–163] 10-,[163] 13-,[119] and 16-membered[164] rings are also formed with this method (Scheme 7). Simple reduction of alkenyl iodides occurs as a side reaction when intramolecular cyclization does not occur smoothly (equation 38).[163]



(38)

Five-[165] and six-membered[145,166] rings containing nitrogen atoms are also constructed with the chromium(II)-nickel(II) system (Scheme 7).[167,168]



Scheme 6 Carbocycles produced by intramolecular cyclization with the Cr-Ni method.

1.06.2.4 Alkynylchromium Reagents

1.06.2.4.1 Comparison with other alkynylmetals

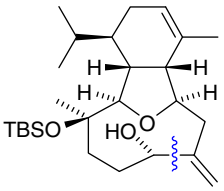
Such alkynylmetals as alkynyllithium, -sodium, and -magnesium compounds are easily generated by treatment of the corresponding 1-alkynes with alkylmetals or metal amides, and are generally used *in situ* for preparation of propargylic alcohols by reaction with carbonyl compounds. Due to the strong basicity of the alkylmetals and metal amides, base-induced side reactions sometimes follow. Although intramolecular cyclization between an alkynylmetal and an aldehyde group can be accomplished with lithium or sodium hexamethyldisilazide,[169,170] milder preparation of alkynylmetals is desirable, especially when electrophilic functionalities exist in the same molecule. Alkynylchromium reagents are prepared *in situ* by reduction of 1-halo-1-alkynes with chromium(II) under mild conditions. The starting halides, 1-iodo-1-alkynes, are prepared either by treatment of 1-alkynes with butyllithium and iodine in tetrahydrofuran, or under milder conditions, with morpholine and iodine in benzene,[171] potassium carbonate, copper(I) iodide, and iodine,[172] or with *N*-iodosuccinimide and silver(I) nitrate in acetone.[173]

1.06.2.4.2 Preparation

Although reactions between simple 1-halo-1-alkynes and aldehydes proceed without a catalytic amount of nickel(II) chloride,[174] the chromium(II) chloride-nickel(II) chloride system is suitable for highly oxygenated substrates[175,176] and for intramolecular cyclizations.[177,178] The amount of nickel(II) chloride used for iodoalkyne addition to carbonyl groups should be smaller (0.01–0.2% w/w) than that for iodoalkenes, otherwise homocoupling of the iodoalkyne to the symmetrical 1,3-diyne occurs.

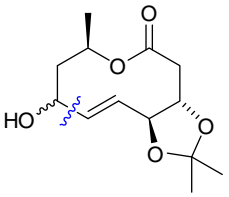
1.06.2.4.3 Typical features of alkynylchromium reagents

Typical features of alkynylchromium reagents are almost the same as those of alkenylchromium reagents. The alkynylchromium reagents can be prepared from iodoalkynes having many oxygen functionalities (equations 39–41).[135,179–181] Potential problems, such as epimerization and dehydration associated with enolization, do not occur.[175,176] The diastereofacial selectivity of the addition of alkynylchromium reagents to aldehydes is moderate, and the diastereomeric ratio varies with the aldehyde structure (equations 39–41).[175,176,182] In some cases, Kishi's modification using lithium chloride and Bu_3BnNCl as additives enhances the efficiency of the catalytic redox cycle of $CrCl_2$, Mn, and Me_3SiCl (equation 41).[181]



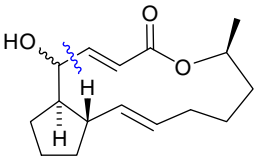
61% (*dr* = >20/1)[127,162]

$CrCl_2$ (56 equivalents), $NiCl_2$ (6.4 mol%)
DMSO, Me_2S (1% v/v)
r.t., 36 h

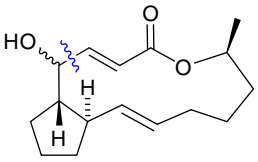


54% (α/β = 2/1)[167]

$CrCl_2$ (15 equivalents), $NiCl_2$ (0.5 mol%)
DMF, r.t., overnight

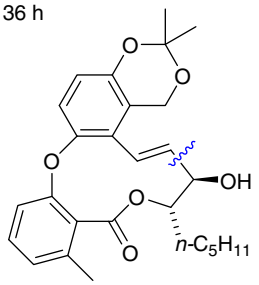


60% (α/β = 1/4)[119]



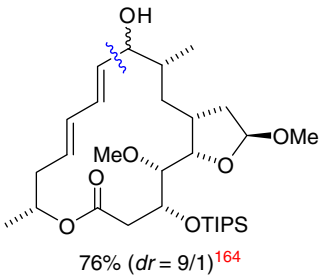
70% (α/β = 1/ >10)[119]

$CrCl_2$, $Ni(acac)_2$ (0.1 mol%), DMF



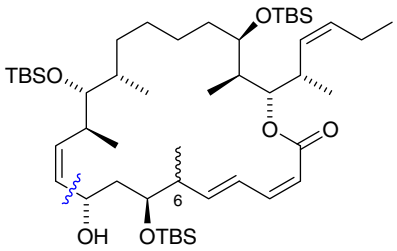
79% (*anti*/*syn* = >95/5)[168]

$CrCl_2(thf)_{1.8}$ (10 equivalents)
$NiCl_2$ (2–4 mol%), DMF (0.02 M)
r.t., 4 h



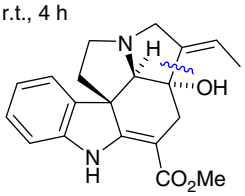
76% (*dr* = 9/1)[164]

$CrCl_2$ (100 equivalents), $NiCl_2$ (1 mol%)
DMSO, r.t., 7 h



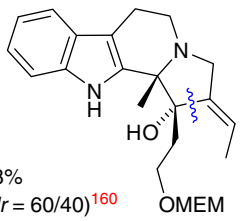
C6 (*S*): 53% or C6 (*R*): 22%[157]

$CrCl_2$ (15 equivalents), $NiCl_2$(dppf) (1 mol%)
4,4'-^{t}Bu$_2$-2,2'-dipyridyl (15 equivalents)
THF (0.001 M), r.t., 5 day



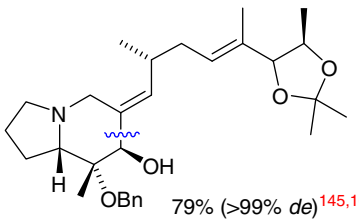
86%[165]

$CrCl_2$ (12 equivalents), $NiCl_2$ (2.2 mol%)
DMSO, r.t., 2 h



88%
(*dr* = 60/40)[160]

$CrCl_2$ (5 equivalents), $NiCl_2$ (38 mol%)
DMSO, r.t., 24 h

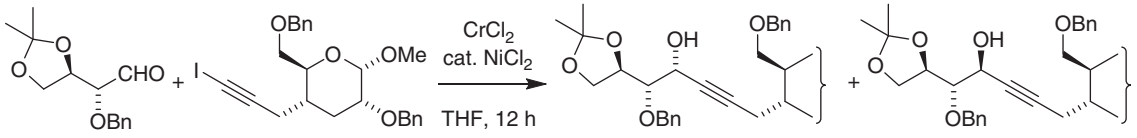


79% (>99% *de*)[145,166]

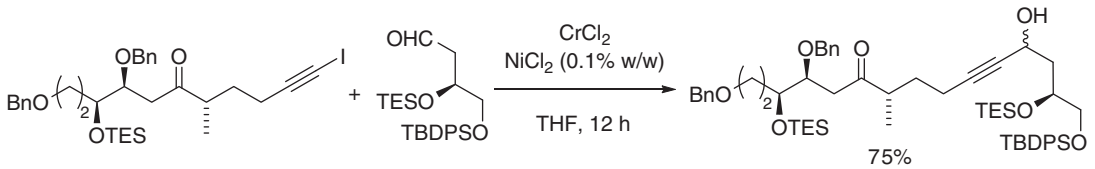
$CrCl_2$ (5 equivalents), $NiCl_2$ (0.58 mol%)
DMF, r.t., 40 h

MEM: $MeO(CH_2)_2OCH_2$

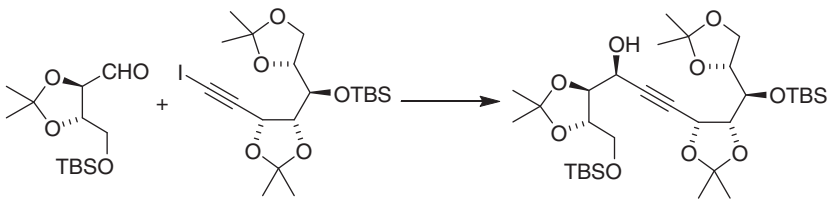
Scheme 7 Heterocycles produced by intramolecular cyclization with the Cr-Ni method.



65% (*dr* = 2/1) (39)



75% (40)

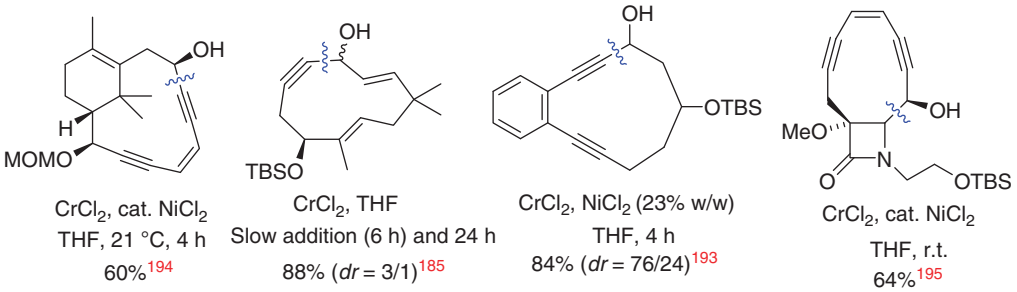


$CrCl_2$, cat. $NiCl_2$ (below 0.2 mol% of $CrCl_2$), THF 82% (>95% *de*)
cat. $CrCl_2$, cat. $NiCl_2$, Bu_3BnNCl, LiCl, Mn, Me_3SiCl, THF 88% (~90% *de*) (41)

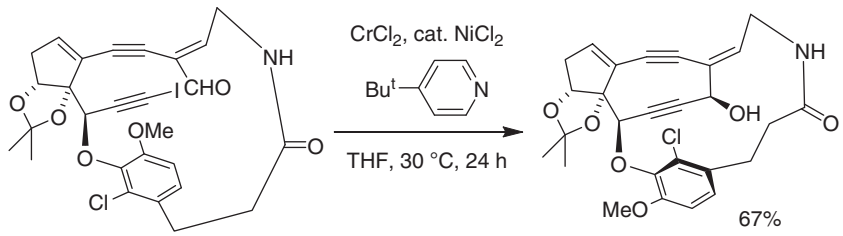
TES: Et_3Si

1.06.2.4.4 Intramolecular cyclization

The starting 1-iodo-1-alkynes can be prepared from 1-alkynes with iodine and morpholine in excellent yields under mild conditions.[176] Thus, the reaction is suitable for intramolecular cyclization.[183–185] The 9-,[186,187] 10-,[177,178,188–192] 11-,[185,193] and 12-membered[194] rings are prepared by intramolecular cyclization with chromium(II) chloride and a catalytic amount of nickel(II) chloride. Notably, this method has been used to synthesize strained molecules such as enediynes.[194] A low concentration of the ω-iodoalkynyl aldehyde is occasionally required to prevent intramolecular coupling and/or dehalogenative reduction.[186,188] Several examples are shown in Scheme 8 and equation 42.[185,187,193,195]



Scheme 8

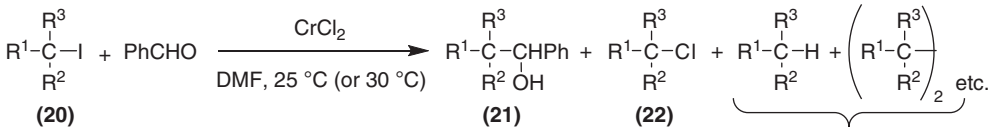


(42)

1.06.2.5 Alkylchromium Reagents

1.06.2.5.1 Preparation under cobalt catalysis[8]

Alkylchromium compounds can be prepared by treating a chromium(III) salt, such as chromium(III) chloride or chromium(III) acetylacetonate, with an organomagnesium,[196] -lithium, or -aluminum compound.[14,197] The transmetalation method, however, requires the use of strong bases or reductants for the preparation of the starting alkylmetal compounds. In contrast to reactive substrates such as allylic or alkynyl halide, it is difficult to reduce alkyl halides to alkylchromium reagents with chromium(II) in aprotic solvents. In addition, the course of the reaction differs depending on the substitution of the carbon attached to the halogen atom (usually iodine). In the case of primary iodides, for example, treatment of a mixture of 1-iodododecane [(**20a**): $R^1 = n\text{-}C_{11}H_{23}$, $R^2 = R^3 = H$] with chromium(II) chloride in dimethylformamide at 30 °C for 16 h produces only 7% of adduct (**21a**), whereas most of the material is recovered as 1-chlorododecane (**22a**, 88%) (equation 43).[38]

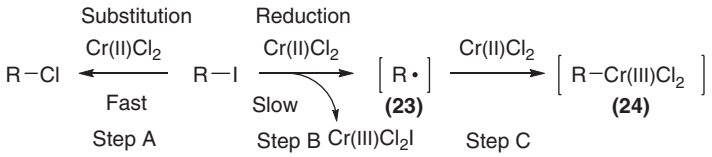


Primary (**a**: $R^1 = n\text{-}C_{11}H_{23}$, $R^2 = R^3 = H$)	16 h	7%	88%	<2%
Secondary (**b**: $R^1 = n\text{-}C_{11}H_{23}$, $R^2 = Me$, $R^3 = H$)	20 h	27%	29%	44%
Tertiary (**c**: $R^1 = n\text{-}C_{10}H_{21}$, $R^2 = R^3 = Me$)	5 h	9%	<1%	84%

(43)

This result suggests that the rate of substitution by chloride ion (step A in Scheme 9) is higher than the rate of reduction with chromium(II) ion (step B). The reduction of the alkyl radical (**23**) with chromium(II) ion leading to an alkylchromium(III) species (**24**) (step C) is rapid.

Addition of a catalytic amount of vitamin B_{12} (B_{12}) or cobalt phthalocyanine (CoPc) accelerates the formation of alkyl radicals from alkyl halides, especially 1-iodoalkanes (step B), and the Barbier-type reaction of alkylchromium reagents then proceeds smoothly. The reactivity of alkyl halides is in the order I > Br > Cl ≈ OTs. The reaction rate is affected by the substitution at the

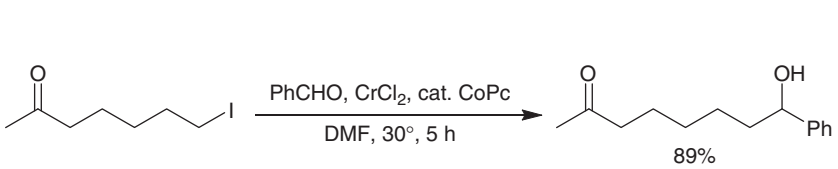


Scheme 9

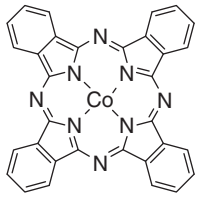
β-position of the iodide. The reaction with isobutyl iodide proceeds more slowly than that with an *n*-alkyl iodide. There are some differences between the two catalysts. Iodo, bromo, chloro, and tosyloxy compounds are reduced to give the alkylchromium reagents with chromium(II) chloride under B_{12} catalysis, while the two latter compounds remain unchanged in the presence of CoPc.

The cobalt-catalyzed reaction cannot be applied to tertiary and secondary alkyl iodides due to the low thermal stability of the carbon–chromium σ bond. Although a chemoselective reaction between isopropyl iodide and benzaldehyde proceeds without affecting the coexisting acetophenone, the yields of the reaction drop considerably when further substituted iodides or aldehydes are employed.[198,199]

Reduction of alkyl halides to the corresponding chromium reagents under mild conditions enables the Barbier-type reaction to proceed without protection of the coexisting ketone and ester groups (equation 44).[8]



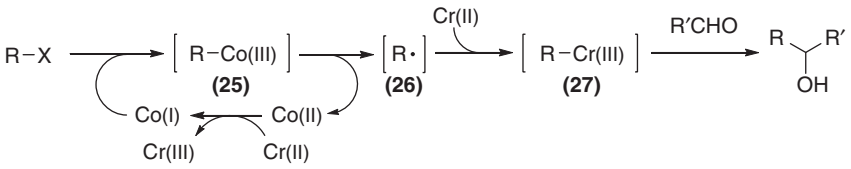
(44)



Cobalt(II) phthalocyanine (CoPc)

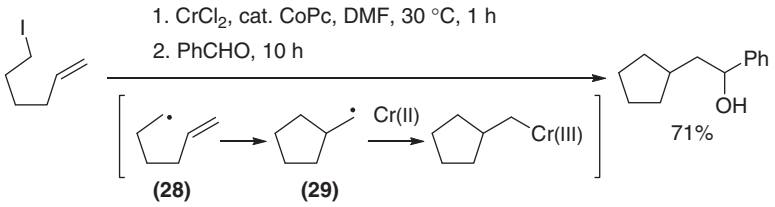
1.06.2.5.2 Mechanism

A possible mechanism for the formation of alkylchromium reagents under cobalt catalysis is shown in Scheme 10. It involves: (1) reduction of cobalt(III) or cobalt(II) into cobalt(I) by chromium(II); (2) nucleophilic substitution of an alkyl halide with cobalt(I) to give the alkylcobalt species (**25**); (3) homolytic cleavage of the carbon–cobalt(III) bond to yield the alkyl radical (**26**) and cobalt(II); (4) reductive trapping of the alkyl radical (**26**) with chromium(II) to generate the alkylchromium (**27**) which then couples with an aldehyde; and (5) regeneration and recycling of cobalt(I) from cobalt(II) by chromium(II).



Scheme 10

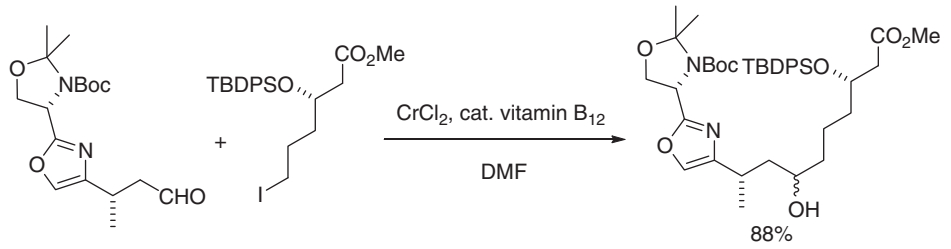
When 6-iodo-1-hexene is used, the 5-hexenyl radical (**28**) cyclizes to the corresponding cyclopentylmethyl radical (**29**), which is trapped by chromium(II) before carbonyl addition occurs (equation 45).[8]



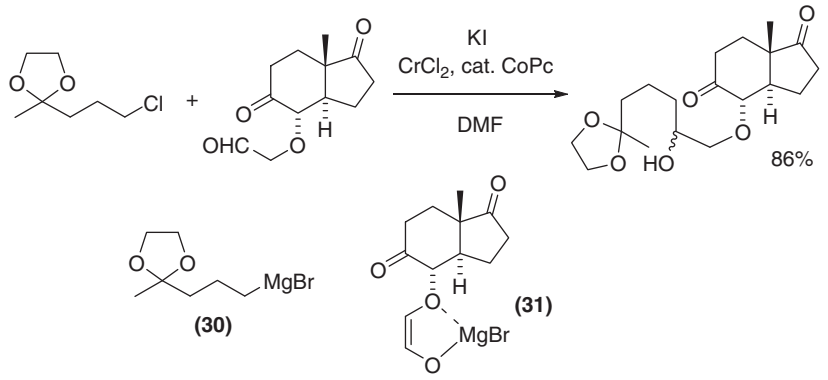
(45)

1.06.2.5.3 Synthetic application

The reaction can be applied to the coupling reaction having oxygen or nitrogen functional groups (equation 46).[200] In the reaction shown in equation 47, the desired product is not obtained with Grignard reagent (**30**) due to the formation of (**31**) by deprotonation with (**30**).[201]

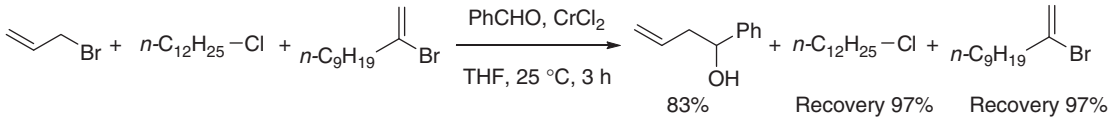


(46)

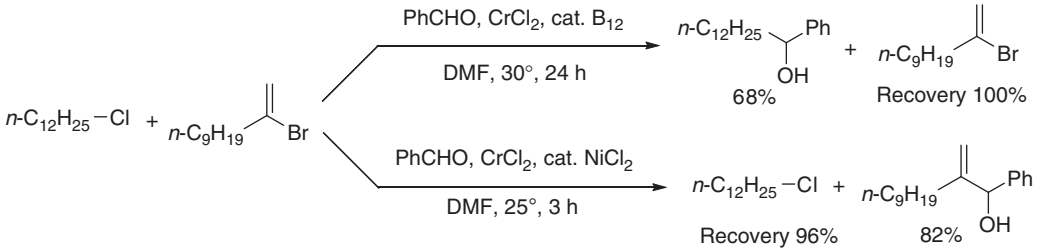


(47)

Organochromium reagents can be prepared chemoselectively by changing either the catalyst or the solvent. Alkenyl and alkyl halides remain unchanged under the conditions of allylchromium preparation (equation 48). However, alkenyl- and alkylchromium reagents are produced selectively under nickel and cobalt catalysis, respectively (equation 49).[8]



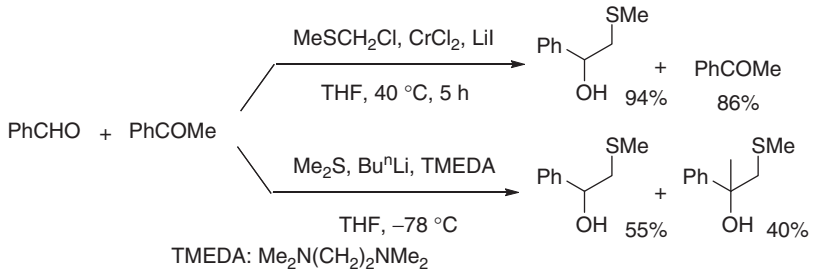
(48)



(49)

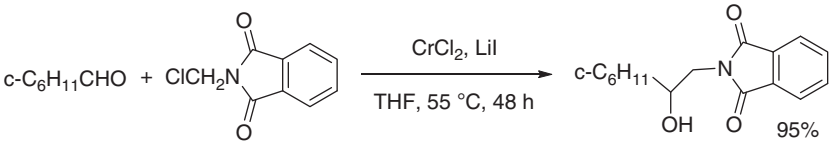
1.06.2.6 Heterosubstituted Alkylchromium Reagents

Compared to their sulfinyl and sulfonyl counterparts, the preparation of α-sulfenyl carbanions by deprotonation requires strong base combinations such as *n*-butyllithium and 1,4-diazabicyclo[2.2.2]undecane,[202] or tetramethylethylenediamine.[203] In contrast, the reduction of α-haloalkyl phenyl or methyl sulfides proceeds smoothly with chromium(II) chloride in the presence of lithium iodide to generate the corresponding α-thioalkylchromium reagents. These agents add to aldehydes in a chemo- and stereoselective manner unattainable under highly basic conditions (equation 50).[204]



(50)

The reduction of *N*-(chloromethyl)succinimide or -phthalimide with $CrCl_2$ in the presence of LiI provides the corresponding α-nitrogen-substituted organochromium reagent, which reacts *in situ* with aldehydes to give protected amino alcohols in good yields (equation 51).[205] The reaction tolerates the presence of functional groups such as nitriles and esters.

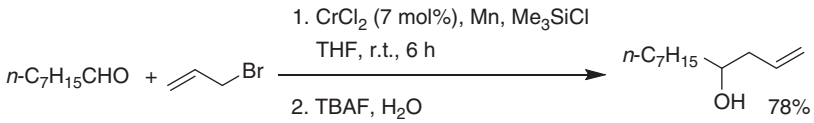


(51)

1.06.2.7 Construction of Catalytic Cycles

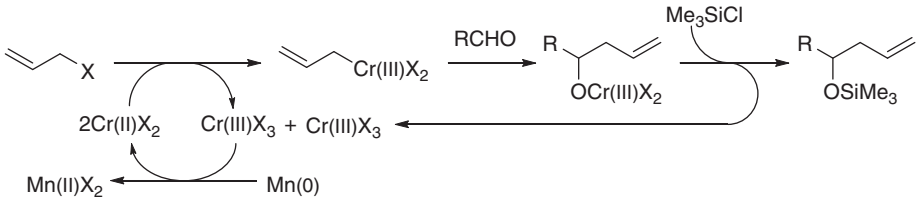
1.06.2.7.1 Catalytic cycle of allylation

Chromium(II) is a one-electron reductant; therefore two equivalents are required for the formation of organochromium reagents. This means that large amounts of chromium(II) salt must be used, which produces large amounts of chromium(III) salt waste. From an economical and ecological view, a catalytic version of the chromium(II)-mediated reaction is desired. Among the methods to recycle the chromium,[206–208] a combination of manganese and chlorotrimethylsilane developed by Fürstner is the most popular (equation 52).[9,43] The work is seminal, especially for asymmetric addition of organochromium compounds.



(52)

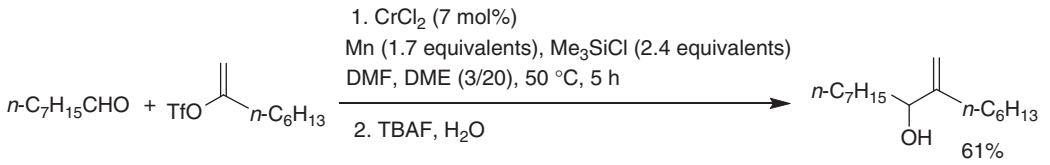
There are two important points in Fürstner's method (Scheme 11): (1) In order to recycle a catalytic amount of chromium(III), manganese metal with its stronger reduction potential is employed. However, the direct reduction of allylic halides with manganese does not occur (or is at least very sluggish) under the reaction conditions. Therefore, for example, zinc metal cannot be employed instead of manganese because zinc reduces allylic halides directly to generate allylic zinc species, and thus the merits of the allylic chromium compounds disappear. (2) The chromium(III) bound to the oxygen of the initial carbonyl addition is not reduced smoothly. Therefore, the alkoxy group on chromium(III) is replaced with chloride by silyl transfer to chlorotrimethylsilane, and an easily reduced chromium(III) salt is liberated.



Scheme 11

1.06.2.7.2 Catalytic cycle of alkenylation

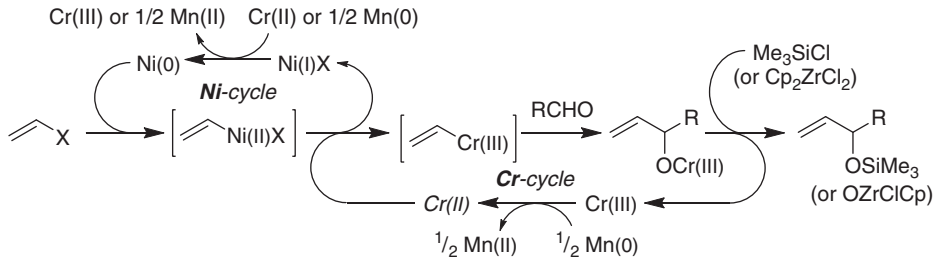
Fürstner's method using manganese and Me_3SiCl can be applied to chromium(II)–nickel and chromium(II)–cobalt-mediated reactions. In the stoichiometric reaction, the suitable solvents are limited to DMF or DMSO in order to dissolve the chromium salt. Thus, development of a catalytic system widens the range of solvents in which the major component can be 1,2-dimethoxyethane (DME) or THF (equation 53).



(53)

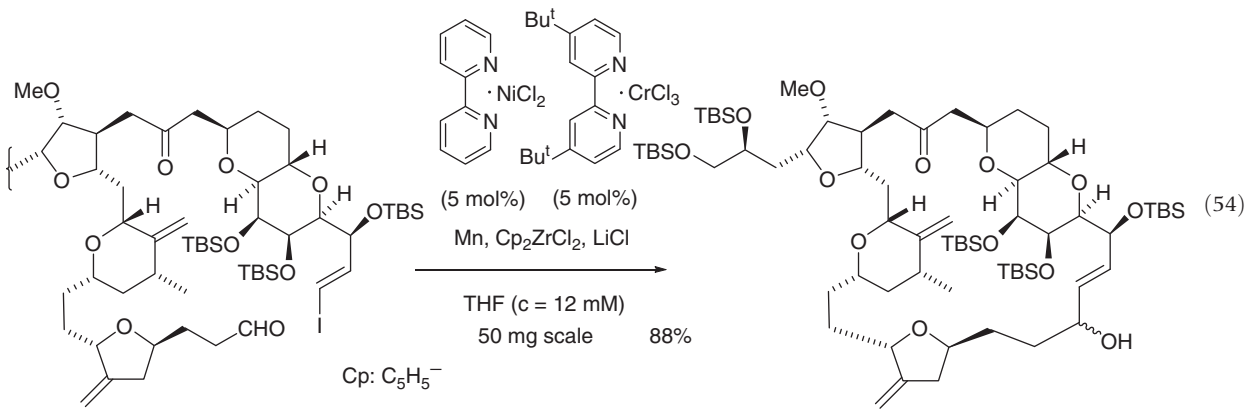
Improving the efficiency of the catalytic cycle is indispensable for the development of catalytic asymmetric reactions. Therefore, Kishi has studied this issue extensively and found several important points in the catalytic reaction.[209] (1) Complexation of both chromium(III) and nickel(II) accelerates the catalytic cycles. The structure of ligands and the solvent affects the efficiency considerably. (2) Using Cp_2ZrCl_2 instead of Me_3SiCl, undesirable side reactions caused by the formation of silyl enol ethers are suppressed.

The mechanism for the catalytic cycle for the coupling between alkenyl halides and aldehydes proposed by Kishi is shown in Scheme 12. In this cycle, transmetalation of an alkenyl group on Ni(II) to Cr(III) occurs with the reduction of the Ni(II) to Ni(I) by Cr(II). Catalytic cycles of both nickel and chromium are highly efficient under appropriate conditions.



Scheme 12

Through research on the development of catalytic cycles, an advantage for intramolecular cyclization was discovered. If an aldehyde coordinates to chromium (chromium(II) (shown in italics in the Cr-cycle)) before the formation of the alkenylchromium species by transmetalation from the alkenylnickel species, and the precursor for the addition is formed in the transmetalation step, the real concentrations of the electrophile and nucleophile do not exceed the concentration of the Cr and Ni catalysts, respectively. Under these highly efficient catalytic conditions, both concentrations of Cr and Ni catalysts are very low, and therefore, intramolecular cyclization proceeds preferentially over intermolecular coupling without the use of high-dilution methods (equation 54).[159]

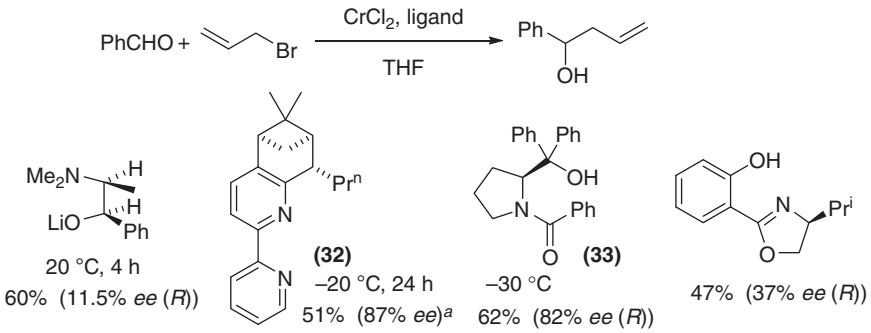


(54)

1.06.2.8 Enantioselective Addition of Organochromium Compounds

1.06.2.8.1 Stoichiometric reactions with chiral ligands

As stoichiometric reactions require stoichiometric amounts of chiral ligands, studies on asymmetric reactions have been limited to those with relatively simple ligands having one or two chiral centers. Among those examined, some chiral bidentate ligands give moderate asymmetric induction. For example, the addition of allylic chromium reagents to aldehydes in the presence of 2,2′-dipyridyl (**32**) or an aminoalcohol-type ligand (**33**) showed a good level of asymmetric induction (equation 55).[210–212]



(55)

[a]The absolute configuration is not established

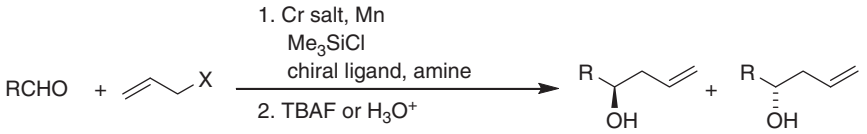
In the case of reactions between alkenylchromium reagents to aldehydes, addition of a catalytic amount of nickel is necessary. As in the allylic case, the coupling reaction between an iodoalkene and an aldehyde proceeds smoothly in the presence of a stoichiometric amount of 2,2′-dipyridyl ligands such as (**32**) with a substituent at the 6-position.[211] This observation is in sharp contrast to the reactions with 2,2′-dipyridyl, 1,10-phenanthroline, CHIRAPHOS, or 4,4′-disubstituted bis(oxazoline) as ligands, for which no coupling is observed. The structure of the ligand strongly affects the asymmetric addition.

1.06.2.8.2 Catalytic allylation with chiral ligands

Since the discovery that the amount of the chiral compounds can be reduced by a catalytic cycle of chromium, research on asymmetric addition of chromium reagents has made remarkable progress.[213]

Allylation and propargylation proceed without addition of nickel salts (or complexes). Chiral ligands that coordinate to a chromium center were designed to improve the efficiency and *ee* values. Representative examples are shown in **Table 1**.

Table 1 Asymmetric allylation of aldehydes with chiral allylchromium reagents



X	*Cr salt*	*Ligand*	*Amine*	*Solvent*	*Conditions*	*R=Ph*		*R=c-C6H11*		*References*
						Yield (%)	ee	*Yield (%)*	ee	
Cl	$CrCl_3$	(**34**)	Et_3N	MeCN	1. r.t. 2. HCl or TBAF THF	67	84 (*R*)	42	89 (*R*)	214
Br	$CrCl_3$	(**35**)	Et_3N	THF	1. 5 °C 2. Aqueous HCl, THF	72	90 (*R*)			219
Br	$CrCl_2$	(**38**)	Pr^iNEt_2	THF	1. r.t., 12–20 h 2. TBAF	89	93 (*S*)	95	92 (*R*)	216
Br	$CrCl_3$	(**39**)	Et_3N	THF	1. r.t., 12–20 h 2. TBAF	95	92 (*R*)	81	89 (*S*)	217
Br		(**37**) (1–3 mol%)		DME-MeCN (3/1)	1. r.t., 24–40 h 2. H^+	91[a]	96 (*R*)	90[a]	98 (*R*)	220
Br	$CrCl_3$	(**40**)	Pr^iNEt_2	THF-MeCN (7/1)	1. r.t., 16 h 2. Aqueous HCl, THF	87	87 (*R*)	64	90 (*R*)	218
Cl	$CrCl_3$	(**36**)	Et_3N	THF	1. r.t., 24 h 2. TBAF	83	95 (*S*)	80	>99 (*S*)	215

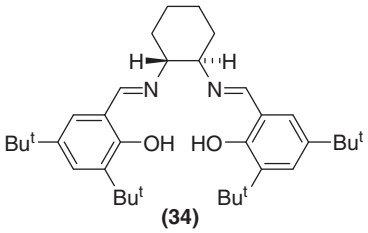
[a]Et_3SiCl.

Note: $CrCl_2$ or $CrCl_3$ (5–10 mol%), ligand (10–12 mol%).

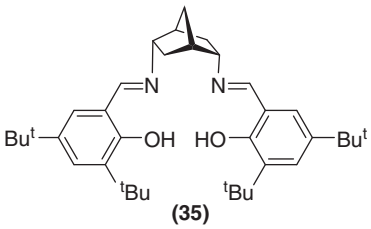
The transition state of the addition of an allylchromium compound to an aldehyde should be an octahedron in which both allyl and aldehyde groups coordinate to the chromium atom. Therefore, the remaining number of coordination sites is four. A catalytic asymmetric reaction is first achieved with 10 mol% of a chromium-salen complex (**34**), a tetradentate ligand, using manganese as a reductant.[214] The enantioselectivity of the first catalytic reaction is, however, not generally high (65–89% *ee*), probably due to the dimeric active species derived from the ligand. A more rigid salen complex (**35**) gives a higher enantiomeric excess under similar conditions.[219] Bipyridyl ligands such as (**36**) are also employed for the catalytic asymmetric addition and give high enantioselectivity.[215] Because there are three ways for a tetradentate ligand to coordinate to an octahedral chromium atom,

i.e., *trans*, *cis*-α, and *cis*-β, it is necessary to control the distribution of coordination patterns. A chromium(III) complex having a N_2O_2-type tetradentate ligand (**37**) was prepared by Yamamoto.[220] The coordination pattern was found to be *cis*-β among the three possible geometric isomers. The lowest catalyst/substrate ratio in this system is 0.5 mol%. In contrast to the reaction with allyl bromide, the yield of homoallylic alcohol with allyl chloride decreases due to the competitive pinacol coupling of the aldehyde.

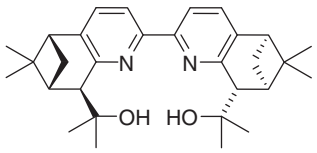
As tridentate ligands, those having oxazoline moieties were extensively examined. Reactions with ligand (**38**) gives high enantioselectivity (86–95% *ee*) with allyl bromides and chlorides. The selectivity decreases in the case of allyl iodide due to the formation of an achiral allylmanganese species. The chiral chromium complex can be reused without decreasing the selectivity.[216] One component of ligand (**39**) is an amino acid, thus, a variety of asymmetric ligands could be prepared and examined.[217] Guiry prepared symmetric and unsymmetric tridentate ligands having bisoxazoline groups, and observed the highest *ee* value with unsymmetrical ligand (**40**).[218]



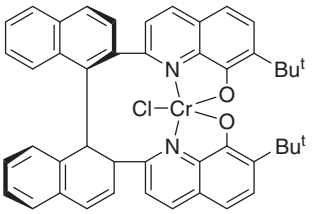
(**34**)



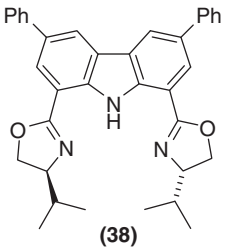
(**35**)



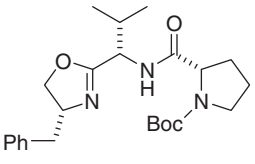
(**36**)



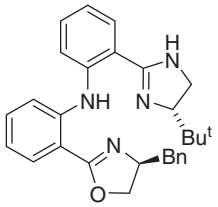
(**37**)



(**38**)

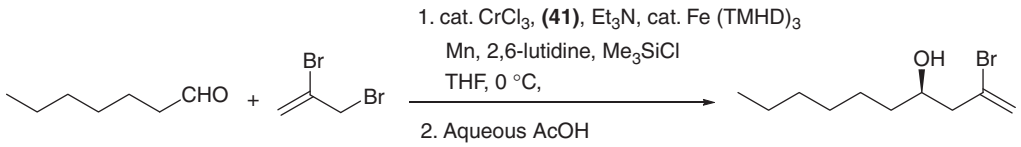


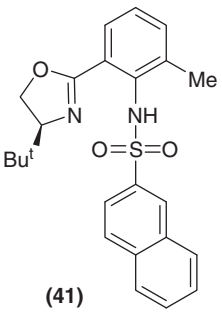
(**39**)



(**40**)

Highly effective bidentate ligand (**41**) was developed by Kishi. Because chiral ligands such as (**41**) can be easily prepared from several components, a variety of ligands are accessible, facilitating the tuning process by a tool-box approach for enantioselectivity. A reaction between 2-haloallylbromide and an aliphatic aldehyde is shown in equation 56.[221] The process is accelerated by addition of cobalt phthalocyanine (CoPc) or iron tris(2,2,6,6-tetramethyl-3,5-heptanedione) [Fe(TMHD)$_3$].





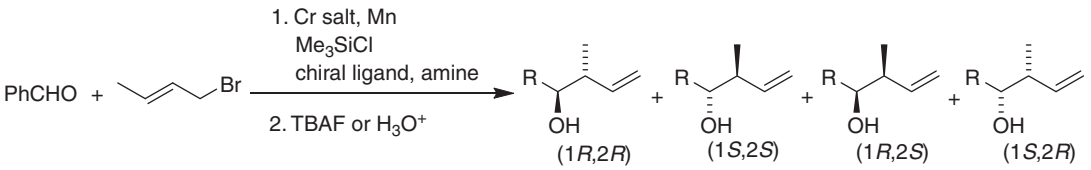
(**41**)

(56)

In contrast to simple allyl halides and 2-substituted allyl halides, the problem of diastereoselectivity arises when crotyl halides are used. The *syn*/*anti* selectivities of the reactions between crotylchromium species and aryl aldehydes depend on the salen complex used, and *syn* adducts are produced predominantly when 2 equivalents of salen based on chromium(II) are used.[222] Other ligands (**37**)–(**40**) show *anti* selectivity as with simple chromium(II) chloride in THF (**Table 2**).

Propargylchromium can be prepared with only chromium(II). Thus, catalytic asymmetric addition of propargyl bromide to aldehydes leading to homopropargyl alcohols is accomplished with a chromium complex coordinated by several chiral ligands such as oxalate (**38**)[223] and sulfonamide (**41**).[224] Similar asymmetric propargylation proceeds with chromium complex (**37**). In the latter case, addition of a cobalt complex (**42**) accelerates the reaction and improves the enantioselectivity.[225] Asymmetric addition of allenyl and alkynyl groups is also accomplished with a manganese-mediated chromium (**37**) catalyzed system (**Scheme 13**).[226]

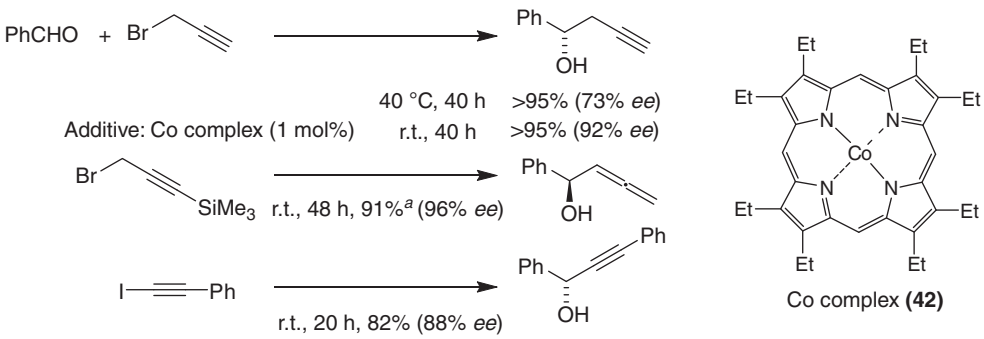
Table 2 Asymmetric allylation of benzaldehyde with chiral crotylchromium reagents



Cr salt	*Ligand*	*Amine*	*Solvent*	*Conditions*	*Yield (%)*	Anti/syn	*ee (%)*		*References*
							Anti	Syn	
$CrCl_3$	(**34**)	Et_3N	MeCN	1. r.t. 2. HCl, THF	56	17/83	36 (1*S*,1*S*)	89 (1*R*,2*S*)	214
$CrCl_2$	(**38**)	Pr^iNEt_2	THF	1. r.t., 16 h 2. TBAF	38	73/27	75 (1*S*,1*S*)	21 (1*R*,2*S*)	216
$CrCl_3$	(**39**)	Et_3N	THF	1. r.t., 20 h 2. TBAF	88	70/30	91 (1*R*,1*R*)	95 (1*R*,2*S*)	217
	(**37**) (3 mol%)		DME-MeCN (3/1)	1. r.t., 36 h 2. H^+	76[a]	85/15	95 (1*R*,1*R*)	96	220
$CrCl_3$	(**40**)	Pr^iNEt_2	THF-MeCN (7/1)	1. r.t., 16 h 2. Aqueous HCl, THF	77	77/23	82 (1*R*,1*R*)	90 (1*R*,2*S*)	218

[a]Et_3SiCl.

Note: $CrCl_2$ or $CrCl_3$ (5–10 mol%), ligand (10–12 mol%).



1. Cr complex **(37)** (3 mol%), Mn, Et_3SiCl, THF; 2. TBAF, THF. [a]Cr complex **(37)** (5 mol%)

Scheme 13

1.06.2.8.3 Catalytic alkenylation and alkylation with chiral ligands

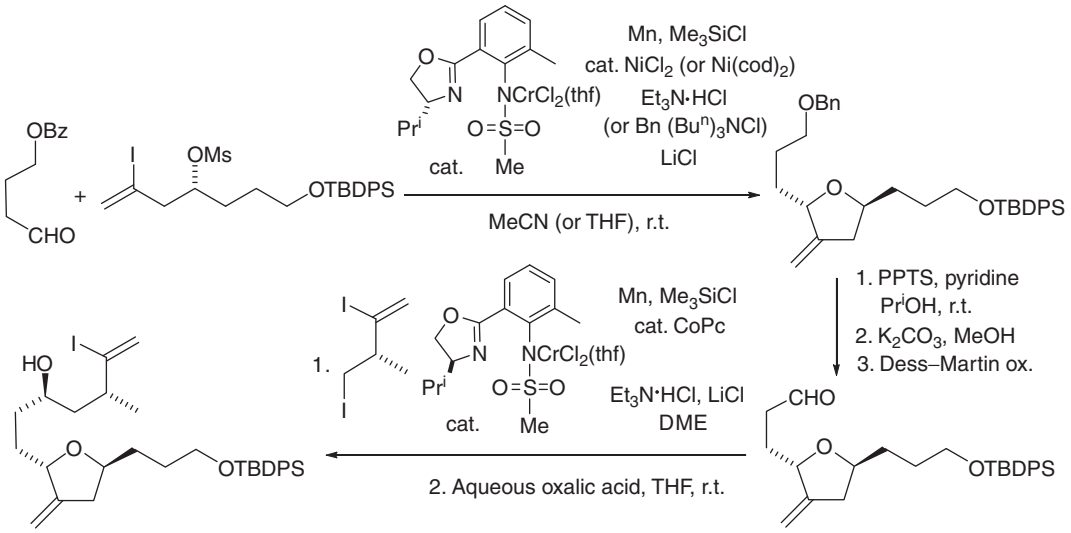
Although the nickel-catalyzed chromium reaction becomes a catalytic process using manganese and chlorotrimethylsilane, some issues still remain. First, both the nickel-catalyst and chromium-catalyst cycles should work efficiently in order to construct a highly efficient catalytic cycle. Second, it is necessary that the chromium complex coordinated by the chiral sulfonamide not be affected by addition of the nickel bipyridyl complex. Kishi investigated the effects of several bipyridyl nickel complexes on the reaction between an alkenyliodide and aldehyde using a chiral sulfonamide-coordinated chromium complex-manganese system. As a result, bipyridyl ligands can be divided into two groups, one of which does not affect the chromium complex coordinated by a chiral sulfonamide. Using the chiral chromium complex and the suitable nickel bipyridyl complex, Kishi developed a new process.[227] Furthermore, the catalytic asymmetric system using a chromium complex coordinated by a chiral sulfonamide can be applied to the cobalt-catalyzed Barbier-type addition of alkyl iodides to aldehyde. These general and reliable methods were employed in the total synthesis of halichondrin[228] and E7389 (Scheme 14).[229]

1.06.3 C–C Double Bond Formation

1.06.3.1 Formation of (*E*)-Olefins

1.06.3.1.1 Preparation of geminal dichromium reagents

The reduction of 1,1-diiodoethane with chromium(II) chloride in THF proceeds smoothly at room temperature. In contrast to the reaction under aqueous conditions, protonation does not take place before workup, and further reduction occurs to give



Scheme 14

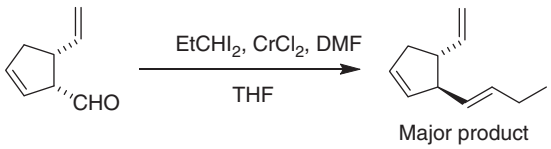
1,1-dichromioethane, a geminal dichromium compound.[12] The reagent reacts with aldehydes to furnish ethylidenation products in high yield.[11] Reduction of other *gem*-diiodoalkanes with chromium(II) chloride proceeds rather slowly, and the desired olefins are obtained in only 10–50% yields. However, activation of chromium(II) chloride with 1 equivalent of dimethylformamide permits a range of *gem*-diiodoalkanes to be used.[11] This effect is attributed to the enhanced reducing ability of chromium(II) by coordination to donor ligands. The reactivity of 1,1-dihaloalkanes toward chromium(II) chloride decreases in the order I > Br > Cl. For example, reaction of 4-isopropylbenzaldehyde with 1,1-diiodo-, 1,1-dibromo- and 1,1-dichloroethane at 25 °C for 10–24 h affords 97, 14, and 0% yields of the ethylidenation product, respectively. When diiodomethane is used as the diiodoalkene, methylenation of the aldehyde proceeds smoothly in the presence of chromium(II) chloride (or chromium(II) chloride treated with dimethylformamide).[11,230]

Olefins are obtained from aldehydes using zinc and a catalytic amount of chromium(III) chloride, but the *E*/*Z* ratios of the resulting olefins are lower than those obtained with chromium(II) chloride.[11,231] In contrast to the chromium(II)-mediated reaction, 1-iodobutane is observed by GLPC analysis during the reaction containing zinc. These results suggest that the mechanism of the olefination with chromium(III) and zinc is different from that for the reactions of geminal dimetallic species and aldehydes.

1.06.3.1.2 Typical features of olefination with geminal dichromium reagents

Stereoselectivity: In contrast to *Z*-olefins, which can be prepared from aldehydes with nonstabilized phosphorus ylides (Wittig reagent) under lithium salt-free conditions,[232,233] *E*-olefins are rather difficult to prepare selectively. Selective preparation of *E*-olefins is accomplished by Schlosser's *β*-oxido ylide method[234,235] or Julia olefination.[236,237] The 1,1-diiodoalkane-chromium(II) chloride-DMF method provides alkylidenation products with a high level of *E* -selectivity, especially when applied to aliphatic aldehydes. The *E*/*Z* ratios increase as the bulkiness of the substituent on the aldehyde (R^1) is enhanced (**Table 3**).[11] It is difficult to obtain *E*-alkylidenation products from pivalaldehyde even with the *β*-oxido ylide method.[238] However, the chromium-mediated olefination proceeds smoothly with the sterically congested tertiary aldehyde, pivalaldehyde, and the corresponding *E*-olefin is produced almost exclusively (**Scheme 15**).[239,241–247] However, when the aldehyde is highly hindered, the alkylidenation is sluggish; in such cases, stepwise reactions via chromium-mediated iodoolefination are employed (**Scheme 16**).[240]

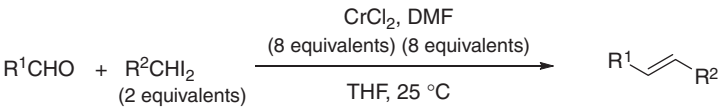
Functional Group Selectivity: Because the olefination proceeds under mild conditions, functional groups indicated in the haloform-chromium(II) chloride section (see Section 1.06.3.2.3) are also tolerated here.[239–247] Epimerization at the *α* position of aldehydes does not normally take place,[241,242,246,247] except in cases where the aldehyde is highly prone to enolization (equation 57).[248]



(57)

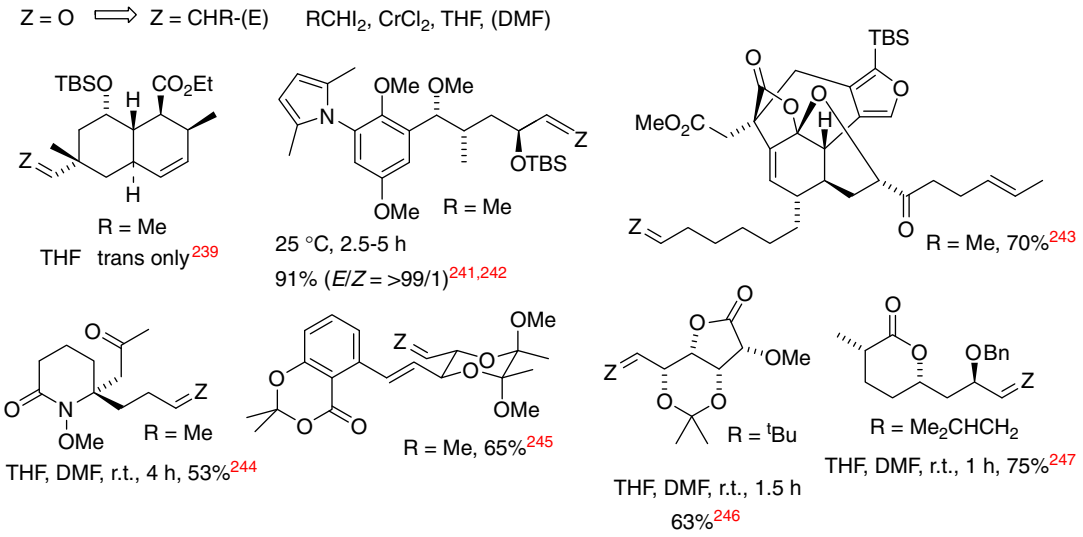
Oxygen-functional groups such as acetals, silyl ethers, acetyl, and even formyl esters can be present not only on the aldehyde but also on the 1,1-diiodo compound (equations 58 and 59).[249–251] However, when protected hydroxyl groups, such as acetoxy or acetal groups, are present next to the diiodo group, *β*-elimination proceeds smoothly on treatment with chromium(II) and DMF to give a mixture of (*E*)- and (*Z*)-1-iodoalkenes.[252]

Table 3 Alkenylation of aldehydes with geminal dichromium reagents

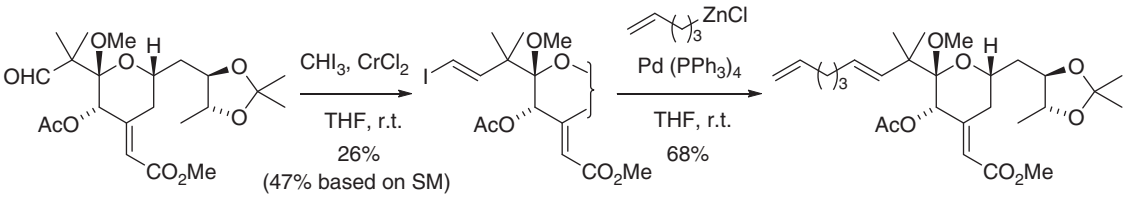


R^1	R^2	*Time (h)*	*Yield (%)*	E/Z
n-C_8H_{17}	Pr^n	1.5	85	96/4
Ph	Pr^n	1	87	88/12
		0.5	60[a]	51/49
Bu^t	Pr^n	1	96	99/1
n-C_5H_{11}	Pr^i	1	74[b]	93/7
Ph	Pr^i	2	79[b]	88/12
Pr^n	Bu^t	0.5	90	94/6
Ph	Bu^t	2	80	96/4

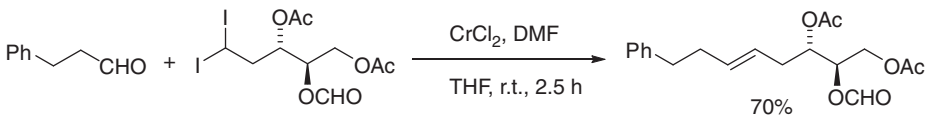
[a]$CrCl_3$, Zn instead of $CrCl_2$, R^2CHI_2 (4 equivalents), $CrCl_2$ (16 equivalents), DMF (16 equivalents). *Source*: Reproduced from Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951–953, with permission from ACS.



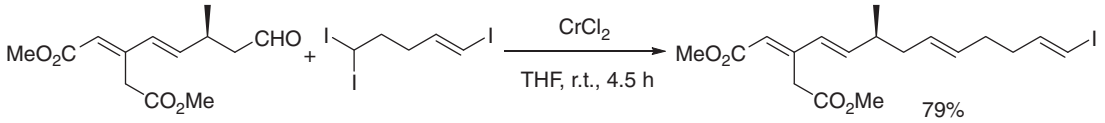
Scheme 15



Scheme 16



(58)



(59)

The ethylidenation of ketones with 1,1-diiodoethane and chromium(II) chloride proceeds in good yield, even with easily enolizable ketones.[11] However, yields of the olefination products of ketones with other 1,1-dichromium reagents are rather low.

1.06.3.2 (*E*)-Selective Formation of Alkenyl Halides

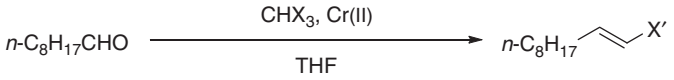
1.06.3.2.1 Comparison with other methods

Several reproducible methods have been reported to obtain (*E*)-1-halo-1-alkenes: (1) formal addition of hydrogen iodides (or bromides) to 1-alkynes, e.g., hydroboration,[253] alumination,[254] and zirconation[255,256] of 1-alkynes followed by trapping with electrophiles, such as iodine and *N*-bromosuccinimide; (2) treatment of stereodefined alkenylsilanes or alkenylstannanes with iodine or *N*-bromosuccinimide. In the case of (*E*)-1-chloro-1-alkenes, partial reduction of 1-chloro-1-alkynes with lithium aluminum hydride can be employed.[257] Compared to these methods, the chromium method is mild enough to be used with highly functionalized substrates, and in addition, the carbon chain increases by one carbon to directly afford (*E*)-1-halo-1-alkenes from aldehydes.

1.06.3.2.2 Preparative method and mechanism

Chromium(II) chloride reduces two of the three halogens of haloform (CHX_3) to form geminal dichromium reagents $XCH(CrL_n)_2$.[12] Since chromium(II) is a one-electron reductant, four equivalents of chromium(II) are required based on the haloform. The second reduction of halogen leading to the geminal dichromium reagents proceeds faster than the first step. The geminal dichromium reagents prepared from iodoform and chloroform react with aldehydes to give iodo- and chloroalkenes, respectively (Table 4).[12]

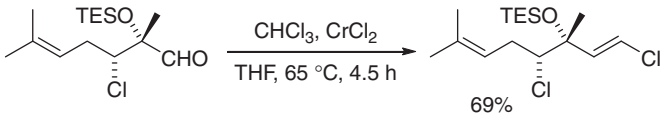
Table 4 Preparation of (E)-alkenyl halides with geminal dichromium reagents



CHX_3		Cr(II)	Temperature (°C)	Time (h)	Yield (%)	E/Z
X = X′ = I		$CrCl_2$	0	2	82	83/17
X = Br	X′ = Br	$CrCl_2$	25	2	37	89/11
	X′ = Cl				32	90/10
X = X′ = Br		$CrBr_3$, $LiAlH_4$	50	2	61	87/13
X = X′ = Cl		$CrCl_2$	65	4	76	94/6
X = X′ = I		cat. $CrCl_3(thf)_3$, Zn NaI, Me_3SiCl	25	2	84[a]	95/5

[a]$Ph(CH_2)_2CHO$ was used instead of nonanal. Solvent: dioxane. Slow addition (4 h).

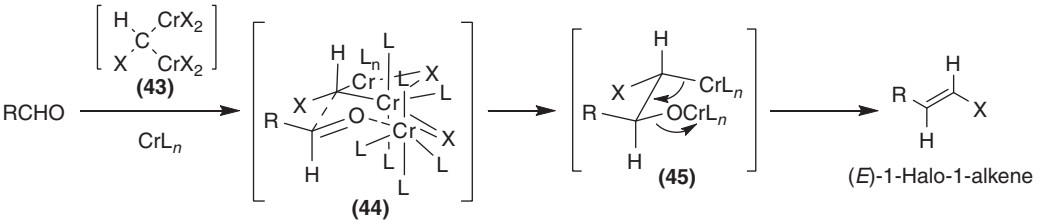
When a combination of bromoform and chromium(II) chloride is used, a partial halogen exchange of bromoform with chloride anion occurs before the reaction with the aldehyde to afford a mixture of bromo- and chloroalkenes (Table 4). This exchange is suppressed using a combination of chromium(III) bromide and lithium aluminum hydride instead of chromium(II) chloride (Table 4).[12,258] The rates of reaction of the haloform decrease in the sequence I > Br > Cl. Heating a mixture of chloroform and chromium(II) chloride in tetrahydrofuran to reflux before adding the aldehyde reportedly accelerates the reaction.[259] Chloroolefination of aldehydes with chloroform and chromium(II) chloride requires heating to promote the reaction (equation 60).[12,260,261]



(60)

Because the reduction rate of iodoform with zinc is considerably slower than that with chromium(II), use of catalytic amounts of chromium salt in the transformation of aldehydes to iodoalkenes is possible in the presence of zinc, Me_3SiCl, and NaI in dioxane (Table 4).[262] Manganese cannot be used as the reductant in place of zinc due to the formation of Me_3SiCHI_2 and contamination of the corresponding alkenylsilanes.[263]

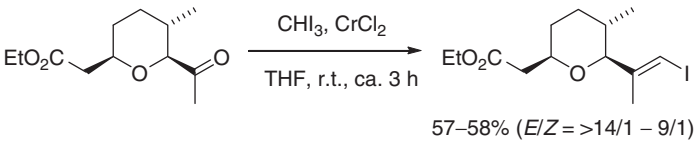
High *E*-selectivity in the formation of 1-halo-1-alkenes with the *gem*-dichromium species is explained by the mechanism summarized in Scheme 17.[264,265] Addition of the *gem*-dichromium species [(**43**), $XCH(CrL_n)_2$] to an aldehyde (RCHO) proceeds *via* a six-membered pseudo-chair transition state (**44**) containing two chromium ions bridged by a halogen. Both substituents R and X occupy stable equatorial positions in the transition state. *Syn*-elimination of $(L_nCr)_2O$ from the adduct (**45**) takes place smoothly, before rotation at the formed single bond, to give an *E*-1-halo-1-alkene.



Scheme 17

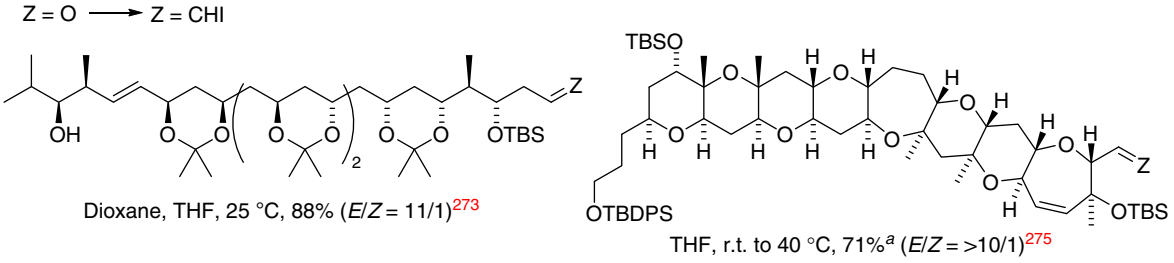
1.06.3.2.3 Typical features

Functional Group Selectivity: Alkenyl iodides can be formed from ketones (equation 61).[266–268] However, ketones are less reactive than aldehydes, and an aldehyde can be selectively converted into an (*E*)-iodoolefin in the presence of a ketone.[12,269–271]



(61)

The following functional groups are also tolerated during the reaction: ester, lactone, amide (e.g., Weinreb amide), nitrile, 1,3-diene, acetylene, olefin, cyclopropane, epoxide, alkyl bromide, alkyl chloride, ethylene glycol acetal, dithioacetal, phenylsulfonyl, and 1,1,1-trichloroalkyl groups. Hydroxyl groups can be protected by the following groups: –OMe, –OBn, –OTES, –OTIPS, –OTBDMS, –OTBDPS, –OAc, –OCOPh, –OMOM, –OTHP, and –OPMB. The iodoolefination proceeds in some cases in the presence of an unprotected hydroxy group.[272–274] Two examples of the iodoolefination from substrates having highly oxygenated functionalities are shown in Scheme 18.[273,275]



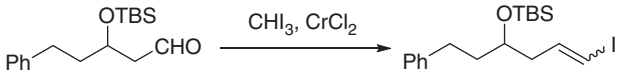
Scheme 18

Because the geminal dichromium reagent is not highly basic, epimerization at the α position of the aldehyde does not normally occur. In the case of β,γ-unsaturated aldehydes, partial isomerization to conjugated dienes can occur as a side reaction.[276,277]

Stereoselectivity: The haloform-chromium(II) chloride reagent produces *E*-alkenyl halides with *E*/*Z* ratios of 83/17 to 95/5. The proportion of *E*-alkenyl halides, which depends on the steric size of the aldehyde R substituent, increases in the order I < Br < Cl (Table 4). As the bulkiness of the substituent R of the aldehyde increases, the *E*/*Z* ratio of the alkenyl halides increases. For example, the *E*/*Z* ratios of the iodoalkanes produced from nonanal and cyclohexanecarboxaldehyde are 83/17 and 89/11, respectively.[12,278,279] The reaction of aldehydes having α-hydroxyl groups protected with TBDMS and Bn groups affords the corresponding *E*-iodoalkenes almost exclusively. Although the iodoolefination is not very sensitive to the bulkiness near the aldehyde group, the reaction does not proceed with a highly sterically hindered aldehyde.[280]

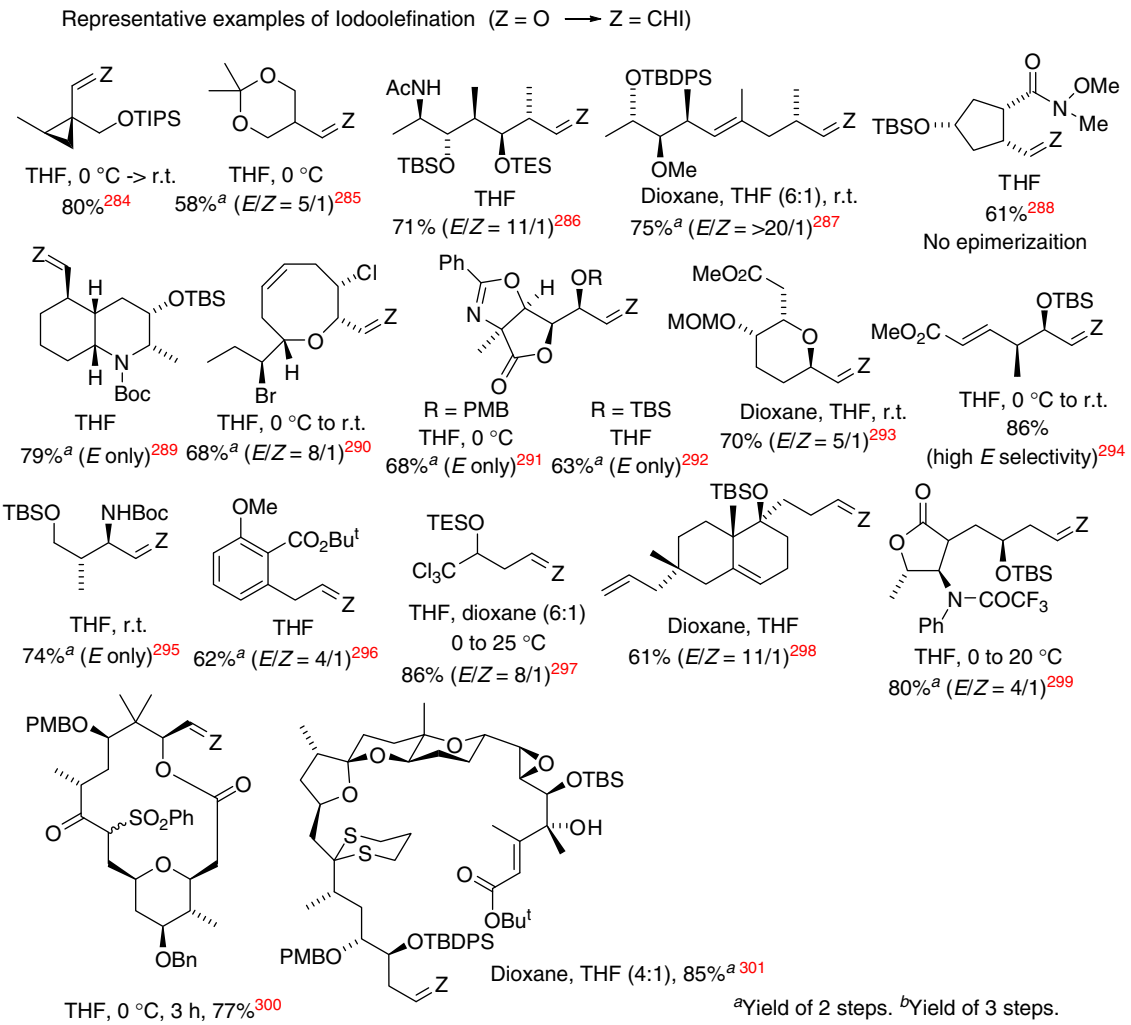
Two methods reportedly improve the *E*/*Z* ratio in acyclic systems: (1) use of a dioxane-tetrahydrofuran solvent mixture (dioxane-THF, 6/1) retards the reaction rate, but considerably improves the *E*/*Z* ratio (equation 62)[281]; and (2) treatment of the

iodoalkane mixture with sodium hydroxide in *n*-butanol selectively consumes the minor (*Z*)-iodoalkene, thereby providing the product with a high *E*/*Z* ratio.[282,283]



(62)

Representative examples of iodoolefination are shown in Scheme 19.[286–303]



Scheme 19

Although α,β-unsaturated aldehydes can usually be converted to the conjugated *E*-iododienes with the reagent (Scheme 20),[284,285,302–308] isomerization to *Z* isomers occurs in some cases. In such cases, the reactions must be protected from light.

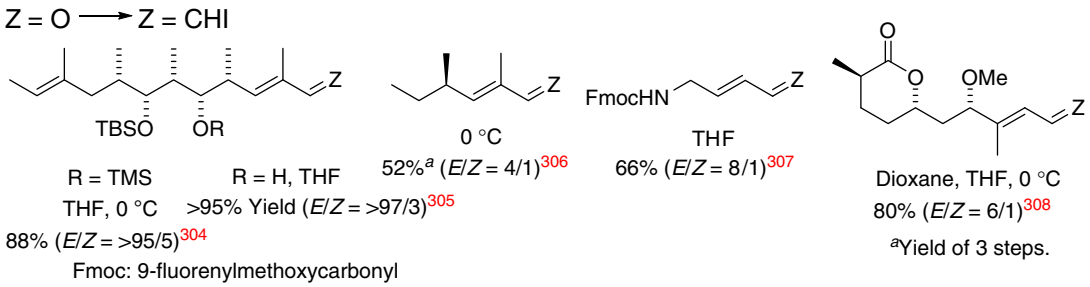
1.06.3.2.4 Applications to synthesis

The alkenyl iodides prepared with iodoform and chromium(II) chloride are used for cross-coupling reactions such as palladium-catalyzed Suzuki–Miyaura or Negishi reactions and chromium-mediated nickel-catalyzed reactions (see Section 1.06.2.3).

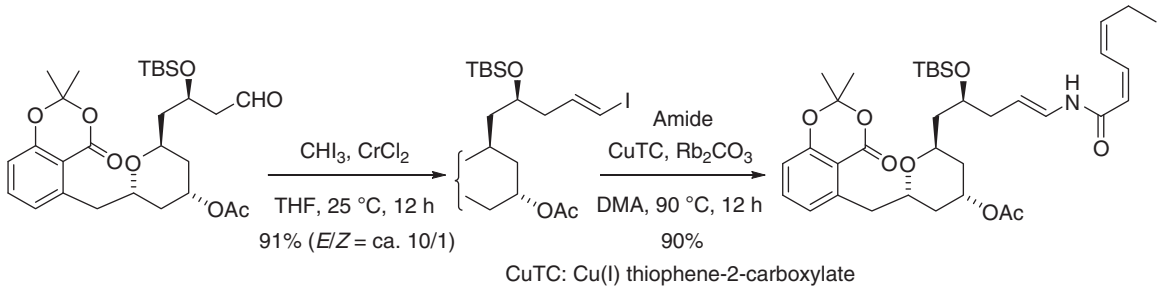
The iodoolefination has also been utilized for the synthesis of the labile enamide linkage connecting polyunsaturated domains of such compounds as salicylihalamide,[309] apicularen A (Scheme 21),[310–312] and palmerolide A.[313]

1.06.3.2.5 (E)-Heterosubstituted olefins from aldehydes

As olefination with one-carbon homologation using heteroatom-substituted phosphorus ylides are not always highly stereoselective, these heteroolefins are usually prepared from aldehydes by the following sequence: (1) one-carbon homologation of aldehydes to terminal acetylenes (RCHO→RCH=CBr_2→RC≡CH) and (2) the stereoselective conversion of the terminal



Scheme 20

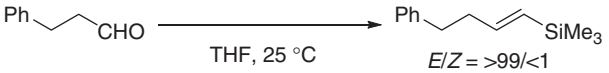


Scheme 21

acetylenes to the heterosubstituted olefins. The chromium-olefination method is applicable to the formation of heterosubstituted olefins, such as alkenylsilanes,[314] alkenyl sulfides,[314] alkenylstannanes,[364,315,316] and alkenylboronic esters[265] with high *E*-selectivity. The chromium reactions proceed under mild conditions, and thus, an aldehyde can be selectively transformed to a heterosubstituted *E*-olefin without affecting coexisting functional groups such as ketone, cyano, ether, acetal, and ester groups.

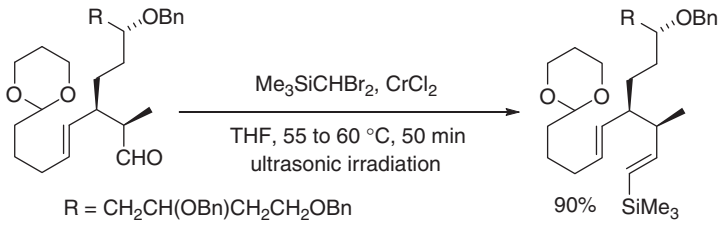
1.06.3.2.6 Formation of (E)-alkenylsilanes

(*E*)-Alkenylsilanes are produced stereoselectively from aldehydes with (dibromomethyl)trimethylsilane[317] and chromium(II) chloride (equation 64).[314,318] *E*-Alkenylsilanes are produced exclusively owing to the steric demand of the trimethylsilyl group. This group also facilitates the reduction of geminal dihalogen compounds with chromium(II) chloride, and thus (dibromomethyl)trimethylsilane can be used instead of the corresponding diiodo compound[263] although a long reaction time is required. The amount of chromium salt can be reduced to a catalytic amount using manganese as a reductant. The easily handled and less hygroscopic chromium(III) salt, $CrCl_3(thf)_3$, can be used for the transformation.[319] Because iodoform is reduced with manganese in the presence of chlorotrimethylsilane to give (diiodomethyl)trimethylsilane, a one-pot transformation of aldehydes to (*E*)-alkenylsilanes is achieved by treatment with iodoform, manganese, chlorotrimethylsilane, and a catalytic amount of chromium(II) chloride in THF, via the *in situ* formation of (diiodomethyl)trimethylsilane (equation 63).[263]



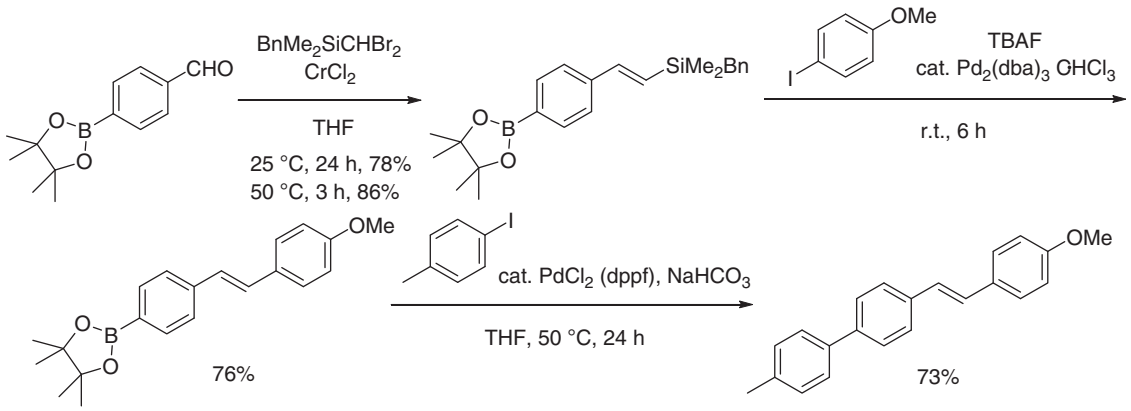
Me_3SiCHX_2 (2 equivalents), $CrCl_2$ (8 equivalents)	X = Br	24 h	86%	(63)
	X = I	4 h	90%	
Me_3SiCHI_2 (2 equivalents), Mn (6 equivalents), Me_3SiCl (6 equivalents), $CrCl_3(thf)_3$ (0.2 equivalent)		5 h	86%	
CHI_3 (3 equivalents), Mn (9 equivalents), Me_3SiCl (9 equivalents), $CrCl_2$ (0.16 equivalent)		24 h	74%	

Ultrasonic irradiation of the mixture at 55–60 °C accelerates the reaction and sometimes minimizes epimerization at the α position of the aldehyde (equation 64).[320]



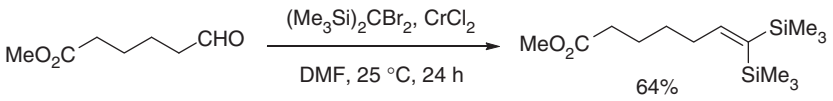
(64)

Because the trimethylsilyl group is not suitable for further homologation by Hiyama coupling, a benzyldimethylsilyl group has been introduced (Scheme 22).[321]



Scheme 22

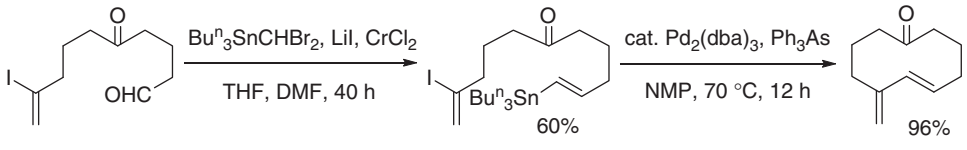
When $(Me_3Si)_2CBr_2$ is used instead of $Me_3SiCHBr_2$, aldehydes are converted to 1,1-bis(trimethylsilyl)alkenes under similar conditions (equation 65).[322]



(65)

1.06.3.2.7 Formation of (E)-alkenylstannanes

The conversion of aldehydes to alkenylstannanes with one-carbon homologation proceeds when (dibromomethyl)- or (diiodomethyl)tributylstannane is used instead of (dibromomethyl)trimethylsilane.[264,315,323] As (dibromomethyl)tributylstannane is not easy to reduce with chromium(II) chloride in tetrahydrofuran, chromium(II) chloride must first be treated with 1 equivalent of dimethylformamide and lithium iodide. In contrast, a geminal dichromium reagent is smoothly generated using (diiodomethyl)tributylstannane in dimethylformamide. The transformation is useful for the preparation of alkenylstannanes having ketone, ester, cyano, or acetal groups.[264] Utilization of the alkenylstannane for the intramolecular Migita–Stille coupling is shown in Scheme 23.[324]



NMP: *N*-methyl-2-pyrrolidone

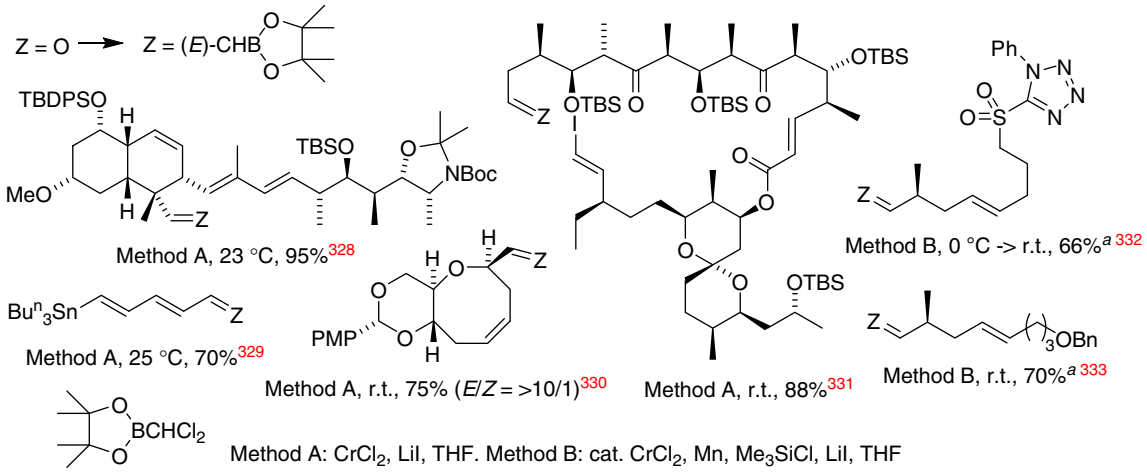
Scheme 23

1.06.3.2.8 Formation of (E)-alkenylboronic esters

(*E*)-Alkenylboronic esters are prepared from aldehydes with high stereocontrol using dichloromethylboronic esters,[325,326] chromium(II) chloride, and LiI in THF.[265] Lithium iodide, which converts the dichloromethyl compound to a diiodomethyl one, is

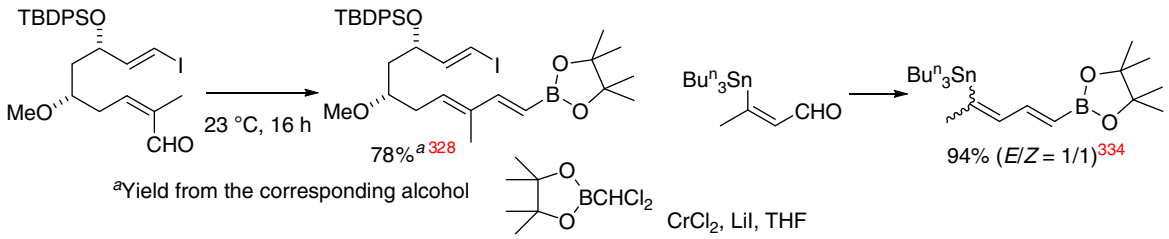
essential to promote the reaction. The synthesis of (*E*)-alkenylboronic esters can also be accomplished using a catalytic amount of a chromium salt, manganese and Me_3SiCl.[319]

The bulkiness of the pinacol group is important for the high *E*-selectivity. For example, the reaction of hexanal with $(RO)_2BCHCl_2$ [$(RO)_2{=}OCH_2CMe_2CH_2O$] gives a 3:1 mixture of the corresponding alkenylboronic esters under the same reaction conditions.[327] Almost the same functional groups as in the case of iodoolefination of aldehydes with iodoform and chromium(II) chloride are tolerated during the transformation (Scheme 24).[328–333]



Scheme 24

In the case of α,β-unsaturated aldehydes, isomerization to the more stable 1,3-dienylboronic esters can occur (Scheme 25).[328,334]



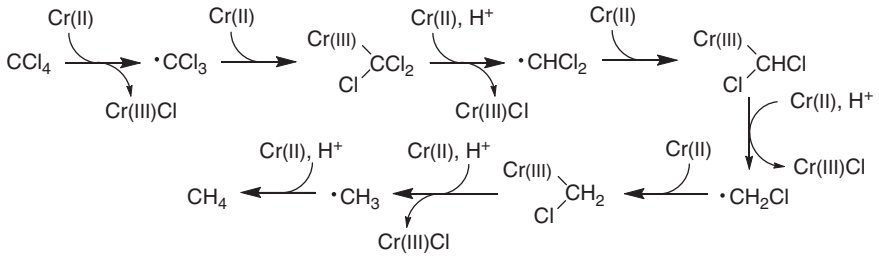
Scheme 25

1.06.4 Miscellaneous Carbon–Carbon Bond Formation

1.06.4.1 Carbon–Carbon Bond Formation via Carbene, Carbenoid, and Carbyne Species

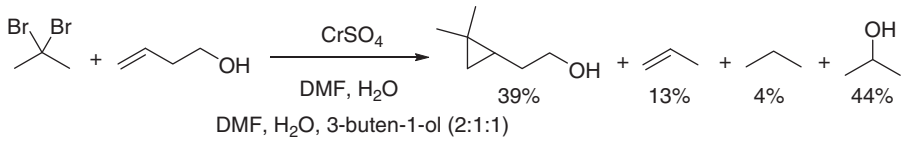
1.06.4.1.1 Reduction of geminal polyhalides

The reduction of geminal polyhalides such as diiodomethane, dibromomethane, chloroform, and carbon tetrachloride with chromium(II) sulfate in aqueous dimethylformamide proceeds rapidly at room temperature to give methane.[335] The reduction involves α-halomethyl radicals and the corresponding carbenoid species (Scheme 26).



Scheme 26

The carbenoids generated under these conditions are electrophilic. Thus, Simmons–Smith-type cyclopropanation takes place in the presence of 3-buten-1-ol (equation 66).[335]

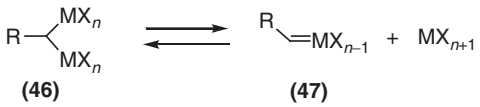


(66)

The mechanism for reduction of geminal polyhalides in aprotic solvents is different from that in Scheme 26. First, protonation does not take place before workup, and second, chromium(II) chloride reduces two of the three (or more) halogens of the polyhalides to form geminal dichromium compounds (see Section 1.06.3.1.1).[11,12] Such successive reduction leading to geminal dichromium compounds is also observed with 1,1,1-trichloroalkanes[336,337] and carbon tetrachloride.[338]

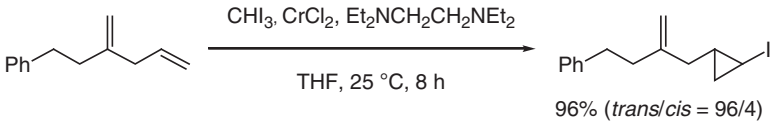
1.06.4.1.2 α-Elimination of geminal dichromium leading to chromium-alkylidene species

The dimetallic species (**46**) of early transition metals like the Tebbe complex are postulated to be in equilibrium with the metal-alkylidene (or carbene) complex (**47**) and MX_{n+1} (equation 67), and the equilibrium shift is caused by the addition of an appropriate amine.

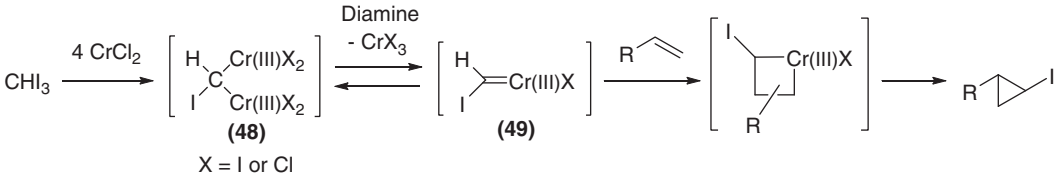


(67)

In the case of a geminal dichromium compound derived from iodoform and chromium(II) chloride, the nucleophilic reactivity of the compound changes markedly by addition of a Lewis base, TMEDA (or *N*,*N*,*N*′,*N*′-tetraethylethylenediamine (TEEDA)), and *trans*-iodocyclopropanes are produced stereoselectively from terminal alkenes by treatment with the base-added reagent system. The iodocyclopropanation proceeded smoothly with a terminal double bond in the presence of di- or trisubstituted ones and without the presence of a hydroxy or an alkoxy group near the double bond (equation 68). This reactivity contrasts with that of the Simmons–Smith zinc carbenoid. The chromium-mediated iodocyclopropanation reaction proceeds without affecting the following functional groups: benzyl and silyl ethers, tertiary amine, ester, amide, and an unprotected hydroxyl group. Because the iodocyclopropanation occurs after generation of the *gem*-dichromium species (**48**), the reaction proceeds via formation of chromium-alkylidene species (**49**), [2 + 2]cycloaddition, and reductive elimination (Scheme 27).

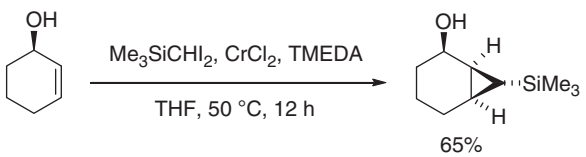


(68)



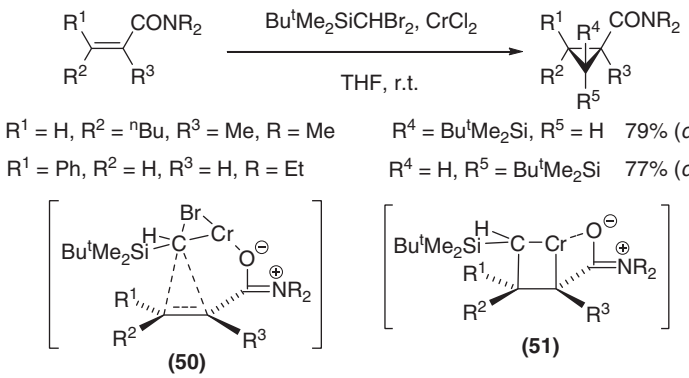
Scheme 27

Silyl- and boryl-substituted cyclopropanes are produced using R_3SiCHI_2 and $(RO)_2BCHCl_2$-LiI instead of iodoform, respectively. However, the stereoselectivities for the reactions of terminal double bonds are not high compared with the iodocyclopropanation except in the case of the hydroxy-directed reaction (equation 69).[339,340]



(69)

Treatment of α,β-unsaturated amides with a reagent derived from $R_3SiCHBr_2$ and chromium(II) chloride gives the corresponding silylcyclopropanes stereoselectively where the silyl group is located to avoid steric interaction (equation 70).[341] The reactive intermediate and transition states ((**50**) or (**51**)) of the silylcyclopropanation are still unclear.

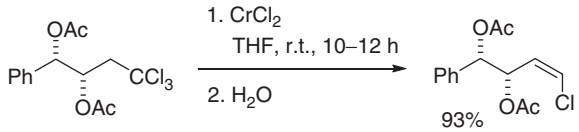


(70)

When a combination of carbon tetrabromide and chromium(II) bromide is used instead of $BuMe_2SiCHBr_2$ and chromium(II) chloride, and heated at reflux for 16 h, bromocyclopropanation proceeds via one-electron reduction of carbon tetrabromide and proton abstraction from THF.[342]

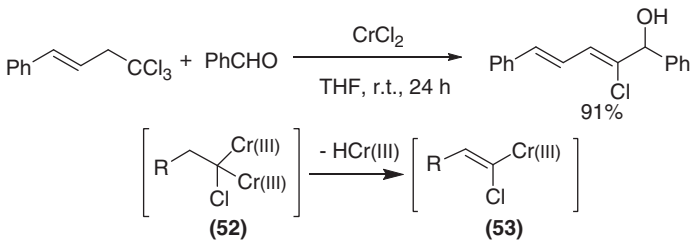
1.06.4.1.3 Reduction of geminal trichloroalkanes to alkylidene-carbenoid species and carbyne equivalents

Treatment of 1,1,1-trichloroalkenes with chromium(II) chloride in THF followed by aqueous workup gives (*Z*)-1-chloro-1-alkenes in high yields (equation 71).[343]

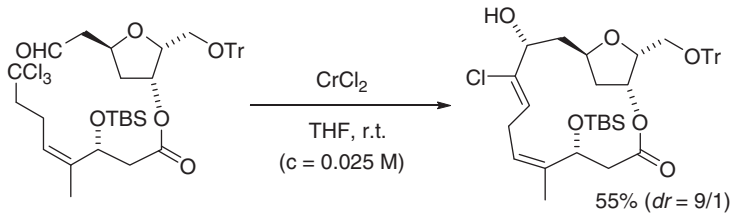


(71)

When the reaction of equation 71 is conducted in the presence of an aldehyde, 1-chloro-2-alkene-1-ol derivatives are produced (equation 72).[337,344] This result suggests the generation of dichromium compounds (**52**) with a geminal chlorine atom which undergoes the β-elimination smoothly to give a (*Z*)-α-chloro-substituted alkenylchromium compound (**53**), or an alkylidene carbenoid. The chromium compound adds to an aldehyde to afford a (*Z*)-2-chloro-2-alken-1-ol stereoselectively. Application to an intramolecular cyclization is shown in equation 73.[345]

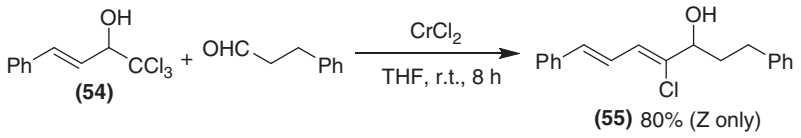


(72)



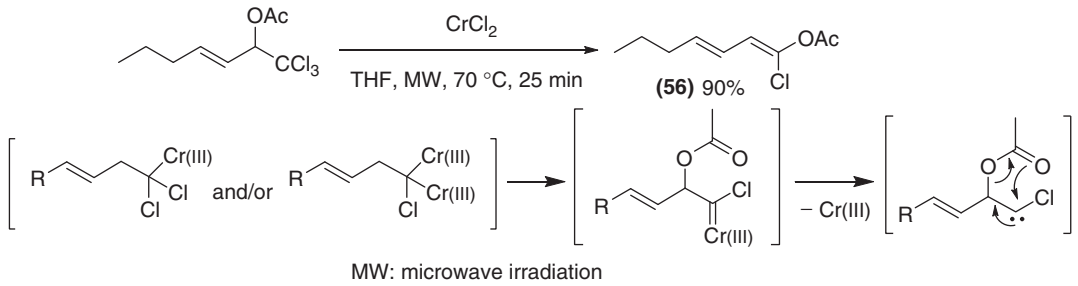
(73)

A similar coupling reaction proceeds with 1,1,1-trichloroalkanes having potential leaving groups such as OH[346] and OCO_2Me[336] on the carbon adjacent to the chlorine atoms. For example, treatment of a mixture of an aldehyde and 1,1,1-trichloro compound (**54**) derived from cinnamaldehyde and chloroform with chromium(II) chloride in THF gives (*Z*)-2-chloro-propen-1-ol derivative (**55**) stereoselectively (equation 74).[346]



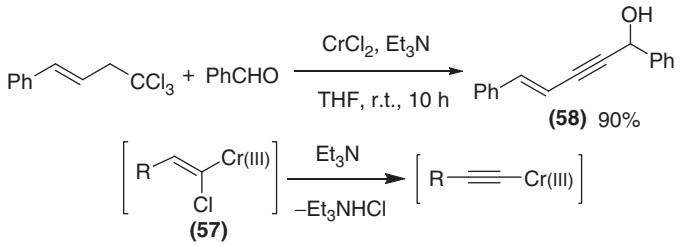
(74)

When the hydroxy group is protected as an acetoxy group, 1,2-rearrangement of the acetoxy group occurs smoothly to give 1-acetoxy-1-chlorobutadiene (**56**) (equation 75).[347]



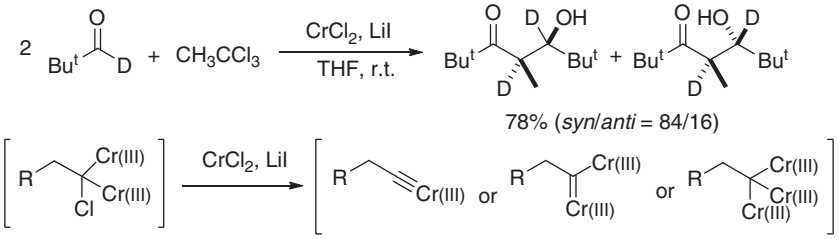
(75)

When the reaction of equation 75 is conducted in the presence of triethylamine, elimination of hydrogen chloride from the alkylidene carbenoid (**57**) occurs before the addition to an aldehyde, and thus, propargyl alcohol (**58**) is produced (equation 76).[348]



(76)

Further reduction of 1,1,1-trichloroalkanes to a chromium-carbyne species (or related species) occurs in the presence of lithium iodide (or in ionic liquid). The generated species reacts with deuterated pivalaldehyde to give a one-to-two adduct of the 1,1,1-trichloroalkane and the aldehyde in good yield (equation 77).[349]



(77)

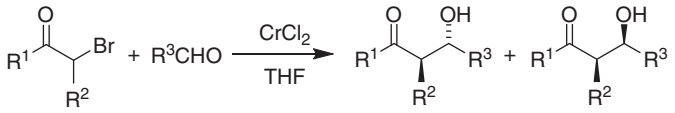
1.06.4.2 Chromium Enolates and Related Species

1.06.4.2.1 Reformatsky-type reaction

Reduction of α-bromoketones with chromium(II) chloride in THF smoothly affords the debrominated ketone in excellent yields.[22] Although trapping of the chromium enolate by addition of either iodomethane, trimethylsilyl chloride, or an aldehyde fails to give products of enolate functionalization,[32] *in situ* trapping with an aldehyde can be accomplished. A mixture of *anti* and *syn* β-hydroxyketones is produced, with the isomer ratios dependent on the structure of the α-bromoketones (Table 5).[350]

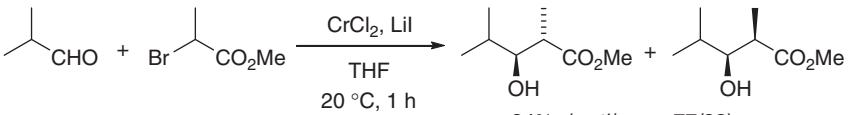
Reactions between α-bromoesters and aldehydes proceed smoothly at 20 to 50 °C by addition of lithium iodide in THF to form *anti* adducts preferentially (equation 78).[351] The *anti* selectivity is in contrast to the *syn* selectivity obtained with lithium or zinc enolates of esters. Similar to previously obtained organochromium reagents, chromium enolates of esters show aldehyde selectivity (>50:1 vs. methyl ketone).[352,353]

Table 5 Reformatsky-type reaction mediated with $CrCl_2$



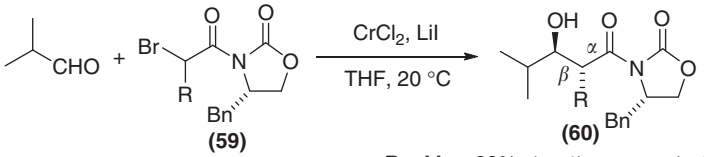
R^1	R^2	R^3	*Yield (%)*	Anti/syn
Bu^t	Me	Et	81	0/100
Ph	Me	Ph	68	50/50
$-(CH_2)_4-$		Ph	75	100/0

Source: Reproduced from Dubois, J.-E.; Axiotis, G.; Bertounesque, E. *Tetrahedron Lett.* **1985**, *26*, 4371–4372.



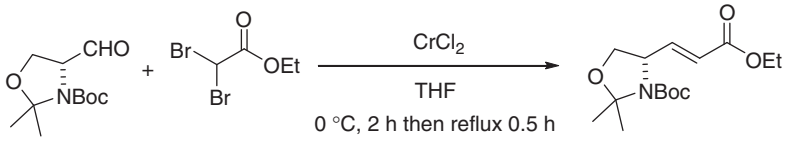
84% (*anti*/*syn* = 77/23) (78)

High diastereofacial selection is achieved with chiral *N*-acyloxazolidinones. Reactions with α-alkyl substituted α-bromoacyloxazolidinones (**59**) afford mainly *anti* adducts (**60**), and chirality induction at the α position of the *anti* isomers by 4-substituted (4*S*)-oxazolidinone is (*R*):(*S*) = > 98:2. The selectivity is opposite to that with the boron enolate of the same chiral *N*-acyloxazolidinone (equation 79).[354,355] Reactions of α-bromoacetate having the (4*S*)-oxazolidinone with aldehydes produce β-(*S*) adducts.



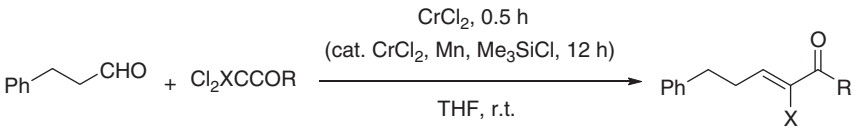
R = Me 88% (*anti*/*syn* = >95/<5)
(α–(*R*)/α–(*S*) = >98/<2)
R = H 91% (β–(*R*)/β–(*S*) = <4/>96) (79)

Treatment of a mixture of an α,α-dihalo (or α,α,α-trihalo) carbonyl compound (i.e., ester, amido, or ketone) and an aldehyde with low-valent metals such as zinc and samarium(II) iodide gives the corresponding α,β-unsaturated carbonyl compound stereoselectively via Reformatsky-type addition and a reduction–elimination step.[356] The reaction also proceeds with chromium(II) chloride in THF (equation 80). Epimerization at the α-position of the aldehyde does not occur during the reaction.[357]



51% (*E*/*Z* = >99/1, >99% *ee*) (80)

A similar reaction between a 1,1,1-trihalo carbonyl compound (ester, amido, or ketone) occurs to give the (*Z*)-isomer of the corresponding α-halo-α,β-unsaturated carbonyl compound in a stereoselective manner (equation 81).[358,359] The selectivity arises at the second elimination step where the sterically less congested transition state is favored.



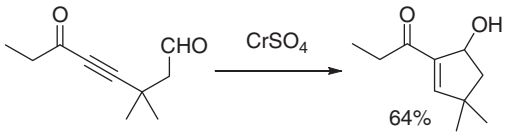
Cl_3CCO_2Me	X = Cl	R = OMe	99%
Cl_2FCCO_2Et	X = F	R = OEt	98%
$Cl_3CCH(OH)OEt$ (= Cl_3CCHO EtOH)	X = Cl	R = H	71%

((*E*)-isomer: 5–7%) (81)

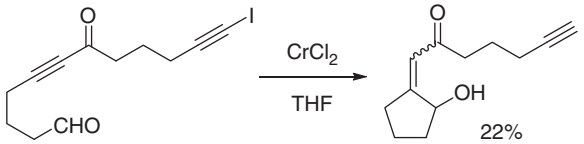
1.06.4.2.2 Enolate equivalents

The reduction of carbon–carbon multiple bonds with chromium(II) under protic conditions was extensively studied by Castro and House.[360–362] The electron transfer from chromium(II) is accelerated when electron-withdrawing groups, such as carbonyl and nitrile groups, are attached to the unsaturated bonds, and by addition of electron-donating ligands such as ethylenediamine.[361]

One-electron reduction of α,β-unsaturated ketones with chromium(II) generates a chromium enolate radical. In the case of acetylenic ketones, the resulting enolate reacts with the internal carbonyl moiety at the α-position to form five-membered hydroxy enones in good yield (equation 82),[363] or at the β-position when the α-position is difficult for cyclization (equation 83).[183]

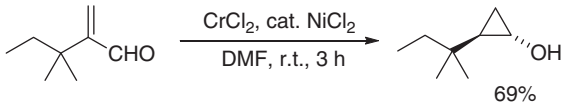


(82)



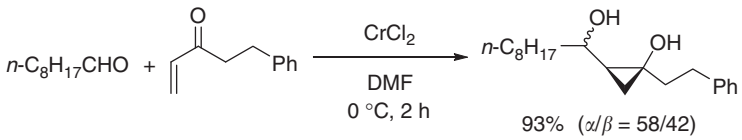
(83)

Reduction of α,β-unsaturated aldehydes with chromium(II) chloride and a catalytic amount of nickel(II) chloride was reported to provide cyclopropanol derivatives in good yields (equation 84).[364] It has been proven that the addition of the nickel salt is not necessary but water is indispensable to promote the cyclopropanol formation.[365] *Trans* isomers are selectively produced from α- or β-substituted aldehydes. However, no reaction occurs in the case of unsaturated α,β-disubstituted aldehydes.



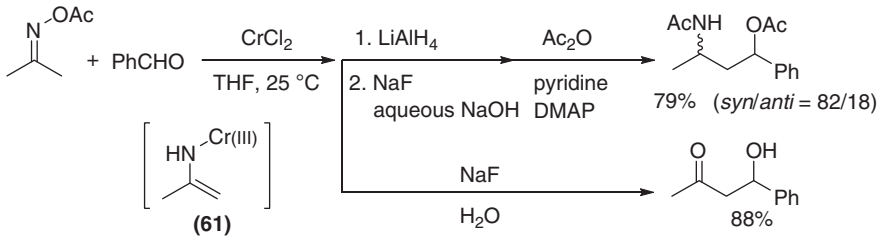
(84)

When the electron transfer from chromium(II) to an α,β-unsaturated ketone is conducted in the presence of an aldehyde under strictly water-free conditions, a *cis*-2-hydroxyalkyl-substituted cyclopropanol is produced (equation 85).[365] The cyclopropanol is produced via an intermolecular aldol reaction of a radical enolate generated by the one-electron transfer to the enone from chromium(II), followed by further one-electron reduction at the β-position of the enone and intramolecular cyclopropanol formation.



(85)

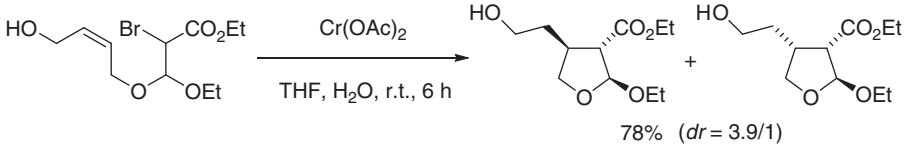
An enamine-type species (**61**) is produced by treating an *O*-acetyl oxime with chromium(II) chloride.[23,366] Trapping of the presumed chromioenamine intermediate (**61**) with an aldehyde followed by reduction with lithium aluminum hydride produces a mixture of β-amino alcohols in good yield (equation 86). Hydrolysis of the initial aldehyde adduct with aqueous sodium fluoride affords a β-hydroxy ketone.



(86)

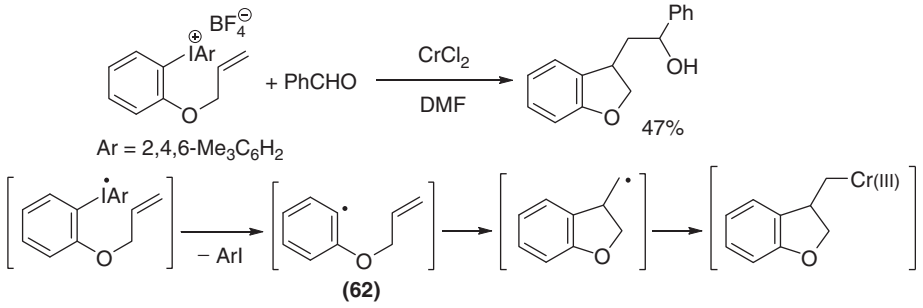
1.06.4.3 Carbon–Carbon Bond Formation via Radical Intermediates

Because chromium(II) is a one-electron reductant, reduction of organic halides (and pseudo halides) gives carbon radicals as intermediates, which are not as sensitive to proton sources. Thus, when unsaturated bonds are located at appropriate positions of the radicals, radical cyclization can occur, and carbon–carbon bond formation can proceed even under aqueous conditions (equation 87).[2,367,368]

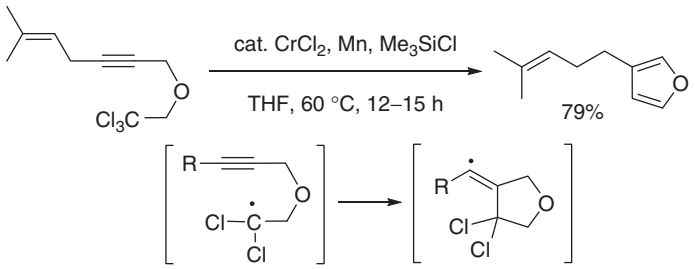


(87)

Treatment of electron-deficient diaryliodonium salts with chromium(II) generates arylchromium(III) species via aryl radicals. The intermediate aryl radical (**62**) can be trapped in an intramolecular manner (equation 88).[369,370] In the reaction of equation 89, furan is produced via radical cyclization.[371]

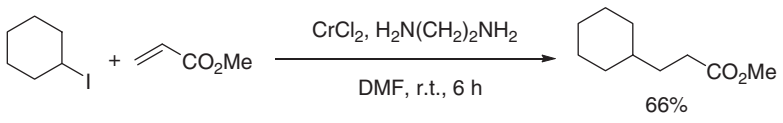


(88)

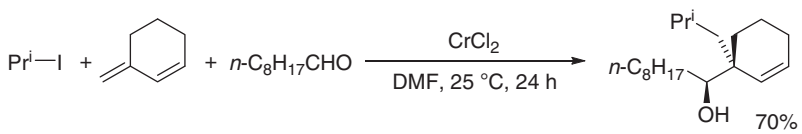


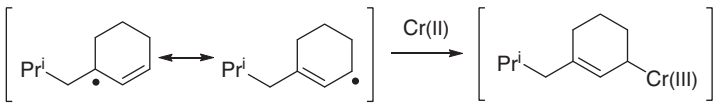
(89)

In the case of secondary and tertiary alkyl iodides, the generated radicals have a sufficient lifetime to add to α,β-unsaturated esters (equation 90)[372,373] or 1,3-dienes intermolecularly. For example, in the treatment of tertiary or secondary alkyl iodides with chromium(II) in DMF in the presence of a 1,3-diene and an aldehyde, the generated alkyl radicals add to the diene. Because the generated allylic radicals are easily reduced with chromium(II), successive one-electron reduction leading to allylic chromium species proceeds. Therefore, three-component addition of the allylic chromium compounds and the aldehyde occurs (equation 91).[38] Because the second one-electron reduction proceeds smoothly under these conditions, polymerization does not occur.



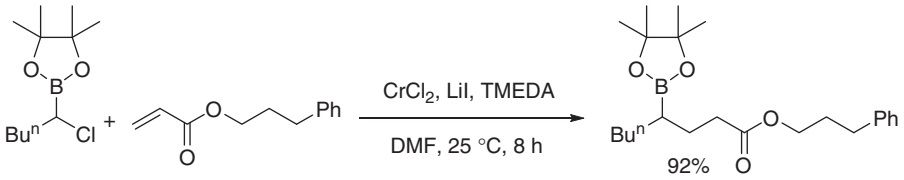
(90)





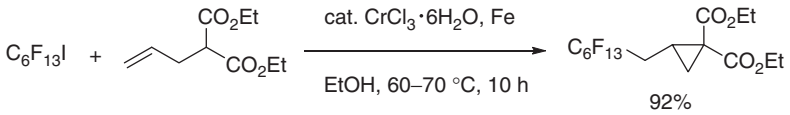
(91)

In contrast to sulfur and nitrogen atoms (see Section 1.06.2.6), an α-boronate substituent does not accelerate the second one-electron reduction leading to the corresponding organochromium compound, and the generated α-boryl radical adds to the α,β-unsaturated ester in a 1,4 fashion (equation 92).[374]



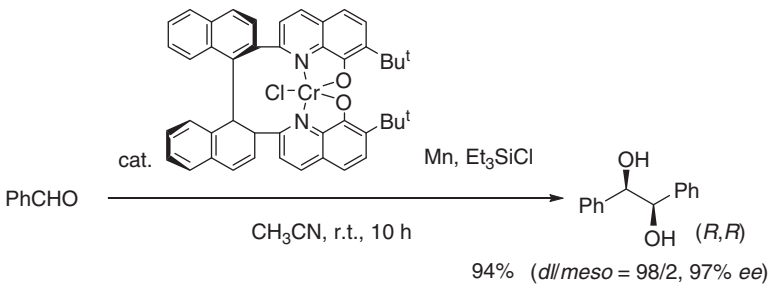
(92)

Treatment of perfluoroalkyl iodides with chromium(II) derived from chromium(III) chloride and iron also generates the corresponding radicals, which add to allyl-substituted malonates to form cyclopropyl compounds in good yield (equation 93).[375]



(93)

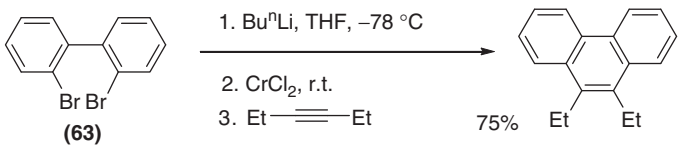
Although chromium(II) is inert to aldehydes under the usual conditions, chromium(II) having electron-rich ligands causes one-electron transfer to aldehydes leading to 1,2-diols, or self-coupling pinacol dimers.[9,43,376] By properly designing the chromium ligand, diastereo- and enantioselective coupling of aldehydes is accomplished (equation 94).[377]



(94)

1.06.4.4 Miscellaneous Reactions

Transmetalation to chromium from other metals sometimes changes the reactivity of the carbanion moiety. For example, treatment of (**63**) with butyllithium followed by chromium(III) chloride and 3-hexyne gives phenanthrene derivative in 75% yield (equation 95).[378]



(95)

Because organochromium species are intermediates of polymerization of ethene (Philips catalysts), trimerization or similar oligomerization is accomplished by designing the ligands for appropriate β-elimination.[379]

1.06.5 Conclusion

The allyl-, alkenyl-, alkyl-, and geminal-dichromium reagents discussed in this chapter can be prepared by treatment of the corresponding organic halides with chromium(II) chloride under appropriate conditions, nickel or cobalt catalysis, as necessary. Chromium(II) chloride has moderate reducing ability. The formed organochromium reagents have mild nucleophilicity, weak basicity, and not so sensitive to water. In addition, the generated chromium(III) salt has moderate Lewis acidity. Because of these advantages, organochromium reagents show chemo- and stereoselectivity and can be prepared from the substrates having many oxygen-functional groups. And therefore, the reagents are complementary to organolithium and -magnesium reagents of strong nucleophilicity and basicity.

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1.07 Recent Advances in Organozinc Reagents

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Glossary

$A^{1,3}$ strain Also known as 1,3-allylic strain, it is caused by steric repulsion between a substituent on a 1-position and that on a 3-position of the allyl moiety. When this repulsion is large enough, conformation of the compound is highly restricted.

Autocatalytic reaction A chemical reaction that is catalyzed by the reaction product itself. When the reaction

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affords a chiral product, the initial small degree of chirality bias can be amplified to give a product with high enantiomeric purity.

Brook rearrangement A rearrangement reaction in which an organosilyl group transfers onto the oxygen atom of a neighboring hydroxy group under basic conditions, affording a silyl ether.

Chirality switching reaction An asymmetric reaction in which structurally similar chiral ligands with the same absolute configuration but partially different chemical structures show reversed chiral induction ability. This is also known as a dual stereoselective reaction.

Domino reaction A chemical reaction that consists of several successive intramolecular reactions. It allows syntheses of highly functionalized cyclic compounds without isolation of the intermediates. This is also known as a tandem reaction or cascade reaction.

Electron spin resonance Physical phenomenon whereby electron spins are excited by absorption of a photon on microwave irradiation, followed by its subsequent emission. This phenomenon allows detection of unpaired electrons. It is also known as electron paramagnetic resonance.

5-*exo*-trig cyclization A type of intramolecular nucleophilic reaction that affords a cyclic structure. The reaction proceeds via attack on the electrophilic trigonal (sp^2) atom, forming a 5-membered ring transition state, followed by cleavage of the covalent bond outside (*exo*) of the ring to give the product.

1.07.1 Introduction

Over the past two decades, the chemistry of organozinc reagents has developed rapidly, and numerous catalytic asymmetric addition reactions have been reported. Notably, since the first report by Oguni and Omi,[1] and discovery of an efficient chiral ligand by Noyori et al.[2] the study of enantioselective addition reactions of dialkylzinc reagents to aromatic aldehydes has grown significantly. This is mainly because many effective chiral catalysts have been developed, and the addition reaction of diethylzinc has subsequently become a typical test used in the design of new chiral ligands. The emphasis now seems to have swiftly moved onto new aspects, namely, the autocatalytic reaction and chirality switching, in addition to overcoming challenges such as selective catalytic reactions of aliphatic aldehydes, ketones, ketoesters, imines, and nitrones.

Considering these research trends, this chapter begins by introducing some characteristic asymmetric addition reactions of dialkylzinc reagents to aromatic and aliphatic aldehydes. In particular, the authors have tried to summarize the results of reactions of various systems according to the particular ligand and substrate. The reactions focused on here are those that have been developed in the period since the first edition of this book series was published.[3] The present section is followed by a discussion of the reactions of vinyl-, alkynyl-, and arylzinc reagents with various aldehydes. Although the basic preparative procedures for organozinc reagents are summarized in the first edition, some new methods have been developed and are introduced at the beginning of the relevant sections. This part of the chapter is concluded with reference to the newest developments, namely, the autocatalytic and chirality switching reactions.

In the next section, organozinc addition to the C═O bond of simple ketones is presented, followed by highlights of some applications of the addition products or intermediates for both ketones and aldehydes. These products provide multifunctional compounds that expand the potential of organozinc reagents as powerful synthetic tools. In the following sections, the addition reactions to the ketone C═O bonds of ketoesters and to imine C═N bonds are discussed. Considering the short history of research in these fields, the reactions are summarized more collectively. Reports on chiral catalysis involving macromolecules or inorganic supports are beyond the scope of this chapter, but are reviewed in detail by Pu and Yu.[4]

Reformatsky reagents are well known in the field of organozinc chemistry.[5] As Grignard reagents cannot be formed from α-halo esters, the Reformatsky reaction is extremely useful; however, research involving its use for catalytic asymmetric addition reactions is less established for dialkylzinc reagents. Nevertheless, some recent papers have presented interesting results that suggest that the mechanism of the Reformatsky reaction needs to be revised with respect to its radical character, a discussion of which is included herein.

Finally, the authors summarize recently reported interesting reactions in which dialkylzinc works as a radical initiator. Several research groups have shown the unique ability of dialkylzincs to afford alkyl radicals in the presence of oxygen.[6,7] The authors include the new addition reactions of such radicals to aldehydes, imines, and C═C bonds, as well as radical domino reactions in the present chapter.

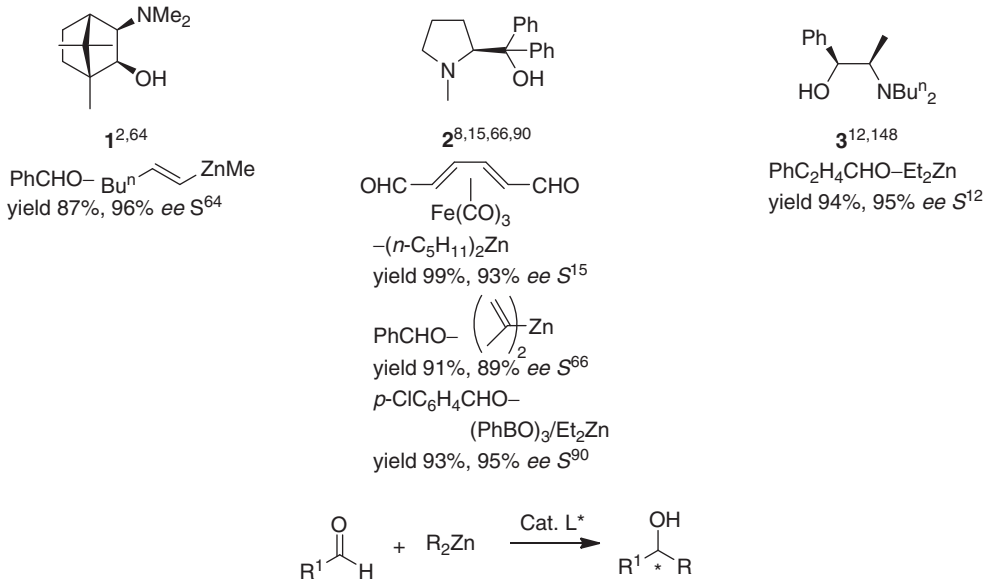
1.07.2 Addition of Organozinc Reagents

1.07.2.1 To Aldehydes

1.07.2.1.1 Introduction

This section provides an introduction to the catalytic asymmetric addition reactions of dialkylzinc reagents to aldehydes (Scheme 1) and the general mechanistic aspects of the transformation.

Since high enantioselectivities were reported by Noyori et al. using (–)-3-*exo*-dimethylaminoisoborneol [(–)-DAIB] (**1**),[2] and by Soai et al. with (*S*)-(+)-(1-methylpyrrolidin-2-yl)diphenylmethanol (**2**) (L* in Scheme 1),[8] *β*-amino alcohols have become a major class of chiral ligand for the addition of organozinc reagents to aldehydes. However, a wide variety of new chiral ligands that contain different functional groups have now been developed. This section discusses the catalytic addition of organozinc reagents to aldehydes using distinctive chiral ligands, according to their main functional groups.



Scheme 1

Figure 1 shows the generally accepted mechanism for the addition reaction involving dialkylzinc catalyzed by a chiral *β*-amino alcohol proposed by Yamakawa and Noyori[9] In the first step, the chiral ligand reacts with dialkylzinc (R_2Zn) to form complex **I** with release of an alkane. Coordination of another R_2Zn species to **I** gives dinuclear zinc complex **II**. The alkoxide zinc atom becomes a Lewis acid to which an aldehyde coordinates to form complex **III**, activating the carbonyl group. In the transition state,

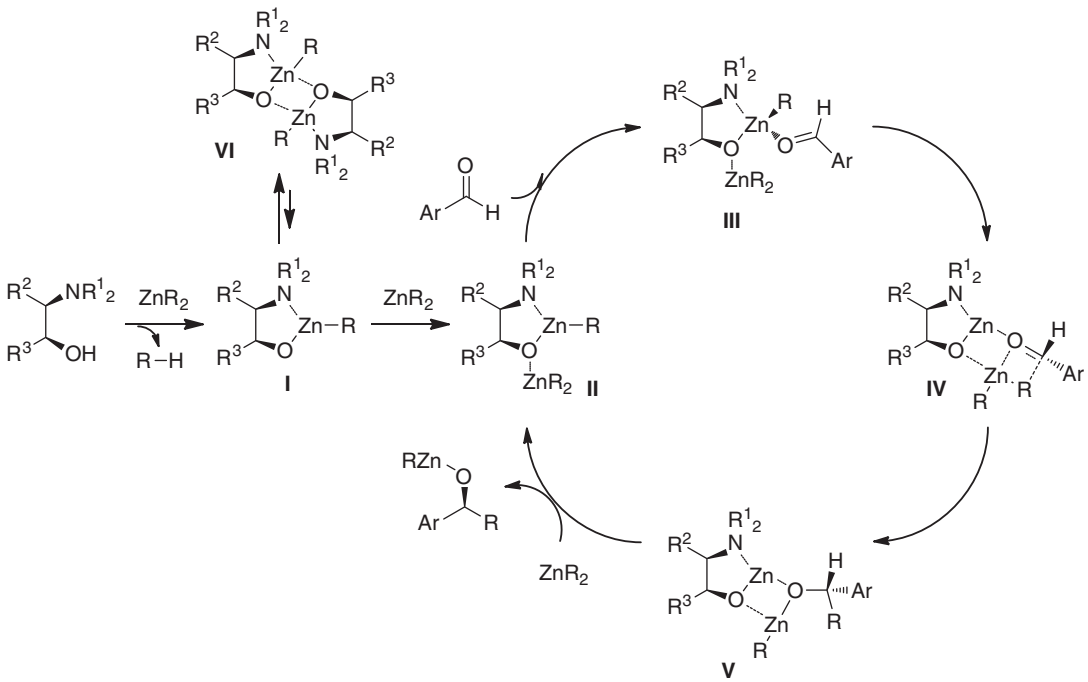


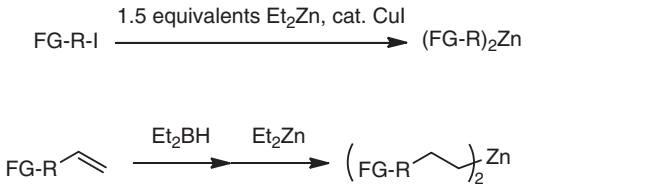
Figure 1 Proposed mechanism for the catalytic dialkylzinc addition to an aromatic aldehyde using a chiral *β*-amino alcohol ligand.[9] Reproduced with permission from Figure 2 in Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*(23), 6327–6335.

anti-5/4/4 tricyclic structure **IV** was calculated to be most favorable for allowing an alkyl group to migrate from the *Si* face to give complex **V**.[9] Soai et al. proposed a 6-membered transition state for their ephedrine-derived ligand,[10] which produces the same chirality, but Noyori et al. did not find this to be favorable using their own calculations.[9] Coordination of a new R_2Zn regenerates **II** and releases the zinc alkoxide of a chiral secondary alcohol as a product.

Complex **I** forms a chiral homodimer (**VI**) in equilibrium. When an enantiomer of a chiral ligand is present, a meso heterodimer can be formed, which is expected to be more stable and less reactive than **VI**. This effectively explains the nonlinear effect observed in the reaction.[9]

1.07.2.1.2 Dialkylzinc

The variety of known dialkylzinc reagents has been greatly expanded by Knochel et al.[10,11] In addition to the basic preparation methods for alkylzinc halides and simple R_2Zn,[3] they have developed the methodology to provide dialkylzinc reagents functionalized with ester, vinyl, allyl, silyl ether, and stannyl groups, in addition to halogen atoms, by applying halogen–zinc[10] and boron–zinc[11] exchange reactions (Scheme 2).

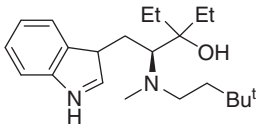


Scheme 2

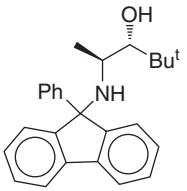
1.07.2.1.2.1 β-Amino alcohol ligands

Since the pioneering studies mentioned in Section 1.07.2.1.1,[1,2,8] many types of β-amino alcohols have been developed for use in the addition reactions of dialkylzinc reagents to aldehydes.

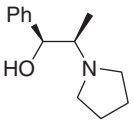
Soai et al. prepared various *N*,*N*-dialkylnorephedrines such as **3**, and have shown that they are effective ligands for the highly enantioselective addition of R_2Zn to aromatic and aliphatic aldehydes.[12] The β-amino alcohol bearing a 3-indolylmethyl group, **4**, developed by Dai et al.[13] has shown high enantioselectivity for diethylzinc (Et_2Zn) addition to various aromatic aldehydes and cyclohexanecarboxaldehyde; however, the large indole unit is not thought to contribute to the transition state. However, Sardina et al. found that β-amino alcohol **5**, with a large phenylfluorenyl group as a nitrogen substituent, achieved high enantioselectivities for both aromatic and aliphatic aldehydes.[14] It was speculated that these results were due to the combination of the bulky *tert*-butyl (Bu^t) group on the carbinol stereocenter (R^3 in Figure 1) and the presence of a small substituent at the α position (R^2 in Figure 1) of the phenylfluorenyl group.



4[13]
p-ClC_6H_4CHO–Et_2Zn
yield 99%, 96.9% *ee R*

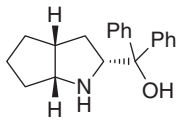


5[14]
n-$C_8H_{17}CHO$–Et_2Zn
yield 98%, 98% *ee S*

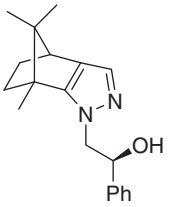


6[12]
n-$C_8H_{17}CHO$–Et_2Zn
yield 87%, >95% *ee S*

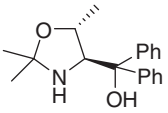
Cyclic β-amino alcohol ligands have often been prepared and applied to the enantioselective addition of R_2Zn to aldehydes, with 5-membered ring proline being the most commonly used amine. After **2**,[8] Soai et al. developed another proline-based β-amino alcohol **6**, which allowed for the addition of Et_2Zn to nonanal in high enantioselectivity.[12] Takemoto et al. prepared a number of different proline-based ligands such as **2**, and demonstrated that they were effective in the dialkylzinc addition to aldehydes bearing iron–diene complexes.[15] Wallbaum and Martens studied a series of bicyclic proline analogs and showed that **7** could achieve high selectivity in addition reactions of aromatic and aliphatic aldehydes.[16] Other 5-membered cyclic amines have also been investigated for use in similar reactions. Kotsuki et al. developed tricyclic pyrazole-based ligand **8**, which gave high enantioselectivity for Et_2Zn addition to benzaldehyde.[17] In comparison with the diastereomeric ligand, product chirality was shown to be controlled by the configuration of the alcohol moiety. Falorni et al. presented oxazolidinyl methanol **9** as an efficient chiral ligand for Et_2Zn addition to both aromatic and aliphatic aldehydes.[18]



7[16]
p-MeC_6H_4CHO–Et_2Zn
yield 87%, 100% *ee R*

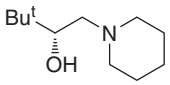


8[17]
$PhCHO$–Et_2Zn
yield 99%, 93% *ee S*

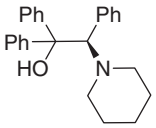


9[18]
n-$C_6H_{13}CHO$–Et_2Zn
yield 100%, 81% *ee S*

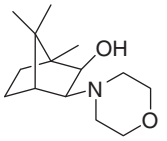
Amino alcohols based on 6-membered piperidine and morpholine have also been developed, with **10** being shown to be highly effective for the addition of Et_2Zn and dimethylzinc (Me_2Zn) to ferrocene and ruthenocene carbaldehydes,[19] and **11** affording excellent reactivity and enantioselectivity in the addition of Et_2Zn to both aromatic and aliphatic aldehydes.[20a] It was subsequently reported that the same ligand worked well for the addition of Me_2Zn to a variety of aldehydes.[20b] Tricyclic (+)-3-*exo*-morpholinoisoborneol [(+)-MIB] (**12**), developed by Nugent, achieved high enantioselectivity for the reaction of Et_2Zn with various aldehydes and Me_2Zn with *m*-tolualdehyde.[21]



10[19]
$FcCHO$–Et_2Zn
yield 96%, >96% *ee R*

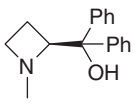


11[20]
p-MeC_6H_4CHO–Et_2Zn
yield 100%, 98% *ee S*[20a]
p-$CF_3C_6H_4CHO$–Me_2Zn
yield >99%, 91% *ee S*[20b]
o-MeC_6H_4CHO–$PhZnEt$
yield 99%, 97% *ee S*[20b]

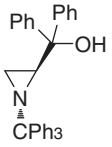


12[21]
Me_2CHCHO–Et_2Zn
yield 94%, 99% *ee R*

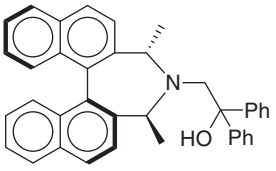
Smaller 4- and 3-membered cyclic amines have also been used as components of chiral *β*-amino alcohols.[22,23] Martens et al. developed the lithium salt of azetidine derivative **13**, which enantioselectively afforded 1-arylpropanols from various aromatic aldehydes and Et_2Zn.[22] Zwanenburg et al. synthesized *N*-tritylaziridine-based *β*-amino alcohol **14** from serine, and reported that it catalyzed the addition of Et_2Zn to various aromatic and aliphatic aldehydes with high enantioselectivity.[23] Moreover, Pisani and Superchi reported that the 7-membered cyclic *β*-amino alcohol with an axially chiral 1,1′-binaphthylazepine structure, **15**, produced a rapid reaction that afforded good results in the asymmetric addition of dialkylzinc reagents to aromatic aldehydes.[24]



13[22]
p-$MeOC_6H_4CHO$–Et_2Zn
100% *ee S*

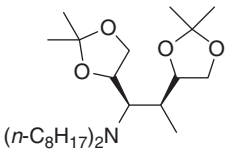


14[23]
c-$C_6H_{11}CHO$–Et_2Zn
yield 90%, 99% *ee S*



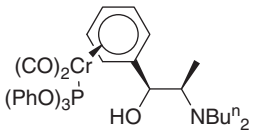
15[24]
$PhCHO$–$Bu^n{}_2Zn$
yield 90%, 96% *ee S*

Various structures and additional functional groups have been introduced to the *β*-amino alcohol ligand platform. Cho et al. reported that *β*-amino alcohol **16**, prepared from D-mannitol, gave high enantioselectivity for the addition of R_2Zn to both aromatic and aliphatic aldehydes,[25] while *β*-amino alcohols bearing a metal complex unit have also been shown to work as chiral ligands. Jones et al. demonstrated that the η^6–arene–chromium complexes of *β*-amino alcohols such as **17** have high enantioselectivity for various aldehydes via conversion to the zinc salt.[26] The attractive dipole–dipole interaction between the chromium complex and Et_2Zn in the transition state is thought to contribute to the improved enantioselectivity compared to the corresponding non-complexed *β*-amino alcohol. Wang et al. showed that *β*-amino alcohols bearing a ferrocenylmethyl group on the aziridine nitrogen, as in the case of **18**, are highly effective for the enantioselective ethylation of aromatic aldehydes.[27] It was speculated that it is the sterically congested zinc alkoxide, rather than the 3-membered ring, that controls the stereochemistry of the product.



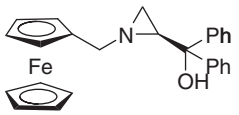
16[25]

n-$C_{10}H_{21}CHO$–Et_2Zn
yield 81%, 90% *ee R*



17[26b]

$Ph_3COC_3H_6CHO$–Me_2Zn
yield 87%, 98% *ee S*

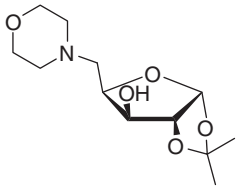


18[27,100]

m-ClC_6H_4CHO–Me_2Zn
yield 82%, 99.8% *ee S*[27]
m-$PhOC_6H_4CHO$–
$PhB(OH)_2/Et_2Zn$
yield 93%, 95.7% *ee S*[100]

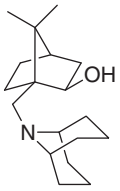
1.07.2.1.2.2 γ-Amino alcohol ligands

Motivated by the success of β-amino alcohol chiral ligands, a variety of γ-amino alcohols and γ-amino phenols have been prepared and investigated for the asymmetric addition of R_2Zn to aldehydes. Cho et al. developed some γ-amino alcohols from D-mannitol and showed that morpholine moiety-containing **19** afforded high enantioselectivity for the addition of Et_2Zn[28a] and diisopropylzinc[28b] to aromatic and aliphatic aldehydes. Hari and Aoyama demonstrated that 10-dialkylaminoisoborneol **20**, with a bulky bicyclic amino group, was the most effective ligand among the γ-amino alcohols prepared for the enantioselective addition of Et_2Zn to a range of different aldehydes.[29] In addition, γ-amino naphthol **21**, a Betti base derivative, and γ-amino phenol **22**, with two stereocenters, were developed and shown to be efficient for the enantioselective addition of a variety of dialkylzincs to aromatic aldehydes.[30,31] Aoyama et al.[29] and Palmieri[31] explained the product configuration by applying Noyori's tricyclic transition state[9] that was proposed for β-amino alcohols (Figure 2 for **22**[31]).



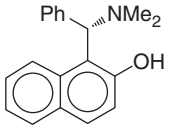
19[28]

n-$C_6H_{13}CHO$–$Pr^i{}_2Zn$
yield 88%, 96% *ee S*[28b]



20[29]

o-MeC_6H_4CHO–Et_2Zn
yield 99%, 95% *ee R*



21[30]

o-$MeOC_6H_4CHO$–Et_2Zn
yield 93%, 96% *ee R*

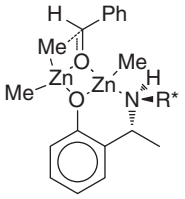
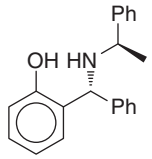


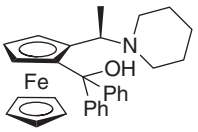
Figure 2 Proposed transition state of the dimethylzinc addition to benzaldehyde in the presence of γ-amino phenol ligand **22**.[31] Reproduced with permission from Scheme 2 in Palmieri, G. *Tetrahedron Asymmetry* **2000**, *11*(16), 3361–3373.

1.07.2.1.2.3 δ-Amino alcohol ligands

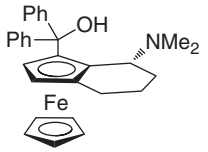
There are a number of reports demonstrating the high efficiency of δ-amino alcohol ligands for the enantioselective addition of dialkylzinc reagents to aldehydes. Three types of ferrocene-based ligands with one stereocenter have been reported. Watanabe reported that **23**, with a piperidine moiety, can effectively catalyze the enantioselective addition of both Et_2Zn and Me_2Zn to metallocene carboxaldehydes and benzaldehyde.[32] Both δ-amino alcohols **24** by Schlögl et al.[33] with a chiral cyclic structure, and **25** by Bolm et al.[34] with a chiral oxazoline unit, achieved good to high enantioselectivity in the addition of Et_2Zn to various aldehydes. The product stereochemistry was attributed to the formation of a 7-membered cyclic transition state containing oxygen, zinc, and nitrogen atoms, which is also in agreement with Noyori's model.[9]



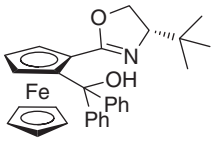
22[31]
$Me_2CHCHO–Et_2Zn$
yield 86%, 97% *ee S*



23[32]
$FcCHO–Me_2Zn$
yield 96%, 97% *ee S*



24[33]
$PhCH=CHCHO–Et_2Zn$
yield 86%, 87% *ee S*



25[34,71,89,98]
$n\text{-}C_6H_{13}CHO–Et_2Zn$
yield 94%, 87% *ee R*[34]
$p\text{-}ClC_6H_4CHO–p\text{-}MeC_6H_4$–ZnEt
yield 62%, 75% *ee R*[71]
$p\text{-}PhC_6H_4CHO–Ph_2Zn/Et_2Zn$
yield 98%, 97% *ee R*[89a]
$p\text{-}ClC_6H_4CHO–PhB(OH)_2/Et_2Zn$
yield 93%, 97% *ee R*[89b]
$p\text{-}MeC_6H_4CHO–Ph_3B/Et_2Zn$
yield 97%, 98% *ee R*[89c]
$FcCHO–p\text{-}ClC_6H_4B(OH)_2/Et_2Zn$
yield 98%, 94% *ee R*[98]

1.07.2.1.2.4 N,O-multidentate ligands

After the success of this wide variety of amino alcohols in the catalytic asymmetric addition of R_2Zn, the logical next step was to investigate *N,O*-multidentate ligands. Hoshino et al. developed N,O_2-tridentate pyridyl alcohols and showed that **26** efficiently worked for the addition of Me_2Zn to benzaldehyde, as well as for the addition of Et_2Zn to both aromatic and aliphatic aldehydes.[35] Compared with **27**,[36] the increased reaction efficiency was attributed to both the coordination ability and the steric effect of the ligand (**Figure 3**). The tetracyclic transition state is thought to saturate the coordination of the zinc atom of the alkoxide, which reduces formation of the less effective dimeric zinc complex, with two aryl groups working to promptly release the alkoxide product. Ferrocene-type N,O_2-ligand **28** by Fu et al. appeared to work similarly well for the addition of Et_2Zn and Me_2Zn to aromatic aldehydes.[37] M. Hayashi et al. developed chiral Schiff-base-type N,O_2-tridentate ligands such as **29** for highly enantioselective addition of Et_2Zn and di-*n*-butylzinc (Bu^n_2Zn) to various aromatic and aliphatic aldehydes.[38] The N,O_2-tridentate amino bisphenol, **30**, developed by Hirose et al. was found to be more effective for the addition of Et_2Zn to aromatic and aliphatic aldehydes than *N,O*-bidentate *γ*-amino phenol.[39a,b] Wu et al. demonstrated that the N_2,O-tridentate *N*-pyridylmethyl *β*-amino alcohol, **31**, could also give high enantioselectivity in the addition reactions with a number of different aromatic aldehydes.[40] The complex in which zinc is coordinated to two nitrogen and one oxygen atoms is quite similar to that of **26**, and is suggested to control the reaction pathway to the carbonyl group.

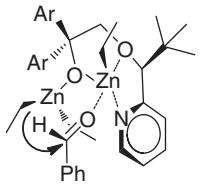
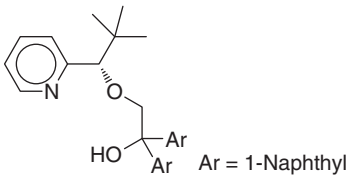
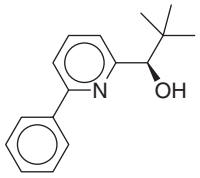


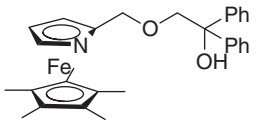
Figure 3 Proposed transition state of the diethylzinc addition to benzaldehyde in the presence of tridentate ligand **26**.[35] Reproduced with permission from Figure 1 in Ishizaki, M.; Fujita, K.; Shimamoto, M.; Hoshino, O. *Tetrahedron Asymmetry* **1994**, *5*(3), 411–424.



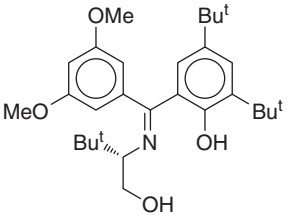
26[35,76]
PhCHO–Me_2Zn
yield 93%, 92% *ee S*[35]
PhCHO–
Ph—≡—ZnMe
yield 93%, 81% *ee R*[76]



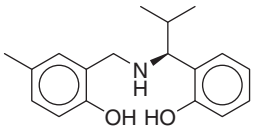
27[36]



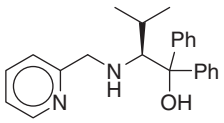
28[37]
p-ClC_6H_4CHO–Et_2Zn
yield 94%, 90% *ee S*
p-ClC_6H_4CHO–Ph_2Zn
yield 99%, 57% *ee S*



29[38]
2-ThienylCHO–$Bu^n{}_2Zn$
yield 82%, 98% *ee R*

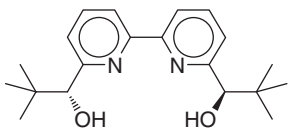


30[39a]
PhC_2H_4CHO–Et_2Zn
yield 81%, 95% *ee R*

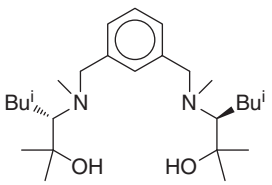


31[40]
p-MeC_6H_4CHO–Et_2Zn
yield 98%, 96% *ee R*

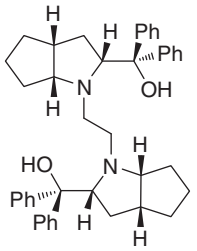
Various N_2,O_2-tetradentate chiral ligands have been prepared as the dimeric forms of β-amino alcohols, that is, as C_2-symmetric ligands. In the early stages of their work, Bolm et al. prepared N_2,O_2-bipyridine diols such as **32**, and employed them as chiral ligands for the enantioselective addition of Et_2Zn to aromatic aldehydes in the presence of nickel(II) acetylacetonate [$Ni(acac)_2$].[36] They discussed the reaction mechanism along with the structural effect of the chiral ligand in detail. Pedrosa et al. reported that C_2-symmetric ligands of aliphatic amines, **33**, for example, worked efficiently for the enantioselective reaction of Et_2Zn with aromatic aldehydes.[41] In other work, Martens et al. found that the tertadentate ligand of cyclic amine **34** was more effective for the enantioselective ethylation of benzaldehyde than is its monomeric form.[42] Liu and Wolf developed unique bis(oxazolidine) N_2,O_2-ligand **35**.[43] Although it has no dissociable protons on the oxygen or nitrogen atoms, the ligand provided high enantioselectivity in the addition of Et_2Zn and Me_2Zn to aromatic aldehydes and cyclohexanecarbaldehyde.



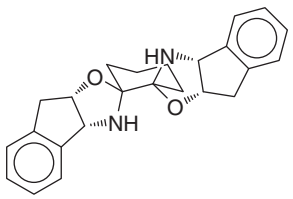
32[36]
PhCHO–Et_2Zn
yield 94%, 97% *ee R*



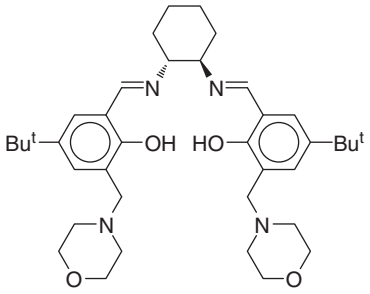
33[41]
p-ClC_6H_4CHO–Et_2Zn
yield 81%, 98% *ee R*



34[42]
PhCHO–Et_2Zn
yield 73%, 100% *ee R*



35[43,86]
p-FC_6H_4CHO–Me_2Zn
yield 95%, 92% *ee*[43]
PhCHO–
Bu^n—≡—ZnMe
yield 96%, 92% *ee*[86]



36[44]
Et_2CHCHO–Et_2Zn
yield 84%, 91% *ee S*

Salen is a well known and highly useful N_2,O_2-tetradentate ligand platform for the asymmetric addition of R_2Zn to carbonyl groups. DiMauro and Kozlowski developed several salen-type chiral ligands and showed that the zinc complex of **36** provided high enantioselectivity in the ethylation of aromatic and aliphatic aldehydes.[44] The nitrogen atom of a morpholinomethyl substituent is proposed to work as a Lewis base to activate Et_2Zn, with the aldehyde being activated at the a pical coordination site of the zinc complex, as shown in **Figure 4.** Cozzi and Kotrusz demonstrated that the chromium(III) complex of commercially available chiral salen, **37**, achieved high enantioselectivity in the addition of Me_2Zn to various aldehydes.[45]

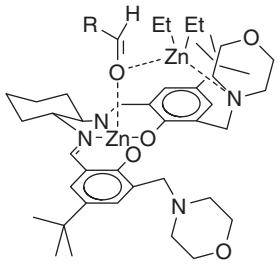
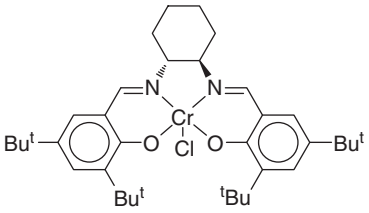


Figure 4 Proposed major transition state of the diethylzinc addition to benzaldehyde in the presence of salen-type ligand **36**.[44] Reproduced with permission from Figure 2 in DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*(19), 3053–3056.



37[45]
Bu^{t}CHO–Me_2Zn
yield 75%, 97% *ee R*

1.07.2.1.2.5 Amide ligands

In addition to amino alcohols, there are a variety of other functional groups and their combinations that have been introduced within the chiral ligands of catalysts for the asymmetric addition of R_2Zn to aldehydes. Knochel et al. achieved the catalytic enantioselective addition of such functionalized zinc reagents to aromatic, aliphatic, and functionalized aldehydes,[10,11,46] applying the chiral bis(trifluoromethanesulfonamide) of *trans*-1,2-diaminocyclohexane **38** and titanium(IV) complex system developed by Ohno et al.[47] The transition state and its stereochemistry were proposed as the coordination of R_2Zn and aldehyde to the titanium complex (**Figure 5**).[48] Recently, other researchers have introduced amide moieties as metal-chelating groups. Singh et al. prepared unsymmetrical bis(sulfonamide) of the same diamine, for example, **39**, and demonstrated that their titanium(IV) complexes gave very good enantioselectivity in the asymmetric addition of Et_2Zn to aromatic aldehydes and cyclohexanecarbaldehyde.[49] Gau et al. prepared a number of β-hydroxy sulfonamides from 10-camphorsulfonic acid and found that the titanium(IV) complex of **40** worked effectively in the enantioselective addition of Et_2Zn to aromatic aldehydes.[50]

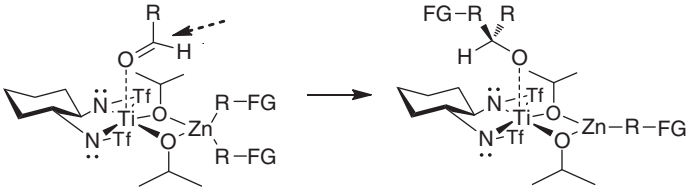
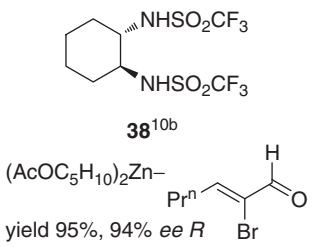
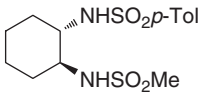


Figure 5 Proposed transition state of the functionalized dialkylzinc addition to an aldehyde in the presence of 1,2-bis(sulfonamide) **38**.[48] Reproduced with permission from Scheme 12 in Ostwald, R.; Chavant, P.-Y.; Stadtmüller, H.; Knochel, P. *J. Org. Chem.* **1994**, *59*(15), 4143–4153.



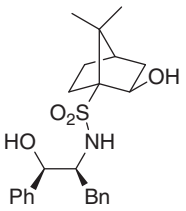
38[10b]

yield 95%, 94% *ee R*



39[49]

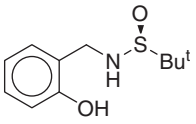
p-ClC$_6$H$_4$CHO–Et$_2$Zn
yield 98%, 96% *ee R*



40[50]

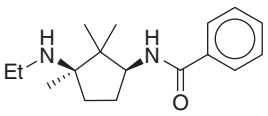
p-ClC$_6$H$_4$CHO–Et$_2$Zn
yield 90%, 94% *ee R*

Chiral sulfinamidophenol **41** was shown by Qin et al. to work as a good ligand in the Et$_2$Zn addition to various aromatic aldehydes, without the need for other metal ions.[51] The authors suggested that two oxygen atoms and one nitrogen atom of the ligand coordinated to zinc to form an *O,N,O*-chelating 6/4 bicyclic transition state (Figure 6).[51] Murtinho et al. introduced a benzamide structure in the chiral ligand and showed that γ-amino amides such as **42** work well for the enantioselective addition of Et$_2$Zn to aromatic aldehydes.[52]



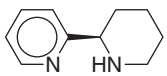
41[51]

p-ClC$_6$H$_4$CHO–Et$_2$Zn
yield 90%, 96% *ee R*



42[52]

m-MeC$_6$H$_4$CHO–Et$_2$Zn
yield 88%, 99% *ee S*



43[53]

2-ThienylCHO–Et$_2$Zn
yield 89%, 88% *ee R*

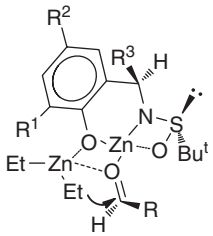


Figure 6 Proposed transition state of the diethylzinc addition to an aldehyde in the presence of sulfinamidophenol **41**.[51] Reproduced with permission from Figure 2 in Huang, Z.; Lai, H.; Qin, Y. *J. Org. Chem.* **2007**, *72*(4), 1373–1378.

1.07.2.1.2.6 Diamine ligands

Few chiral *N,N*-bidentate ligands that selectively work for the addition of R$_2$Zn to aldehydes have been reported. Gao et al. synthesized 2-(2′-piperidinyl)pyridine **43**, a β-diamine ligand, and demonstrated its effectiveness for the enantioselective addition of Et$_2$Zn to various aldehydes.[53] They presented a transition state in which the alkylzinc coordinated to a piperidyl nitrogen for the ethylation of benzaldehyde (Figure 7). More recently, Qi and Judeh developed some 1,1′-bis(isoquinoline)-based ligands and showed that **44** works well for the enantioselective ethylation of aromatic aldehydes.[54]

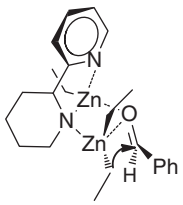
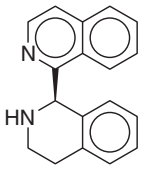


Figure 7 Proposed transition state of the diethylzinc addition to benzaldehyde in the presence of diamine ligand **43**.[53]

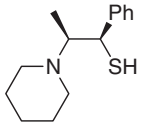
1.07.2.1.2.7 β-Amino thiol ligands

Some β-amino thiols and their derivatives or analogs have been shown to be effective as ligands for the enantioselective addition of dialkylzinc reagents to aldehydes. Kang et al. studied some β-amino secondary thiols with bulky cyclic amino groups and showed that **45** achieved the highly enantioselective addition of Et$_2$Zn to aromatic and aliphatic aldehydes, and ferrocene

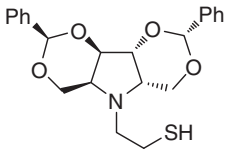
carbaldehydes.[55] Masaki et al. demonstrated that pyrrolidine-based primary thiol **46**, derived from D-mannitol, worked well as a chiral ligand for Et_2Zn addition to both aromatic and aliphatic aldehydes.[56] The catalytic ability was found to be much better than that of the corresponding β-amino alcohol in the addition reaction with benzaldehyde. In other work, Kellogg et al. found that the disulfides derived from ephedrine, such as **47**, worked as chiral ligands for the reaction with benzaldehyde,[57] and speculated that the disulfide bond was cleaved by Et_2Zn to form thiolates.



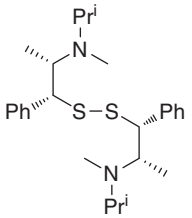
44[54]
PhCHO - Et_2Zn
y. 96%, 85% *ee R*



45[55]
c-$C_6H_{11}CHO$ - Et_2Zn
y. 97%, 100% *ee R*



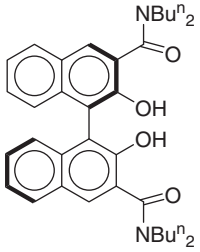
46[56]
n-$C_8H_{17}CHO$ - Et_2Zn
y. 91%, 88% *ee S*



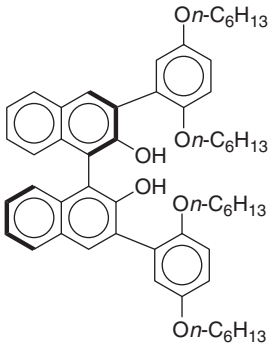
47[57]
PhCHO–Et_2Zn
yield 97%, 89% *ee R*

1.07.2.1.2.8 Diols: BINOLs and TADDOLs

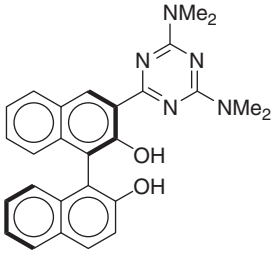
Binaphthols (BINOLs) and $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs) are families of chiral diol scaffolds that have been applied as chiral ligands for the enantioselective addition of dialkylzinc reagents to aldehydes. Katsuki et al. found that BINOL derivatives containing amide functional groups at the 3,3′-positions, such as **48**, are efficient ligands for Et_2Zn addition to various aldehydes, with the exception of linear aliphatic aldehydes.[58] It was indicated that coordination of the amide carbonyl groups and a solvent molecule to the zinc atoms in the intermediate was important in the transformation (**Figure 8(a)**). Pu et al. discovered that another 3,3′-substituted BINOL ligand, **49**, achieved excellent enantioselectivity in Et_2Zn addition to a number of different aldehydes.[59]



48[58,99]
o-FC_6H_4CHO–Et_2Zn
yield 86%, 95% *ee R*[58]
2-NaphthylCHO–$PhB(OH)_2$/Et_2Zn
yield 100%, 96% *ee S*[99]



49[59]
n-$C_8H_{17}CHO$–Et_2Zn
yield 91%, 98% *ee R*



50[60]
1-NaphthylCHO–Et_2Zn
yield 99%, 95% *ee R*

To date, a wide variety of BINOL derivatives that bear other functional groups, including aminotriazine (**50**),[60] phosphoramide (**51**),[61] and pyridyl (**52**)[62] groups at the 3,3′-positions, have been synthesized and employed as highly effective chiral ligands. J.-S. Li et al. applied the titanium(IV) complex of **50** to the enantioselective addition of Et_2Zn to aromatic aldehydes.[60] However, both

ligands **51** and **52** are able to work without other Lewis acids such as titanium isopropoxide [$Ti(OPr^i)_4$]. Based on the optimized transition model of **52**, Snieckus et al. proposed an alternative transition model (Figure 8(b)),[62] in which the roles of the coordinated zinc atoms were switched from those of the Katsuki's model.[58]

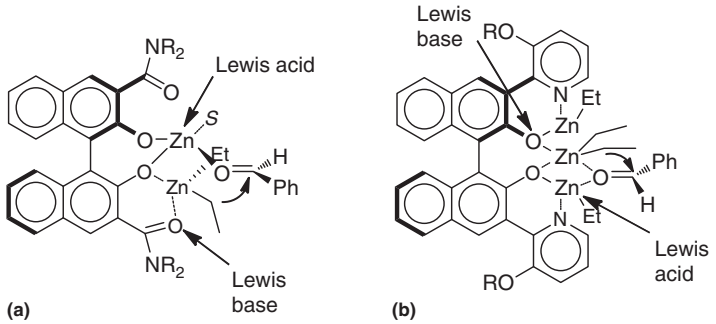
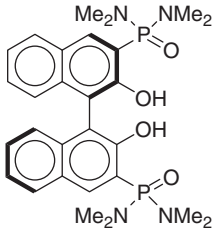
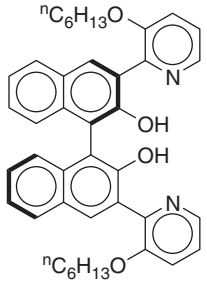


Figure 8 Proposed transition states of the diethylzinc addition to benzaldehyde in the presence of salen-type ligands (a) **48**[58] and (b) **52**.[62] Reproduced with permission from Figure 5 in Kitajima, H.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*(1), 207–217, and Scheme 3 in Milburn, R. R.; Hussain, S. M. S.; Prein, O.; Ahmed, Z.; Snieckus, V. *Org. Lett.* **2007**, *9*(22), 4403–4406.



51[61]

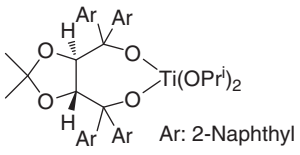
p-$CF_3C_6H_4CHO$–$Bu^n{}_2Zn$
yield 91%, 97% *ee R*



52[62]

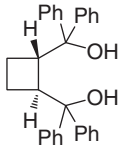
o-$MeOC_6H_4CHO$–Et_2Zn
yield 99%, 97% *ee R*

In contrast to the BINOL derivatives mentioned above, most TADDOL derivatives have no additional coordinating atoms other than the two hydroxyl oxygen atoms, and have mostly been used as titanium(IV) complexes. Seebach et al. extensively studied many TADDOL–titanium complexes such as **53**, and reported highly enantioselective addition of Et_2Zn to aromatic and aliphatic aldehydes.[63a] Some analogs such as **54** were also shown to be good chiral ligands for Et_2Zn addition to benzaldehyde.[63b] The reactivity and selectivity were speculated to be controlled by the steric interaction between the aryl substituents on the 7-membered metallacycle and aldehyde coordinated to the titanium.[63b]



53[63a]

PhC_2H_4CHO–Et_2Zn
yield 89%, 96% *ee S*



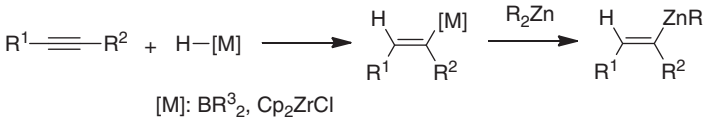
54[63b]

PhCHO–Et_2Zn
yield 79%, 88% *ee R*

1.07.2.1.3 Vinylzinc

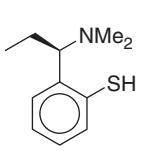
In addition to direct preparation of vinylzinc reagents by oxidative addition, methods such as the hydrometalation of alkynes and transmetalation have been developed (Scheme 3).[64,65] Oppolzer and Radinov prepared alkenylzinc reagents by hydroboration of alkynes followed by boron–zinc metal exchange, achieving good enantioselectivity in the asymmetric addition to aromatic and aliphatic aldehydes in the presence of DAIB (**1**).[64] Later, Wipf and Ribe developed a method to prepare vinylzinc reagents by treatment of terminal alkynes with zirconocene hydrochloride followed by transmetalation with Me_2Zn. They studied several β-amino alcohols and γ-amino thiophenols as chiral ligands, and found that **55** was highly efficient for the enantioselective addition of vinylzinc reagents to aromatic aldehydes.[65] In other work, Soai et al. directly prepared diisopropenylzinc by the

reaction of zinc bromide ($ZnBr_2$), isopropenyl bromide, and lithium. They used chiral β-amino alcohols such as **2** as the ligands to catalyze the reaction of the divinylzinc reagent with benzaldehydes in high enantioselectivity.[66]



Scheme 3

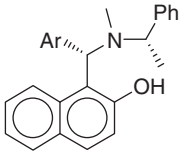
Many research groups have utilized Oppolzer's procedure for their newly developed ligands. Chan's group prepared Betti base derivative **56a** as a ligand for the highly enantioselective addition of vinylmethylzinc to various aldehydes.[67] Uang et al. achieved high enantioselectivity in the vinylation of aromatic aldehydes and cyclohexanecarbaldehyde by using γ-amino thiol ligand **57**.[68] They also succeeded in the preparation of the vinylzinc of an internal alkyne, 3-hexyne. Seto et al. developed many dipeptide-based amino thioether ligands and showed that **58** was effective for both aromatic and α-branched aldehydes.[69] Bräse's group prepared paracyclophane-based γ-imino phenols such as **59**, also achieving high enantioselectivity in the addition of various vinylzinc reagents (prepared by hydroboration of alkynes) to aliphatic aldehydes and benzaldehydes.[70]



55[65]

p-ClC_6H_4CHO–Bu^n–ZnMe

yield 83%, 97% *ee S*



56[67,96a]

Ar = Ph **56a**[67]

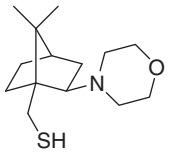
o-ClC_6H_4CHO–PhC_2H_4–ZnMe

yield 90%, >99% *ee R*

Ar = 1-Naphthyl **56b**[96a]

o-MeC_6H_4CHO–$PhB(OH)_2/Et_2Zn$

yield 95%, 99% *ee R*



57[68,84,95,144]

p-$CF_3C_6H_4CHO$–n-C_6H_{13}–ZnMe

yield 90%, >99.5% *ee R*[68]

p-$CF_3C_6H_4CHO$–Ph—≡—ZnMe

yield 84%, 87% *ee S*[84]

o-MeC_6H_4CHO–$PhB(OH)_2/Et_2Zn$

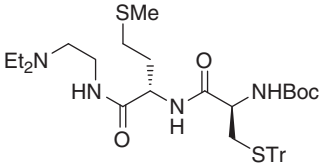
yield 95%, >99.5% *ee R*[95]

p-$MeC_6H_4COCO_2Me$–Me_2Zn

yield 84%, 85% *ee S*[144]

A vinylboronic acid/Et_2Zn system for the preparation of vinylzinc reagents was developed by Bolm et al. They succeeded in achieving asymmetric addition to aromatic aldehydes using the oxazoline alcohol with a ferrocene unit, **25**, as a chiral ligand.[71] Moreover, Sato et al. recently developed a new method to directly prepare terminal and branched vinylzinc reagents by transmetalation between trivinylbismuthine and Me_2Zn, and achieved high enantioselectivity for aromatic aldehydes by using **60** (the enantiomer of **2**) as a chiral ligand.[72]

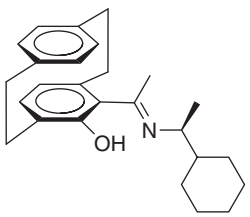
The vinylzinc reagents prepared by hydrometalation of alkynes and transmetalation provide the (*E*)-vinylzinc reagents. However, Walsh et al. prepared the (*Z*)-vinylzinc reagents from the reaction of dicyclohexylborane and 1-halo-1-alkyne followed by treatment with *tert*-butyllithium and transmetalation with Et_2Zn. The (*Z*)-vinylzinc reagents and β-amino alcohol (–)-MIB **61** (the enantiomer of **12**) effectively reacted to afford enantioenriched (*Z*)-allyl alcohols in the presence of tetraethylethylenediamine, which is critical for the prevention of racemization by the lithium salt (LiX) (**Scheme 4**).[73a] Recently, they also showed that the addition of a vinylzinc reagent to chiral α-silyloxy aldehydes proceeded with high diastereoselectivity through chelation control.[73b]



58[69]

p-ClC_6H_4CHO–Bu^t–ZnMe

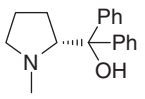
yield 86%, 95% *ee R*



59[70]

Me_2CHCHO–n-C_6H_{13}–ZnEt

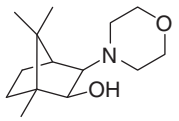
yield 70%, 94% *ee* (+)



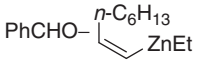
60[72]

p-BrC_6H_4CHO–ZnMe

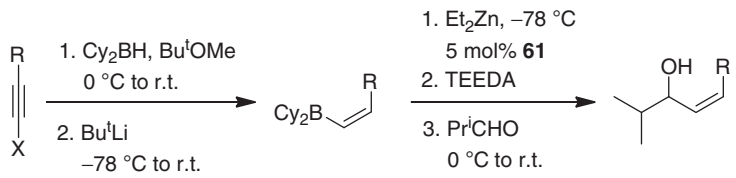
yield 81%, 97% *ee S*



61[73a,91,137,138b,139]



yield 63%, 93% *ee S*[73a]
2-Naphthyl CHO–Ph_2Zn
yield 86%, 93% *ee S*[91]
2-NaphthylCHO–$PhZnBu^n$
yield 86%, 93% *ee S*[91]

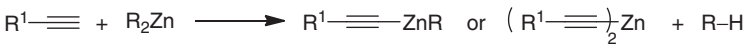


TEEDA: $Et_2NCH_2CH_2NEt_2$

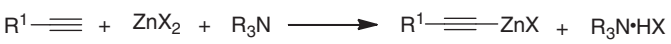
Scheme 4

1.07.2.1.4 Alkynylzinc

Alkynylzinc reagents are generally prepared by one of two methods: (1) the reaction of 1 or 2 equivalents of a terminal alkyne with R_2Zn, leading to alkylalkynylzinc or dialkynylzinc, respectively (Scheme 5)[74]; or (2) the reaction between a terminal alkyne and zinc salt in the presence of an amine (Scheme 6).[75]

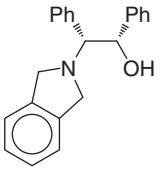


Scheme 5



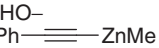
Scheme 6

Ishizaki and Hoshino found that tridentate pyridyl alcohol **26** was effective for the enantioselective alkynylation of aromatic and aliphatic aldehydes by alkynylethylzinc reagents, but not by dialkynylzinc reagents.[76] Several bidentate chiral ligands have also been developed, similar to those used for the addition of R_2Zn. Li et al. showed that ephedrine derivatives such as **62** can catalyze the enantioselective addition of terminal alkynes to various aromatic aldehydes in good enantioselectivity using alkynylmethylzinc reagents.[77] Chan et al. studied a number of binaphthyl-derived *β*-amino alcohols with 7-membered cyclic tertiary amines as chiral ligands for asymmetric alkynylation, and found that **63** was effective for the enantioselective addition of phenylacetylene to aromatic aldehydes.[78]

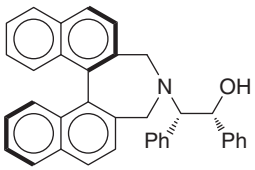


62[77]

o-FC_6H_4CHO–



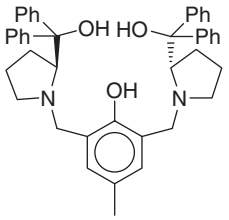
yield 90%, 82% *ee* (–)



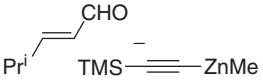
63[78,96b]

o-ClC_6H_4CHO–

yield >95%, 93% *ee* (+)[78]
p-PhC_6H_4CHO–$PhB(OH)_2/Et_2Zn$
yield 95%, 99% *ee R*[96b]



64[79]



yield 100%, 94% *ee R*

Trost et al. synthesized phenol ligand with two prolinol units (**64**), and applied it to the asymmetric alkynylation of unsaturated aldehydes.[79] They proposed a catalytic mechanism in which the dinuclear zinc complex of **64** coordinated by 2 equivalents of zinc alkynylide works to control the stereochemistry (Figure 9). γ-Amino phenol **65**, developed by Hirose et al. was also seen to achieve good selectivity for the enantioselective alkynylation of aromatic aldehydes using the phenylacetylene/Et_2Zn system.[80]

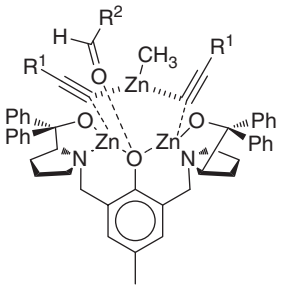
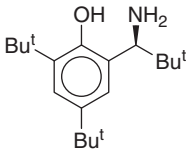


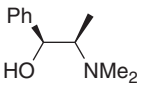
Figure 9 Proposed transition state of the alkynylation to aldehyde by the dinuclear zinc complex of **64**.[79] Reproduced with permission from Scheme 2 in Trost, B. M.; Weiss, A. H.; von Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*(1), 8–9.

Carreira et al. developed the terminal alkyne/zinc triflate [$Zn(OTf)_2$] system for preparation of alkynylzinc reagents.[75] This system is interesting because only a catalytic amount of zinc is necessary, and the resulting alkynylzinc triflate is easy to handle because it is more tolerant of oxygen and moisture than R_2Zn. Using *N*-methylephedrine **66** as a chiral ligand, they achieved highly enantioselective alkynylation of aromatic and aliphatic aldehydes by various terminal alkynes, including one containing a hydroxyl group.[75] Applying their method, Jiang et al. showed that β-amino alcohol **67** with a silyl ether group at the γ-position was highly effective for the alkynylation of aromatic and aliphatic aldehydes.[81]



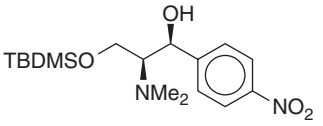
65[80,97]

p-BrC_6H_4CHO–
Ph—≡—ZnEt
yield 98%, 89% *ee R*[80]
p-BrC_6H_4CHO–
p-$ClC_6H_4B(OH)_2/Et_2Zn$
yield 92%, 99% *ee R*[97]



66[75]

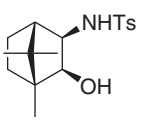
c-$C_6H_{11}CHO$–
PhC_2H_4—≡—ZnOTf
yield 98%, 99% *ee R*



67[81,147]

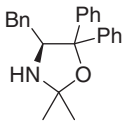
Me_2CHCHO–
PhC_2H_4—≡—ZnOTf
yield 99%, >99% *ee R*[81]
$PhCOCO_2Me$–
PhC_2H_4—≡—ZnOTf
yield 88%, 94% *ee* (+)[147]

Various chiral ligand–titanium(IV) systems have also been applied for the asymmetric alkynylation of aldehydes. Wang et al. showed that chiral hydroxyl sulfonamide **68** can allow highly enantioselective addition of phenylacetylene to aromatic and aliphatic aldehydes using Et_2Zn in the presence of $Ti(OPr^i)_4$.[82a] They found that simple oxazolidine ligand **69**, prepared from natural phenylalanine, also worked effectively toward aromatic aldehydes under similar conditions, but without the titanium(IV).[82b] In other work, Hui et al. also showed that C_2-symmetric tetradentate amido alcohols such as **70** could afford high enantioselectivity in alkynylation using the phenylacetylene/Et_2Zn system in the presence of $Ti(OPr^i)_4$.[83a] They also found that β-hydroxy amide **71** allowed highly enantioselective addition of propiolate to aliphatic aldehydes under similar conditions.[83b]



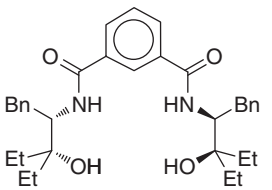
68[82a]

PhCHO–
Ph—≡—ZnEt
yield 93%, 97% *ee R*



69[82b]

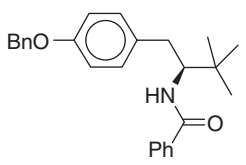
p-BrC_6H_4CHO–
Ph—≡—ZnEt
yield 74%, 91% *ee*



70[83a]

p-MeC_6H_4CHO–
Ph—≡—ZnEt
yield 94%, 98% *ee*

Uang et al. demonstrated that γ-amino thiol **57** worked as a chiral ligand for the addition of aromatic and aliphatic terminal alkynes to a variety of aldehydes with good enantioselectivity.[84] Hou et al. showed that chiral ferrocene derivatives with an oxazoline unit, such as **72**, were good ligands for the asymmetric addition of phenylacetylene to aromatic and aliphatic aldehydes.[85]

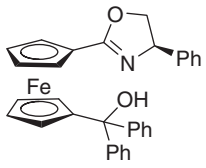


71[83b]

Me_2CHCH_2CHO–

MeO_2C—≡—ZnEt

yield 88%, 88% *ee*

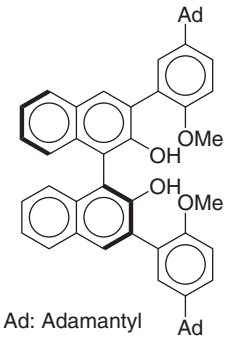


72[85]

1-Naphthyl CHO–

Ph—≡—ZnEt

yield 86%, 93% *ee* (–)



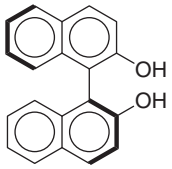
73[87]

o-ClC_6H_4CHO–

Ph—≡—ZnEt

yield 74%, 94% *ee*

A number of tetradentate chiral ligands have also been prepared. Liu and Wolf successfully achieved catalytic addition of various acetylenes to both aromatic and aliphatic aldehydes in high enantioselectivity using their N_2O_2-ligand **35**.[86] Pu et al. found that BINOL derivative **73** with bulky substituents at the 3- and 3′- positions worked very well for the enantioselective addition of phenylacetylene to aromatic aldehydes without $Ti(OPr^i)_4$,[87] while Yu et al. showed that BINOL **74**, in the presence of the titanium species, itself allowed highly enantioselective addition of linear aliphatic terminal alkynes to various aromatic aldehydes.[88]



74[88]

m-FC_6H_4CHO–

n-C_6H_{13}—≡—ZnEt

yield 92%, 94% *ee* (–)

1.07.2.1.5 Arylzinc

Although diphenylzinc (Ph_2Zn) is commercially available, functionalized arylzinc reagents must be prepared when required. Several methods have been reported for preparing such reagents, the first of which is the use of a diarylzinc (Ar_2Zn)/Et_2Zn mixture (Scheme 7). Here, the presence of Et_2Zn effectively decreases the nucleophilicity of Ar_2Zn.[89a] The second preparation method, and probably the most commonly used, is the transmetalation of arylboron compounds such as boronic acid,[89b] triarylborane,[89c] or boroxine[90] with R_2Zn (Scheme 8). Direct arylation of zinc halide (Scheme 9)[91] and reaction of aryl iodide (ArI) and R_2Zn in the presence of lithium acetylacetonate [Li(acac)] as a catalyst (Scheme 10)[92] have also been employed.

$$Ar_2Zn + Et_2Zn \longrightarrow 2\ ArZnEt$$

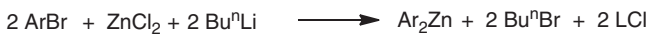
Scheme 7

$$ArBX_2 + R_2Zn \longrightarrow ArZnR + RBX_2$$

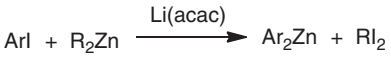
X: OH, Ar

X_2: $(OBAr)_2O$

Scheme 8



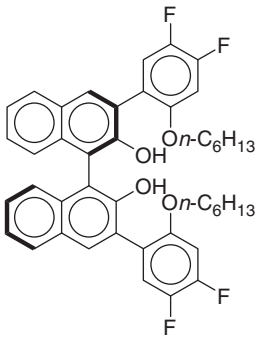
Scheme 9



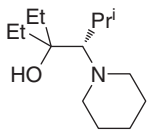
Scheme 10

Fu et al. first succeeded in affecting the catalytic asymmetric addition of Ph_2Zn to *p*-chlorobenzaldehyde using ferrocene-type amino alcohol **28**.[37] Later, Bolm et al. showed that chiral ferrocenyl oxazoline alcohol **25** was able to achieve highly enantioselective arylation of various aldehydes using the Ph_2Zn/Et_2Zn system.[89a] They also demonstrated that the same ligand worked efficiently for arylboronic acid $[ArB(OH)_2]$[89b] or triphenylborane (Ph_3B)[89c] combined with Et_2Zn for the enantioselective arylation of various aldehydes. In the latter system, they demonstrated that approximately two-thirds of the phenyl groups of Ph_3B could be used for phenylation.

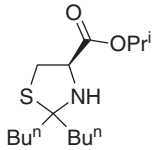
Huang and Pu found that zinc complexes of BINOL derivatives such as **75**, that contain electron-withdrawing fluorine atoms, could catalyze the highly enantioselective addition of Ph_2Zn to aromatic aldehydes, giving diarylmethanols.[93] They proposed a transition state similar to that described for **52**.[62] It is clear that chiral amino alcohols are efficient ligands for the enantioselective arylation of various aldehydes. Using the Ph_2Zn/Et_2Zn system, Pericàs et al. successfully achieved the enantioselective phenylation of aromatic and aliphatic aldehydes by using β-cyclic amino alcohols such as **11**.[20b] Braga et al. also developed various chiral ligands starting from natural amino acids,[94] and showed that not only β-amino alcohols such as **76**[94a] but also thiazolidine esters such as **77**[94b] worked for the enantioselective arylation of aromatic aldehydes using the $ArB(OH)_2/Et_2Zn$ system. In addition, Uang et al. showed that γ-amino thiol **57** was also very useful for the enantioselective arylation of various aromatic aldehydes using the same system.[95]



75[93]
p-ClC_6H_4CHO–Ph_2Zn
yield 92%, 95% *ee S*



76[94a]
p-MeC_6H_4CHO–
$PhB(OH)_2/Et_2Zn$
yield 97%, 97% *ee R*



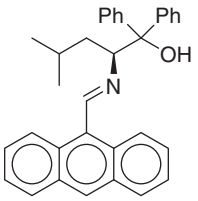
77[94b]
PhCHO–
p-$MeOC_6H_4B(OH)_2/Et_2Zn$
yield 90%, 80% *ee R*

Chan et al. demonstrated that γ-amino naphthol **56b**[96a] and β-amino alcohol **63**[96b] were effective for the highly enantioselective arylation of various aromatic aldehydes using the $ArB(OH)_2/Et_2Zn$ system. They demonstrated that ligand **63** was able to work for not only $ArB(OH)_2$ but also *n*-butylboronic and ferrocenylboronic acids, giving moderate *ee*.[96b] Hirose et al. found that γ-amino phenol **65** was also useful for the highly enantioselective arylation of aromatic aldehydes using the same arylzinc-supplying system.[97] Recently, Šebesta et al. demonstrated that various aryl groups could be enantioselectively added to ferrocenecarboxaldehyde using **25**, a ferrocene unit that bears a δ-amino alcohol.[98]

Several more research groups demonstrated the applicability of the $ArB(OH)_2/Et_2Zn$ system. It was shown that 3,3′-dicarboxamido BINOL **48** worked well for achieving highly enantioselective phenylation of aromatic and aliphatic aldehydes,[99] and that arylation of aromatic aldehydes could be carried out with chiral ferrocenyl aziridine alcohol **18**.[100] In other work, Wang et al. demonstrated that highly enantioselective addition of a thienyl group to various aromatic aldehydes could be achieved using the 2-thienylboronic acid/Et_2Zn combination with chiral imino alcohol **78** as a ligand.[101]

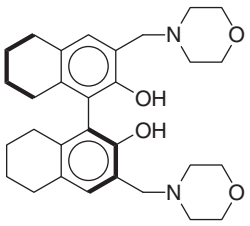
Zhao et al. used the arylboroxine $[(ArBO)_3]/Et_2Zn$ system as an aryl source for the enantioselective addition reactions of aromatic aldehydes using proline-derived β-amino alcohol **2**.[90] Kim and Walsh compared two different arylzinc reagents, Ar_2Zn and aryl-*n*-butylzinc, which were prepared by the direct arylation of zinc halide and by the reaction of arylzinc halide and Bu^nLi, respectively, and achieved highly enantioselective arylation of various aldehydes using both reagents with β-amino alcohol ligand **61**.[91] In another study, Pu et al. prepared Ar_2Zn from Et_2Zn and a functionalized ArI in the presence of Li(acac), and

succeeded in achieving the highly enantioselective arylation of aromatic and aliphatic aldehydes by using the morpholino BINOL analog **79**.[102]



78[101]

p-MeOC$_6$H$_4$CHO–
2-ThienylB(OH)$_2$/Et$_2$Zn
yield 81%, 96% *ee* (–)



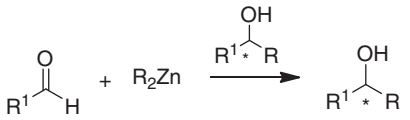
79[102]

c-C$_6$H$_{11}$CHO–
(*m*-MeOC$_6$H$_4$)$_2$Zn
yield 93%, > 99% *ee R*

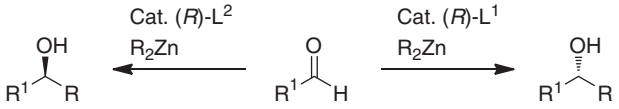
As seen thus far, many efficient chiral ligands are available for organozinc addition to aldehydes. For reasons of availability and flexibility, however, aminoisoborneol derivatives **1**,[2,64] **12**,[21] and **61**[73a,91] seem to be ligands of choice when attempting the synthesis of chiral secondary alcohols. Norephedrine and ephedrine derivatives such as **3**[12], **6**[12], and **66**[75] are also efficient ligands if the starting materials are easily obtainable.

1.07.2.1.6 Autocatalytic and chirality switching reactions

Autocatalytic alkylation and chirality switching, or dual stereoselectivity, are extremely interesting topics in the addition of R_2Zn to aldehydes. The former is a self-replicating system where the product itself plays the role of the chiral catalyst (Scheme 11).[103] It is not only a synthetically important system that can lead to chirality amplification but is also scientifically interesting when considering the origin of homochirality. The latter also provides product chirality control, but in this case by the structural change or modification of a chiral ligand while retaining its absolute configuration (Scheme 12). Although these topics are relatively new, a few studies were reported approximately two decades ago and have since been referred in a review by Kim.[104] Chirality switching expands the synthetic versatility of chiral compounds such as natural products that only have one enantiomer.



Scheme 11



Scheme 12

1.07.2.1.6.1 Autocatalytic reaction

Since the observation of the first autocatalytic system,[105a] Soai et al. have developed the methodology and achieved several new systems, with that employing pyrimidyl alkanol **80**[105b,c] affording the highest enantioselectivity. As they have already comprehensively reviewed their own work on autocatalysis,[103] the work of other research groups is focused on in this section.

Jiang et al. found that (*R*)-1-phenylpropanol was capable of effecting asymmetric autocatalysis, but with low levels of chemical activity and chiral induction. However, interestingly, addition of sterically bulky achiral amines, such as dicyclohexylamine, improved both the chemical reactivity and asymmetric autoinduction, quantitatively providing 51% *ee*.[106]

Ferrocene carbaldehydes have also been shown to be effective substrates for autocatalytic reactions.[107] Brocard et al. found that ferrocene-based δ-amino alcohol **81** worked as an autocatalytic ligand in the enantioselective addition of ethylmetal reagents, with especially high activity demonstrated for the addition of Et_2Zn to aldehydes.[107a] Fukuzawa et al. observed that a highly similar reaction occurred for Me_2Zn and Et_2Zn when using **82** with an additional stereocenter, and they proposed the mechanism shown in Figure 10.[107b]

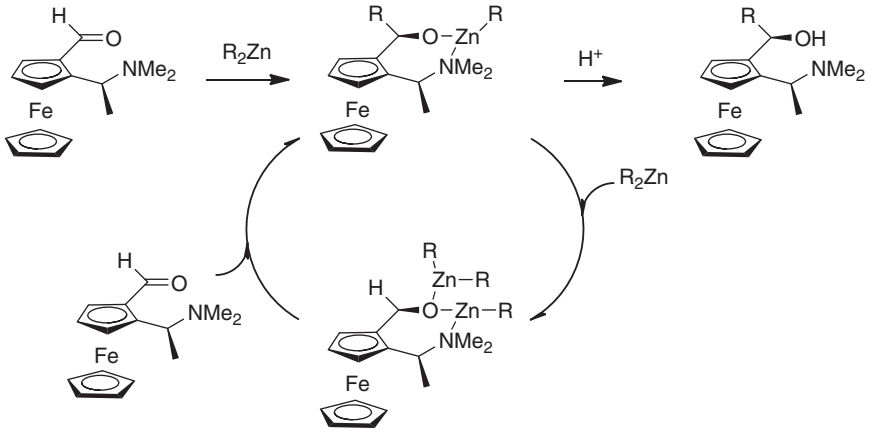
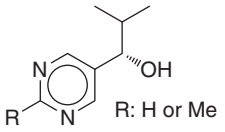
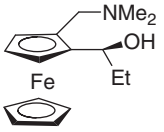


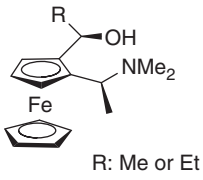
Figure 10 Autocatalytic mechanism of the enantioselective addition of dialkylzinc by **82**.[107b] Reproduced with permission from Scheme 3 in Fukuzawa, S.-i.; Tsuchiya, D.; Sasamoto, K.; Hirano, K.; Ohtaguchi, M. *Eur. J. Org. Chem.* **2000**, *2000*(16), 2877–2883.



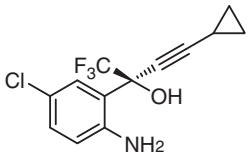
80[105c]
R = H
yield 87%, 94.7% *ee*
R = Me
yield 103%, 95.9% *ee*



81[107a]
yield 98%, >98% *de*



82[107b]
R = Me
yield 80%, >99% *de*
R = Et
yield 96%, >99% *de*

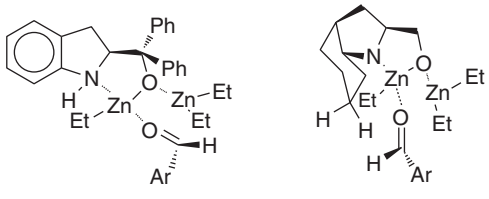


83[108a]
yield 79%, 99.6% *ee*

Recently, an advanced system was reported for application to ketones by Carreira et al.[108a] They developed the stoichiometric enantioselective synthesis of tertiary alcohol **83**, which is a key intermediate in the synthesis of the drug efavirenz,[108b,c] by using a system of cyclopropylacetylene, *n*-hexyllithium, and Et_2Zn, in the presence of small amount of **83** and (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)propanol, which is the enantiomer of **6**. They found that the system was effective on a 250 mmol scale in 99.5% *ee* but nonenantioselective in the absence of the second chiral catalyst. Considering the difference in the effect of the external catalyst to the *N*-pivaloyl system of **83** and the corresponding ketone, further investigation is necessary to elucidate the apparently complex mechanistic feature of this particular autocatalytic system.

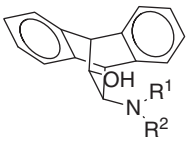
1.07.2.1.6.2 Chirality switching reaction

Kunieda et al. found that *β*-amino alcohol ligands **84a** and **84b** afforded the opposite enantiomers in the addition of Et_2Zn to benzaldehyde and heptanal in high enantioselectivity.[109] Although the authors did not discuss the mechanism in detail, the electronic effect of the substituents on the nitrogen atom of the ligands was speculated to contribute significantly to these results. Kim et al. reported that *β*-amino alcohols **85** and **86**,which have hydroxymethyl groups with the same chirality, selectively gave (*R*)- and (*S*)-1-phenylpropanols, respectively.[110] From the transition state models shown in **Figure 11**, the phenyl groups in **85** and the cyclohexyl group in **86** were deduced to contribute to the chirality of the products.

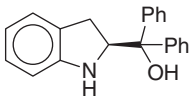


85 **86**

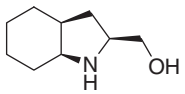
Figure 11 Comparison of the transition states of **85** and **86** for diethylzinc addition.[110] Reproduced with permission from Figure 1 in Kim, Y. M.; Park, D. H.; Byun, I. S. *Heteroatom Chem.* **2004**, *3*(1), 51–54.



84[109]
PhCHO–Et_2Zn
84a: $R^1 = R^2$ = Me
yield 91%, 96% *ee S*
84b: $R^1 = SO_2CF_3$, R^2= H
yield 80%, 98% *ee R*

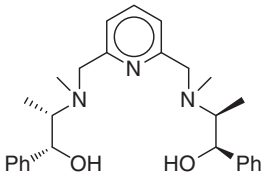


85[110]
p-ClC_6H_4CHO–Et_2Zn
yield 93%, 97% *ee S*

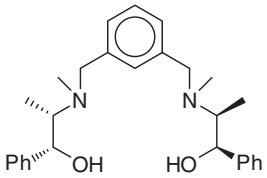


86[110]
p-ClC_6H_4CHO–Et_2Zn
yield 92%, 92% *ee R*

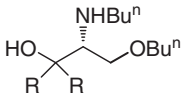
In another study, Williams and Fromhold found that C_2-symmetric N_2,O_2-ligands **87** and **88** provided the opposite enantioselectivity in the addition of R_2Zn to aromatic aldehydes.[111] Sibi et al. reported that N,O_2-tridentate β-amino alcohols **89a** and **90**, with the same chirality, afforded (*S*)- and (*R*)-1-phenylpropanols in the presence of Bu^nLi, respectively.[112] In addition to the steric factors present at the stereocenter, that is, the substituent(s) on the nitrogen atom and butoxymethyl group, the chiral control was attributed to the weak interaction and/or steric difference between the aromatic and aliphatic substituents (**Figure 12**).[112] However, the mechanism for this particular reaction is not completely clear because of the opposite selectivity between **89a** and **89b**.



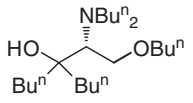
87[111]
PhCHO–Et_2Zn
yield 82%, 90% *ee S*



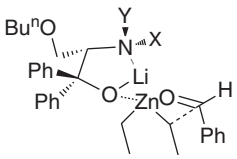
88[111]
PhCHO–Et_2Zn
yield 72%, 76% *ee R*



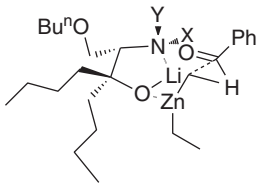
89[112]
PhCHO–Et_2Zn
89a: R = Ph
yield 95%, 83% *ee S*
89b: R = Bu^n
yield 88%, 26% *ee R*



90[112]
PhCHO–Et_2Zn
yield 92%, 79% *ee R*



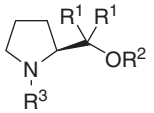
89a



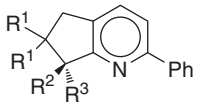
90

Figure 12 Proposed transition states of the diethylzinc addition to benzaldehyde in the presence of **89a** and **90**.[112] Reproduced with permission from Sibi, M. P.; Chen, J.-X.; Cook, G. R. *Tetrahedron Lett.* **1999**, *40*(17), 3301–3304.

Wang et al. reported similar results using cyclic amino alcohols, proline-based β-*N*,*O*-bidentate ligands, where they found that **91a** afforded the (*S*)-enantiomer, while **91b** and **91c** gave the (*R*)-enantiomer.[113] It was suggested that the bulkiness of the dialkyl methanol moiety controlled the product stereochemistry in combination with a bulky substituent on the nitrogen atom. In other work, Kang et al. found that pyridyl alcohol ligands **92a** and **92b**, with the opposite chirality, afforded the same product for the addition of Et_2Zn to benzaldehydes.[114] The substituent effect of the two geminal ethyl groups is apparent.



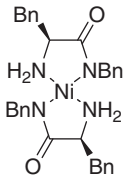
91[113]
PhCHO–Et_2Zn
91a: R^1 = Ph, R^2 = Me, R^3 = Bn
yield 94.6%, 85.3% *ee S*
91b: R^1 = Me, R^2 = H, R^3 = Bn
yield 97.7%, 99.2% *ee R*
91c: R^1 = Ph, R^2 = Me, R^3 = H
yield 95.9%, 93.7% *ee R*



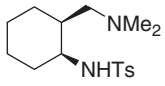
92[114]
PhCHO–Et_2Zn
92a: R^1 = H, R^2 = OH, R^3 = H
yield 82%, 90% *ee R*
92b: R^1 = Et, R^2 = H, R^3 = OH
yield 80%, 87% *ee R*

Burguete et al. reported interesting results showing that the monomeric nickel complex **93** and dimeric nickel complex **94** of α-amino amide produced the opposite enantiomers of 1-arylpropanol.[115] Although the structures of the active catalysts seem to be very different, it is interesting that the same ligands afford both enantiomers of a target molecule. Recently, Hirose et al. reported that (*R*)- and (*S*)-*sec*-alcohols were produced by enantioselective addition of Et_2Zn to a variety of aldehydes using the regioisomers of γ-amino sulfonamides **95** and **96**, which have the same chirality.[116]

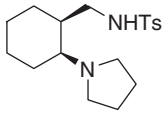
93[115]
PhCHO–Et_2Zn
yield 97%, 97% *ee S*



94[115]
PhCHO–Et_2Zn
yield 96%, 96% *ee R*

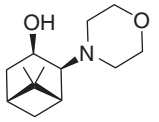


95[116]
PhCHO–Et_2Zn
yield 91%, 83% *ee S*

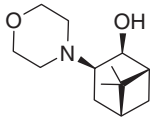


96[116]
PhCHO–Et_2Zn
yield >99%, 91% *ee R*

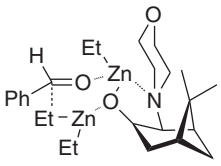
Singaram et al. prepared the regioisomeric amino alcohol ligands **97** and **98** and applied them to the addition of Et_2Zn and Me_2Zn to aromatic and aliphatic aldehydes to obtain opposite enantiomers in very high selectivity.[117] They appeared to work almost as enantiomers in the stereocontrol (**Figure 13**). Considering that they are prepared from the same starting material, β-pinene, the opposite enantioselectivity is synthetically extremely useful.



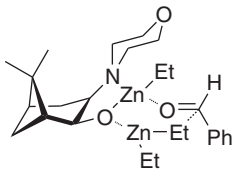
97[117]
PhCHO–Et_2Zn
yield 100%, 99% *ee R*



98[117]
PhCHO–Et_2Zn
yield 100%, 99% *ee S*



97



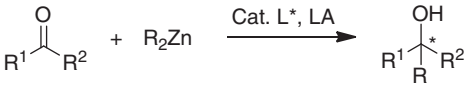
98

Figure 13 Proposed transition states in the reaction of diethylzinc and benzaldehyde in the presence of **97** and **98**.[117] Reproduced with permission from Figure 6 in Binder, C. M.; Bautista, A.; Zaidlewicz, M.; *et al. J. Org. Chem.* **2009**, *74*(6), 2337–2343.

1.07.2.2 To Ketones

1.07.2.2.1 Introduction

The enantioselective reaction of R_2Zn with ketones is more challenging than that with aldehydes owing to their lower reactivity and the extra steric crowding at the carbonyl group. This problem was first solved by the activation of ketones with $Ti(OPr^i)_4$,[118] which is a stronger Lewis acid than zinc derivatives, and then by the development of well-designed active chiral ligands (**Scheme 13**). However, the nucleophilicity of Ph_2Zn is higher than R_2Zn, and the reaction is able to take place without activation of the ketone carbonyl group, providing an adequate ligand is utilized.[119] Compared to aldehydes, however, this area of chemical synthesis still possesses a number of challenges that need to be overcome, including improved reaction conditions, higher efficiency, and the scope of the ketones and organozinc reagents that can be successfully employed.

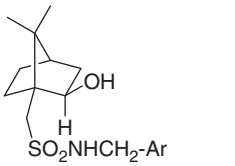


L*: Chiral ligand
LA: Lewis acid

Scheme 13

1.07.2.2.2 Dialkylzinc

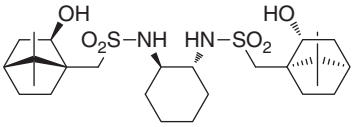
Using chiral hydroxy sulfonamides such as **99**, Ramón and Yus achieved the first enantioselective addition of Et_2Zn and Me_2Zn to ketones in the presence of $Ti(OPr^i)_4$.[118a] They subsequently applied bis(hydroxy sulfonamide) ligands such as **100** for the same reactions.[118b] Walsh et al. also used **100** to achieve higher enantioselectivity in the addition of not only Et_2Zn and Me_2Zn[120a,b] but also various functionalized alkylzinc reagents,[120b] to aromatic ketones and α,β-unsaturated ketones using $Ti(OPr^i)_4$. Ishihara later succeeded in achieving the highly enantioselective ethylation of various aromatic ketones by using chiral amino phosphoramide **101**, without the additional Lewis acid.[121] The zinc complex of the ligand was speculated to work as the Lewis acid–Lewis base catalyst by coordination of the phosphoramide oxygen to Et_2Zn (**Figure 14**).



Ar: 1-Naphthyl

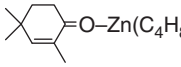
99[118a]

$PhCOBu^n$–Me_2Zn
yield 95%, 83% *ee R*

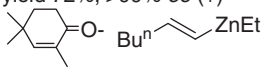


100[118b,120,122a,128,129,138a]

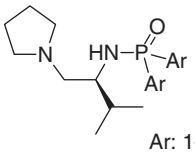
$PhCOC_2H_5$–Me_2Zn
yield >95%, 97.5% *ee R*[118b]
m-$MeC_6H_4COCH_3$–Et_2Zn
yield 82%, 99% *ee* (–)[120a]



yield 72%, >99% *ee* (+)[120b]



yield 94%, 97% *ee* (–)[122a]
2-Naphthyl$COCH_3$–Ph_2Zn
yield 99%, 96% *ee* (+)[128]
p-$BrC_6H_4COCH_3$–Ph_2Zn
yield 98%, 96% *ee* (+)[129]



Ar: 1-Naphthyl

101[121]

m-$ClC_6H_4COCH_3$–Et_2Zn
yield 82%, 99% *ee S*
2-Naphthyl $COCH_3$–PhZnEt
yield 97%, 97% *ee S*

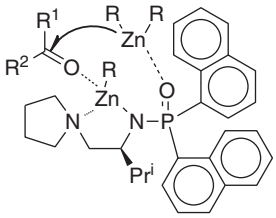
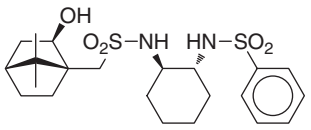


Figure 14 Proposed mechanism of the alkylation of ketone by R_2Zn using a chiral ligand **101**.[121] Reproduced with permission from Scheme 1 in Hatano, M.; Miyamoto, T.; Ishihara, K. *Org. Lett.* **2007**, *9*(22), 4535–4538.

1.07.2.2.3 Vinylzinc and alkynylzinc

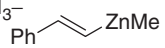
There is also a limited number of systems reported for the catalytic asymmetric addition of vinylzinc and alkynylzinc reagents to ketones. Three types of chiral ligands, hydroxy sulfonamide, amino alcohol-type, and salen-type ligands, have been used, with the alkynylzinc reagents being prepared *in situ* from terminal alkynes and R_2Zn.

Walsh et al. successfully achieved the enantioselective addition of various vinylzincs to aromatic, aliphatic, and α,β-unsaturated ketones by using **100** in the presence of $Ti(OPr^i)_4$.[122a] In this case, the vinylzinc reagents were prepared by Oppolzer's method.[64] Recently, they also achieved the highly diastereoselective addition of vinylzinc reagents to chiral α-silyloxy ketones through chelation control.[122b] In other work, Ramón et al. developed new chiral disulfonamide ligands such as **102**, and demonstrated that they work not only for alkylation but also for vinylation and alkynylation of aromatic ketones in the presence of $Ti(OPr^i)_4$.[123] The vinylzinc and alkenylzinc reagents were prepared from the reaction of Et_2Zn with the corresponding alkenylzirconium reagent[65] and phenylacetylene. Chan et al. revealed that hydroxy sulfonamide **103** (the enantiomer of **99**) was a highly effective chiral ligand for the enantioselective addition of phenylacetylene to aromatic ketones, using Me_2Zn in the presence of copper(II) triflate.[124]



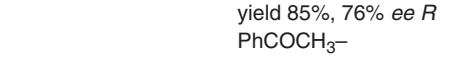
102[123]

PhCOCH$_3$–



yield 85%, 76% *ee R*

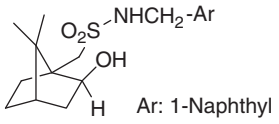
PhCOCH$_3$–



yield 77%, 20% *ee R*

p-BrC$_6$H$_4$OCH$_3$–PhZnEt

yield 90%, >99% *ee S*

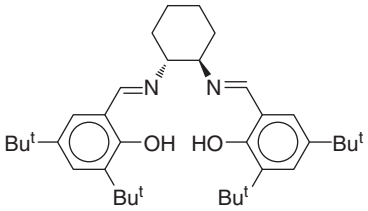


103[124]

o-ClC$_6$H$_4$COMe–

yield 94%, 97% *ee* (–)

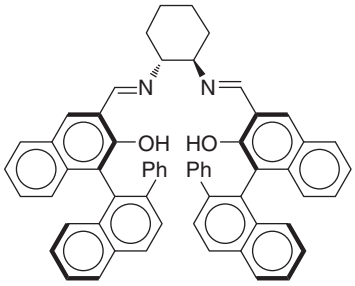
Cozzi showed that chiral salen derivative **104** worked well for the direct addition of some terminal alkynes to various methyl ketones, in the absence of other metal ions.[125] It was suggested that the *in situ* formation of the alkynylzinc reagent resulted from Me_2Zn coordination by two oxygen atoms, with the ketones activated at the apical position of the zinc complex of the ligand (Figure 15).[125] Saito and Katsuki applied salen-type bis(imino binaphthol) **105** to the asymmetric alkynylation of aliphatic ketones using various terminal alkynes in combination with Me_2Zn.[126]



104[125]

Bu^{t}COMe–

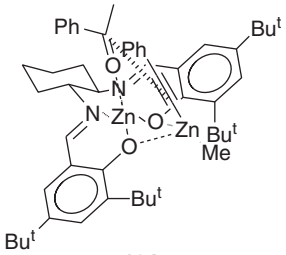
yield 89%, 80% *ee* (–)



105[126]

Bu^{t}COMe–

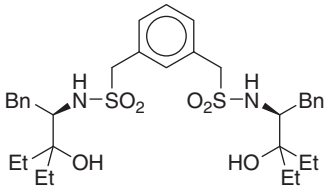
yield 75%, 91% *ee* (+)



104

Figure 15 Proposed transition state of the alkynylation to a acetophenone in the presence of **104**.[125] Reproduced with permission from Cozzi, P. G. *Angew. Chem. Int. Ed.* **2003**, *42*(25), 2895–2898.

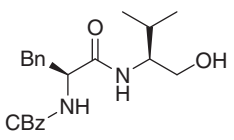
Wang et al. used bis(hydroxy sulfonamide) **106** for the asymmetric alkynylation of methyl ketones as well as various aldehydes, using the phenylacetylene/Et_2Zn system together with Ti(OPr^i)$_4$.[127a] They also showed that hydroxy amino amides, N_2,*O*-ligands such as **107**, worked for the enantioselective addition of phenylacetylene to aromatic ketones using the same system.[127b]



106[127a]

m-BrC$_6$H$_4$COMe–

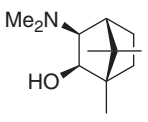
yield 74%, 77% *ee*



107[127b]

o-BrC$_6$H$_4$COMe–

yield 85%, 86% *ee*



108[119]

m-BrC$_6$H$_4$COEt–Ph$_2$Zn

yield 91%, 91% *ee* (–)

1.07.2.2.4 Arylzinc

Dosa and Fu first discovered that Ph_2Zn reacts enantioselectively with various methyl ketones and ethyl ketones in the presence of a catalytic amount of (+)-DAIB **108** (the enantiomer of **1**) and methanol (1.5 equivalents), which was speculated to work by reducing the reactivity of Ph_2Zn.[119]

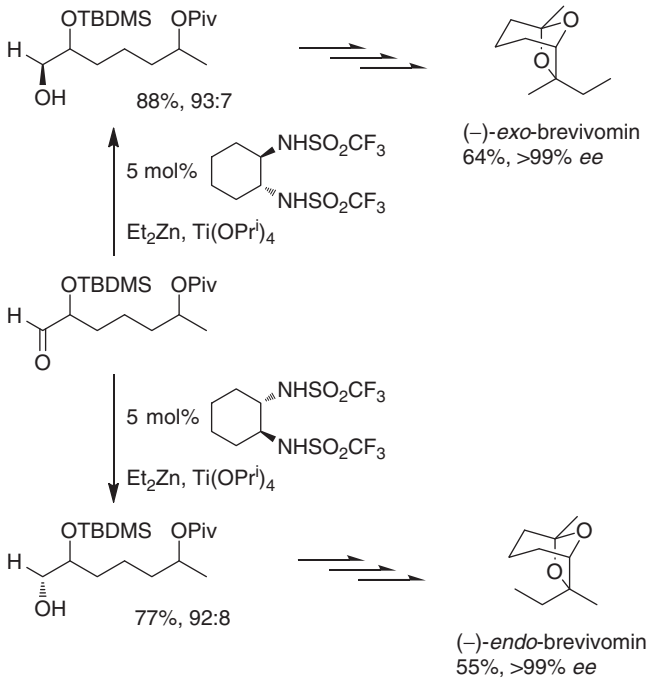
Some amide ligands have also been shown to work for the addition of arylzinc to ketones. Walsh et al. demonstrated that **100** effected the catalytic asymmetric addition of Ph_2Zn to ketones in the presence of $Ti(OPr^i)_4$.[128] Yus et al. also succeeded in the enantioselective arylation of aryl methyl ketones and aryl ethyl ketones by using **100** with Ph_2Zn and the $ArB(OH)_2/Et_2Zn$ system.[129] They subsequently applied **102** for the highly enantioselective arylation of aryl methyl ketone using the BPh_3/Et_2Zn system as an aryl source and $Ti(OPr^i)_4$ as a Lewis acid center.[123] Amino phosphoramide **101**, reported by Ishihara et al., also effectively worked for the enantioselective phenylation of ketones using the Ph_2Zn/Et_2Zn system in the absence of additives.[121]

For the enantioselective addition to alkyl aryl ketones, **99**[118a] (**103**[124]), **100**,[118b,120,122a,128,129] and **108**[119] (**1**) seem to be efficient and useful ligands. The high utility of **100** and **108** (**1**), along with **61** (**12**), is discussed further in the next section.

1.07.2.3 Applications

The enantioselective addition of organozinc reagents to the C═O bond is an extensively studied method for achieving the synthesis of chiral secondary and tertiary alcohols. This is because they are milder and more selective than the corresponding organolithium and Grignard reagents. When the products or intermediates can be further transformed into other structures, the synthetic utility of the reactions is greatly expanded. This is termed as a domino reaction. Here, the authors highlight several applications of organozinc addition to C═O bonds.

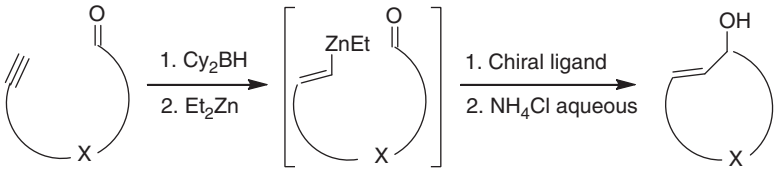
Knochel et al. are the pioneers in this field, having prepared many different polyfunctional chiral alcohol derivatives such as diols,[130] allyl alcohols,[10b,46b,48] propargyl alcohols,[131] amino alcohols,[132] and other related compounds from the addition products with silyl, stannyl, and halogen groups. They took advantage of their developed methodology to synthesize the natural products, ginnol[11b] and (–)-*exo*- and (–)-*endo*-brevicomins[133] (**Scheme 14**), and a structurally interesting C_3 symmetrical triol[134] in high optical purity.



Scheme 14

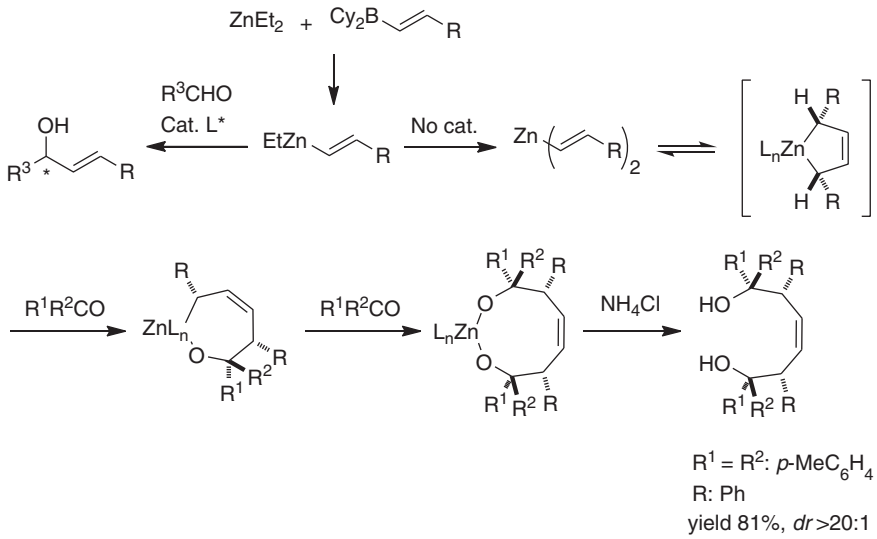
Oppolzer et al. applied their vinylzinc preparation method to the construction of chiral macrocyclic (*E*)-allylic alcohols.[135] Starting from ω-alkynals, terminal vinylzinc reagents were prepared and reacted with the formyl group in the presence of **1** (**Scheme 15**). The reaction was able to be carried out in one pot to form 13- to 21-membered rings in only low to moderate chemical yield, but in high *ee*.

Walsh et al. extensively studied the applications of both the products and intermediates of the enantioselective addition of alkenylzinc reagents to C═O bonds. They successfully introduced additional functional groups and stereocenters and further expanded the versatility of organozinc reagents in synthetic organic chemistry. In addition, they achieved the diastereoselective



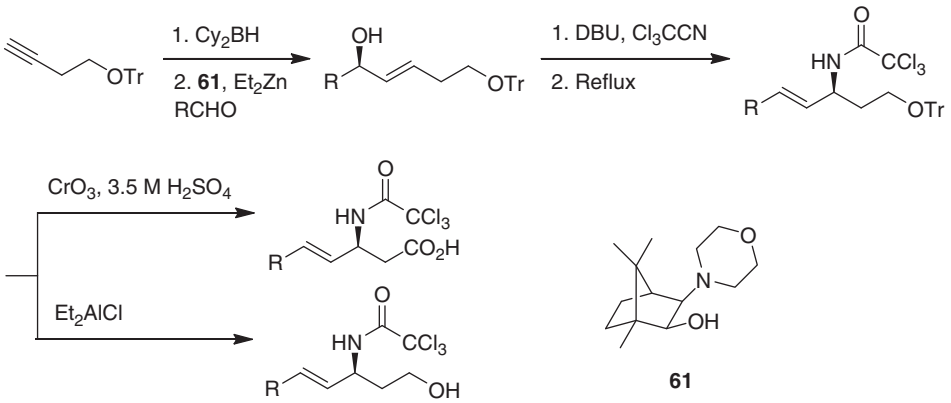
Scheme 15

formation of *cis*-3-hexene-1,6-diols in the absence of a ligand.[136] It was proposed that a metallacyclopentene formed from ethylvinylzinc as the reactive organozinc intermediate, followed by reaction with 2 equivalents of ketone or aldehyde (Scheme 16).

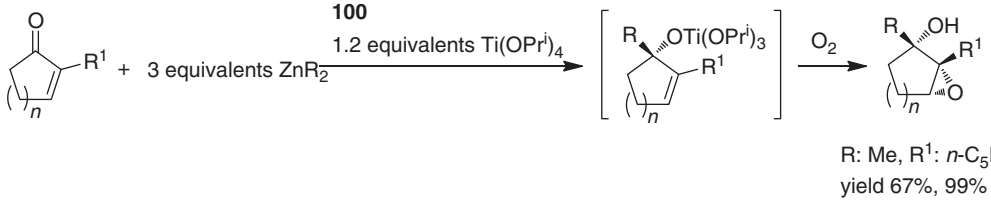


Scheme 16

They also utilized allyl alcohols or their zinc alkoxides for further functionalization of the C=C bond.[137,138] After the enantioselective addition of vinylzinc to aldehydes in the presence of **61**, the products were converted into γ-unsaturated β-amino acid derivatives and their corresponding 1,3-amino alcohols by applying Overman's [3,3]-sigmatropic trichloroacetimidate rearrangement (Scheme 17).[137] They also demonstrated that the chiral allyl alcohols prepared from cyclic α,β-unsaturated ketones using **100** can be diastereoselectively epoxidized by molecular oxygen (Scheme 18).[138a] It was shown that the resulting epoxy alcohols rearranged to β-hydroxy-α,α-disubstituted ketones as single diastereomers. The same alkylation/epoxidation reactions were extended to acyclic α,β-unsaturated aldehydes using **61**.[138b] At the same time, they reported an alternative route to epoxy alcohols that proceeded via vinylation/epoxidation of simple aldehydes.[138b]

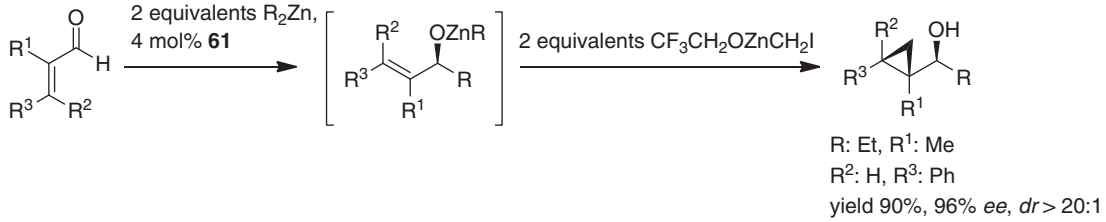


Scheme 17

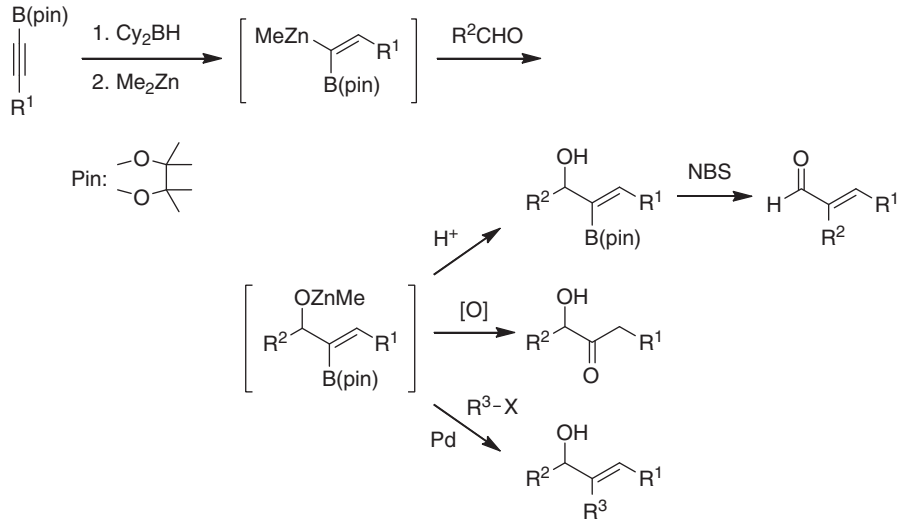


Scheme 18

In other work, Katsuki et al. and Walsh et al.[139] showed that treatment of chiral allyl alcohols with iodomethylzinc resulted in highly diastereoselective cyclopropanation in the presence of chiral ligands. Scheme 19 shows an example of the tandem enantioselective alkylation/cyclopropanation of α,β-unsaturated aldehydes.[139] In addition, the authors developed a preparation method and one-pot reaction involving 1-alkenyl-1,1-boron/zinc bimetallic reagents to afford (*E*)-trisubstituted α,β-unsaturated aldehydes, α-hydroxy ketones, and trisubstituted allyl alcohols (Scheme 20).[140] These extremely interesting organometallic reagents were generated by hydroboration of 1-alkynyl-1-boronate esters with dicyclohexylborane and *in situ* transmetalation with dialkylzinc reagents to furnish 1-alkenyl-1,1-heterobimetallic intermediates.



Scheme 19



Scheme 20

1.07.2.4 To α-Ketoesters

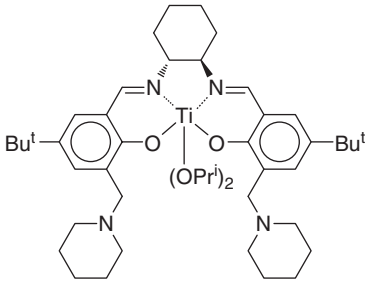
1.07.2.4.1 Introduction

The ketone carbonyl group of α-ketoesters is more electrophilic than simple ketones because of the electron-withdrawing property of the ester group. For this reason, the main challenge associated with the alkylation of α-ketoesters is the prevention of side reactions such as noncatalytic reactions and reduction. As a result, the combination of the zinc reagent and chiral ligand becomes more important, with limited successful examples having been reported.

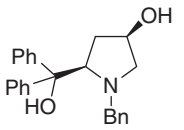
1.07.2.4.2 Dialkylzinc

DiMauro and Kozlowski first found that the titanium(IV) complex of piperidino salen ligand **109** worked in the enantioselective addition of Et$_2$Zn to various α-ketoesters in the presence of Ti(OPr^i)$_4$.[141] The titanium complex was speculated to activate the

ketone carbonyl group at the apical site, with Et_2Zn being activated by the piperidine nitrogen atom, similar to the mechanism suggested for the zinc(II) complex of **36** (Figure 4).[44]



109[141,165]
$PhCOCO_2Me$–Et_2Zn
yield 99%, 78% *ee R*[141]
p-$MeOC_6H_4N{=}CHCO_2Et$-Et_2Zn
yield 63%, 80% *ee S*[165]



110[142]
$PhCOCO_2Me$–Me_2Zn
yield 95%, 92% *ee R*

As mentioned above, the specific combination of substrate, alkylzinc reagent, ligand, and additive is a key factor in the outcome of the reaction. Shibasaki et al. studied various chiral ligands and showed that dihydroxy proline ligand **110** worked for the highly enantioselective methylation of aromatic and heteroaromatic α-ketoesters using Me_2Zn with isopropyl alcohol (Pr^iOH) as a Lewis base.[142] Hoveyda et al. developed **111**, an imino phenol ligand bearing a dipeptide moiety, for highly enantioselective ethylation and methylation of various α-ketoesters using the combination of aluminum isopropoxide as a Lewis acid and diethylphosphoramidate as a Lewis base.[143] The additive was suggested to bind to the aluminum catalytic center and activate the dialkylzinc reagent (Figure 16). Uang et al. used γ-amino thiol **57** as a chiral ligand for the addition of Me_2Zn to α-ketoesters, and observed an enhancement in both yield and enantioselectivity by the addition of triethyl borate.[144]

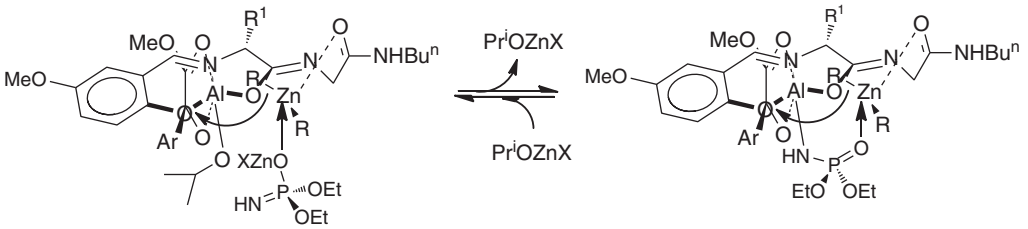
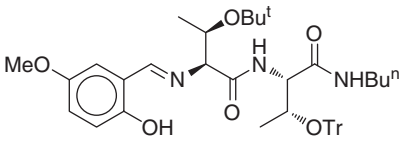
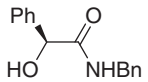


Figure 16 Proposed transition state for the addition of dialkylzinc to a ketoester catalyzed by the Al complexes of **111**.[143] Reproduced with permission from Scheme 1 in Wieland, L. C.; Deng, H.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*(44), 15453–15456.

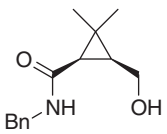
Pedro et al. applied mandelamide **112** as a chiral ligand and succeeded in effecting enantioselective methylation of various aromatic α-ketoesters using Me_2Zn in the absence of other additives.[145] It is interesting that Me_2Zn is activated not only by the ligand but also by the ester group of the substrate coordinated to the zinc complex (Figure 17). Wang et al. developed *cis*-cyclopropane-based hydroxy amide ligand **113** and achieved the enantioselective addition of Me_2Zn to aromatic α-ketoesters.[146]



111[143]
$PhCOCO_2Me$–Me_2Zn
yield >98%, 95% *ee R*



112[145]
p-$MeOC_6H_4COCO_2Et$–Me_2Zn
yield 82%, 90% *ee S*



113[146]
$PhCOCO_2Bu^t$–Me_2Zn
yield 85%, 81% *ee R*

1.07.2.4.3 Alkynylzinc

Jiang et al. demonstrated that **67** was highly effective for the enantioselective addition of prepared alkynylzinc reagents to various α-ketoesters,[147] as well as to aldehydes.[81]

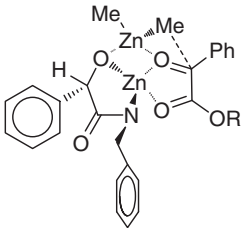
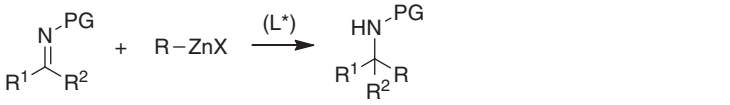


Figure 17 Proposed transition state for the addition of dimethylzinc to ethyl benzoylformate in the presence of **112**.[145] Reproduced with permission from Figure 2 in Blay, G.; Fernández, I.; Marco-Aleixandre, A.; Pedro, J. R. *Org. Lett.* **2006**, *8*(7), 1287–1290.

1.07.2.5 To C–N π-Bonds

1.07.2.5.1 Introduction

In comparison with the addition of organozinc reagents to carbonyl compounds, the direct reaction with simple imine C═N bonds is more challenging because of their lower electrophilicity. To overcome this problem, suitable activation and/or protection of the imino group as a phosphinoylimine, sulfonylimine, acylimine, or *o*-anisidinylimine (Scheme 21), or as a nitrone (Scheme 22), has been employed. Two decades ago, Katritzky and Harris[148] and Soai et al.[149a] first successfully achieved enantioselective addition to the C═N bond. As this area is still in its developmental stages, in this chapter both stoichiometric and catalytic reactions are summarized without regard to enantioselectivity.

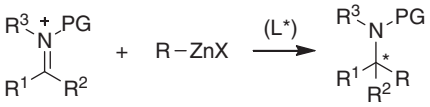


PG: Protecting group

PG: $P(O)R^3{}_2$, SO_2R^3, SOR^3, *o*-$MeOC_6H_4$, COR^3, R^3

R: alkyl, alkynyl, aryl

Scheme 21



PG: Protecting group

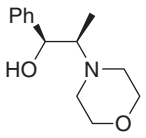
PG: O^-

R: vinyl, alkynyl, aryl

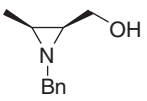
Scheme 22

1.07.2.5.2 Dialkylzinc

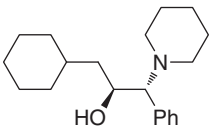
Soai et al. successfully achieved highly enantioselective alkylation of the C═N bonds of *N*-diphenylphosphinoylimines with R_2Zn promoted by β-amino alcohol ligands such as **114**, and converted the products into chiral amines.[149a] They also showed that the *N*-diphenylphosphinoylimine of ferrocenecarbaldehyde could be alkylated by Et_2Zn, Me_2Zn, and Bu^n_2Zn.[149b] *N*-Diphenylphosphinoylimines are some of the most frequently used substrates for the addition of a variety of organozinc reagents to the C═N bond, and a number of different chiral ligands have been developed for this transformation. Andersson et al. achieved the enantioselective addition of Et_2Zn and Me_2Zn to *N*-phosphinoylimines using aziridino alcohols such as **115** as ligands.[150] Pericàs demonstrated that the dual-catalyst system of β-amino alcohol/halosilane, for example, **116**/triisopropylsilyl chloride, also effectively improved the enantioselectivity of the addition of Et_2Zn.[151] The silylating agent was speculated to increase the substrate reactivity by silylation at the phosphinoyl oxygen. In other work, Beresford examined four cinchona alkaloids, which are also β-amino alcohols, as chiral ligands for the enantioselective addition of Et_2Zn to *N*-phosphinoyl benzaldimine, and showed that cinchonidine **117** gave the best results.[152] Gong et al.[153] and Wu et al.[154] found that chiral hydroxy oxazolines, β-imino alcohols **118** and **119**, respectively, allowed highly enantioselective Et_2Zn addition to various *N*-phosphinoyl arylimines, with a potential transition state for the reaction of **118** shown in Figure 18.[153]



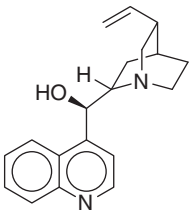
114[149a]
PhCH=NP(O)Ph_2–Et_2Zn
yield 89%, 90% *ee S*



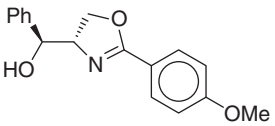
115[150]
PhCH=NP(O)Ph_2–Et_2Zn
yield 76%, 87% *ee R*



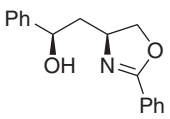
116[151]
p-MeC_6H_4CH=NP(O)Ph_2–
Et_2Zn/Pr^i_3SiCl
yield 63%, 92% *ee R*



117[152]
PhCH=NP(O)Ph_2–Et_2Zn
yield 76%, 93% *ee R*



118[153]
PhCH=NP(O)Ph_2–Et_2Zn
yield 72%, 93% *ee S*
p-BrC_6H_4CH=NP(O)Ph_2–Et_2Zn
yield 75%, 95% *ee*



119[154]
PhCH=NP(O)Ph_2–Et_2Zn
yield 80%, 91% *ee S*
p-BrC_6H_4CH=NP(O)Ph_2–Et_2Zn
yield 85%, 94% *ee*

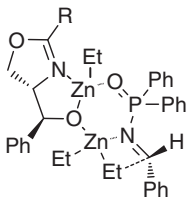
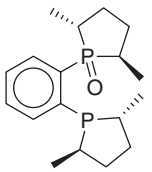
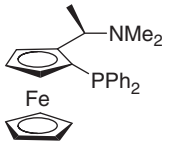


Figure 18 Proposed transition state for the addition of diethylzinc to *N*-diphenylphosphinoylimine in the presence of **118**.[153] Reproduced with permission from Figure 2 in Zhang, X. M.; Zhang, H. L.; Lin, W. Q.; *et al. J. Org. Chem.* **2003**, *68*(11), 4322–4329.

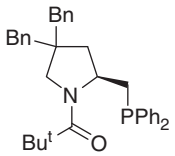
To enhance reaction efficiency, the use of other metal complexes of chiral ligands or metal salts became popular. Charette et al. reported that methyl-DuPHOS[155a] and its monoxide **120**[155b] were effective chiral ligands for the enantioselective addition of R_2Zn to *N*-phosphinoyl aromatic and aliphatic imines in a copper(II)-catalyzed system. Wang et al. applied the copper(II) and copper(I) salts of ferrocenyl γ-amino phosphine ligands such as **121** to the enantioselective addition of Et_2Zn to *N*-phosphinoylimines derived from various aromatic aldehydes.[156] Tomioka et al. demonstrated that *N*-sulfonyl arylimines can be substrates in the highly enantioselective addition of Et_2Zn in the presence of the copper(II) complex of β-amide phosphine **122**.[157] In another study, Wang and Shi showed that the copper(I) salts of binaphthyl-based amino thiophosphoramides such as **123**[158] achieved the enantioselective addition of Et_2Zn to *N*-tosylimines from various aromatic aldehydes. Gong et al. showed that the copper(II) complexes of tridentate pyridino dioxazoline ligands such as **124** allowed the enantioselective addition of Et_2Zn to *N*-sulfonylimines.[159] In another study, Hoveyda et al. developed a zirconium(IV)-catalyzed system for the enantioselective addition of R_2Zn to various arylimines of *o*-anisidine using dipeptide-based Schiff base ligands such as **125** in the presence of Pr^iOH.[160a] They extended this system and reported that the hafnium(IV) salt is effective for the alkylation of aliphatic imines.[160b] Hayashi et al. developed an interesting system in which a rhodium(I) complex coordinated to chiral diene **126** efficiently catalyzed the asymmetric addition of Me_2Zn to *N*-tosyl arylimines.[161]



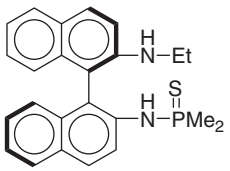
120[155b]
PhCH=NP(O)Ph_2–
$Et_2Zn/Cu(OTf)_2$
yield 96%, 98% *ee S*



121[156]
o-$MeOC_6H_4$CH=NP(O)Ph_2–
$Et_2Zn/Cu(OTf)_2$
yield 95%, 97% *ee R*

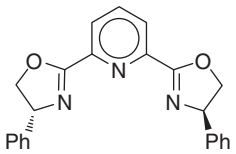


122[157]
p-ClC_6H_4CH=NSO_2Me–Et_2Zn
yield 95%, 94% *ee S*



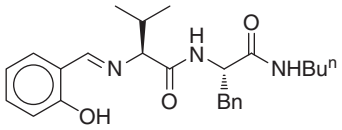
123[158]

p-$CF_3C_6H_4CH$=NTs–
$Et_2Zn/Cu(MeCN)_4BF_4$
yield >98%, 94% *ee S*



124[159]

1-NaphthylCH=NTs–
$Et_2Zn/Cu(OTf)_2$
yield 51%, 82% *ee S*

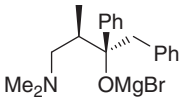


125[160b]

PhCH=N(*o*-$MeOC_6H_4$)–
$Et_2Zn/Zr(OPr^i)_4{\cdot}Pr^iOH$
yield >98%, 94% *ee S*

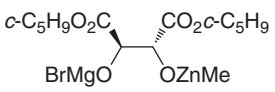
126[161]

p-FC_6H_4CH=NTs–
$Me_2Zn/[RhCl(C_2H_4)_2]_2$
yield 84%, 98% *ee S*

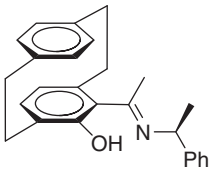


127[162b]

In other work, Ukaji et al. developed the enantioselective alkylation of nitrones.[162] By using the magnesium(II) salt of γ-amino alcohol **127**, they achieved the catalytic addition of Et_2Zn and Me_2Zn to the C=N bonds of 3,4-dihydroisoquinoline *N*-oxide derivatives.[162a,b] They later showed that the magnesium(II) and zinc(II) salts of dicyclopentyl tartrate **128** afforded higher yields and enantioselectivities in chirality, opposite to that achieved with **127** (Scheme 23).[162c] They presented a proposed transition state for the reaction of **128** by considering reversal of the enantioselectivity depending on the amount of Et_2Zn (Figure 19).

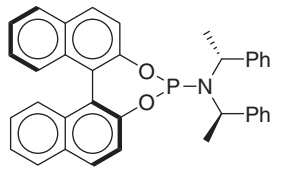


128[162c]



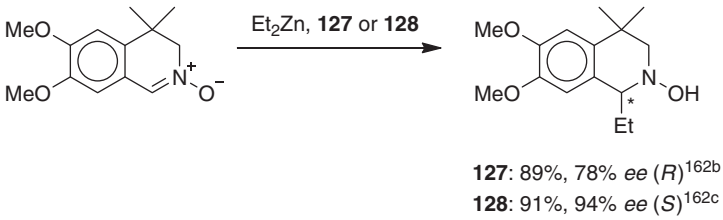
129[163,181]

PhCH(Ts)NHCHO–Et_2Zn
yield >99%, 95% *ee R*[163]
p-MeC_6H_4CH(Ts)NHCHO–
PhZnEt
yield 98%, 97% *ee* (+)[181]



130[164]

p-BrC_6H_4CH(Ts)NHCHO–Et_2Zn
yield 94%, 99% *ee R*



127: 89%, 78% *ee* (*R*)[162b]
128: 91%, 94% *ee* (*S*)[162c]

Scheme 23

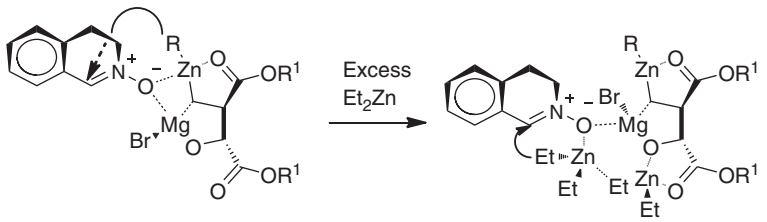
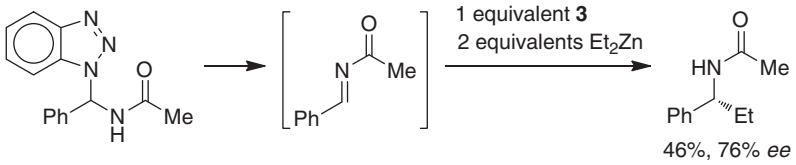
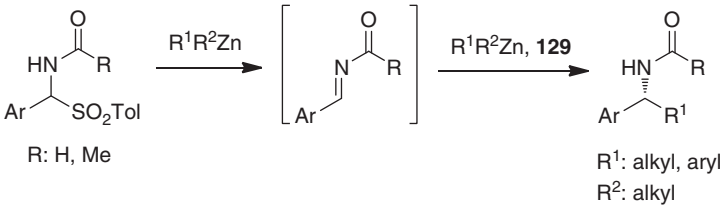


Figure 19 Proposed transition state for reversal of enantioselectivity in the addition of diethylzinc to 3,4-dihydroisoquinoline *N*-oxide in the presence of **128**.[162c] Reproduced with permission from Figure 1 in Ukaji, U.; Shimizu, Y.; Kenmoku, Y.; Ahmed, A.; Inomata, K. *Chem. Lett.* **1997**, *26*(1), 59–60.

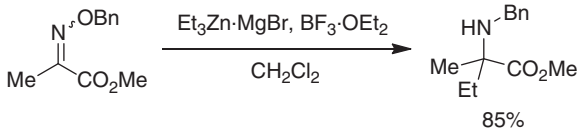
A number of groups have reported the alkylation of C=N bonds of other substrates. Katritzky and Harris applied *N*-(amidobenzyl)benzotriazole as a substrate, forming *N*-acyl benzaldimine *in situ* by reaction with Et_2Zn.[148] Using 2 equivalents of the zinc species and 1 equivalent of **3** as a chiral ligand, they achieved enantioselective ethylation (Scheme 24). Dahmen and Bräse found that *N*-formyl-α-(tosyl)arylamine was a possible substrate for generating *N*-formylimine *in situ* by reaction with 1 equivalent of R_2Zn.[163] A second equivalent of the zinc species then enantioselectively added to the arylimine (Scheme 25). In addition, in the presence of [2.2]paracyclophane-based γ-imino phenol ligands such as **129**, they achieved highly enantioselective addition of R_2Zn to *N*-formyl aryl- and alkylimines.[163] Feringa et al. extended this system by using a combination of a copper(II) salt and phosphoramidite ligands such as **130**.[164] Kozlowski et al. demonstrated that α-aldiminoesters (imines of glyoxylate) can undergo enantioselective alkylation of the C=N bond by Et_2Zn using titanium(IV) complex **109** with an alcohol (0.5 equivalent) as an additive.[165] In other work, Mitani et al. developed an interesting addition reaction of alkylzinc reagents to the ethers of α-oxime esters (Scheme 26).[166] The α-oxime esters could be prepared from acetylene carboxylate and methyl pyruvate. Both trialkylzincates and dialkylzinc reagents react with the C=N bond in the presence of a Lewis acid to afford α,α-disubstituted α-amino acid derivatives.



Scheme 24

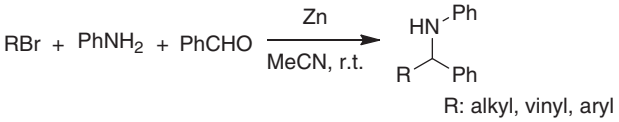


Scheme 25



Scheme 26

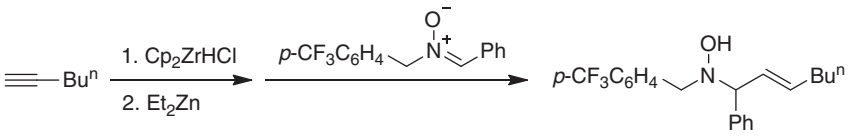
Recently, Le Gall et al. developed the Mannich-type reaction for use in the efficient preparation of α-branched amines from various organic halides, aldehyde derivatives, and amines in the presence of zinc dust (Scheme 27).[167a] The reaction was achieved by the addition of *in situ* prepared organozinc reagents to the C=N bond. The reaction was found to also work on the direct addition of vinylzinc and arylzinc reagents. This reaction was applied for ethyl glyoxylate and benzylic organozinc reagents to obtain phenylalanine ethyl ester deivatives.[167b]



Scheme 27

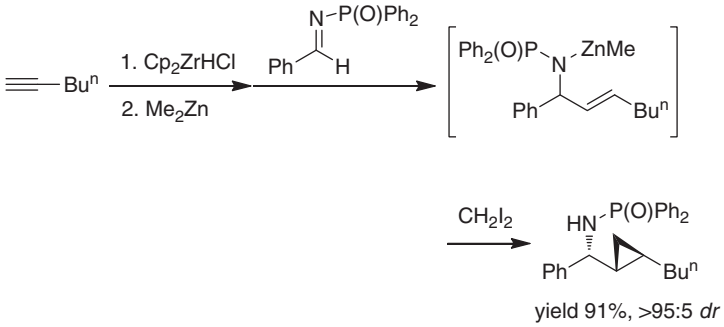
1.07.2.5.3 Vinylzinc

Vallée et al. utilized the addition of vinylzinc reagents to the C=N bond of nitrones to obtain (*E*)-*N*-allylhydroxylamines (Scheme 28).[168a] The vinylzinc reagents were prepared by the hydrozirconation of terminal alkynes and metal exchange with zinc by reaction with Et_2Zn (the Wipf procedure).[65] The authors also showed that the vinylation of nitrones occurred in good yields using vinylzinc reagents prepared from vinylboronic esters of pinacol,[169] and Me_2Zn and Et_2Zn.[168b]



Scheme 28

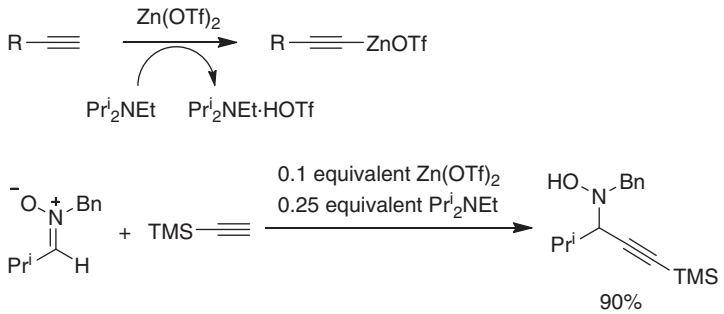
Wipf et al. also achieved the vinylation of C=N bonds of *N*-phosphinoyl arylimines using the alkenylzirconocene/Me_2Zn system.[170] They discovered that *C*-cyclopropylalkylamide can be directly prepared from the intermediate, the *N*-zinc salt of the allylamide, in high yield and diastereoselectivity (Scheme 29).



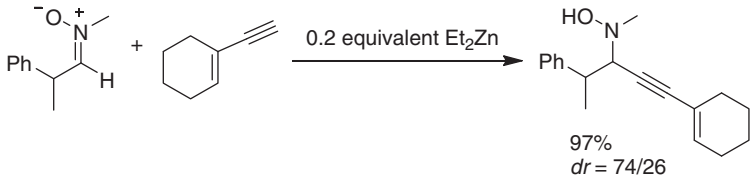
Scheme 29

1.07.2.5.4 Alkynylzinc

Carreira et al. developed a catalytic system for the preparation of an alkynylzinc reagent from the corresponding terminal alkyne, $Zn(OTf)_2$, and amine *in situ*, and achieved its addition to *N*-benzyl nitrones (Scheme 30).[171a] They further extended the system to the highly stereoselective synthesis of optically active secondary propargylic *N*-hydroxylamines using a mannose-derived glycoside as a chiral auxiliary.[171b] Vallée et al. showed that the reactions between terminal alkynes and nitrones could occur with a catalytic amount of Et_2Zn in high yield (Scheme 31).[172]

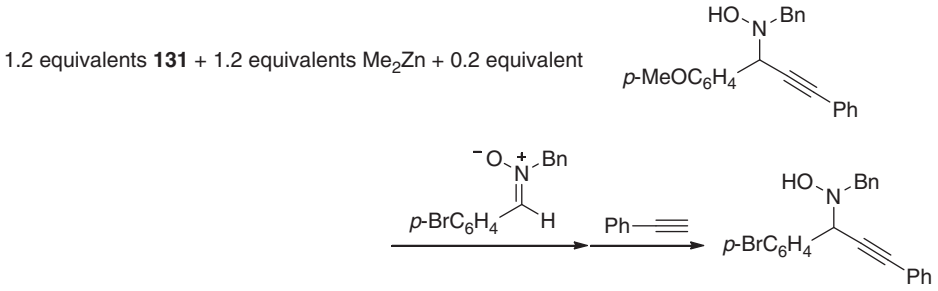


Scheme 30



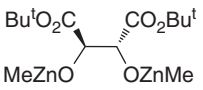
Scheme 31

In other work, Inomata et al. achieved the enantioselective alkynylation of arylnitrones by using alkynylzinc reagents prepared from terminal alkynes and Me_2Zn with the bis(methylzinc) salt of di(*tert*-butyl) (*R,R*)-tartrate **131** as a ligand (**Scheme 32**).[173] Interestingly, the addition of a product-like racemic substrate increased the enantioselectivity.



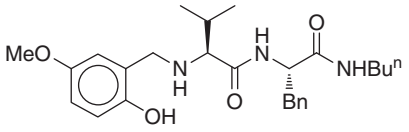
Scheme 32

In addition to nitrones, several other types of imines have also been studied. Hoveyda et al. found that the enantioselective alkynylation of *o*-anisidine arylimines can be achieved by using the zirconium complex of dipeptide-based ligand **132**.[174] Bolm et al. developed a catalytic one-pot enantioselective alkynylation of various *o*-anisidylimines without any ligands[175a] by using *β*-amino alcohols such as **133**.[175b] In another study, Pedro et al. also showed that BINOL-based ligands such as **134** work for the highly enantioselective alkynylation of *N*-sulfonyl arylimines by using the alkynylzinc reagents in the same way.[176] Wang et al. prepared proline-derived amino alcohols such as N_2,O_2-tetradentate **135**[177a] and *N,O,S*-tridentate **136**[177b] as chiral ligands. They were found to be effective for the highly enantioselective addition of trimethylsilylacetylene and arylacetylenes to *N*-phosphinoyl alkylimines with Et_2Zn, respectively, with **Figure 20** showing the transition state proposed for **135**.[177a]



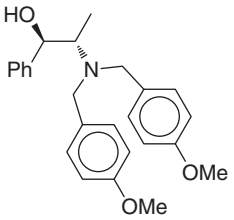
131[173,184]

p-$BrC_6H_4CH{=}N^+(Bn)O^-$ –
Ph—≡—ZnEt
yield 92%, 91% *ee R*[173]
PhC≡CCH=$N^+(Bn)O^-$ –PhZnMe
yield 75%, 92% *ee S*[184]



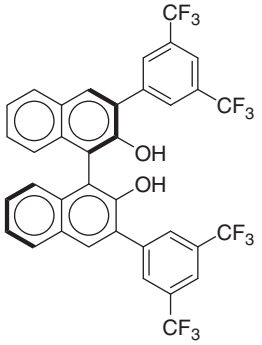
132[174]

o-$MeOC_6H_4N{=}CHPh$–
(TMS—≡—)2Zn
yield 84%, 98% *ee S*



133[175b]

p-$ClC_6H_4CH{=}N(o\text{-}MeO)C_6H_4$ –
Ph—≡—ZnMe
yield 83%, 87% *ee* (–)



134[176]

p-$BrC_6H_4CH{=}NTs$ –
Ph—≡—ZnMe
yield 84%, 97% *ee S*

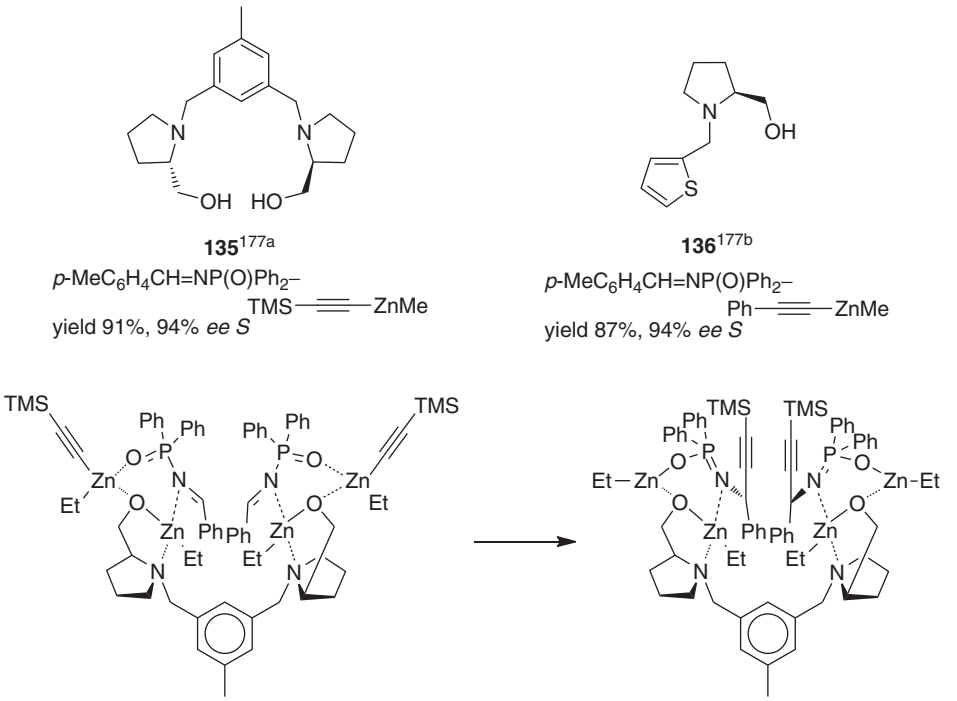
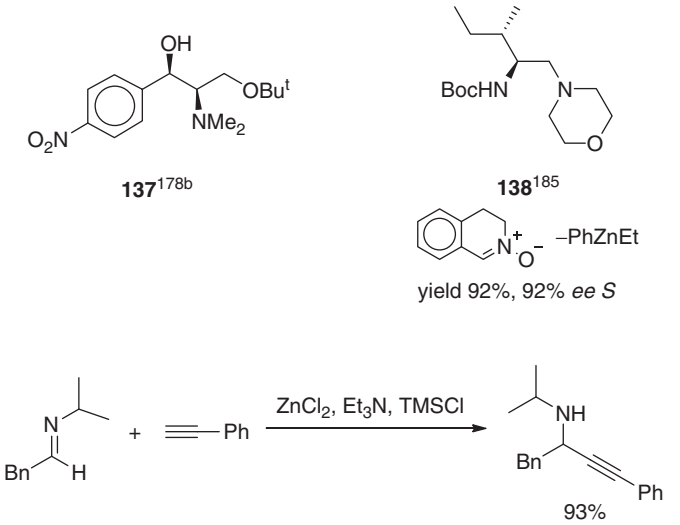


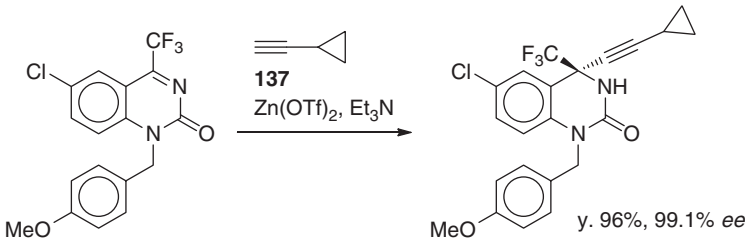
Figure 20 Proposed transition state for the addition of alkynylalkylzinc to *N*-diphenylphosphinoylimine in the presence of **135**.[177a] Reproduced with permission from Scheme 5 in Zhu, S.; Yan, W.; Mao, B.; Jiang, X.; Wang, R. *J. Org. Chem.* **2009**, *74*(18), 6980–6985.

Jiang and Si developed a terminal alkyne/zinc chloride ($ZnCl_2$)/triethylamine (Et_3N) system for the preparation of alkynylzinc reagents, and achieved the alkynylation of simple benzaldimine with trimethylsilyl chloride (TMSCl) as an activator (Scheme 33).[178a] They studied the diastereoselectivity of the reaction by using imines prepared from chiral amines, and achieved enantioselective addition to the cyclic *N*-acyl ketimine by using $Zn(OTf)_2$ and a stoichiometric amount of tridentate alkoxy *β*-amino alcohols such as **137** as chiral ligands (Scheme 34).[178b] The synthesis of tertiary amines was achieved in high yield and enantioselectivity, even on a 100 g scale, and **137** was recovered and recycled.

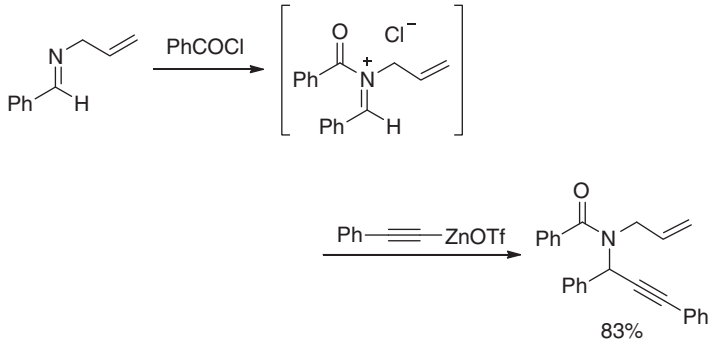


Scheme 33

Fischer and Carreira found that alkynylzinc reagents can add to acyl iminium salts, which can be prepared *in situ* from imines and acid halides (Scheme 35).[179] The reaction was also shown to be effective for preparation of a cyclic substrate by alkynylation of isoquinoline. Kim et al.[180] and Bolm et al.[175a] both applied imines bearing sulfonyl groups, such as *N*-tosylimine, as substrates for alkynylation. The alkynylzinc reagents were prepared using a terminal alkyne/$ZnBr_2$/tertiary amine system in acetonitrile,[180] or a terminal alkyne/Me_2Zn system.[175a]



Scheme 34



Scheme 35

1.07.2.5.5 Arylzinc

The addition of arylzinc reagents to the C═N bond has been achieved by applying methods similar to those reported for alkylation reactions. Bräse et al. extended their alkylation method to the arylation of *N*-formyl arylsulfone (Scheme 25)[163] and achieved the first catalytic asymmetric addition of phenylzinc using **129** in high yields and enantioselectivities.[181] The Mannich-type reaction (Scheme 27) by Le Gall et al.[182a] was first reported for arylation of the C═N bond by arylzinc bromide[183] directly prepared from arylbromide. Recently, they extended their method to the preparation of various chiral amines containing aryl group(s) using chiral amines such as an ester derivative of L-proline.[182b]

In other work, Inomata et al. modified their alkynylzinc addition (cf. Scheme 32) for the enantioselective addition of phenylzinc to *C*-alkynyl nitrones using **131** in the presence of a product-like additive.[184] Seto et al. developed the enantioselective arylation of 3,4-dihydroisoquinoline *N*-oxide with arylzinc reagents prepared from boronic esters and Et_2Zn using a zinc salt of chiral *β*-amino amide ligand **138**.[185]

As seen above, many types of substrates have been examined for the addition of organozinc reagents to the C═N bond. This situation makes it difficult to choose appropriate reaction systems, and therefore to list good chiral ligands for a particular C═N bond. Nevertheless, the norephedrine derivatives **114**[149a] and **133**[175b] and dipeptides of **125**[160b] and **132**[174] can be singled out as convenient starting points in the search for an optimal reagent.

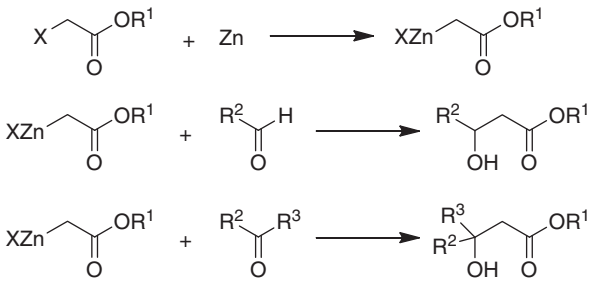
1.07.3 Addition of Reformatsky Reagents

1.07.3.1 Introduction

Since it was initially reported in 1887, the Reformatsky reaction has been one of the most useful methods for C–C bond formation to afford *β*-hydroxy esters.[5] The classical reaction involves insertion of zinc into the halogen–carbon bond of α-haloesters and subsequent nucleophilic addition of the organozinc enolate to aldehydes or ketones (Scheme 36). As the Reformatsky reaction requires only mild reaction conditions and inexpensive zinc metal, it can be a useful alternative to the aldol reaction, which is conducted under basic conditions. It has therefore been applied to industrial-scale production and total synthesis of natural compounds. As illustrated in a number of previous reviews, this reaction has a wide scope, and a range of haloesters, electrophiles (nitriles, phosphonates, amides, imides, azomethines, etc.), and even various metals (Cr, In, SmI_2, Co complexes, etc.) can be used.[186] In this section of the chapter, the authors summarize advances in which the Reformatsky reaction is mediated by organozinc reagents.

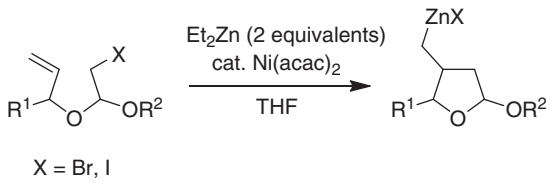
1.07.3.2 Reformatsky Reactions of Carbonyl Compounds Mediated by Organozinc Compounds

The Reformatsky reaction can be conducted under neutral conditions and has high functional group tolerance. However, at the same time, it suffers from problems of low yield and stereoselectivity. This is often attributed to the low solubility of zinc metal in



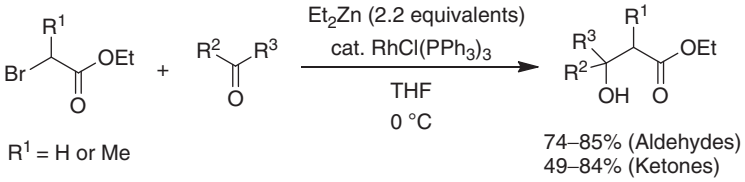
Scheme 36

typical organic solvents, with the resulting heterogeneous system significantly inhibiting the reaction. To avoid this drawback, the zinc metal can be replaced by activated zinc species such as Rieke zinc (zinc chloride reduced by potassium) or a copper–zinc couple.[187] Dramatic advancement in the Reformatsky reaction has occurred since homogeneous reaction conditions were established. In this context, Knochel et al. reported the synthesis of organozinc reagents by radical cyclization, where a practical method for the activation of zinc involved the use of 2 equivalents of diethylzinc (Et_2Zn) in the presence of a catalytic amount of nickel(II) acetylacetonate ($Ni(acac)_2$) (Scheme 37).[188]



Scheme 37

This convenient method has been commonly applied to the activation of zinc metal. Honda et al. first reported the combination of Et_2Zn and a catalytic amount of chlorotris(triphenylphosphine) rhodium(I) ($RhCl(PPh_3)_3$, Wilkinson's catalyst) to develop a homogeneous Reformatsky-type reaction between α-haloesters and aldehydes or ketones (Scheme 38).[189] Adrian et al. later showed that dichlorobis(triphenylphosphine) nickel(II) ($NiCl_2(PPh_3)_2$) could effectively replace Wilkinson's catalyst, providing a faster reaction rate at reduced cost.[190] These reports have stimulated the design of various chiral ligands and have led to the development of the stereoselective Reformatsky reactions described in Sections 1.07.3.3–1.07.3.5.

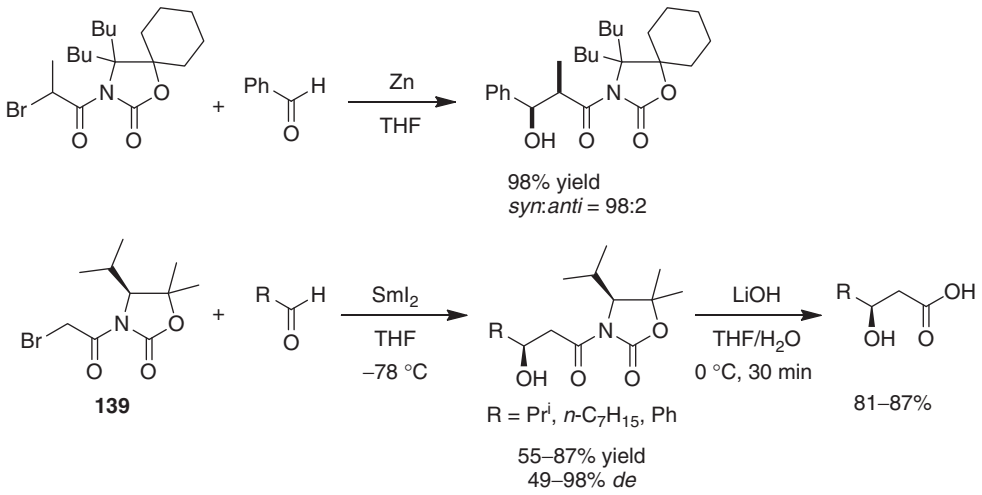


Scheme 38

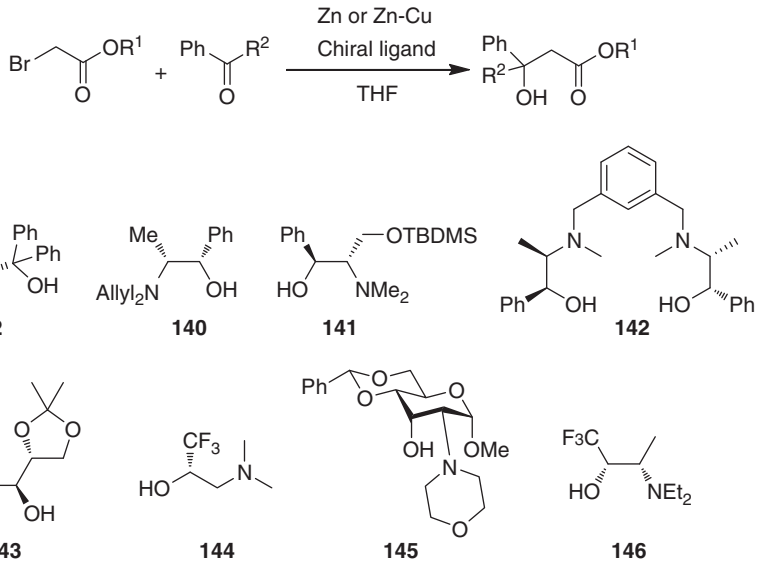
1.07.3.3 Stereoselective Reformatsky Reactions

As the demand for enantiopure compounds intensifies throughout a wide range of scientific and medical fields, increasing attempts have been made to achieve highly efficient stereoselective Reformatsky reactions. Primitive examples of these have been conducted with halocarbonyl compounds bearing chiral auxiliaries such as Evans-type chiral oxazolidinones.[191a–d] Further derivatization or removal of the chiral auxiliaries from **139** afforded the desired chiral products in high purity (Scheme 39).[191e]

Another method for chiral induction is the addition of chiral ligands to the reaction mixture. Various chiral alcohols and amino alcohols (**2** and **140–146**) have been tested for zinc- or zinc–copper-mediated Reformatsky reactions between α-bromo esters and benzaldehyde or acetophenone (Scheme 40).[192]



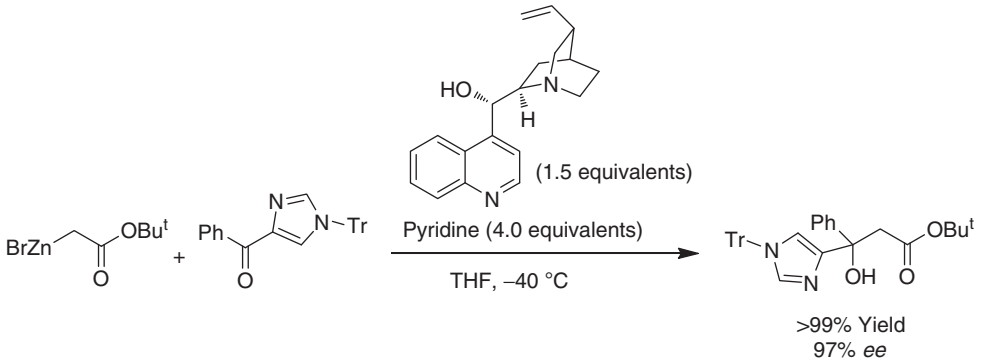
Scheme 39



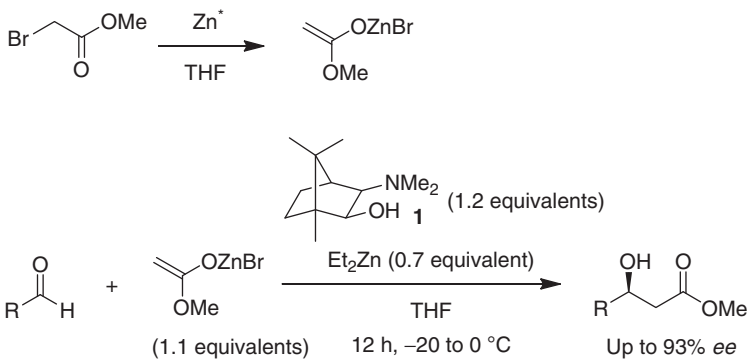
Entry	R^1	R^2	Mediator	Chiral ligand	Yield	*ee*
1	Bu^t	H	Zn-Cu	**2**	91%	75%
2	Bu^t	Me	Zn-Cu	**140**	65%	74%
3	Bu^t	H	Zn	**141**	100%	65%
4	Bu^t	H	Zn	**142**	90%	62%
5	Et	H	Zn	**143**	58%	30%
6	Et	H	Zn	**144**	80%	81%
7	Et	H	Zn-Cu	**145**	10%	74%
8	Et	H	Zn-TMSCl	**146**	89%	86%

Scheme 40

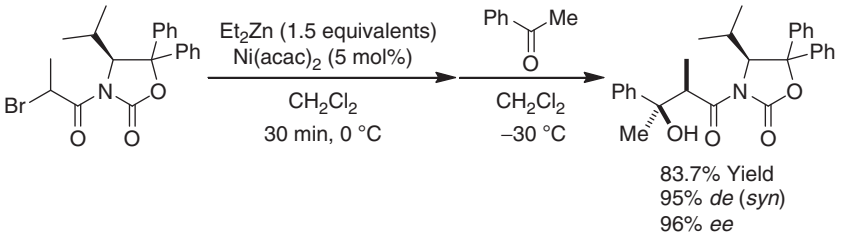
The best chiral induction of up to 97% *ee* was observed when cinchonine was used for the zinc-mediated reaction with a diarylketone at $-40\ ^{\circ}C$ (Scheme 41).[193] In addition, Knochel et al. reported that the use of Et_2Zn to deprotonate chiral amino alcohol **1** was effective for the enantioselective reaction between benzaldehyde and the zinc Reformatsky reagent, affording *β*-hydroxy esters in up to 93% *ee* (Scheme 42).[194] For most of these examples, however, it was necessary to use stoichiometric amounts of chiral additive because of the heterogeneous reaction conditions. The subsequent development of homogeneous reaction conditions has enabled the precise design of stereoselective Reformatsky reactions. Yang et al. reported a diastereoselective Et_2Zn-mediated Reformatsky reaction between Evans chiral imide and acetophenone, catalyzed by 5 mol% of $Ni(acac)_2$ (Scheme 43).[195]



Scheme 41

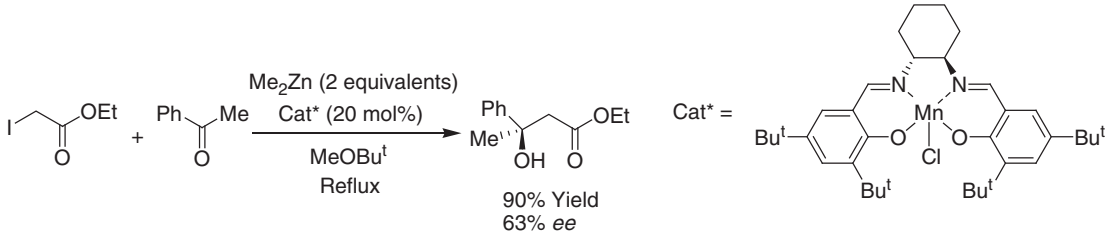


Scheme 42



Scheme 43

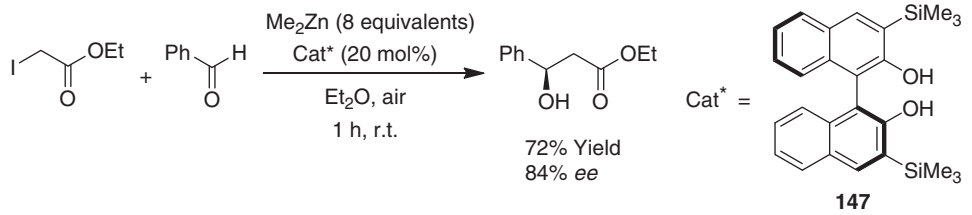
From the viewpoint of reducing the amount of chiral auxiliary, Cozzi et al. reported the enantioselective Me_2Zn-mediated Reformatsky reaction with aromatic or aliphatic ketones catalyzed by 20 mol% of chiral manganese (salen)chloride complex (Scheme 44). Moderate to high enantioselectivities were obtained on addition of 25 mol% of 4-phenylpyridine *N*-oxide at room temperature.[196]



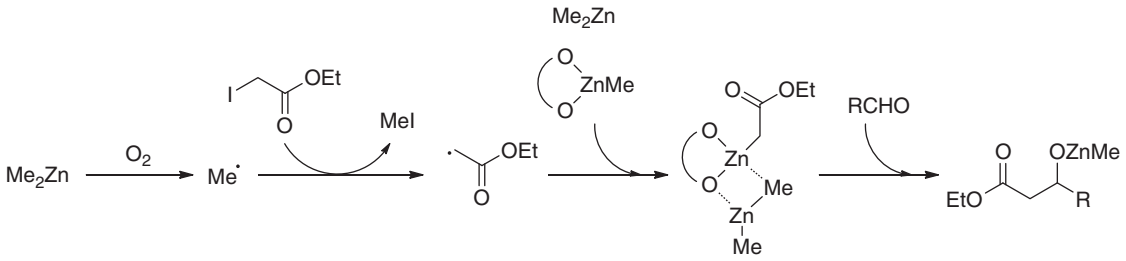
Scheme 44

Feringa et al. first reported catalytic enantioselective Reformatsky reactions with aldehydes.[197a] Typically, they conducted the reaction with ethyl iodoacetate, Me_2Zn, and benzaldehyde in the presence of a catalytic amount of a chiral BINOL derivative,

147 (Scheme 45). This reaction afforded the *β*-hydroxy ester in low yield under a nitrogen atmosphere, whereas high conversion to the product (72% yield, 84% *ee*) was observed under an air atmosphere. As will be discussed in Section 1.07.4.2 in the chapter, Me_2Zn can be a good radical initiator on reaction with molecular oxygen. This reaction was conducted with various aromatic and aliphatic aldehydes under optimized reaction conditions, giving the products in moderate to high enantioselectivities (up to 84% *ee*). According to a plausible catalytic cycle of this reaction, a generated methyl radical affords an ethyl acetate radical by iodine atom transfer, which is followed by complexation with Me_2Zn and reaction with benzaldehyde to give the product (Scheme 46). Similar chiral BINOL ligands were applied to catalytic enantioselective Reformatsky reactions with ketones to yield tertiary alcohols of high purities in the presence of air.[197b,c]

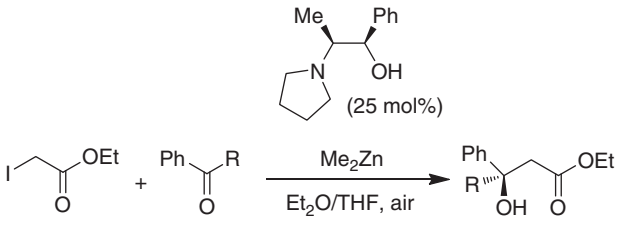


Scheme 45



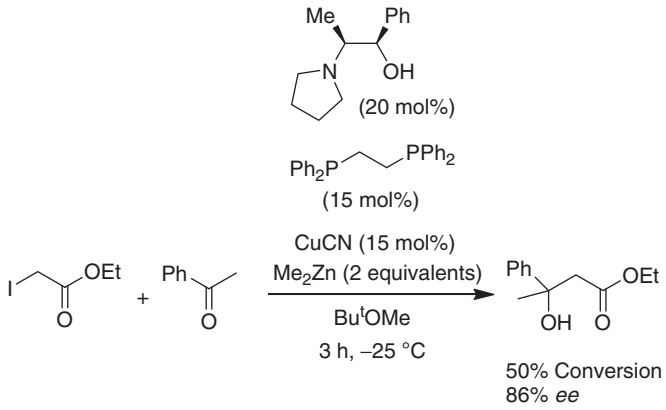
Scheme 46

Cozzi et al. similarly focused on the radical nature of Me_2Zn and developed enantioselective reactions of ethyl iodoacetate with aldehydes or ketones using 25 mol% of chiral *N*-pyrrolidinylephedrine (the enantiomer of **6**) under oxidative conditions.[197d,e] They revealed that the use of air, and also *tert*-butyl hydroperoxide (Bu^tOOH) or ceric ammonium nitrate (CAN) as an oxidant, were effective for obtaining higher yields, and that addition of triphenylphosphine oxide/sulfide can further accelerate the reaction (Scheme 47). After optimization of the reaction conditions, various aldehydes afforded *β*-hydroxy esters in up to 93% *ee*. It was found that a combination of copper(I) salts and bidentate phosphines could also be used as a reliable promoter and an alternative to other oxidants (Scheme 48).[197f] Since these studies were reported, various different types of chiral ligand, including Schiff base **148**,[197g] *β*-amino alcohols **149**,[197h] and oxazolidine **35**,[197i] have been developed for catalytic enantioselective Reformatsky reactions with aldehydes or ketones (Scheme 49).

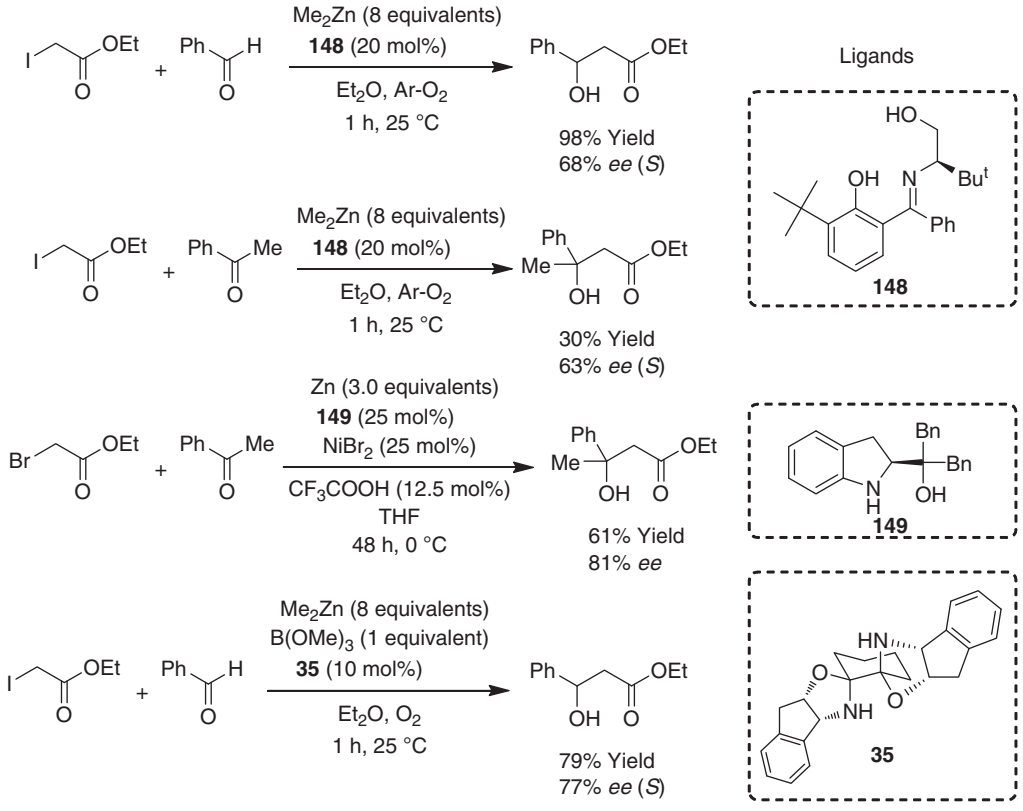


Entry	R	Me_2Zn	Additive	Temp.	Time	Yield	*ee*
1	H	1.5 equivalents	Ph_3PO (10 mol%)	–14 °C	71 h	70%	76%
2	H	1.5 equivalents	Ph_3PO (10 mol%)	–25 °C	70 h	40%	84%
3	Me	2 equivalents	Ph_3PO (20 mol%)	0 °C	40 h	50%	57%
4	Me	2 equivalents	Ph_3PO (20 mol%)	–25 °C	87 h	57%	81%
5	H	1.5 equivalents	Ph_3PS (10 mol%)	–25 °C	70 h	30%	80%
6	H	1.5 equivalents	Ph_3PS (30 mol%)	0 °C	3 h	90%	75%

Scheme 47



Scheme 48

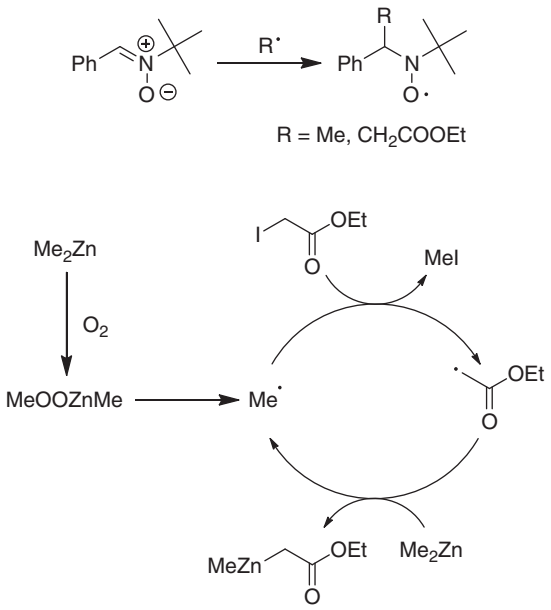


Scheme 49

Recently, clear experimental evidence for the generation of radicals by Me_2Zn was provided by the acquisition of electron paramagnetic resonance (EPR) spectra by using phenyl *tert*-butyl nitrone as a radical trap. It was suggested that Me_2Zn and molecular oxygen first interact to afford methyl radicals, which subsequently react with ethyl iodoacetate to give ethoxycarbonylmethyl radicals under the conditions of the Reformatsky reaction (Scheme 50).[198]

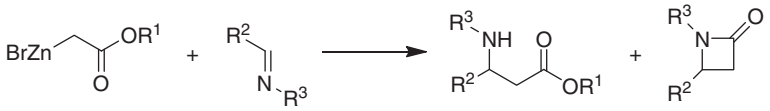
1.07.3.4 Addition of Reformatsky Reagents to Imines

Imines, like carbonyl compounds, are good candidates as substrates for the production of β-amino acid derivatives using the Reformatsky reaction. In fact, several examples of the Reformatsky reaction with imines have been presented since the first report by Gilman et al.[199a] However, it was known that not only β-amino esters but also β-lactams were often produced simultaneously (Scheme 51).[199b–d] Adrian et al. showed highly selective synthesis of β-amino esters by using imines prepared from



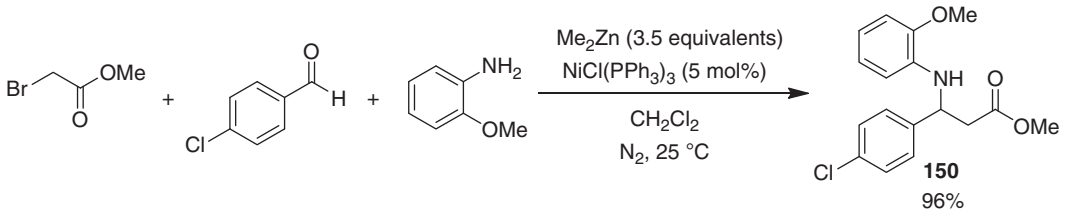
Scheme 50

2-methoxyaniline.[200] The electronegative oxygen atom of the *ortho*-methoxy group had an inductive effect, which played a key role in decreasing the nucleophilicity of the imino nitrogen and preventing cyclization to afford lactams.



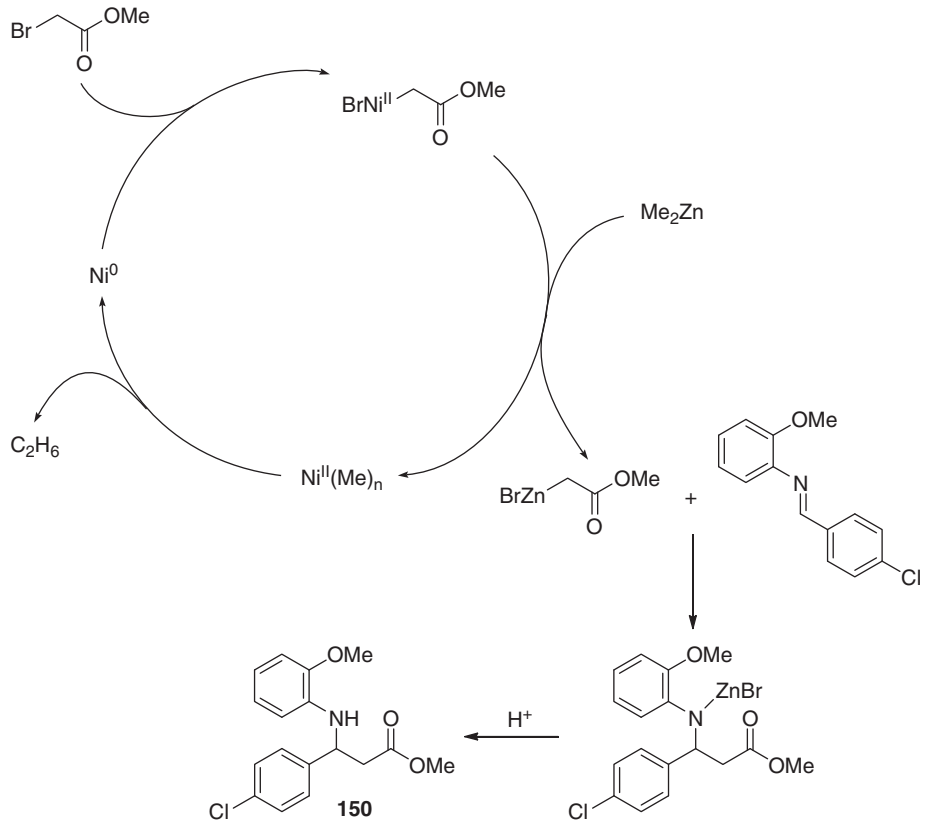
Scheme 51

As both imines and Reformatsky reagents can be generated *in situ*, the same authors also applied this reaction to the one-pot, three-component imino-Reformatsky reaction involving an aldehyde, aniline, and an α-haloester compound (Scheme 52).[190] The combination of Me_2Zn and a catalytic amount (5 mol%) of chlorotris(triphenylphosphine)nickel(II) ($NiCl(PPh_3)_3$) afforded the corresponding *β*-aminocarbonyl compound **150** in high yields. It is notable that the less nucleophilic Me_2Zn was used instead of Et_2Zn in order to prevent addition of an alkyl group to the imino group. The mechanism of the homogeneous catalytic reaction that was proposed is shown in Scheme 53. The catalytic cycle is initiated by the formation of a nickel(0) species, which undergoes oxidative addition to an α-bromocarbonyl compound to afford the nickel(II) complex. After ligand exchange with Me_2Zn, the zinc enolate and methylated nickel(II) complex is formed. This then undergoes reductive elimination to release ethane, regenerating the initial nickel(0) species.

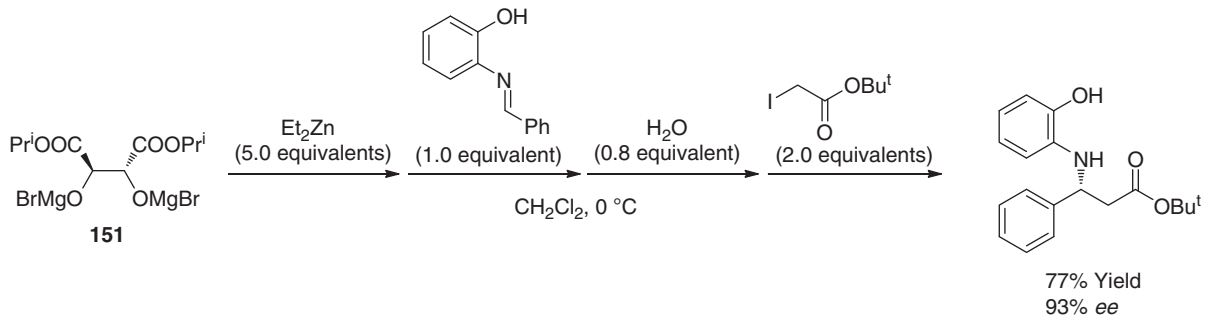


Scheme 52

Recently, stereoselective Reformatsky reactions with imines have also been developed. Ukaji et al. reported the enantioselective addition of Reformatsky reagents prepared *in situ* from Et_2Zn and *tert*-butyl iodoacetate, to 3,4-dihydroisoquinoline *N*-oxides and imines in the presence of an equimolar amount of diisopropyl-L-tartrate **151** as a chiral source.[201] For the latter reaction, addition of a small amount of water improved the product yield and enantioselectivity, probably because the dissociation of aggregates formed from the metal salt of tartrate and imines enhanced the reaction (Scheme 54).[201b]



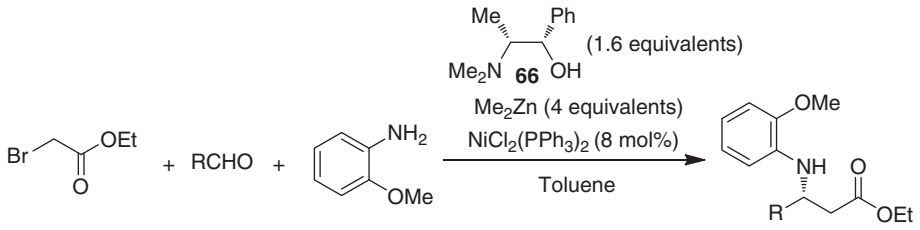
Scheme 53



Scheme 54

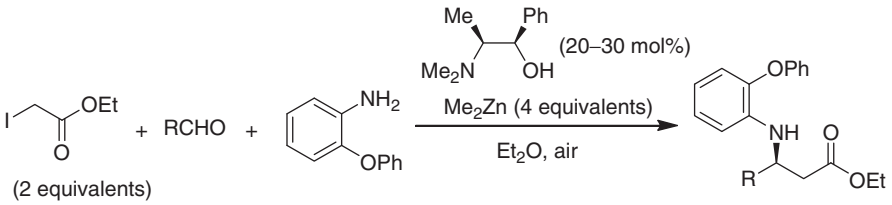
Cozzi et al. first reported the Me_2Zn-mediated one-pot enantioselective three-component imino-Reformatsky reaction promoted in the presence of a stoichiometric amount of *N*-methylephedrine **66** and 8 mol% of the nickel(II) salt (Scheme 55).[202a,b] Various aldehydes were reacted with 2-methoxyaniline and ethyl bromoacetate to give *β*-amino esters in good enantioselectivities (64–92% *ee*). They also successfully developed a catalytic version of this reaction by employing ethyl iodoacetate and 2-phenoxyaniline as substrates, and conducting the reaction in the presence of dry air (Scheme 56).[202c] High yields (67–93%) and enantioselectivities (80–95% *ee*) were observed for the *β*-amino ester products. This reaction was found to be inhibited by the addition of a radical trap, 1,4-cyclohexadiene, indicating that the reaction proceeded via a radical mechanism.

Synthesis of fluorinated *β*-amino acids and *β*-lactams by an imino-Reformatsky reaction has also been reported. In particular, *α*,*α*-difluoro-*β*-amino acids **152** are of interest owing to their unusual structures. Traditionally, Reformatsky reactions of ethyl bromodifluoroacetate with imines or *N*-(*α*-aminoalkyl)benzotriazoles have been used for their synthesis.[203a,b] Quirion et al. first reported enantioselective synthesis of *α*,*α*-difluoro-*β*-amino acids **152** by Reformatsky reaction with oxazolidines modified with a chiral auxiliary (Scheme 57).[199d,203c] They obtained corresponding *β*-lactams **153** as major products with high diastereoselectivity, and further conversion to enamides followed by acidic hydrolysis afforded fluorinated *β*-amino acids **152** without racemization. To obtain **152** more directly, enantiopure sulfinimines were applied as chiral auxiliaries. It was found that Ellman's



Entry	R	Temp.	Time	Yield	*ee*
1	Ph	–30 °C	48 h	63%	83%
2	4-ClPh	–25 °C	3 h	62%	90%
3	PhCH=CH	–20 °C	48 h	60%	85%
4	2-Naphthyl	–5 °C	16 h	40%	84%
5	2-Thiophene	–28 °C	16 h	49%	92%
6	Pr^i	–10 °C	48 h	57%	64%
7	Pr^i	–20 °C	48 h	52%	74%

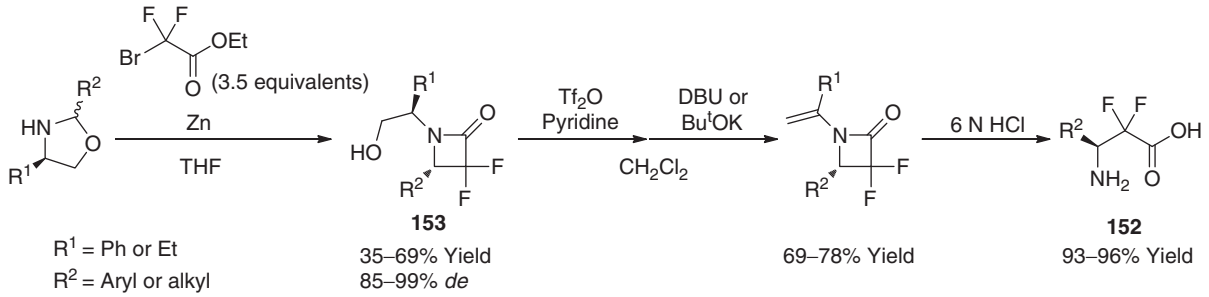
Scheme 55



Entry	R	Ligand	Temp.	Time	Yield	*ee*
1	Ph	30 mol%	–30 °C	24 h	80%	93%
2	4-$Pr^iC_6H_4$	30 mol%	0 °C	3 h	84%	80%
3	4-$Pr^iC_6H_4$	30 mol%	–25 °C	24 h	81%	90%
4	PhCH=CH	30 mol%	0 °C	8 h	93%	83%
5	4-$CF_3C_6H_4$	20 mol%	0 °C	8 h	90%	95%
6	2-Naphthyl	30 mol%	0 °C	8 h	90%	94%
7	*c*-Hex	30 mol%	0 °C	60 h	67%	90%
8	Pr^i	30 mol%	0 °C	60 h	78%	88%

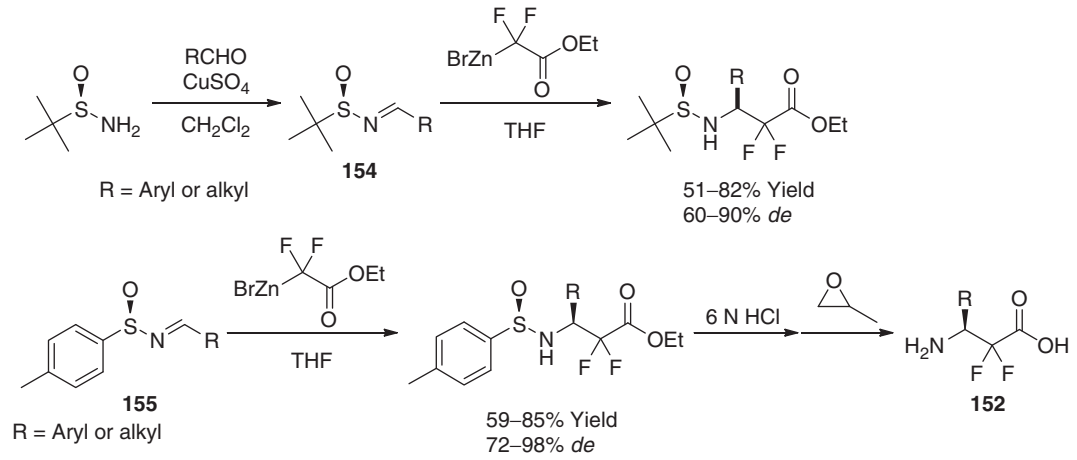
Scheme 56

N-tert-butylsulfinimines **154** and *p*-toluenesulfinimines **155** induced a diastereoselective Reformatsky reaction, and subsequent deprotection of the sulfinyl group gave **152** in high yield and enantiopurity (Scheme 58).[203d–f]



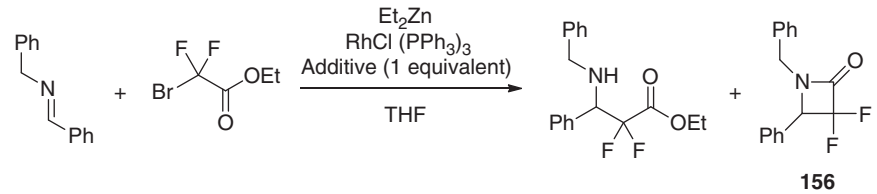
Scheme 57

Kumadaki et al. applied a combination of Et_2Zn and Wilkinson's catalyst to the highly chemoselective imino-Reformatsky reaction.[204a] When it was conducted in anhydrous solvents, the reaction gave α,α-difluoro-β-lactam **156**, while



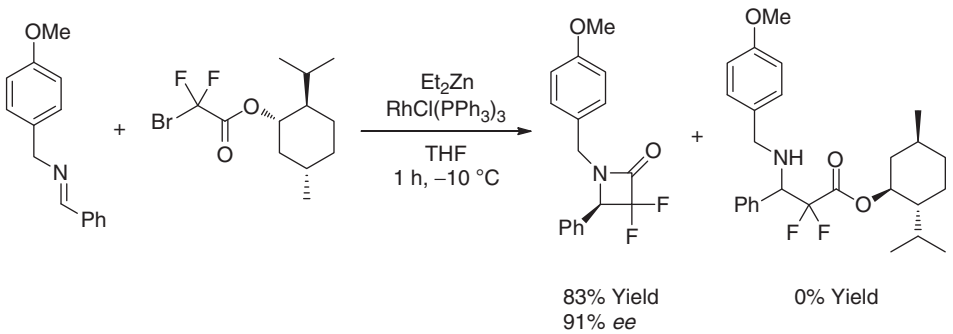
Scheme 58

α,α-difluoro-β-amino ester was produced in a good yield upon addition of magnesium sulfate heptahydrate ($MgSO_4 \cdot 7H_2O$) (Scheme 59). They further developed an enantioselective version of this reaction by introduction of an enantiopure menthyl group into the bromodifluoroacetates (Scheme 60).[204b] In addition, they changed the substrate ester to ethyl dibromofluoroacetate, which underwent a highly chemo- and diastereoselective imino-Reformatsky reaction to afford α-bromo-α-fluoro-β-lactams **157**. This reaction proceeded without addition of the rhodium catalyst, and noncyclized α-bromo-α-fluoro-β-amino esters were not detected at all; however, a small amount of aziridine **158** was produced by aza-Darzens-type reaction (Scheme 61).[204c]



Entry	Additive	Time	Yield	Yield
1	None	1 h	Trace	83%
2	H_2O	2 h	48%	16%
3	$MgSO_4 \cdot 7H_2O$	1 h	65%	Trace

Scheme 59

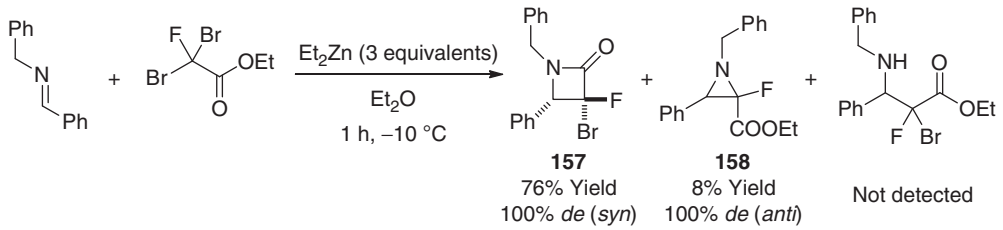


Scheme 60

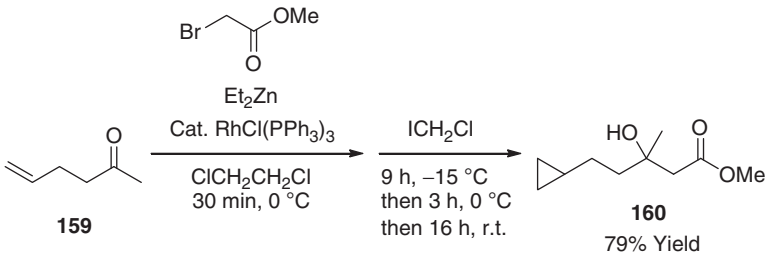
1.07.3.5 Other Types of Zinc-Mediated Reformatsky Reactions

Recently, several tandem reactions involving the Reformatsky reaction have been reported. Cossy et al. studied a one-pot tandem Reformatsky/cyclopropanation reaction of ω-unsaturated carbonyl compounds **159** to give ω-cyclopropyl alcohols **160** (Scheme 62).[205a] The first reaction occurred with methyl bromoacetate and Et_2Zn catalyzed by $RhCl(PPh_3)_3$ in dichloroethane,

with the second reaction being initiated by the addition of chloroiodomethane. The product was obtained in higher yield than when the reactions were carried out separately. It is also notable that both reactions were mediated by Et_2Zn.

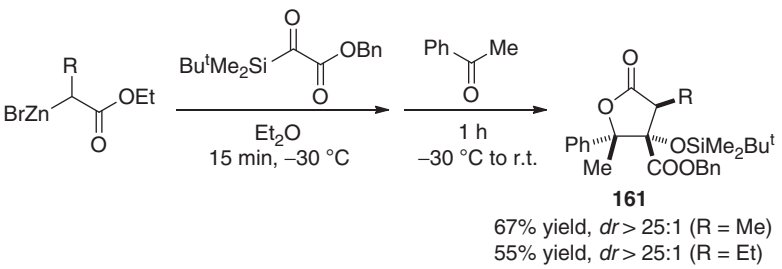


Scheme 61

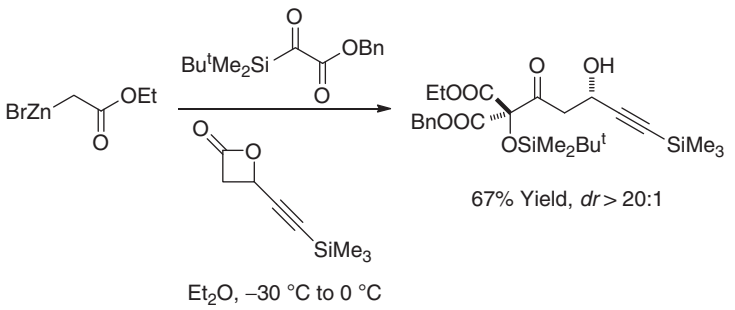


Scheme 62

Johnson et al. reported a double Reformatsky reaction of zinc enolates of bromopropionates with silyl glyoxylates and aryl ketones to afford pentasubstituted γ-butyrolactones **161** in a highly diastereoselective manner (Scheme 63).[205b] This reaction proceeds via nucleophilic addition of Reformatsky reagents to silyl glyoxylates to afford the first zinc aldolates. These then undergo a [1,2]-Brook rearrangement to give new zinc Reformatsky reagents, which subsequently react with aryl ketones, with the product obtained after lactonization. The authors changed the electrophile from an aryl ketone to a β-lactone and showed tandem Reformatsky/Claisen condensation reactions of Reformatsky reagents and silyl glyoxylates.[205c] As β-lactones are not reactive with Reformatsky reagents, these could be added at the same time, with substituted ketones being obtained. The reaction was highly diastereoselective and the stereochemistry of the emerging quaternary α-carbon was controlled by the β-lactone (Scheme 64).



Scheme 63



Scheme 64

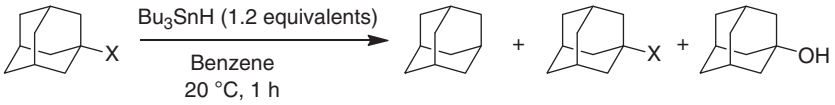
1.07.4 Applications of Dialkylzincs as Radical Reagents

1.07.4.1 Introduction

Radical-mediated reactions are a highly important and unique class of reactions in the field of organic synthesis as they can offer mild reaction conditions, high product yield, and chemoselectivity.[206] The development of stereoselective free-radical reactions began in the 1980s and has been thoroughly studied in the three decades since.[207] Peroxides, azo compounds, and triethylborane (Et_3B) are the most frequently used radical sources for this purpose. Dialkylzinc reagents (R_2Zn), however, have weak Lewis acidity and are often used for alkylation of aldehydes with the aid of complexation with Lewis bases, as stated in the in Section 1.07.2.1 of this chapter. Recently, dialkylzinc has become another choice when selecting a radical initiator. There are several examples that show the unique reactivity and selectivity of dialkylzincs compared with other radical initiators, making them appealing alternatives. In this section, the authors summarize recent studies in which dialkylzinc reagents are used as radical initiators.

1.07.4.2 Radical Reactions Mediated by Dialkylzinc Reagents

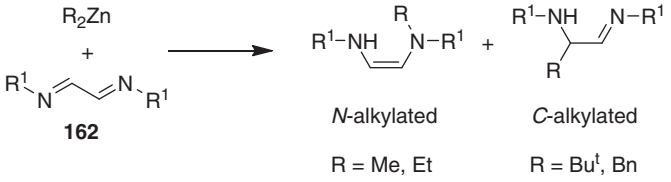
The utility of dialkylzinc as a radical source has been recognized since 1984. It was known that radical polymerization of vinyl compounds was promoted by Et_2Zn in air.[208] Inspired by this result, Komatsu et al. applied the Et_2Zn/air system to tributyltin hydride–mediated radical reactions, and showed its potential as a radical initiator (Scheme 65).[209] Reductive dehalogenation of 1-haloadamantane was promoted with the tributyltin hydride (1.2 equivalents) in the presence of Et_2Zn (5 mol%) and air to afford adamantane. It is notable that bubbling air through the reaction mixture significantly increased the product yield. The absence of Et_2Zn resulted in low product yield and an undesirable side reaction to afford 1-adamantanol by an aerobic radical reaction.



X = Br	Et_2Zn (5 mol%)	28%	67%	
X = Br	Et_2Zn (5 mol%)/air	97%	2%	
X = I	Et_2Zn (5 mol%)/air	94%	0%	
X = I	air	41%	41%	10%

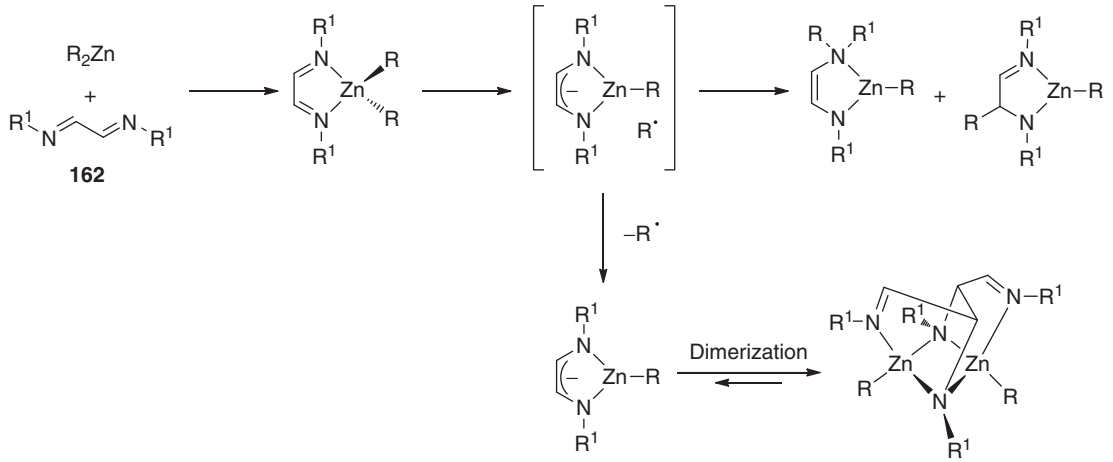
Scheme 65

Direct addition reactions of alkyl radical species promoted by dialkylzincs have also been investigated. The reactions of dialkylzincs with α-diimines and α-imino ketones were first studied by van Koten et al.[210] For example, the reaction between R_2Zn and 1,4-diaza-1,3-butadiene **162** could afford both the corresponding *C*-alkylated and *N*-alkylated products. Intramolecular charge transfer in the coordination complex R_2Zn–**162** afforded the radical pair, which was subsequently converted to the products. The product ratio was highly dependent on the particular alkyl group of the organozinc reagent (Scheme 66). When primary alkyl groups were used, the *N*-alkylated product was obtained, whereas tertiary and benzylic dialkylzinc compounds gave the *C*-alkylated product. A possible reaction mechanism was proposed on the basis of nuclear magnetic resonance (NMR), electron spin resonance spectroscopy, and the X-ray structure of the intermediate zinc complex (Scheme 67).



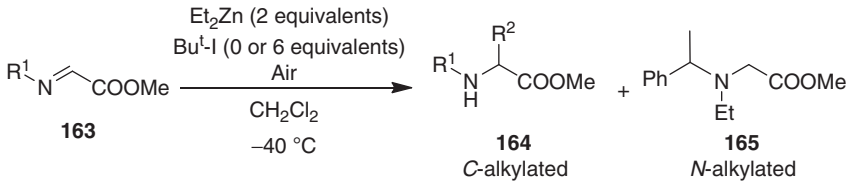
Scheme 66

Similarly, the reaction between Et_2Zn and glyoxylate imines **163** was investigated by Bertrand et al.[211] It was reported that when this reaction was conducted in the presence of air, the *C*-alkylated product **164** was mainly obtained, and its yield increased with increasing amounts of oxygen. Moreover, in the presence of *tert*-butyl iodide, a *tert*-butyl radical was produced by iodine atom transfer to add to the carbon atom of the imino group (Scheme 68). In these reactions, Et_2Zn played multiple roles, acting as a Lewis acid for activating the imine moiety, as a radical initiator, and as a chain-transfer reagent. This reaction could also be applied to glyoxylic acids and hydrazones, providing the products in higher yields. Similar radical addition to the imino group could be mediated by Et_3B; however, Et_2Zn showed high and reverse stereoinduction in the diastereoselective addition reaction (Scheme 69). This can be explained by their different coordination modes to the substrate (monodentate for Et_3B and bidentate for Et_2Zn).[211c] Bertrand et al. indicated the utility of alkyl phenyl tellurides instead of alkyl iodides as the radical precursor,



Scheme 67

while the addition of the primary alkyl radicals was found to be unsuccessful.[211d] Recently, they applied the Me_2Zn/alkyl iodide system to the highly selective *anti*-carbozincation of diethyl acetylenedicarboxylate to form fumaric acid derivatives **166**.[211e] This stereoselectivity can be explained by considering the alkylzinc group transfer in the *cis*-position relative to the carboxylate group, controlled by the coordination of a carbonyl oxygen atom to a zinc atom (Scheme 70). The use of Et_3B instead of Me_2Zn gave a 1:1 mixture of the stereoisomers as minor products and vinyl iodide as the major product. Here again, R_2Zn showed unique and favorable properties as a radical mediator.



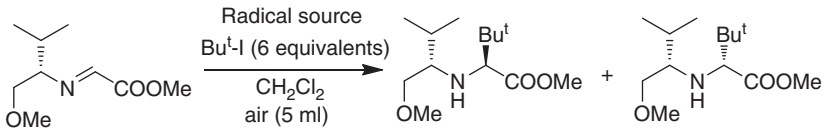
			Product yields		
			164	**164**	**165**
R^1	Additive	Conditions	R^2 = Et	R^2 = Bu^t	
CH(Me)Ph	None	Air	49%	–	9%
CH(Me)Ph	None	Degassed, 20 °C	34%	–	21%
CH(Me)Ph	Bu^t-I (6 equivalents)	Air	0%	66%	0%
OBn	None	Air	88%	–	–
OBn	Bu^t-I (6 equivalents)	Air	16%	74%	–
NPh_2	None	Air	88%	–	–
NPh_2	Bu^t-I (6 equivalents)	Air	17%	72%	–

Scheme 68

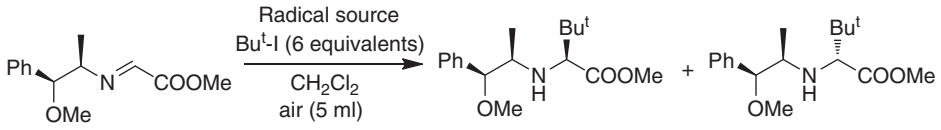
In other work, when the reaction with glyoxylate imines **163** was carried out under an inert atmosphere, zinc enolate was produced and the corresponding *β*-lactam **167** was obtained after reaction with another imine (Scheme 71).[212]

The use of Me_2Zn as a radical source has been extensively studied by Tomioka et al.[213] In the course of their studies involving the asymmetric addition of Me_2Zn to *N*-sulfonyl imines **168**, they noticed the formation of adduct **169** between the substrate imine and the tetrahydrofuran (THF) solvent. The same reaction carried out under an argon atmosphere with silicon grease applied to the connections of the apparatuses gave adduct **169** in very low yield (4%), and the substrate was recovered almost quantitatively; however, the reaction was highly accelerated by bubbling air through the reaction mixture (Scheme 72). These results suggest that Me_2Zn has the ability to abstract a hydrogen atom from an ether to afford an α-alkoxyalkyl radical in the presence of air. It is notable that a similar reaction was not efficiently promoted by other dialkylzinc reagents, with these affording not only adducts of alkyl groups but also the corresponding reduced products. This is because of the instability of methyl radicals, which would rapidly abstract an α-hydrogen atom from the THF. Furthermore, it is preferential for the addition of a α-THF radical to an imine to occur rather than addition to an aldehyde, which differs from the case using Et_3B that promotes both reactions.[213b]

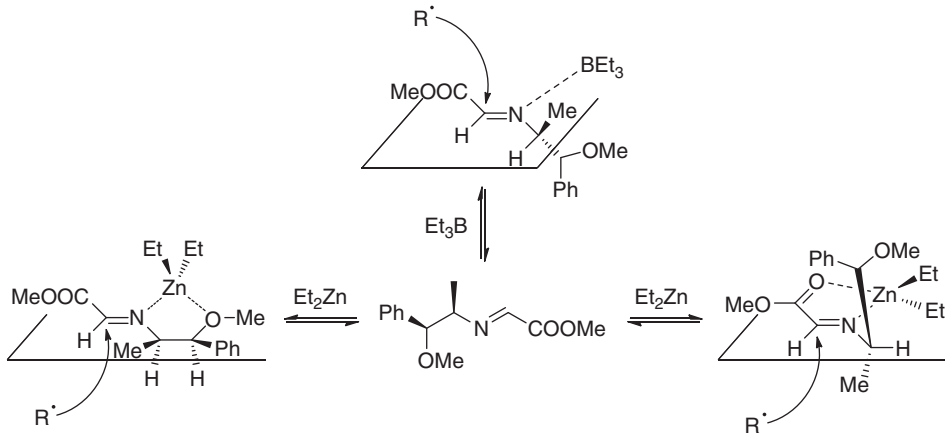
The scope of the addition reaction with the α-THF radical was extended to substrates such as α,*β*-unsaturated imines **170**, which predominantly gave the corresponding 1,4-adduct **171** by slower addition of the substrate (Scheme 73).[213f] It was also observed that alkylidenemalonates **172** could be used as radical acceptors to afford the corresponding conjugate adducts **173** with the



Radical source	Temperature	Yield	Product ratio	
Et_3B (3 equivalents)	20 °C	42%	55%	45%
Et_2Zn (2 equivalents)	20 °C	41%	87%	13%
Et_2Zn (2 equivalents)	–40 °C	67%	92%	8%



Radical source	Temperature	Yield	Product ratio	
Et_3B (3 equivalents)	20 °C	42%	65%	35%
Et_2Zn (2 equivalents)	20 °C	39%	22%	78%
Et_2Zn (2 equivalents)	–40 °C	69%	7%	93%



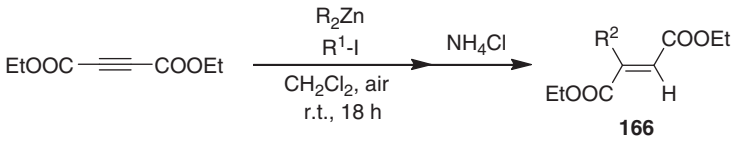
Scheme 69

α-THF radical (Scheme 74). When 8-phenylmenthol was introduced as a chiral auxiliary to the substrate benzylidenemalonate, the diastereoenriched adduct was obtained and later successfully converted into chiral lactone **174** in high yield (Scheme 75).[213g] The conjugate addition reaction was chemoselective and proceeded ahead of the addition to the carbonyl group. A large excess of THF was necessary in order to obtain the product in a high yield; however, the reagent amount could be reduced by the addition of a catalytic amount of iron(III) chloride, using dimethylsulfoxide (DMSO) as a cosolvent.[213h]

This Me_2Zn/air-mediated radical reaction could also be applied to the addition of cycloalkyl radicals to imines **168** (Scheme 76).[213c] The side reaction to give the oxidized product was suppressed by the addition of $BF_3 \cdot Et_2O$, and aminoalkylated cycloalkanes **175** were obtained in moderate yields.

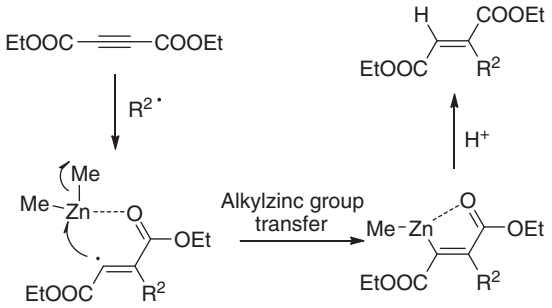
The combination of Me_2Zn and air with alkyl iodides or α-acyloxyalkyl iodides was demonstrated to provide a corresponding alkyl radical to form adducts with imines **168** (Scheme 77).[213d,e] Also, in this case, application of Et_2Zn was associated with the undesirable addition of an ethyl radical, indicating that Me_2Zn was superior as a radical source.

Although these reactions are commonly considered to be simple radical-chain processes mediated by an alkyl radical, little study has focused on the detailed mechanism of these transformations. Recently, spectroscopic analyses and direct crystallographic structure analysis of the reaction intermediates have been reported by Lewinski et al.[214a–e] They showed that in the presence of a Lewis base, the oxidation of R_2Zn by molecular oxygen under controlled conditions proceeded selectively for only one alkyl group. The mixture of Bu^t_2Zn and molecular oxygen afforded $Bu^tZnOOBu^t$ or Bu^tZnOBu^t species depending on the basicity of the Lewis base. Based on this observation, they proposed a mechanism for oxygen insertion into the Zn–C bond (Scheme 78).[214b] From the mixture of Me_2Zn and oxygen in the presence of Bu^t–**162**, crystals of zinc oxo(methylperoxide) with a cubane-like structure were isolated in high yield. In the case of Me_2Zn, the oxygenation process was rather slow and proceeded in

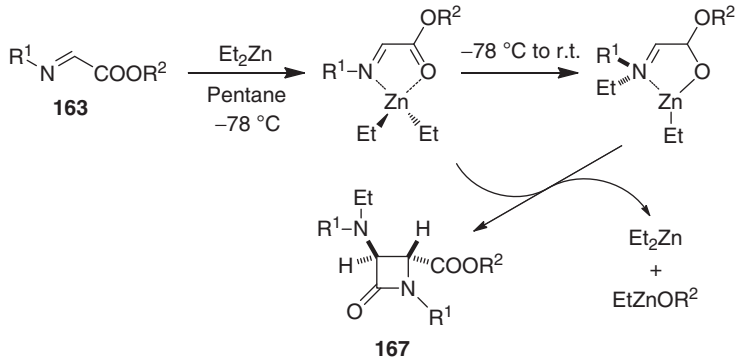


166

R_2Zn (equivalent)	R^1-I (equivalent)	Yield	*E*/*Z* ratio
Et_2Zn (2)	None	89% (R^2 = Et)	100/0
Me_2Zn (5)	None	32% (R^2 = Me)	100/0
Me_2Zn (3)	Bu^t-I (5)	96% (R^2 = Bu^t)	100/0
Me_2Zn (3)	Pr^i-I (5)	97% (R^2 = Pr^i)	98/2
Me_2Zn (3)	Bu^s-I (5)	99% (R^2 = Bu^s)	100/0
Me_2Zn (3)	Et-I (5)	34% (R^2 = Et), 35% (R^2 = Me)	100/0
Me_2Zn (3)	Et-I (10)	51% (R^2 = Et), 33% (R^2 = Me)	100/0



Scheme 70



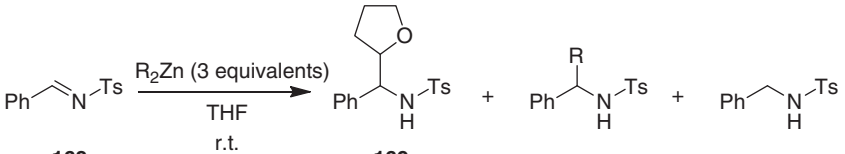
163

167

Scheme 71

several steps, resulting in the formation of many different types of oxygenated species. Time-course ^{1}H NMR analysis showed that MeOOZnMe formed initially and was gradually converted to zinc oxo(methylperoxide). They provided a plausible mechanism for the formation of the zinc oxo(methylperoxide) species: homolytic cleavage of the O–O bond in MeOOZnMe leads to the $MeZnO^•$ radical, which combines with Me_2Zn to give the MeZnOZnMe species and $Me^•$ radical. Subsequently, the resultant MeZnOZnMe species and methylperoxide MeOOZnMe yield the oxo(methylperoxide) species (Scheme 79).[214c] These results indicate that the widely accepted simple mechanism needs to be reconsidered as the nature of the oxidation is highly dependent on the Lewis base, reaction temperature, and alkyl groups on the zinc atom.

Bertrand et al. carried out EPR experiments using 5-diethoxyphosphoryl-5-methyl-1-pyrrolidine *N*-oxide (DEPMPO) as a radical trap and examined the relative concentrations of radical species involved in the reactions between R_2Zn and molecular oxygen (alkyl ($R^•$), alkoxyl ($RO^•$), and alkylperoxyl ($ROO^•$) radical species).[214f] When R_2Zn (R = Me, Et, or Bu^n) was mixed with

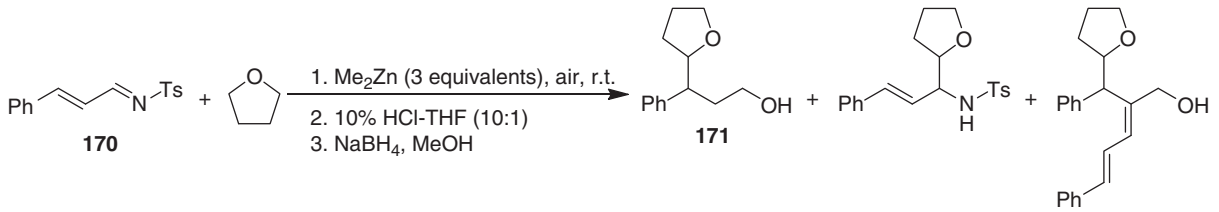


168 169

R_2Zn	Time	Method[a]	Product yields		
Me_2Zn	4 h	A	94%	0%	0%
Me_2Zn	48 h	B	4%	–	–
Me_2Zn	1 h	C	95%	–	–
Et_2Zn	4 h	A	48%	33%	2%
Pr^i_2Zn	4 h	A	6%	34%	27%
Ph_2Zn	4 h	A	0%	7%	0%

[a]Method A: Conducted under an Ar atmosphere, however, a trace amount of air-oxygen seemed to enter the reaction flask through the connections of the apparatuses.
Method B: Conducted under an Ar atmosphere and silicon grease on the connections prevented air invasion.
Method C: Conducted with an air stream of constant bubbling (10 mL/h).

Scheme 72

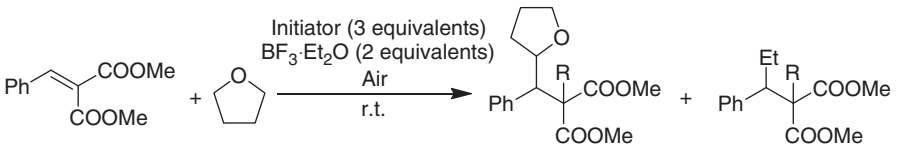


170 171

Method[a]	Product yields		
A	24% (*dr* = 7:3)	3% (*dr* = 3:2)	35% (*dr* = 7:3)
B	68% (*dr* = 7:3)	3% (*dr* = 3:2)	3% (*dr* = 7:3)

[a]Method A: Me_2Zn was added to a THF solution of imine within 1 min.
Method B: A THF solution of imine was was added to a solution of Me_2Zn in THF over 6 h.

Scheme 73

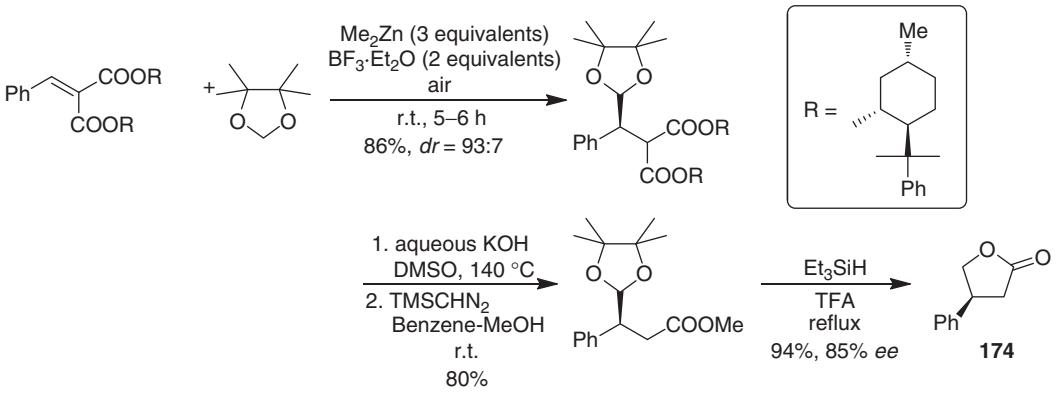


172 173

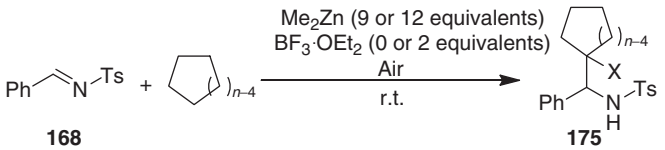
Initiator	Time	Product yields			
		R = H	R = Et	R = H	R = Et
Me_2Zn[a]	6 h	59%	0%	0%	0%
Me_2Zn	1.5 h	86%	0%	0%	0%
Et_2Zn	2.5 h	49%	0%	41%	0%
Et_3B	1 h	34%	26%	14%	18%

[a] Without $BF_3{\cdot}Et_2O$.

Scheme 74



Scheme 75

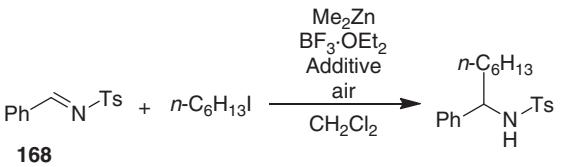


168 **175**

			Product yields	
n	Method[a]	Time	X = H	X = OH
5	A	61 h	59%	12%
5	B	70 h	68%	0%
6	A	48 h	68%	10%
6	B	56 h	80%	0%
7	A	108 h	48%	3%
7	B	72 h	61%	2%
8	B	72 h	54%	1%

[a] Method A: Conducted using Me_2Zn (12 equivalents) and $BF_3{\cdot}Et_2O$ (0 equivalent).
Method B: Conducted using Me_2Zn (9 equivalents) and $BF_3{\cdot}Et_2O$ (2 equivalents).

Scheme 76

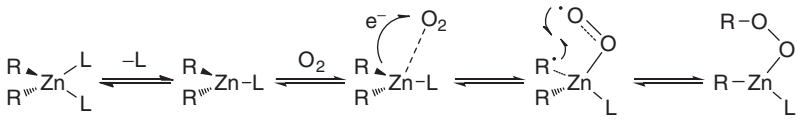


168

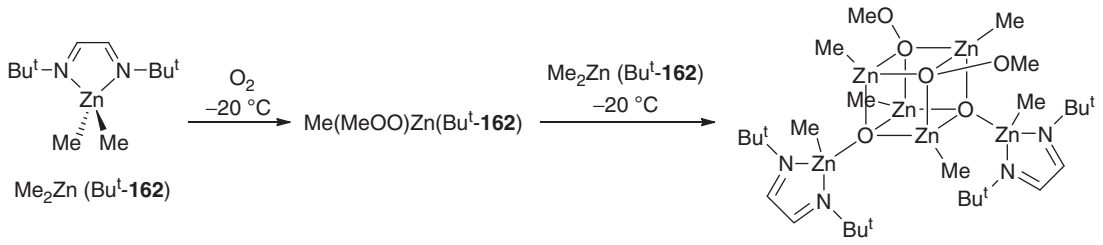
Entry	Me_2Zn (equivalent)	$BF_3{\cdot}Et_2O$ (equivalent)	Additive (equivalent)	Temp.	Time	Yield
1	6	6	None	r.t.	10 h	62%
2	6	6	CuI (0.1)	r.t.	6 h	64%
3	2	2	$Cu(OTf)_2$ (0.1)	r.t.	1.5 h	71%
4	2	None	$Cu(OTf)_2$ (0.1)	r.t.	24 h	45%
5	2	2	$Cu(OTf)_2$ (0.1)	0 °C	1.5 h	74%
6[a]	2	2	$Cu(OT)_2$ (0.1)	0 °C	1.5 h	5%

[a] Reaction conducted under an Ar atmosphere.

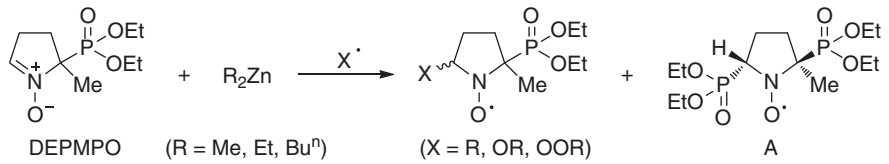
Scheme 77



Scheme 78



Scheme 79



	Relative ratios of the trapped radical X								
Temp. (K)	Me	OMe	OOMe	Et	OEt	OOEt	Bu^n	OBu^n	OOBu^n
183[a]	15	61	24	4	45	51	1	67	32
213[a]	27	42	31	12	55	33	3	73	24
273[a]	44	37	19	8	57	35	4	66	30
290[a]	51	44	5	11	61	28	10	73	17
290[a]	100	–	–	–	–	–	54	40	–
290[b,c]	23	56	16	32	37	9	35	49	–

[a]DEPMPO/R_2Zn used was 5:1.
[b]DEPMPO/R_2Zn used was 1:5. In these cases, a new nitroxide radical A was detected.
[c]The samples were measured after air bubbling.

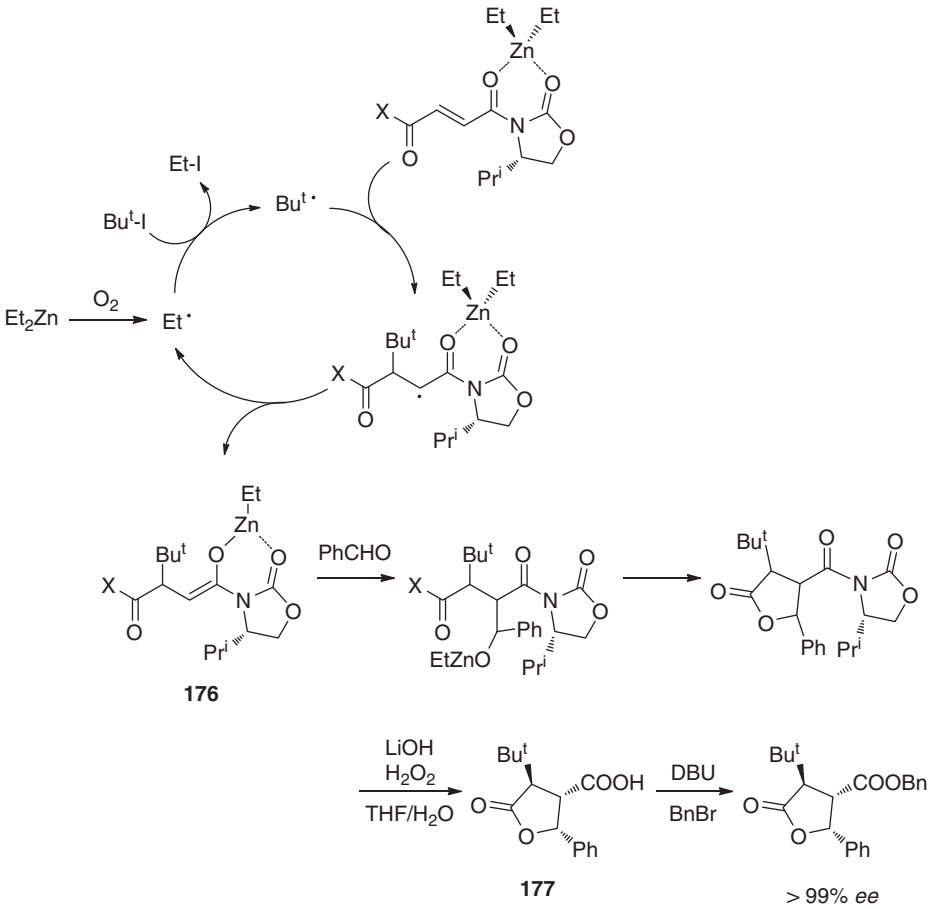
Scheme 80

an excess amount of DEPMPO at 183 K, the ratio of oxygen-centered radical species (RO$^\bullet$ and ROO$^\bullet$) to alkyl radicals was very high in all three cases, and was almost unchanged when the temperature was raised in the case of Et_2Zn and Bu^n_2Zn. This indicated that the adducts were sufficiently stable within this temperature range. In the case of Me_2Zn, the oxidation process to form oxygen-centered radical species was much slower than for the larger alkyl groups, with the rate of methyl radical trapping being seen to increase with temperature, indicating an increase in the quantity of methyl radicals generated. However, when the R_2Zn was used in excess with respect to DEPMPO with air bubbling at 290 K, which is similar to the general experimental conditions, the sum of concentrations of alkoxyl and alkylperoxyl radicals was higher for Me_2Zn (72%) than for Et_2Zn (46%) and Bu^n_2Zn (49%). This high concentration of oxygen-centered radicals probably resulted in the high radical reactivity of the Me_2Zn reagent to abstract hydrogen atoms from substrates such as ethers or alkanes (Scheme 80).

1.07.4.3 Application of Dialkylzinc-Mediated Radical Reactions to Domino Reactions

Recently, much attention has been paid to domino reactions (tandem reactions) because they are highly atom-economical and beneficial from the viewpoint of green chemistry for the preparation of target compounds. Radical reactions are especially useful in these applications because of their mild reaction conditions. Therefore, several radical domino reactions mediated by R_2Zn have been reported.

Bertrand et al. reported a pioneering study that combined 1,4-addition/aldol condensation reactions between *N*-enoyloxazolidinones and benzaldehyde initiated by Et_2Zn.[215a,b] The mechanism of this reaction was proposed as shown in Scheme 81. Ethyl radicals are first generated from Et_2Zn, and molecular oxygen concurrently reacts with *tert*-butyl iodide to give *tert*-butyl radicals. Subsequent 1,4-addition of the radicals to the substrate gives an enoxyl radical, which is converted into zinc enolate **176** by elimination of an ethyl radical. Enolate **176** is immediately trapped by benzaldehyde to give the corresponding aldols after quenching. Bertrand et al. introduced an Evans-type chiral oxazolidinone auxiliary and isolated the product in high stereoselectivity after oxidation. When the substrate was a type of fumarate derivative, further cyclization proceeded from the latter zinc

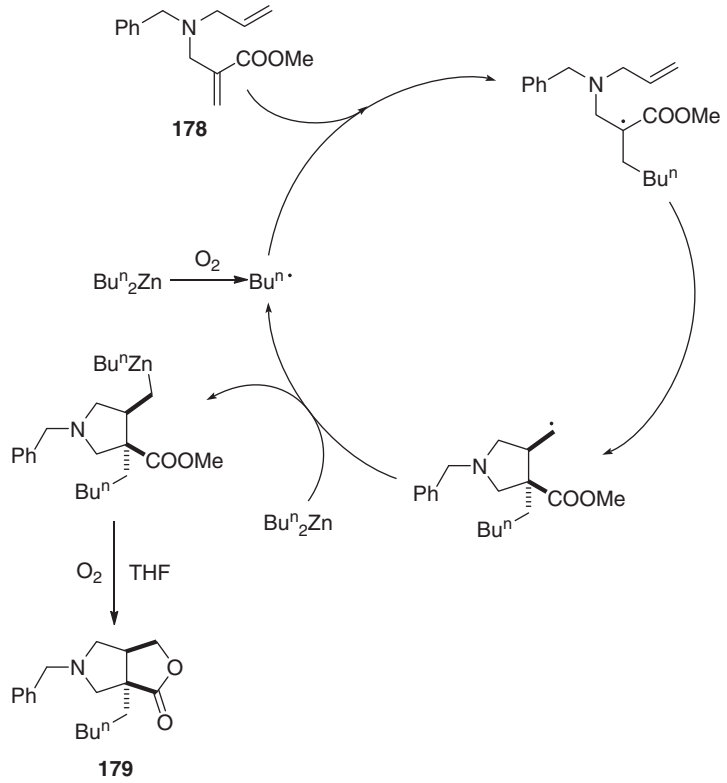


Scheme 81

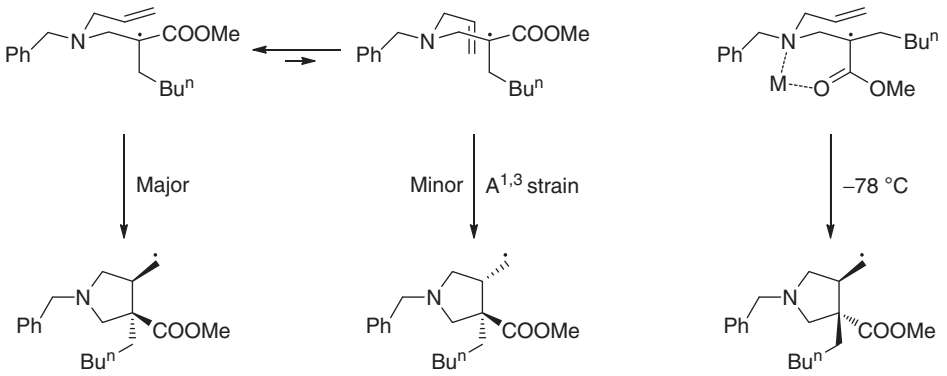
enolate to afford trisubstituted γ-lactones. Although the products were mixtures of five diastereomers, cleavage of the chiral auxiliary gave optically pure γ-lactone carboxylic acid **177**. This is because base-catalyzed epimerization occurs during cleavage of the chiral auxiliary and final stereochemistry would be determined by thermodynamic control.

Chemla et al. reported a radical domino reaction of β-*N*-allyl-*N*-benzyl amino esters **178** and Bu^n_2Zn to yield substituted pyrrolidines (Scheme 82).[215c,d] This reaction first involves the generation of an alkyl radical from Bu^n_2Zn and molecular oxygen, which then reacts with substrate **178** by Michael addition. The resultant radical adds to the unsaturated C═C bond in a 5-*exo*-trig fashion and is further reduced to form an organozinc species. Finally, this reacts with electrophiles to afford substituted *N*-benzyl pyrrolidines. When oxygen is present in the system, oxidation of the intermediate organozinc species further promotes intramolecular cyclization to afford bicyclic lactone **179**. The reaction proceeds stereoselectively, and *cis*-isomers are obtained as major products when the reaction is conducted at room temperature. This diastereoselectivity was found to be determined only by the cyclization step, which could be explained by the minimization of $A^{1,3}$ strain in the intermediate radical species. However, the stereoselectivity was reversed at low temperature, probably because of chelation of the carbonyl oxygen and nitrogen atoms to direct the ester group in a pseudoaxial position (Scheme 83). A similar reaction was conducted for β-allyloxy enoates in which the amino nitrogen was replaced by an oxygen atom to afford substituted furans.[215e]

Such domino reactions can be also applied to processes involving the formation of vinylzinc species. Bertrand et al. reported sequential 1,4-addition/cyclization reactions of *N*,*N*-diallylpropiolamide **180** initiated by R_2Zn to give corresponding 3-alkylidene-2-pyrrolidones **181** (Scheme 84).[216a] They combined R_2Zn and tertiary (or secondary) alkyl iodides to give tertiary (or secondary) alkyl radicals, which added to the triple bond, followed by 5-*exo*-trig cyclization and reduction to afford the corresponding lactams. In this reaction, a catalytic amount of R_2Zn should be enough to complete the reaction; however, the high and low reactivities of Et_2Zn and Me_2Zn, respectively, prevent their catalytic use. When this reaction was carried out for allyl propiolate **182**, which is an analog of *N*,*N*-diallylpropiolamide **180** in that an allylamino nitrogen atom is replaced by an oxygen atom, no cyclized products were obtained, with only the addition of an alkyl radical to the triple bond observed with the allyl



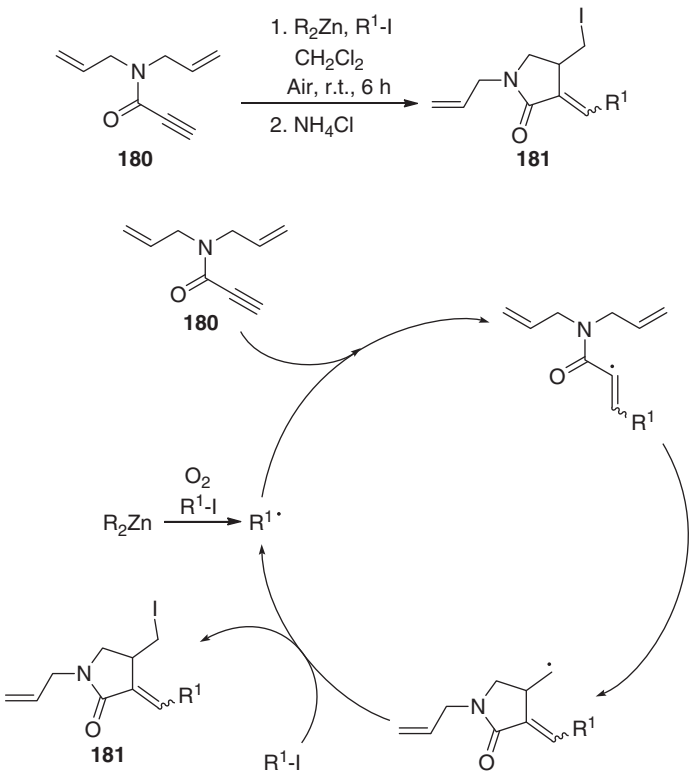
Scheme 82



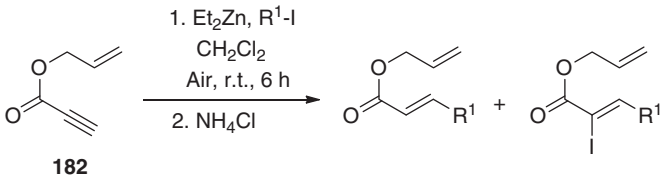
Scheme 83

group left intact (Scheme 85). This is because it is unfavorable for the reaction to proceed via the intermediate α-alkoxycarbonyl radicals to produce the less stable (*E*)-rotamer following 5-*exo*-trig cyclization. Similarly, Chemla et al. showed that R_2Zn-mediated 1,4-addition/cyclization reactions of *β*-(propargyloxy)enoates **183** afford substituted alkylidene tetrahydrofurans **184**.[216b] The 1,4-addition of the alkyl radical afforded the corresponding enoxy radical and subsequent 5-*exo*-dig cyclization and reduction by R_2Zn resulted in the vinylzinc intermediate, which was further trapped by an appropriate electrophile (Scheme 86).

Bertrand et al. presented another example of a radical domino reaction: stereoselective preparation of disubstituted *γ*-lactone **185** from acyloxymethyl iodide and diethyl fumarate mediated by Me_2Zn (Scheme 87).[216c] This reaction involved the generation



Scheme 84



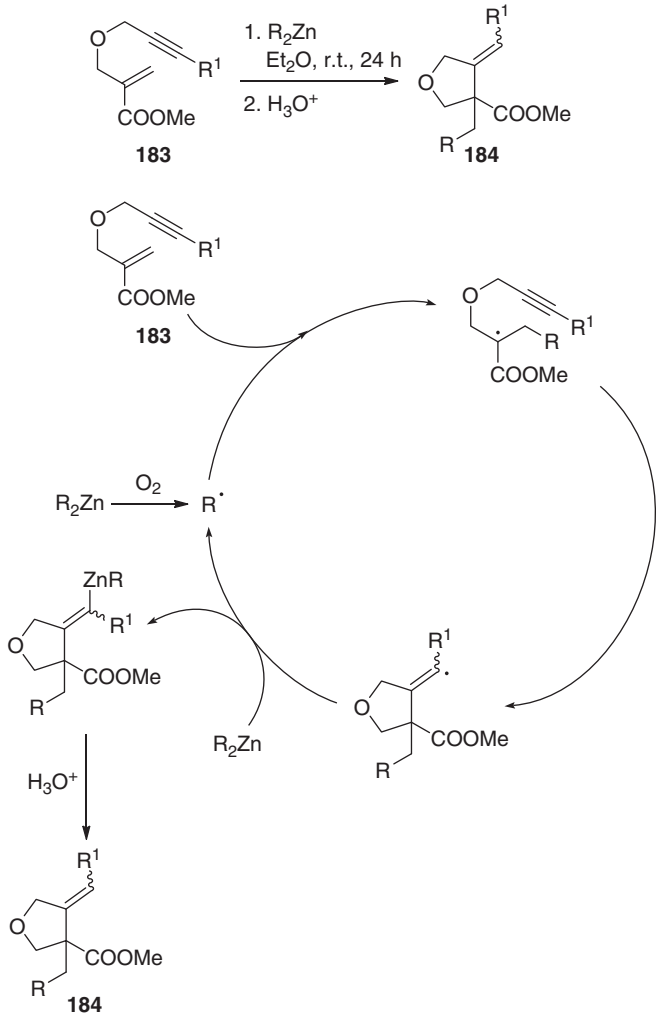
Entry	Et_2Zn (equivalent)	R^1-I (10 equivalents)	Yield[a]	Product ratio
1	1.5	Bu^t-I	89%	98:2
2	0.4	Bu^t-I	73%	27:73
3	0.2	Bu^t-I	79%	13:87
4	1.5	Pr^i-I	87%	83:17
5	0.4	Pr^i-I	78%	28:72
6	0.2	Pr^i-I	70%	14:86

[a] Sum of individual isolated yields.

Scheme 85

of the acyloxymethyl radical and its 1,4-addition to fumarate. A methyl radical was formed from the resulting α-acyloxy radical to give a zinc enolate. Successive intramolecular acyl transfer and nucleophilic substitution gave *trans*-γ-lactones **185**. It is notable that the reaction product was dramatically altered by using additives. Addition of $BF_3 \cdot Et_2O$ afforded lactol **186** that was isolated as the dihydrofuran after dehydration. Addition of ytterbium(III) triflate ($Yb(OTf)_3$) prevented the acyl transfer and only gave adduct **187** of the acyloxymethyl radical and the substrate (Scheme 88).

Tomioka et al. extended their study of α-THF radicals generated from Me_2Zn and THF to the domino reaction of benzylidenemalonate with a formyl group at its *ortho*-position (Scheme 89).[216d] Owing to the high chemoselectivity of the addition reaction of the α-THF radical stated above, sequential 1,4-addition/5-*exo*-trig aldol cyclization reactions proceeded, and indane



Scheme 86

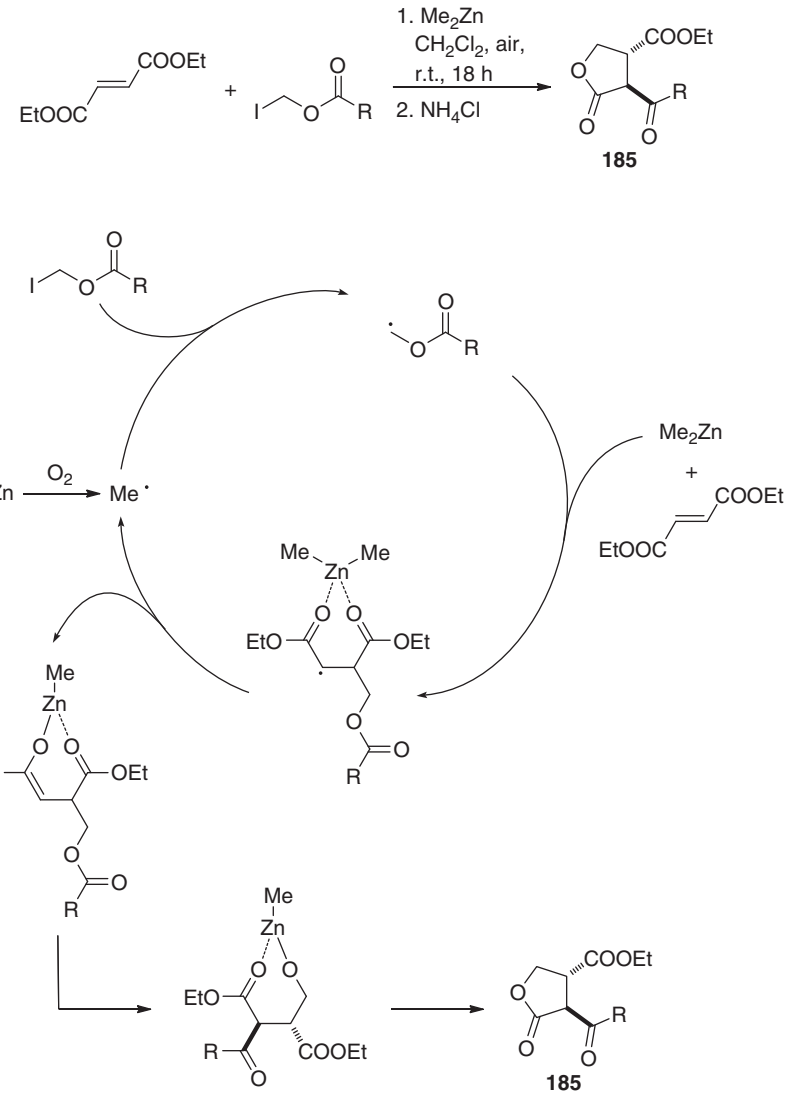
skeleton **188** was constructed as a mixture of four diastereoisomers. They also showed that further reduction of the acetal and benzylic moieties by triethylsilane successfully gave tricyclic lactone **189** (Scheme 90).

1.07.4.4 Other Reactions Involving Organozinc Reagents

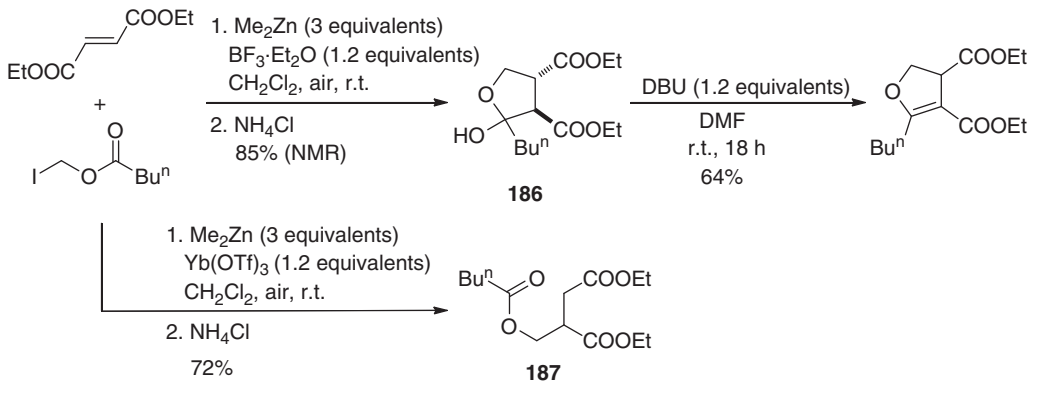
Here the authors summarize some other recent advances using organozinc reagents that could not be classified into the above categories, but are still highly significant in this area of research. Mikami et al. reported radical trifluoromethylation of ketone silyl enol ethers by trifluoromethyl iodide and Et_3B in the presence of air (Scheme 91). In this reaction, addition of Et_2Zn activated the substrate by complex formation and significantly improved the product yield (from 6% to 75%).[217a,b]

Miyabe et al. demonstrated the sequential transformation of arynes to *ortho*-disubstituted aminophenols **190** using formamide and R_2Zn (Scheme 92).[217c] The aryne generated upon elimination of the trimethylsilyl and triflate groups of the precursor by fluoride anions undergoes [2 + 2] cycloaddition with the C═O bond of formamide. The resultant strained four-membered intermediate oxetane is in equilibrium with the more stable quinone methide, which further reacts with R_2Zn to give the alkylated aminophenol **190**. Use of Et_3B instead of Et_2Zn in the reaction afforded only a trace amount of the ethylated product, indicating that the reaction does not involve a radical pathway.

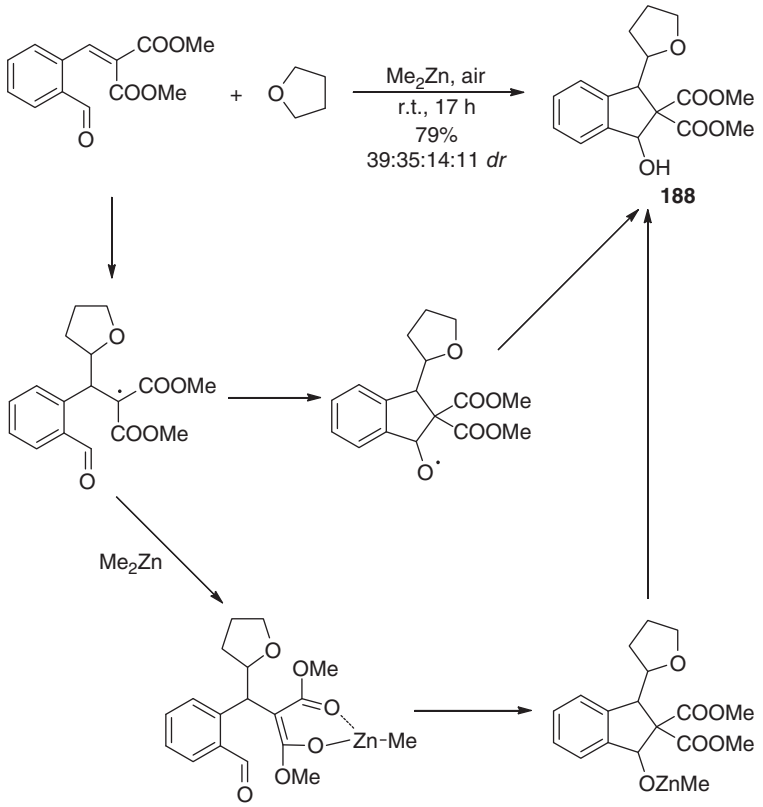
The addition reaction summarized in Section 1.07.2 has been rapidly expanded through investigation of various organozinc reagents, substrates, and ligands. In these reactions, the organozinc reagent shows an ionic character and allows a variety of addition reactions activated by an appropriate ligand. Considering the history, a new aspect of organozinc reagent described in this section, a radical character, enables synthetically useful addition reaction to further expand the potential of organozinc reagent.



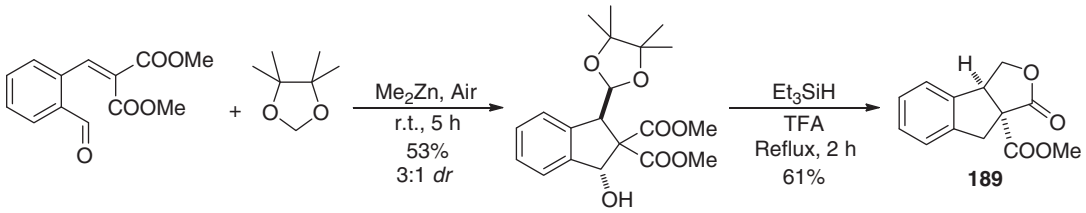
Scheme 87



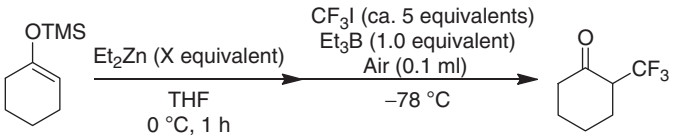
Scheme 88



Scheme 89

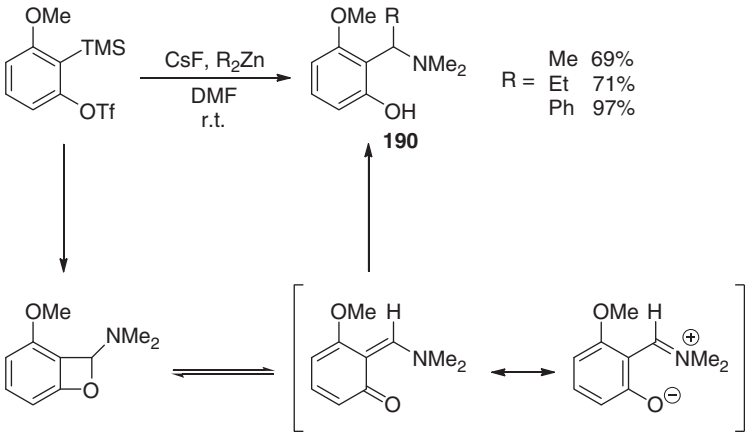


Scheme 90



Entry	Et_2Zn (equivalent)	Time (h)	Yield (%)
1	0	1	6
2	0	6	16
3	0	20	28
4	0.1	1	14
5	0.1	20	43
6	0.5	1	55
7	0.5	20	76
8	1.0	1	75

Scheme 91



Scheme 92

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1.08 Organocerium Reagents

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Glossary

Conjugated systems Molecules that have alternating single and double bonds, and the p electrons can interact with each other to give enhanced stability.
Cyclic compound Molecule that has the two ends of the carbon chain connected together.
Functional group The reactive grouping of atoms in an organic molecule; the functional group changes during the course of an organic reaction.
Heteroatom An atom other than carbon.
Mechanism A proposed pathway for a given reaction.
Multistep synthesis Preparation of a compound by a route that requires several steps.
Natural product A product synthesized in nature.
Nucleophilic addition Reaction in which a nucleophile is added to a multiple bond.
Reagent A compound or mixture added to a system to cause a chemical reaction or test if a reaction occurs.
Target molecule The desired end product of a synthesis.
Transmetallation Metal exchange.

1.08.1 Introduction

Compounds that contain a metal–carbon bond, RM, are known as organometallic compounds, and they provide a source of nucleophilic carbon atoms which can react with electrophilic carbon to form a new carbon–carbon bond. The extensive application of new RM systems has recently received great attention in the synthesis of well-defined molecular species with potential relevance to the chemical biology and the material sciences.[1] The use of organometallics in organic synthesis is an important part of many synthetic processes both in academic and industrial laboratories.[2] However, in spite of their broad utility, RM compounds generally exhibit strong basicity, and, therefore, competition between nucleophilic addition and acid-base type exchange reactions has attracted enormous attention in organic synthesis.[3]

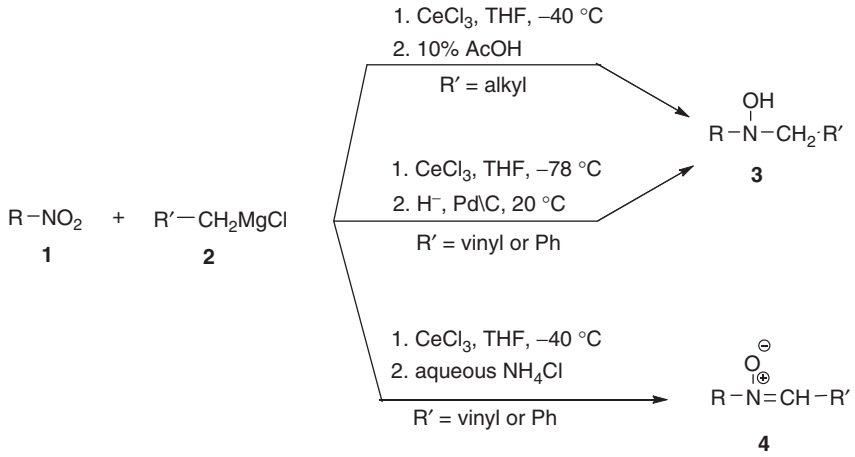
Organolanthanide derivatives are relatively inexpensive organometallic reagents that are useful in carbon–carbon bond-forming reactions. Intense research activity has led to a variety of experimental protocols that have become mainstay methods of choice in organic synthesis.[4] Organolanthanides are organometallic reagents of low toxicity.[5] They readily hydrolyze when exposed to air and moisture, and should routinely be handled under an inert gas atmosphere by application of Schlenk-line either 'and' or 'or' glove-box techniques.

Lanthanides are often called the rare earth elements, but they are not really rare (with the exception of promethium which is radioactive and does not occur naturally). Cerium, which is the most abundant in the lanthanide series, is more abundant than cobalt, tin, and zinc. This chapter will address the utility of organocerium reagents in organic synthesis. With the term 'organocerium reagents' we can include any species made up of an organic fragment and cerium metal, hence not only compounds containing carbon–cerium bonds, but also, for example, oxygen-cerium such as cerium enolates can be included. Other organolanthanide reagents will be covered in other chapters in this volume.

1.08.2 Organocerium Reagents

The three most common cerium reagents in organic synthesis are ceric ammonium nitrate (CAN), cerium trichloride heptahydrate ($CeCl_3 \cdot 7H_2O$), and organocerium reagents.[6] The latter were discovered and first exploited in organic synthesis by Imamoto in 1982.[7] After his pioneering work, these reagents have extensively been used as organocerium species able to add to electrophilic

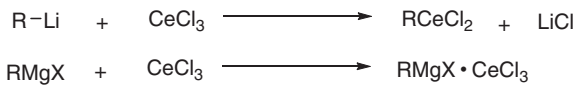
substrates having a high reduction potential or containing acidic hydrogens.[8] Although the treatment of an aliphatic nitro-compound like **1** with a Grignard reagent **2** resulted in an intractable mixture of several products, the reaction between **1** and an organocerium reagent showed interesting synthetic utilities. The course of the reaction depends on the nature of the carbanionic framework (Scheme 1). The use of alkyl organocerium reagents allowed the formation of *N*,*N*-disubstituted hydroxylamines **3** in good yields,[9] and allylic or benzylic organocerium reagents[10] have provided a good approach to the synthesis of nitrones **4** or by reduction to the corresponding hydroxylamines **3**.



Scheme 1

1.08.2.1 Preparation of Organocerium Reagents

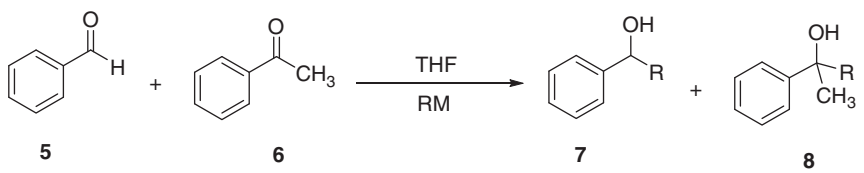
The broad utility of organocerium reagents in nucleophilic additions is possible because they can be easily prepared from the corresponding organomagnesium (Grignard reagents, RMgX) or organolithium compounds (RLi) (Scheme 2). Organocerium reagents derived from RLi are stable only at low temperature, and they are generally used at −78 °C.



Scheme 2

Organocerium compounds derived from RMgX are most stable and are prepared at temperatures ranging from −20 °C to 0 °C, with the exception of alkenyl and alkynyl derivatives, which require reaction temperature below −60 °C. The more convincing evidence supporting the existence of two different structure for organocerium reagents is that the RLi/$CeCl_3$ complexes are better nucleophiles and poor bases than the RMgX/$CeCl_3$ complexes.[11] Although the actual nature of organocerium is not yet well-known, it is a common view that those derived from RLi should have a structure resembling that of a true organocerium species ($RCeCl_2$); whereas those derived from RMgX are *ate*-complexes. In both cases, reagents containing a large variety of carbon frameworks are available, including primary, secondary, and tertiary alkyl groups as well as alkynyl, alkenyl, and aromatic moieties.

The reactivity of organocerium reagents depends significantly on the nature of the coordinating anion of the cerium(III) salt (Scheme 3), and RLi/$CeCl_3$ behaves chemo-randomly in contrast with the >99% aldehyde selectivity displayed by RMgX/$CeCl_3$ (Table 1).[12] (Reaction of organocerium reagents with enones and related compounds leads almost exclusively to 1,2-addition products. The kinetic preference for 1,2-addition has been properly explained on the basis of the Pearson's hard-soft principle: the



Scheme 3

Table 1 Chemoselective reactions of organocerium reagents in THF (Scheme 3)

No	*RM*	***7:8***	*Yield (%)*	*References*
i	$CH_3Li/CeCl_3$	50:50	99	12
ii	$CH_3Ce(OPr^i)_3Li$[a]	82:18	90	12
iii	$CH_3Ce(OPr^i)_3MgCl$[b]	99:1	80	12
iv	$PhLi/CeCl_3$	50:50	95	12
v	$PhMgBr/CeCl_3$	99:1	81	12
vi	$PhCe(OPr^i)_3MgBr$[c]	99:1	80	12

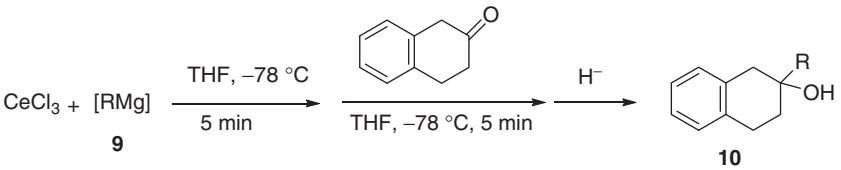
[a]From CH_3Li and $Ce(OPr^i)_3$.
[b]From $CeCl_3 \cdot 3^iPrOH$ and 4 equivalents of CH_3MgCl.
[c]From PhMgBr and $Ce(OPr^i)_3$.

hard cerium compound prefers to add to the hard carbonyl group.) Anhydrous $CeCl_3$ is the common reagent used in the preparation of organocerium reagents, and, although it is commercially available, it can be easily prepared by the dehydration of the heptahydrate form *in vacuo*.[13] Finally, ground $CeCl_3 \cdot 7H_2O$ is heated gradually from 135–140 °C under high vacuum (<0.5 mmHg), and by this thermal dehydration the oxidation of Ce^{3+} to Ce^{4+} has been a drawback. In fact, the thiosulfate titration method has shown that the amount of Ce^{4+} found under these conditions is generally less than 0.5% (w/w) the drying process.[14] Thus, the preparation of organocerium reagents according to the original methods of Imamoto follows:

1. From RMgX: a solution of RMgX (1 equivalent) in THF or Et_2O is added dropwise to a vigorously stirred suspension of anhydrous $CeCl_3$ (1 equivalent) in THF at 0 °C under inert atmosphere, and the stirring is continued for 1.5 h. The reaction mixture usually results in a dark gray suspension.
2. From RLi: a solution of RLi (1 equivalent) in THF or Et_2O is added dropwise to a vigorously stirred suspension of anhydrous $CeCl_3$ (1 equivalent) in THF at −78 °C under argon atmosphere, and the stirring is continued for 30 min. The reaction mixture usually results in a yellow or brownish red suspension.

Organocerium reagents cannot be stored for a long time and must be prepared immediately before use. Generally, the reactions are carried out by adding the THF or Et_2O solution of a given electrophilic substrate to a freshly prepared suspension of organocerium compound in THF at the appropriate temperature. The use of THF leads to improved yields and reduced reaction times, compared to the use of Et_2O. THF is more basic than Et_2O and strongly coordinates metals, especially oxophilic cerium. Even if the material obtained after thermal drying of $CeCl_3 \cdot 7H_2O$ contains water,[15] the suspension of 'dehydrated' $CeCl_3$ in THF is highly efficient without the need for a large excess of organolithium or Grignard reagent. In principle, commercially available anhydrous $CeCl_3$ might be preferred over the heptahydrate because the drying step is eliminated; however, the reaction efficiencies tend to be lower, probably due to nonuniform or excessively large $CeCl_3$ particle size, even after sonication of the commercial reagent. Reuman et al. have observed an incomplete activation of $CeCl_3$ and subsequent incomplete formation of the $RM/CeCl_3$ complex.[16] There were improved results if the dry $CeCl_3$ purchased is ground to a fine powder and sonicated before RM addition. The simultaneous stirring and sonication operations are efficient even for large runs, but when the magnetic stirring is changed to overhead stirring, the $CeCl_3$ would remain well suspended during the reaction.

Finally, Matsubara and coworkers[17] have proposed the use of R_2Mg instead of RMgX in the preparation of organocerium reagents. The combination of R_2Mg, which is formed from RMgX through Schlenk equilibrium, and anhydrous $CeCl_3$ provides the corresponding organocerium reagent efficiently that allows the 1,2-addition to a highly enolizable ketone (Scheme 4).



[RMg]	Yield	References
n-BuMgBr	66%	17
n-Bu_2Mg	81%	17

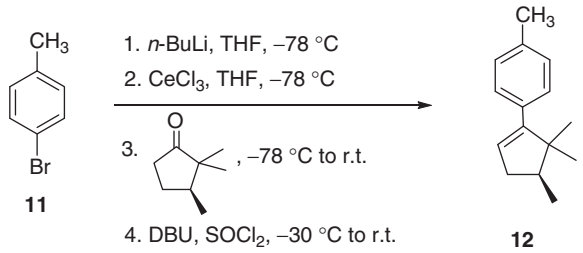
Scheme 4

β-Tetralone (**9**) is one of the most difficult carbonyl compounds for organometallic reagent to carry out a nucleophilic addition owing to the high C-H acidity. To suppress the undesired deprotonation, the illustrated organocerium reagents were tested and

found to deliver the adduct **10** in good yields. The use of R_2Mg, prepared by addition of 1,4-dioxane to an ethereal solution of RMgX, for the preparation of Ce-complex reagents gave better yields than that of RMgX.

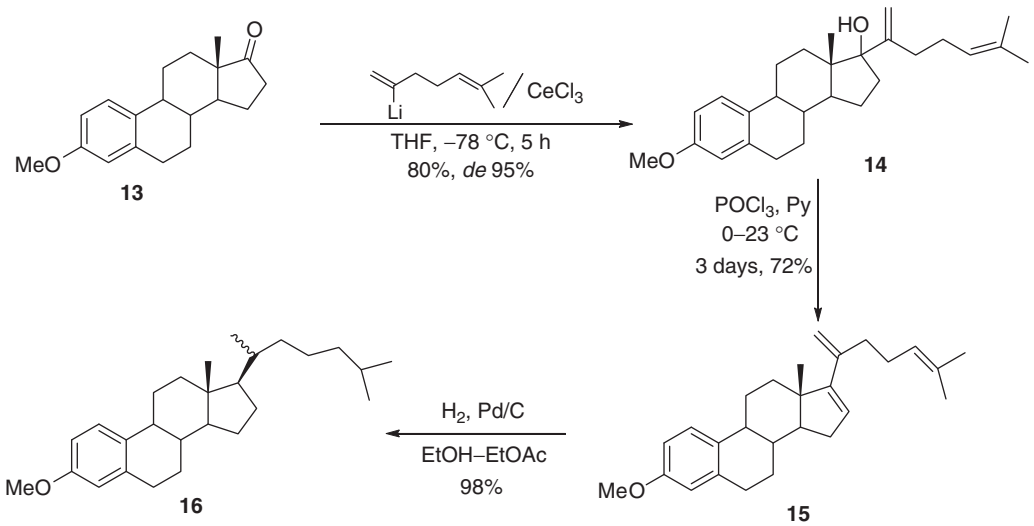
1.08.2.2 Addition to Carbon–Oxygen Double Bond

The organocerium reagent addition to carbon–oxygen double bond has found broad utility in organic synthesis. These additions usually occur much more smoothly than those of the parent organolithium or organomagnesium reagents. The addition to carbonyl compounds with these strongly basic organometallic reagents often leads to unwanted reactions such as enolization, metal-halogen exchange, reduction, and pinacol coupling. Improved yields of the corresponding alcohols from carbonyl compounds have been obtained in the addition of organometallic reagents in the presence of anhydrous cerium(III) species. $Ce(OPr^i)_3$ can sometimes be substituted for $CeCl_3$, but the yields (under the same reaction conditions) can be better for the latter.[18] The use of the organocerium reagent avoids operating in strongly basic conditions and it suggested to Lecourné and coworkers[19] a one-pot method for the preparation of various aryl- and heteroarylcycloalkanes. The lithiation of aryl and heteroaryl bromides with *n*-BuLi is followed by transmetallation with $CeCl_3$, and the addition to cycloalkanones provides the intermediate alkoxide, which is not quenched. Addition of a base and $SOCl_2$ leads to the desired aryl- or heteroarylcycloalkenes, and a short total synthesis of (±)-laurokamurene B (**12**) making use of this procedure has been reported (Scheme 5).



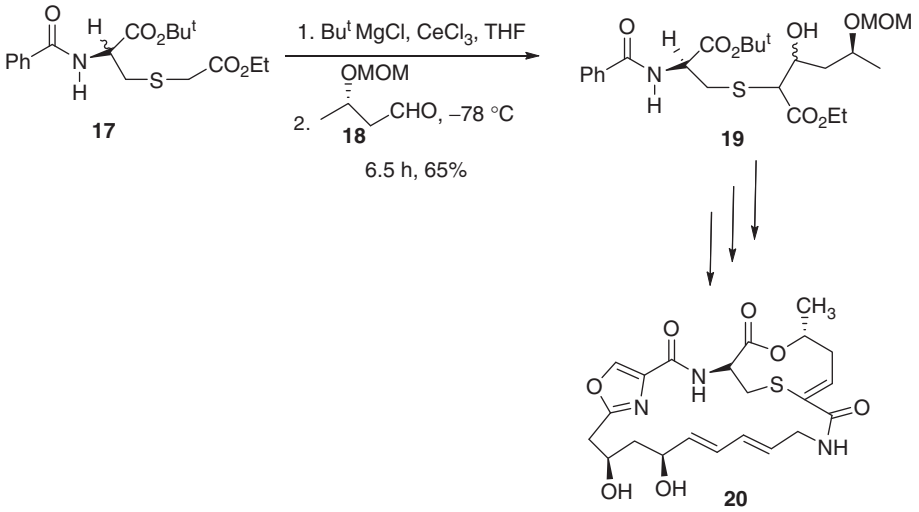
Scheme 5

The construction of quaternary centers is a major contemporary challenge in organic chemistry, in particular when stereogenic centers are involved. Christoffers and coworkers[20] have reported, on the introduction of the saturated 1,5-dimethylhexyl side chain onto an cholestane skeleton (**16**) using transmetalation of an unsaturated organolithium to organocerium reagent as a first step (Scheme 6). The intermediate tertiary alcohol **14** has been obtained without formation of any byproduct and in good yield. This method works very well for preparing allylic alcohols, which are versatile intermediates for the synthesis of biologically active compounds. In this strategy, the organocerium solution developed to overcome initial difficulties in the addition of vinylorganometallic reagents to carbonyl derivatives has served as valuable methodology to obtain polyfunctionalized allylic alcohols.



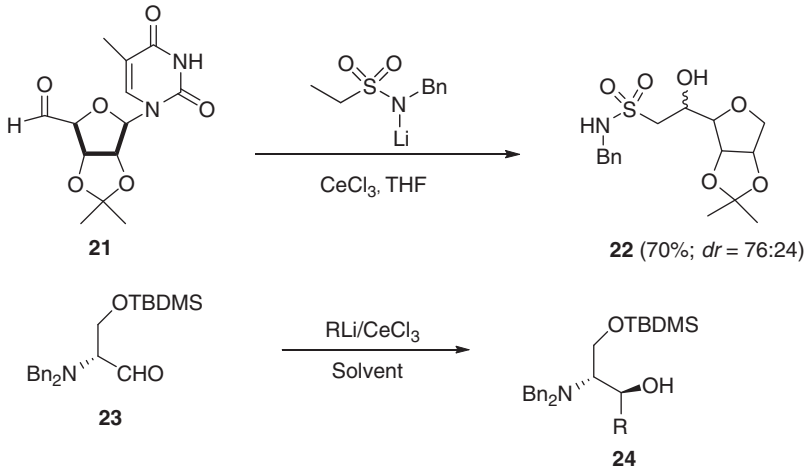
Scheme 6

These observations suggested that dry cerium(III) chloride works as an efficient activator for the addition of carbanion to the carbonyl moiety, and it has been used in promoting the formation of the alcohol **19**. This is a key intermediate of griseoviridin (**20**), the most structurally complex member of streptogramin antibiotics (Scheme 7).[21] The *tert*-butyl Grignard in the presence of $CeCl_3$ has been used as a base to generate the corresponding anion, which, after subsequent transfer by cannula to a mixture of chiral aldehyde **18** and dry $CeCl_3$ in THF at −78 °C, afforded a mixture of desired diastereomeric alcohols **19** in 65% yield. Although the distereomers could be separated by chromatography, such separation has not been necessary because both of them permit access to griseoviridin. Attempts of using Grignard reagent without $CeCl_3$ have not been successful, nor have efforts involving replacement of the Grignard with an alkyllithium. It should be noted that in several other examples the organocerium reagents derived from organolithiums represent a prerequisiste for the positive outcome of the reaction, whereas cerium-magnesium are ineffective;[22] therefore, the evaluation of both reagents is recommended for synthetic applications.



Scheme 7

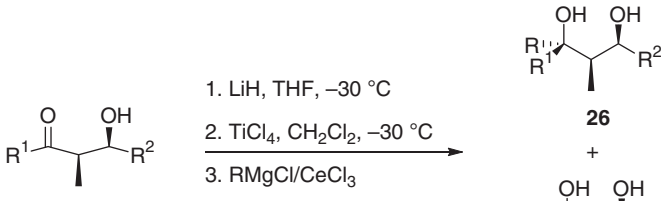
The ability of $CeCl_3$ to mediate high yielding and highly diastereoselective transfer of carbon frameworks to base-sensitive carbonyl compounds has been utilized in the addition to substrates of biological relevance, such as steroids, sugars, nucleosides (**21**), and *N*-protected amino aldehydes (23) (Scheme 8).[23] The usefulness of this procedure resides especially in its compatibility with a range of substrates having base-epimerizable centers adjacent to carbonyl groups, and it demonstrates the high potential for important synthetic applications.



Scheme 8

The presence of $CeCl_3$ in the reaction mixture has improved the efficiency of the reaction mixture and influenced the stereochemical course. Given that the construction of an alcoholic unit with a defined configuration represents an important target in

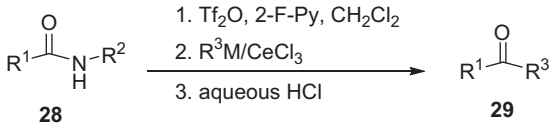
organic synthesis, remarkable importance has received the $TiCl_4$-mediated addition of organocerium reagents to enolizable *syn*-β-hydroxy ketones **25** (Scheme 9). The reaction proceeds with very high diastereoselectivity with exclusive formation of the diastereoisomer derived from the attack of the carbanionic opposite to the α-alkyl group.[24]



R	R^1	R^2	Yield (%)	26:27	References
Me	Et	Ph	77	93:7	24
Bn	Et	Ph	85	96:4	24
PhC≡CH	Et	Ph	95	92:8	24
Et	Et	Et	93	99:1	24

Scheme 9

Ketones are a class of extremely versatile molecules, and as a consequence, the transformation of easily available secondary amides into ketones is of high importance in organic synthesis. After the efficient conversion of Weinreb amides[25] or of morpholine amides[26] to ketones, a general method for the direct conversion of secondary amides into ketones by deaminative alkylation with organocerium reagents has been reported. The efficiency of the method required the treatment of the solution of the amide and 2-fluoropyridine with Tf_2O before and organocerium reagents later (Scheme 10, Table 2).[27] These nucleophiles are more efficient than organomagnesium, organolithium, and organozinc species. The reduced basicity and higher oxophilicity of organocerium reagents, together running the reaction at low temperature such as −78 °C, circumvent the problem of overalkylation of the reaction products to tertiary alcohols even in the presence of an excess of $RM/CeCl_3$ complex. This suitable and general application of organocerium reagents for ketone synthesis is known, although less commonly, for other carboxylic acid derivatives.[6]



Scheme 10

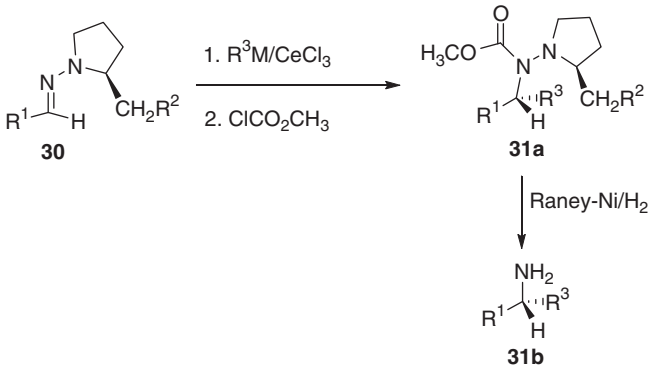
Table 2 One-pot transformation of secondary amides into ketones (Scheme 10)

No	*R^1*	*R^2*	*R^3M*	*Yield (%)*	*References*
i	Ph	*n*-Bu	*n*-BuMgBr	90	27
ii	Ph	*c*-Hex	*n*-BuLi	87	27
iii	4-$NMe_2C_6H_4$	*c*-Hex	EtMgBr	83	27
iv	*n*-$C_{11}H_{23}$	*n*-Bu	Vinyl MgBr	70	27
v	4-NO_2Ph	Bn	BnMgBr	68	27

1.08.2.3 Addition to Carbon–Nitrogen Double Bond

Nitrogen atoms are present in a large number of molecules that are particularly important for their widespread occurrence in natural products and in biologically interesting compounds. Several synthetic methods for introducing nitrogen-containing organic fragments into organic molecules have been reported, and among them the nucleophilic addition of organometallic

reagents to azomethine moieties still occupy a prominent position. Unfortunately, the poor electrophilic character of carbon–nitrogen double bonds often promotes the α-metalation rather than addition of the substrates during the reaction with RMgX or RLi. In this regard, the strong propensity of cerium(III) salts in being coordinated with Lewis bases permitted the addition of functionalized carbanions to the imine function and its derivatives for the generation of amino functions. The groups of Enders[28] and Denmark[29] have studied the enantioselective addition of organocerium reagents derived from both organolithium and organomagnesium precursors to chiral imino functions. The studies have led to an increase in the available methods for the direct formation of chiral amines by asymmetric transformations of azomethine precursors. In particular, organocerium reagents add to chiral 2-alkylpyrrolidine hydrazones **30** in good yield and with high diastereoselectivities (**Scheme 11**, **Table 3**). Adding a second ligating atom one methylene unit away had no effect on the selectivity of the reaction (entry iii).[30] The lowest selectivity has been observed with hydrazones possessing an alkoxide side chain (entry iv).[32] Good selectivity is even observed when a nitrogen replaces an oxygen atom (entry v).[31] The strategy afforded products with >95:5 *dr*, but the diastereoselectivity cannot be due only to binding sites in the auxiliary side chain. For explaining the stereoinduction in the addition described by entry vii, other factors must be considered since no additional Lewis basic atom is present. To illustrate the synthetic utility of this methodology, the crude air-sensitive hydrazines **31a–b** have been hydrogenated over Raney-nickel to afford the free amines.

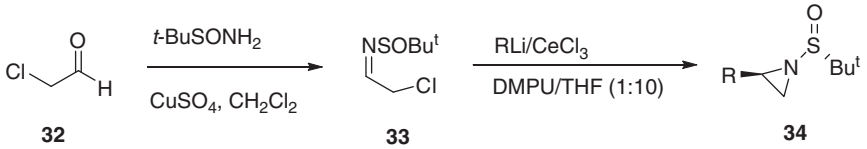


Scheme 11

Table 3 Additions of organocerium reagents to 2-alkylpyrrolidine hydrazones (**Scheme 11**)

No	R^1	R^2	R^3M	dr	*Yield (%)*	*References*
i	$PhCH_2CH_2$	OCH_3	MeLi	98:2	80	29
ii	$PhCH_2CH_2$	OCH_3	MeMgBr	97:3	76	28
iii	$PhCH_2CH_2$	$OCH_2CH_2OCH_3$	*n*-BuLi	97:3	72	30
iv	$PhCH_2CH_2$	H	*n*-BuLi	70:30	75	30
v	$PhCH_2CH_2$	$CH_2CH_2N(CH_3)_2$	*n*-BuLi	90:10	61	31
vi	CH_3	$OCH_2CH_2OCH_3$	$PhCH_2CH_2$	4:96	53	32
vii	$PhCH_2CH_2$	$CH(CH_3)_2$	*n*-BuLi	97:3	95	29

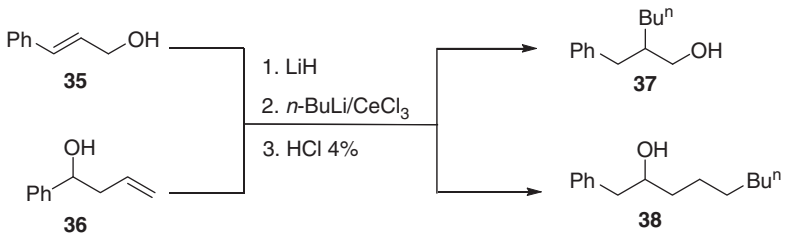
Even if the synthesis of nitrogen-containing organic molecules by double addition of organocerium reagents to nitriles is not very commonly used, in the past years particular attention has received the addition to substrates such as N-sulfenyl imines. Addition to *N-tert*-butylsulfinyl aldimine **33** have been reported. The elcrtophile is prepared from anhydrous chloroacetaldehyde (**32**) and commercially available *t*-$BuSONH_2$ (**Scheme 12**).[33] The reaction allows to obtain *N-tert*-butylsulfinyl aziridines **34** in good yields and with good diastereomeric ratios. The diastereoselectivity in THF could be further improved to >99:1 by addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone (DMPU) as cosolvent, and the aziridines bearing an electron-withdrawing activating group on nitrogen undergo easily ring-opening reactions with nucleophiles.[34]



Scheme 12

1.08.2.4 Addition to Carbon–Carbon Double Bond

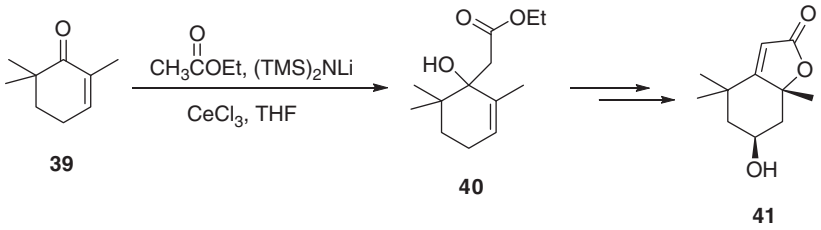
It has been reported so far that $CeCl_3$ is an efficient additive to depress proton abstraction and redox processes in the reaction of organometallic RM precursors with carbonyl and imine compounds. Because of the easy availability of organocerium reagents it seemed of interest to utilize their efficiency in the Michael addition to nitro alkenes[35] and to secondary β-amino ketones.[36] Otherwise, since nonconjugated carbon–carbon double bonds are generally inert toward nucleophilic attack, the addition of organocerium reagents has not yet found general synthetic applications, especially because of the extreme reaction conditions required. In organic synthesis is worthy of note only the combination of both organolithium compounds and lithium hydride with dry $CeCl_3$ and a range of allyl, and homoallyl alcohols (Scheme 13).[37] The formation of a negatively charged oxygen-containing species is essential for the reaction to proceed. It should be noted that when organocerium reagent is prepared from $CeCl_3$ and a Grignard reagent instead of an alkyllithium, the reaction proceeded more slowly and less efficiently.



Scheme 13

1.08.3 Cerium Enolates

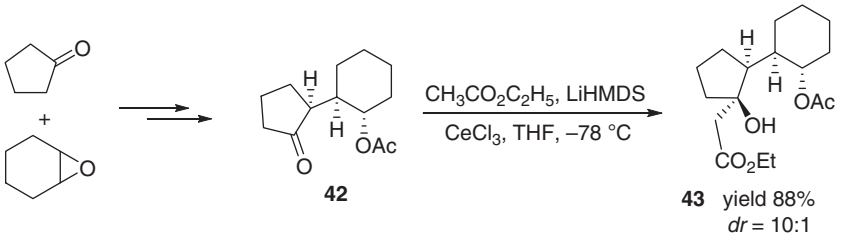
The functionalized β-hydroxy and β-amino carbonyl compounds are in strong demand in the pharmaceutical and agricultural industries. Due to the importance of these classes of compounds, considerable efforts have been directed toward the development of processes for their synthesis. The addition of metal enolates to carbonyl compounds or imines is one of the better methods for the synthesis of β-substituted carbonylic molecules. Many desirable target molecules have stereogenic centers at α- and β-position and may have only one useful stereoisomer. Therefore, it is important that the condensation reaction be stereoselective. Generally, lithium enolates have been the most applicable of these reagents, but their high basicity and poor nucleophilicity limit the applicability of this process. The use of other metal enolates has produced mixed results. Zinc and aluminum enolates react with both enolizable and nonenolizable electrophiles and may produce good yields of products; however, lower stereoselectivity relative lithium enolates has been observed. Boron, tin(II) and zirconium enolates may also produce good yields under certain conditions, but their difficult preparation and the lack of generality have favored the development of a new synthetic strategy. Although the structure and reaction mechanism of organocerium have not been fully clarified, it is certain that their chemical behavior relates to strong coordination of cerium(III) with oxygen and nitrogen. Liu has shown[38] that when the cerium-enolate of ethyl acetate reacted with α,β-unsaturated ketones, the addition took place in the 1,2-mode. Similarly, the lithioacetonitrile in the presence of $CeCl_3$ added cleanly with highly hindered ketones. This opportunity to obtain functionalized tertiary alcohols has suggested to Eidman the synthesis of racemic liolide **41**, a terpene lactone found in many plants including tobacco and tea (Scheme 14).[39] The key transformation in his synthesis is the 1,2-addition of cerium-enolate of ethyl acetate to highly hindered α,β-unsaturated ketone **39**. The tertiary alcohol **40** has been found to readily dehydrate if treated with a strong acid. The cerium salts are insoluble in aqueous ammonium chloride, and, then, the use of 10% aqueous acetic acid as the quenching reagent allowed an easy workup by dissolving the cerium salts without the dehydration of **40**.



Scheme 14

This same diastereoselective addition of cerium enolates to hindered carbonyl compounds has been successfully used in the synthesis of oxygenated phorboid substrates[40] employed in total syntheses of complex diterpenoids of tigliane and daphanone

families. The strategy starts from the coupling of cyclopentanone and cyclohexene oxide giving, after the alcohol acetylation, the illustrated diastereomer **42** (Scheme 15). This ketone undergoes aldol addition with the metal enolate of ethyl acetate and a β-hydroxy carbonyl compound with an alcohol moiety on a tertiary stereogenic center is obtained.[41] The stereoselectivity varies dramatically with the nature of the metal in the enolate, and only cerium-enolate showed a useful diastereofacial selectivity.

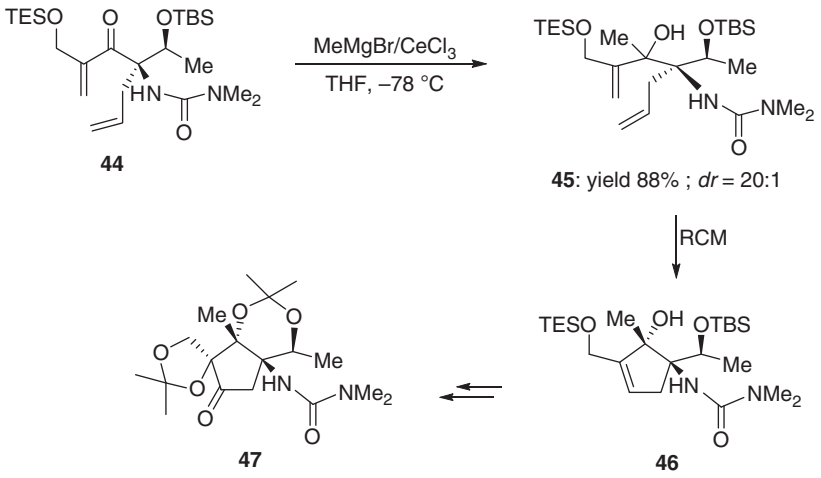


Scheme 15

1.08.4 Application in Organic Synthesis

After the pioneering work of Imamoto appeared around 1980,[42] numerous reports on the utility of organocerium reagents in organic synthesis have been disclosed. Such an intense activity allowed the development of a large variety of processes which are in several cases superior to preexisting procedures; this has led to some of these procedures becoming the methods of common choice in current organic synthesis. Although several total syntheses reported in literature display the use of organocerium reagents, representative examples of chemo-, regio-, and stereoselective applications in organic synthesis are reported here.

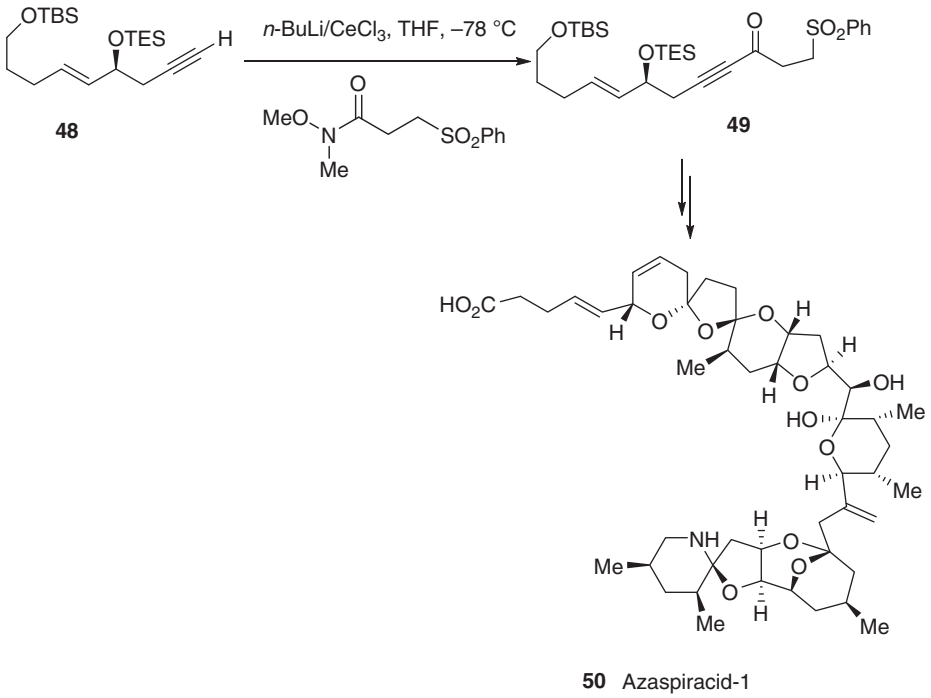
Johnson and coworkers[43] have recently studied an excellent strategy for the synthesis of an advanced intermediate for the preparation of pactamycin (**44**), a potent, universal inhibitor of translocation, which is heteroatom-rich and contains urea, salicylate, and aniline functionality. In the synthesis (Scheme 16), a key bond formation included the addition of a methyl Grignard in the presence of $CeCl_3$ to a hindered α-ureido ketone **44** giving the 1,2-addition product with proper C5 stereochemistry. The subsequent ring-closing metathesis with Grubb's second generation catalyst provided the cyclopentene moiety, a useful handle for elaboration to stereochemically and functionally dense in the pactamycin core. The noesy analysis on this structure **46** showed the desired stereochemistry at C5.



Scheme 16

An interesting application of an organocerium reagent in organic synthesis has been the stereoselective construction of the α,β-ynone **49** (Scheme 17).[44] The strategy utilizes the addition of a precooled solution of Weinreb amide in THF to the organocerium suspension (derived from alkyne **48**) at low temperature. The desired acetylenic ketone represents the key fragment of a new possible synthetic approach toward azaspiracid **50**, an highly oxygenated polyether with biological activity.

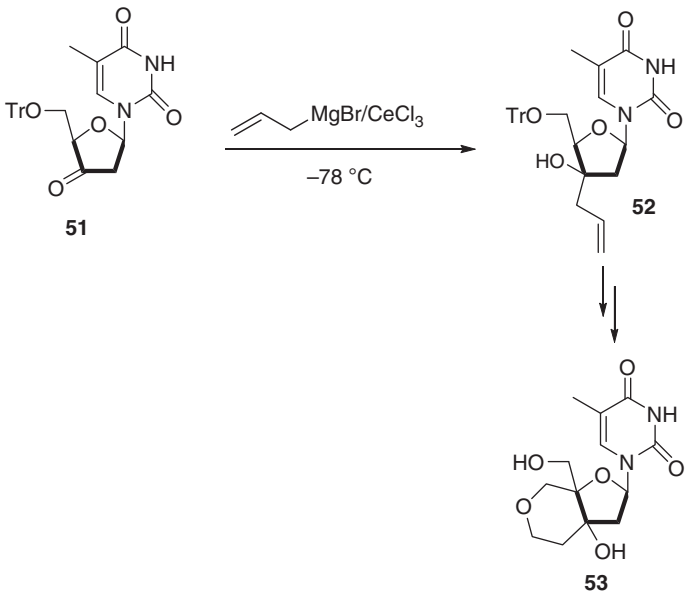
Nucleic acid chemistry has developed by the introduction of conformationally restricted nucleoside building blocks. In particular, locked nucleic acids (LNAs) have demonstrated unprecedented DNA and RNA-recognition and promising results as



50 Azaspiracid-1

Scheme 17

potential antisense therapeutic compounds. The synthesis of these conformationally locked nucleosides required the addition of organometallic nucleophiles to protected 3′-ketonucleosides (Scheme 18).[45] After oxidation of the well-known 5′-tritylated derivative obtained from thymidine, the cerium-assisted Grignard with allylmagnesium bromide to **51** afforded the tertiary alcohol in a reasonable 41% yield. In the absence of $CeCl_3$ the Grignard reaction is accomplished with some difficulties due to the sensitivity of **51** to undergo a β-elimination. The bicyclic nucleoside **53** showed a single incorporation into oligodeoxynucleotides leading to decreased affinity for both DNA and RNA.



Scheme 18

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1.09 Samarium and Ytterbium Reagents

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Glossary

Hexamethylphosphoramide (HMPA) Basic, polar aprotic phosphoramide solvent with the formula $[(CH_3)_2N]_3PO$. The molecule exhibits tetrahedral geometry with a highly polarized P–O bond. It is an important ligand for lanthanides and used as an additive in many lanthanide mediated reactions.

Lanthanides Consist of the elements in the periodic table from atomic number 57 (lanthanum) to 71 (lutetium) and are distinguished by the filling of 4*f* orbitals from 0 to 14 electrons.

Oxophilic Attraction or affinity for oxygen, 'oxygen loving.'

Pinacol Diol product formed through the reductive coupling of two carbonyl-containing substrates.

Proton donors Alcohols, glycols, or water used in reactions to quench carbanions and alkoxides generated through substrate reduction by Sm(II)- and Yb(II)-based reductants.

 doi:10.1016/B978-0-08-097742-3.00111-7

Samarocene An organosamarium coordination compound containing a samarium in the +2 or +3 oxidation state sandwiched between 2 or 3 cyclopentadiene ligands, respectively.

Transmetallation Reaction where one metal is exchanged for another in an organometallic reagent or intermediate.

1.09.1 Introduction and Scope

The application of reagents based on samarium (Sm) and ytterbium (Yb) have a relatively short history in organic synthesis, but their use continues to grow at a rapid pace. Given the increasing complexity of synthetic targets, the search for efficient and selective reagents has led to the use of compounds derived from Sm and Yb. Although initially considered esoteric compounds, reagents based on Sm and Yb are employed in most organic laboratories and their use in synthesis is featured in over 100 publications per year. The unique place held by Sm- and Yb-based reagents in the arsenal of synthetic chemists is a result of their versatility in mediating numerous, fundamentally important C–X π-bond addition reactions. As a result, their use allows for alternative and selective methods for the synthesis of multifunctional targets. Although numerous reactions have been developed utilizing these reagents, their scope in synthesis certainly has not been exhausted and new applications for them are steadily being discovered. In this chapter, a brief overview of lanthanide chemistry will be presented and followed by a discussion of the chemistry and reactions of zero valent Yb and Sm. The main portion of the chapter will focus on divalent Yb and Sm reagents and their reactions, and will conclude with examples of organic reactions using Yb and Sm in the +3 oxidation state. Where possible (and useful), mechanistic studies will be presented to explain the reaction of these reagents to assist those wishing to use the methods described or predict outcomes of reactions being considered. The main focus of this chapter will be on work carried out since the overview of Yb and Sm reagents written for the first edition of this volume and only seminal studies before 1990 will be presented.

1.09.1.1 General Properties of the Lanthanides

The lanthanide series is a unique class of 15 elements with relatively similar chemical properties. They have atomic numbers ranging from 57 to 71, which corresponds to the filling of the 4*f* orbitals with 14 electrons. The lanthanides are sometimes referred to as the 'rare earth elements,' leading to the misconception that they are rare. In fact, many of the rare earth elements are more common than gold, silver, and in some cases, lead. A table of the relative abundance of selective lanthanides versus other common metals in the earth crust is shown below (Table 1).[1] These data show that the term 'rare earth' is a misnomer. In fact, the world reserve of 'rare earths' is estimated to be approximately 150 million metric tons, in the form of rare-earth oxides, although the annual consumption is only approximately 120 000 t.[2] This statistic indicates that an ample supply of lanthanide metals will be available for many years to come as long as political factors do not interfere with their commercial supply. The current world production of Yb is approximately 50 t year^{-1} and the production of Sm is nearly 700 t year^{-1}.[1]

Table 1 Abundance of metals in the earth crust in ppm

Iron	41 000	Samarium	7.9
Chromium	100	Ytterbium	5.3
Nickel	80	Tin	2.2
Cerium	68	Tungsten	1.0
Cobalt	24	Silver	0.07
Lithium	20	Mercury	0.050
Lead	14	Gold	0.0025

The lanthanides are commonly found in nature as a mixture in a number of minerals such as monazite ($LnPO_4$) and bastnaesite ($LnCO_3F$) in the +3 oxidation state. The individual metals can be extracted from the ore as salts using strong acids and bases. Selective, complex-forming ligands can then be added to the extracted metal mixture, followed by elution through a cation exchange column. It is also known that extraction into tri-*n*-butylphosphine oxide can give purities more than 99% for each element.[3] As a consequence, nearly all of the lanthanides are commercially available in pure form at a reasonable cost. Yb was discovered in 1878 by the Swiss chemist Jean Charles Galissard de Marignac and named the element after the Swedish village Ytterby where the element was discovered. Sm was discovered in 1879 by the French chemist Paul Émil Lecoq de Boisbaudran and the element was named after the mineral samarskite in which it was discovered.[1]

The chemical and physical properties of lanthanides provide the unique features that set them apart from other elements. Lanthanides are most stable in the +3 oxidation state. Yb and Sm, though stable in the +3 state, also have accessible +2 oxidation states. The ease of accessibility of both oxidation states is of great importance in chemical synthesis and these elements act as Lewis acids in the +3 state and single electron reductants in the +2 state. The accessibility of the +2 state for each element

is due to the stability of the filled f^{14} orbitals for Yb, and the nearly filled f^6 for Sm. Sm(II) is a strong one-electron reductant (Sm(II)/Sm(III) = − 1.55 V) making it exceptionally useful in synthesis. Yb(II) is more stable but still a strong reductant (Yb(II)/Yb(III) = − 1.15 V).

Another distinguishing feature of lanthanides is that their 4*f* orbitals are shielded by the completely filled $5s^2$ and $5p^6$ orbitals and as a consequence have limited radial extension.[4,5] This configuration leads to the phenomenon known as the 'lanthanide contraction,' which is the steady decrease in ionic radii from lanthanum to lutetium.[4] The lanthanides in the +3 state gradually decrease in size from La^{3+} having an ionic radius of 1.17 Å to Lu^{3+} having a radius of 1.00. Within this group, Sm(III) has an ionic radius of 1.10 Å and Yb(III) has an ionic radius of 1.01 Å.[3] This gradual and steady decrease in size allows the fine-tuning of the reactivity of lanthanide-based reagents by simply changing the metal. An example of the consequences of chemical reactivity as a result of the lanthanide contraction is shown in the work of Evans and coworkers on the hydrogenolysis of lanthanide alkyl complexes.[5] In this work, treatment of $[Cp_2ErCH_3]_2$ with H_2 in toluene/tetrahydrofuran (THF) led to the formation of $[Cp_2Er(\mu\text{-}H)(THF)]_2$ in a 55% yield over a 24-h period, whereas the analogous $[Cp_2YbCH_3]_2$ treated under the same conditions was unreactive. This shows that small changes in the radius of the metal can have significant consequences on reactivity.

Lanthanides have a shell core configuration of [Xe] 4 f^n6 s^2 and in addition to the lanthanide contraction, the shielding of the *f* orbitals results in a behavior similar to that of closed shell inert gases with a tripositive charge. The interaction of lanthanides with ligands is dominated by steric and electrostatic interactions. As a consequence, the large ionic radii enable lanthanides to accommodate up to 12 ligands in the coordination sphere although coordination numbers of 7–9 are more common. Ligands play an essential part in mediating many organometallic reactions. In the area of organolanthanide chemistry, a central role is played by hexamethylphosphoramide (HMPA), which serves as a ligand for the entire lanthanide series. Coordination and crystallographic studies provide an enormous amount of insight into the solid-state structures of lanthanide–HMPA complexes. One striking feature of these complexes is the regularity of the stoichiometry through the series from lanthanum to lutetium. When lanthanide(III) perchlorates were dissolved in HMPA, the entire series from lanthanum to lutetium produced complexes containing six inner-sphere HMPA ligands and three outer-sphere perchlorate ions.[6,7] Other ligands, such as amides and sulfoxides, produce complexes with metal-ligand stoichiometries that depend on the size of the particular lanthanide, i.e., the early lanthanides exhibit higher coordination numbers than the later lanthanides.[8–10] The unique behavior of HMPA makes it an important ligand and additive in reactions of lanthanides, especially samarium diiodide (SmI_2) and related Sm(II)-based reagents.

Although a great deal of this chapter will focus on halide and related triflate ligands since they are commonly employed in Ln-based synthetic reagents, the formulation of ligands plays an important role in lanthanide chemistry. Early work in the field focused on the use of ligands which prevented oligomerization of lanthanides whose coordination spheres were unsaturated with the goal of producing monomeric complexes.[11] A range of sterically encumbered cyclopentadienyl, amide, alkoxide, and pyrazolylborate ligands have been developed, employed and studied.[12] In particular, ligands based on the cyclopentadienyl unit have played an important role in the development of organolanthanide chemistry and their use was critical in understanding the reactivity of lanthanides providing the foundation for their use in organic synthesis.[13]

The chemistry of Ln-based compounds is dominated by interaction with oxygen-containing substrates. Since Ln(III) ions are hard acids they coordinate preferentially to oxygen and other hard bases. The oxophilicity of the lanthanides is a great advantage in organic synthesis and a great deal of their reactions are dominated by reaction with oxygen containing functional groups including ketones, aldehydes, esters, amides, and alcohols. Moreover, oxygen-containing pendant functional groups in close proximity to the primary site of reaction can be used to direct the stereoselectivity of reactions through chelation providing an important advantage for selective synthesis. The feature of lanthanide chemistry is especially important in stereoselective synthesis using SmI_2.[14]

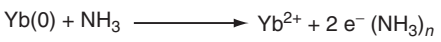
1.09.2 Zero Valent Yb and Sm

Zero valent Yb and Sm have large absolute redox potentials ($Yb^\circ/Yb^{3+} = -2.27$, $Sm^\circ/Sm^{3+} = -2.41$ V)[15] and as a consequence are increasingly being used in organic reactions. One of the potential advantages of using zero valent Yb and Sm is that conversion to the more stable (+2) or (+3) oxidation state makes them two- or three-electron transfer reagents. Work described in this section will focus on the use of Yb and Sm metal and the unique features of reactions that make them advantageous compared to other approaches.

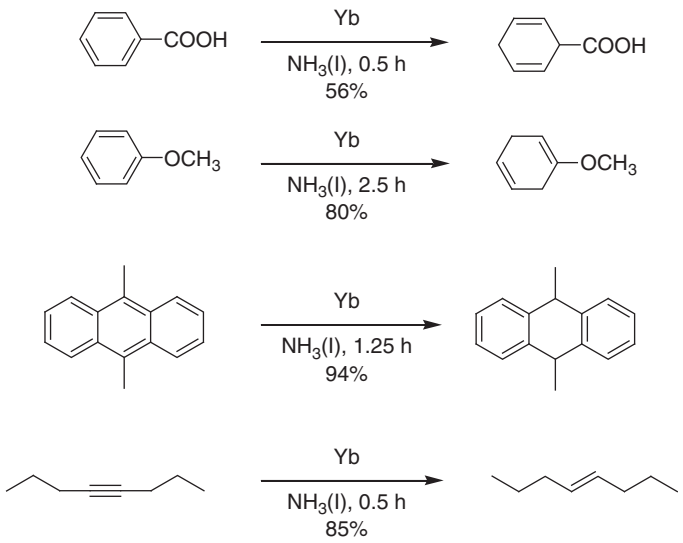
1.09.2.1 Yb(0)

One of the initial applications of Yb metal was as a replacement for sodium metal in dissolving metal reductions.[16] White and Larson reported that dissolution of Yb metal in liquid ammonia yielded a blue solution containing ammoniated electrons through the conversion shown below in **Scheme 1**. The solutions were found to be stable for several hours at − 33 °C and was a very powerful reducing system capable of reducing aromatics, α,β-unsaturated ketones, and aldehydes.[16] A few representative examples of reactions are shown in **Scheme 2**. In the reactions described, aromatic substituents were found to exert a pronounced effect on the rate of reduction with electron-donating substituents leading to slower reactions and electron-withdrawing substituents reacting quickly. Reduction of anthracene and derivatives produced the 9,10-dihydro products, and internal alkynes

produced *trans* alkenes in good yields. The advantages of this procedure were the ease of handling of the system and the avoidance of strongly basic hydroxides in reaction workup.



Scheme 1 Reproduced from White, J. D.; Larson, G. L. *J. Org. Chem.* **1978**, *43*, 4555, with permission from ACS.



Scheme 2 Reproduced from White, J. D.; Larson, G. L. *J. Org. Chem.* **1978**, *43*, 4555, with permission from ACS.

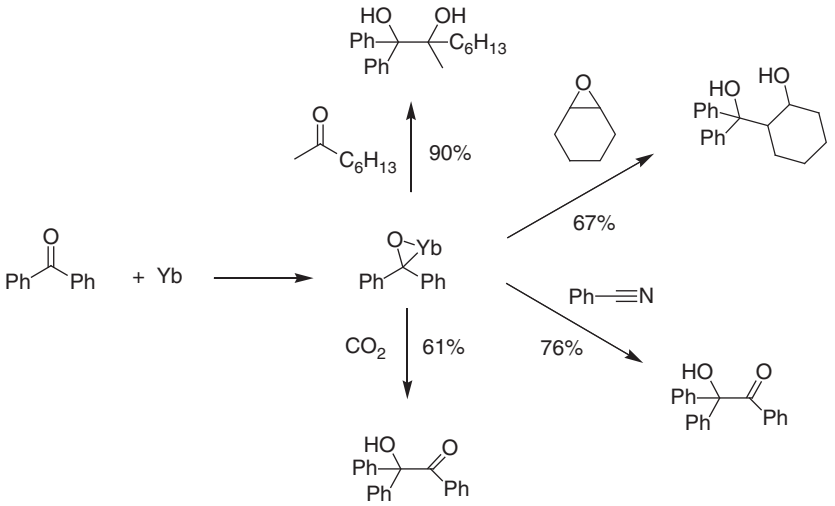
Metallic Yb can also be employed in pinacol coupling and related reactions. Fujiwara and coworkers discovered that treatment of diaryl ketones with 1–2 equivalents of Yb metal react efficiently with ketones, epoxides, nitriles, CO_2, and other electrophiles to produce pinacols, 1,3-diols, α-hydroxyketones, and carboxylic acids in good yields as shown below (Scheme 3) (Ln-0–3).[17] The reactions are proposed to proceed through a bridged alkoxyorganoytterbium intermediate. Although the process provides access to several important products, the reaction is limited in scope since only diaryl ketones can be employed.

In related studies, Fujiwara and coworkers developed a Yb-initiated dimerization/oxidative dehydrogenation of aldimines providing efficient conversion to vicinal diimines (Scheme 4).[18] Reactions of aryl aldimines with Yb in THF containing HMPA provide intermediate diamines, which on reaction with 1-naphthaldehyde produce diimines in good yields. A range of aldehydes were examined, but 1-naphthaldehyde was found to be the most effective oxidant for the reaction. Deuterium labeling and other mechanistic studies showed that the hydride transfer from *C*-deuterated diamine intermediate to the aldehyde was responsible for the oxidation. The authors examined Sm metal and SmI_2 as reductants but found they were significantly less effective in the coupling reaction. They further ascribed the efficiency of the reaction to the Lewis acidity of the oxidized Yb being responsible for coordinating 1-naphthaldehyde and intermediate diamine and facilitating hydride transfer as shown below (Scheme 5).

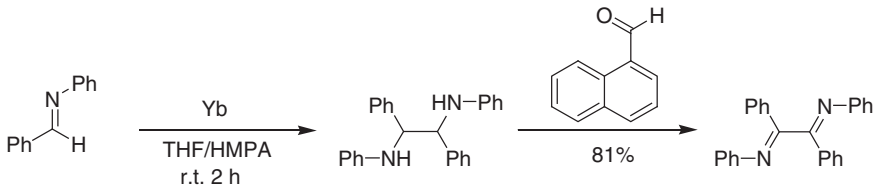
Although this reaction is quite efficient for aromatic imines, it appears to be limited in scope and no reports of reactions on alkyl amines have appeared in the literature.

In 2003, Prajapati and coworkers reported a Yb(0) initiated coupling of α-oxonitriles with allyl bromides to produce, β,γ-unsaturated ketones (Scheme 6).[19] The reaction proceeds smoothly with allyl, crotyl, or prenyl bromides with aromatic α-oxonitriles providing 70–80% yields. A wide range of electron rich and poor aromatic α-oxonitriles work in the process. The reaction contrasts coupling reactions with indium reagents that generate enamino products with the same starting materials. As described in the previous two examples, reactions are quite efficient with aromatic carbonyls, but are not effective with alkyl substituted starting materials.[20]

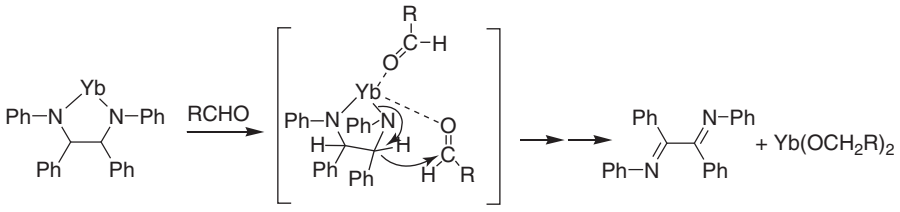
There are several reports of mixed valent systems for the reductive coupling of carbonyls. Ogawa, Sonoda, and coworkers have described the deoxygenative coupling of amides to vicinal diamines by Yb(0)/YbI_2 and Sm(0)/SmI_2.[21] The coupling of aromatic amides and their chalcogen analogs proceeds efficiently with a combination of Yb/YbI_2 or Sm/SmI_2 with the zero valent metal in slight excess (Scheme 7). The reaction provided *e*/*z* ratios of approximately 4:1. Interestingly, replacement of zero valent Yb or Sm with sodium metal led to very low yields of coupled product and use of Mg provided only unreacted starting material.



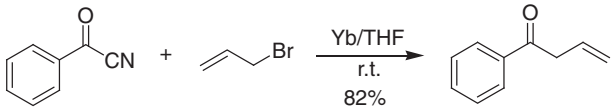
Scheme 3 Reproduced from Hou, Z.; Takamine, K.; Aoki, O.; *et al. J. Org. Chem.* **1988**, *53*, 6077, with permission from ACS.



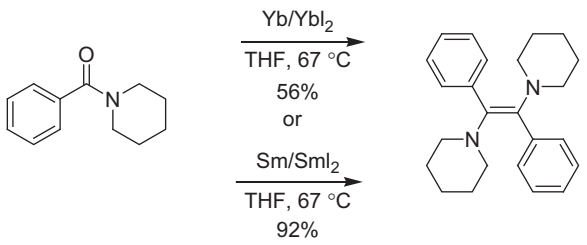
Scheme 4 Reproduced from Jin, W.; Makioka, Y.; Kitamura, T.; Fujiwara, Y. J. *J. Org. Chem.* **2001**, *66*, 514, with permission from ACS.



Scheme 5 Reproduced from Jin, W.; Makioka, Y.; Kitamura, T.; Fujiwara, Y. J. *J. Org. Chem.* **2001**, *66*, 514, with permission from ACS.



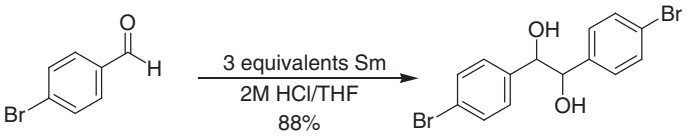
Scheme 6 Reproduced from Gohain, M.; Gogoi, B. J.; Prajapati, D.; Sandhu, J. S. *New. J. Chem.* **2003**, *27*, 1038, with permission from Royal Society of Chemistry.



Scheme 7 Reproduced from Ogawa, A.; Nanke, T.; Takami, N.; *et al. Appl. Organomet. Chem.* **1995**, *9*, 461, with permission from Wiley.

1.09.2.2 Sm(0)

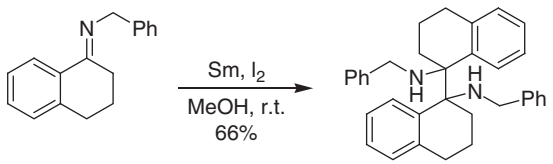
Sm metal has been used for a wide range of coupling reactions and has proven especially effective in pinacol coupling and related reactions. An interesting 'wet' system employing Sm metal in aqueous media was developed by Fang.[22] The metal was activated by running the reaction in 2 M HCl aqueous solution (5:1 HCl(aq):THF). This method was found to be the superior 'activating' system, as compared to activating the Sm metal with I_2, $HgCl_2$, $FeCl_3$, or saturated NH_4Cl. Forming symmetric pinacol products was achieved for aromatic and carbonyls, whereas aliphatic carbonyls provided predominantly reduced products (alcohols) (Scheme 8).



Scheme 8 Reproduced from Talukdar, S.; Fang, J.-J. *J. Org. Chem.* **2001**, *66*, 330, with permission from ACS.

Catalytic amounts of allyl bromide as well as sonication with NH_4Cl have been used to activate Sm metal for pinacol couplings.[23,24]

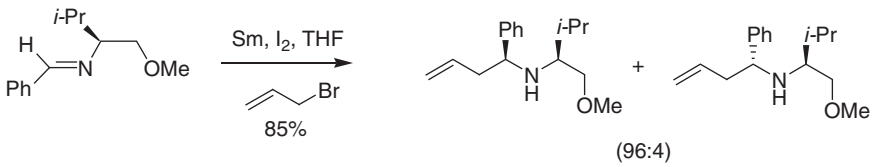
Banik and coworkers have shown that Sm(0) in methanol containing the presence of a catalytic amount of I_2 is capable of coupling aldimines as shown below (Scheme 9).[25]



Scheme 9 Reproduced from Banik, B. K.; Zegrocka, O.; Banik, I.; Hackfield, L.; Becker, F. F. *Tetrahedron Lett.* **1999**, *40*, 6731.

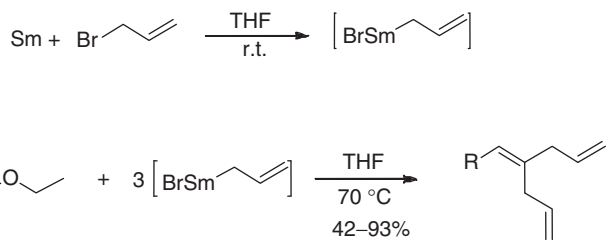
The reactive intermediates in these reactions are not known, but likely proceed through Sm(II) intermediates. In general, reactions work best with aromatic aldimines, but there are some exceptions. Similar reactions have been reported with Sm metal and Cp_2TiCl_2, but these reactions are typically dominated by Ti(III) chemistry.[26]

Although reductions and pinacol reactions are predominately carried out with zero valent Sm and Yb, allylation of imines is also possible with Sm metal (Scheme 10). The reaction uses Sm metal and I_2 as an activating agent to produce coupled products with good control over the diastereoselectivity.[27]



Scheme 10 Reproduced from Negoro, N.; Yanada, R.; Okaniwa, M.; Yanada, K.; Fujita, T. *Synlett* **1998**, 835, with permission from Thieme Publisher.

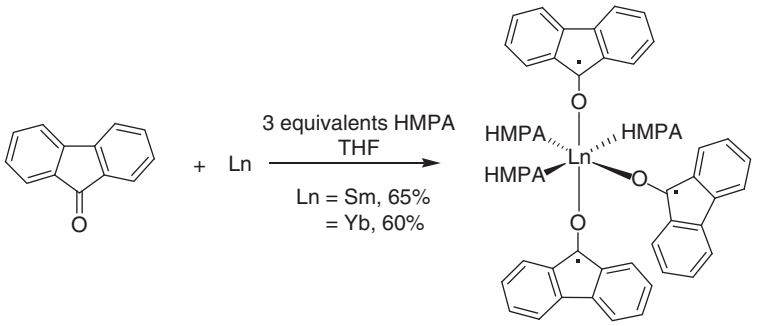
There are several other reports of using Sm metal in conjunction with allylbromide to generate 'allylsamarium regents' that lead to useful conversions. One recent example is the reaction of Sm metal with allylbromide and subsequent addition to α-haloesters to produce trienes in good to excellent yields (Scheme 11).[28] Given the known chemistry of the lanthanides, and their



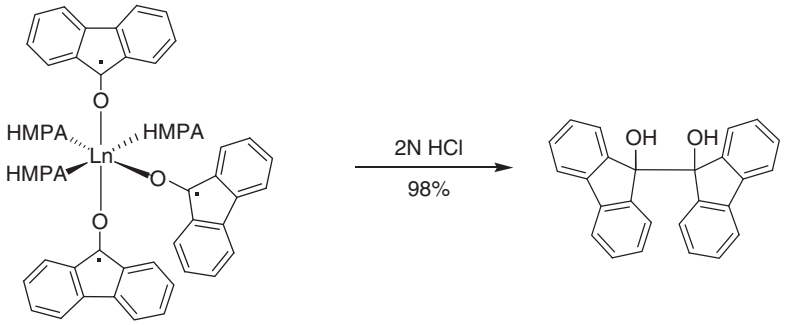
Scheme 11 Reproduced from Hu, Y.; Zhao, T.; Zhang, S. *Chem. Eur. J.* **2010**, *16*, 1697, with permission from Wiley.

tendency to fill their coordination sphere through aggregation and sequestration of solvent, it is unlikely that the combination of Sm(0) and allylbromide produces a structurally well-defined organosamarium species in solution.[29] Regardless of the structure of this combination, the allylbromide-Sm(0) reagent system provides unusual reactivity that can be exploited by synthetic chemists.

One of the advantages of zero valent Sm and Yb is that in some cases, reactions can be carried out in aqueous systems. Additionally, Yb(0) and Sm(0) are reported to be less sensitive to oxygen in comparison to their Ln(II) counterparts.[30] In many cases, an efficient activating species is needed, and there is a limited number of bond-forming reactions that can be carried out. The main issue in fully exploiting the use of zero valent Yb and Sm in synthesis is the lack of mechanistic studies necessary to provide a rational basis to understand the reactivity and selectivity of intermediates generated during the course of such reactions. One of the difficulties in working with zero valent Yb and Sm is that reaction with substrates produces intermediates with no stabilizing ligands to suppress further reaction. The only thorough mechanistic studies to date have been carried out by Hou and coworkers on the generation of ketyls by zero valent Sm and Yb.[31] In this seminal work, Hou found that the use of HMPA as a coordinating ligand sufficiently suppressed follow up coupling reactions in the reduction of flurenone by Yb(0) and Sm(0). Reduction of fluorenone with Sm(0) yielded the Sm(III) tris(fluorenone ketyl) complex in a 65% yield whereas the use of Yb(0) provided the analogous Yb(III) complex in a 60% yield (**Scheme 12**). Hydrolysis of the intermediate tris-ketyl complexes provided nearly quantitative yields of pinacol (**Scheme 13**). Studies of other related ketones such as benzophenone resulted in decomposition products showing that small changes in steric demands of ketones play an important role in the stability and reactivity of intermediates produced in these reactions.



Scheme 12 Reproduced from Hou, Z.; Fujita, A.; Zhang, Y.; *et al. J. Am. Chem. Soc.* **1998**, *120*, 754, with permission from ACS.



Scheme 13 Reproduced from Hou, Z.; Fujita, A.; Zhang, Y.; *et al. J. Am. Chem. Soc.* **1998**, *120*, 754, with permission from ACS.

Additionally, given the stability of benzophenone ketyls derived from Na/HMPA and Ca/HMPA, these studies showed that the lanthanide ketyls derived from Sm(0) and Yb(0) are significantly more reactive than their alkali and alkaline earth counterparts.[32]

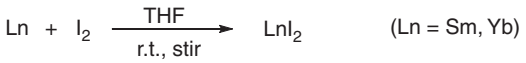
Given the interesting reactivity and paucity of mechanistic knowledge of reactions initiated by zero valent Sm and Yb, this area is ripe for further study. It is likely that additional applications will continue to emerge in the near future as this area is further explored.

1.09.3 Divalent Sm and Yb

Divalent ions of nearly all of the lanthanides have been generated, but only three, Eu, Yb, and Sm, are readily accessible under standard laboratory conditions. More recently divalent Tm, Dy, and Nd have been generated and although they are powerful reductants and have potential for use in organic synthesis, their preparation is somewhat more difficult from the viewpoint of an organic chemist. Among the three former lanthanides that are straightforward to prepare in divalent form, Eu is a weak reductant,

Yb is intermediate, and Sm is a strong reductant ($Eu^{+2}/Eu^{+3} = -0.35$ V, $Yb^{+2}/Yb^{+3} = -1.15$ V, $Sm^{+2}/Sm^{+3} = -1.55$ V vs. NHE). Because of their ease of preparation and stability in many organic solvents, reductants based on Yb(II) and Sm(II) have found important applications in organic synthesis.

The most widely used Ln(II) reductants, SmI_2 and YbI_2, can easily be made through reacting the respective metal with 1,2-diiodoethane or I_2 in THF (Scheme 14). Homogeneous reactions with the divalent species can be carried out at room temperature, under inert atmosphere. Many of the reductions with SmI_2 and YbI_2 are nearly quantitative and can be performed as titrations. Kagan initially described a wide range of reactions with SmI_2 and YbI_2, including deoxygenations, reduction of conjugated double bonds, reduction of carbonyls, reduction of organic halides, and alkylation of carbonyl-containing species with alkyl halides. This section describes the state of the art use of Yb(II) and Sm(II) in carbon–carbon and carbon–heteroatom bond forming reactions. In the 30+ years following the seminal report of Ln(II) by Kagan, over 2000 publications can be found on new adaptations and detailed mechanistic studies of these single-electron reductants. Given the large number of publications describing the use of Sm(II) in organic synthesis, this portion of the chapter will focus predominantly on the use of SmI_2 and important examples of its use. A large number of reviews are available for readers wishing to obtain further insight into the use of the reagent in organic synthesis.[14,33–45] An introductory portion describing the applications of Yb(II)-based intermediates will be followed by an extensive section on the chemistry of SmI_2, followed by a brief section on other Sm(II)-based reductants.

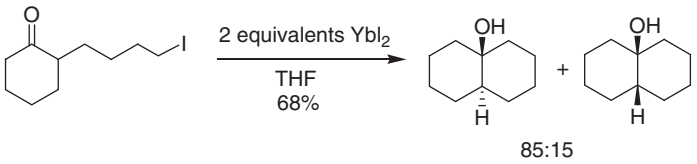


Scheme 14

1.09.3.1 Yb(II)

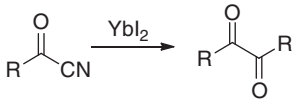
The use of Yb(II) along with Sm(II) as reagents in organic synthesis were introduced by Kagan in 1980. In the ensuing years, Sm(II)-based reductants have been employed significantly more extensively than Yb(II). With that being said, Yb(II) has been employed in C–C bond forming reactions and in a few instances provides better results.

Ytterbium diiodide (YbI_2) is generally not used in the intermolecular reductive coupling of halides and carbonyls, however the reductant works well in intramolecular reactions to form bicyclic compounds (Scheme 15). In some cases it has been found that using YbI_2 over SmI_2 achieves greater diastereoselectivities.[46]



Scheme 15 Reproduced from Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1986**, *51*, 1778, with permission from ACS.

YbI_2 in THF has also been used for the coupling of acyl cyanides to form 1,2-diketones (Scheme 16). In general, this method provides higher yields and greater selectivity than magnesium iodide and other coupling agents.[47]



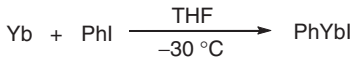
Entry	R	Yield (%)
1	C_6H_5	80
2	4-IC_6H_4	78
3	4-MeC_6H_4	82
4	4-$MeOC_6H_4$	78

Scheme 16 Reproduced from Saikia, P.; Laskar, D. D.; Dipak, P.; Sandhum, J. S. *Tetrahedron Lett.* **2002**, *43*, 7525.

One of the shortcomings of YbI_2 as a reductant is that it is not a strong enough single-electron reductant to reduce most functional groups. Ogawa has shown that irradiation with near –UV light leads to a significant improvement of the reducing ability of YbI_2.[48] Although this approach has not been used in bond-forming reactions it has been used successfully in the reduction of alkyl and aryl bromides. In more recent work, Hilmersson has shown that the combination of $YbI_2/H_2O/Et_3N$ can be

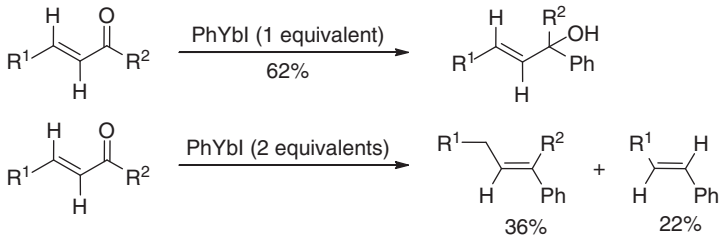
used to reduce aromatic hydrocarbons with redox potentials approaching -2.3 V versus SCE.[49] Although no examples of bond-forming reactions have been published, both of these approaches should provide access to Yb(II)-based reagent systems capable of forming C–C bonds through reductive coupling.

Yb(II) intermediates have been proposed for the addition of Yb(0) to alkyl and aryl iodides through the oxidative metalation of organoiodides as shown in (Scheme 17).[48] The intermediates are often described as 'Grignard-like' and written as RYbI. Given the lack of careful characterization, it is unclear whether these are Yb(II)-based intermediates. Nonetheless, this combination of reagents can be useful in carbonyl additions.



Scheme 17 Reproduced from Ogawa, A.; Ohya, S.; Sumino, Y.; Sandhum, J. S. *Tetrahedron Lett.* **1997**, *38*, 9017.

Phenyl ytterbium iodide has been shown to undergo 1,2-addition with unsaturated carbonyl compounds. When equimolar amounts of PhYbI and α,β-unsaturated carbonyls were reacted, 62% of the 1,2-addition product was obtained as the sole product.[50] When the concentration of PhYbI was increased to 2 equivalents or more, the formation of deoxygenated and C–C cleavage products predominates (Scheme 18).



Scheme 18 Reproduced from Hou, Z.; Fujiwara, Y.; Jintoku, T.; *et al. J. Org. Chem.* **1987**, *52*, 3524, with permission from ACS.

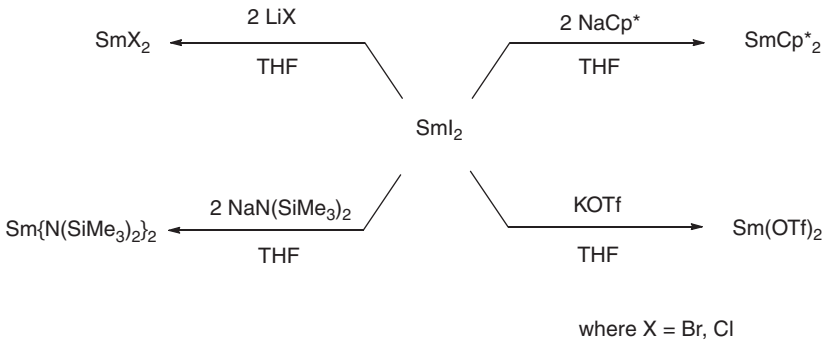
1.09.3.2 Sm(II)

1.09.3.2.1 Sm(II) halides

1.09.3.2.1.1 SmI_2

SmI_2 is a mild and selective reductant that is commonly used in organic synthesis. The versatility of SmI_2 is a result of its ability to initiate a wide range of reductions including C–C bond-forming and cascade or sequential reactions. SmI_2 can reduce sulfoxides and sulfones,[51,52] phosphine oxides,[51,52] epoxides,[53,54] alkyl and aryl halides,[46,54–59] carbonyls,[60–62] and conjugated double bonds.[49,63] The rate of reduction of functional groups varies significantly. As a consequence, SmI_2 can be used for sequential functional group reduction and coupling or to selectively reduce functional groups for follow-up bond-forming reactions in complex substrates. An additional benefit of SmI_2 is that the use of additives can be employed to further tune the rate and selectivity of reductive coupling reactions.

Another benefit of SmI_2 is its ease of preparation. It can be prepared in THF in a number of ways, including reaction of the metal with I_2, 1,2-diiodoethane, and triiodomethane.[14] In all these conditions, a dark-blue solution of SmI_2 in THF is formed. The limiting concentration of the reductant in THF is 0.1 M and the solution is stable for long periods of time if stored in an inert atmosphere. Although the solvent of choice for most reactions is THF, the reagent can be prepared in dimethoxyethane (DME), acetonitrile (CH_3CN), tetrahydropyran (THP), and even benzene. One of the other key features of SmI_2 is that it can be used as a convenient and stable intermediate for the synthesis of other Sm(II)-based reductants as shown below (Scheme 19).



Scheme 19

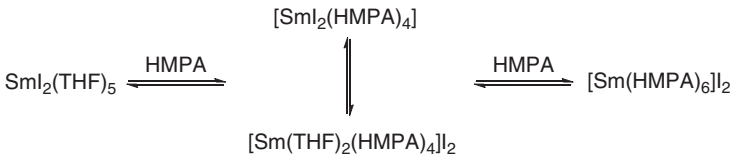
1.09.3.2.1.1.1 Effect of additives and cosolvents

One of the unique features of SmI_2 is that addition of cosolvents or additives can be used to control its reactivity. Remarkable changes in the rate, diastereoselectivity, and chemoselectivity of organic reactions initiated by SmI_2 can be achieved through addition of suitable additives to SmI_2. In fact, nearly all the examples that will be presented herein utilize additives that are critical for the success of reactions. Additives useful in reactions of SmI_2 can be classified into three groups: (1) Lewis bases including HMPA and other electron donor ligands and chelating ethers, (2) proton sources (predominantly water and alcohols), and (3) inorganic additives (NiI_2, $FeCl_3$, etc.). A great deal of synthetic and mechanistic work has been carried out on these reagent systems to determine the mechanistic features critical for reaction success.[50,51,52,64,65] The collection of mechanistic studies on these systems has shown that additives control divalent Sm reactivity through three main avenues: (1) changing the thermodynamic redox potential of Sm,[54–59] (2) controlling the steric bulk around the divalent metal center,[66–68] and interacting with substrates and intermediates along the reaction coordinate.[69] Additional mechanistic roles for additives have been identified and in some cases, the behavior of additives depends on the degree of interactions with Sm(II), substrate, or the solvent milieu.

Lewis bases containing basic oxygen or nitrogen atoms are important promoters of reactions initiated by SmI_2. The most commonly utilized Lewis base used in conjunction with SmI_2 is HMPA. The potential of the SmI_2-HMPA reagent system was first reported by Inanaga who showed that this additive accelerates the rate of reduction of a range of alkyl and aryl halides.[54] Since this seminal report, the SmI_2-HMPA reagent system has played an important role in the development of SmI_2 chemistry given that it accelerates a broad range of functional group conversions and bond-forming reactions. Additionally, the SmI_2-reagent enhances the stereochemical control of bond-forming reactions.

During early synthetic work employing the reagent system, several hypotheses were proposed. A wide variety of experimental studies have examined the role of HMPA and its mechanistic impact on reactions. Given the fact that lanthanides have a propensity to fill their coordination sphere, it was thought that SmI_2 could aggregate in solution in a manner similar to lithium aggregates.[70–79] Since HMPA is sterically encumbered and known to be a good ligand for lanthanides, its addition to SmI_2 could lead to deaggregation. Another supposition was that HMPA could increase the reducing power of SmI_2 by perturbing the electron donating orbital of Sm(II) and increasing the redox potential of the metal. Crystallographic studies by Evans and coworkers showed that the solvated structure of SmI_2 in THF is $[SmI_2(THF)_5]$. Later studies by Flowers employing vapor pressure osmometry established that SmI_2 is monomeric in solution.[66,80] Electrochemical studies by Flowers showed that addition of HMPA creates a more powerful reductant. These experiments demonstrate that deaggregation of SmI_2 by HMPA and other donor ligands is unimportant.

Insight into the structure of the SmI_2-HMPA complex was provided through the crystallographic studies of Hou. Addition of 4 equivalents of HMPA to SmI_2 in THF provided $[SmI_2(HMPA)_4]$ after recrystallization from toluene.[81,82] Careful examination of the complex shows that the Sm-iodide bond distance is increased dramatically upon the addition of HMPA, so it became apparent that in solution, the structure may be best represented by $[Sm(THF)_2(HMPA)_4]I_2$. Hou also found that upon the addition of a 10 equivalents or greater excess of HMPA to SmI_2, $[Sm(HMPA)_6]I_2$ was produced.[81,82] Elegant conductance studies in THF by Daasbjerg and Skrydstrup showed that upon the addition of 4 equivalents of HMPA to SmI_2, $[Sm(THF)_2(HMPA)_4]I_2$ was formed and addition of greater than 10 equivalents of HMPA produced $[Sm(HMPA)_6]I_2$.[83] Taken together, these studies illustrated that a great deal of complexity was possible for this reagent system as illustrated below (**Scheme 20**).



Scheme 20 Reproduced from Flowers, R. A. II *Synlett* **2008**, 1427–1439, with permission from Thieme Publisher.

Depending on the substrates involved, HMPA can act in a variety of ways in a reaction and even interact with substrate. These specific roles will be discussed further in the context of reactions employing HMPA in subsequent sections.

Other Lewis bases such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) and TMU are known to coordinate to Sm(II), producing a more powerful reductant.[84] Measurements of oxidation potentials clearly show that as HMPA, DMPU, TMU, and H_2O are added to SmI_2, the thermodynamic reducing power increases dramatically (**Table 2**). Acceleration of reaction times has been observed for the addition of glycols to SmI_2-initiated reactions.[39] Although oxidation potentials have not been measured for these additives, crystal structures have verified coordination to the metal center occurs, and enhanced reaction rates are observed.[85]

In addition to Lewis bases, many reactions initiated by SmI_2 require proton donors. The most commonly utilized proton donors are alcohols, glycols, and water. It was long thought that the primary role of proton donors was to quench carbanions and alkoxides generated on substrate reduction by SmI_2. It is now recognized that proton donors have a considerable impact on the regiochemical and stereochemical outcome of many SmI_2-mediated reactions and often times changing the proton donor can have a profound impact on product distributions. The complicating feature of these systems is that oxygen-containing proton donors may coordinate to the oxophilic SmI_2 as well as donate a proton to the reduced substrate through heterolytic cleavage of the O–H bond. If proton donor coordination to Sm(II) occurs along the reaction coordinate, its acidity will be enhanced. The

Table 2 Oxidation potentials determined versus $Ag/AgNO_3$[80,84]

Reductant	*Standard potential (V)*
SmI_2 (THF)	−1.33
SmI_2-HMPA (THF)	−2.05
SmI_2-TMU (THF) (60 equivalents)	−2.04
SmI_2-H_2O (THF) (500 equivalents)	−1.9
SmI_2 (acetonitrile)	−0.84
SmI_2-DMPU (acetonitrile)	−1.48

consequences of this complexity are best understood through the seminal mechanistic work of Hoz who showed that the reduction of activated olefins by SmI_2 and proton donors occurred through two mechanistic pathways: one in which free SmI_2 reacted with substrate before protonation and another where the Sm(II)–proton donor complex reacted with substrate.[86,87] The reactant concentration, proton source, and mode of addition were all factors that determined the mechanistic pathway of reductions. Subsequent studies by Hoz have clarified the mechanistic role of proton donors in reductions by SmI_2 and are required reading for chemists considering the use of SmI_2–proton donor systems in bond-forming reactions.[88–90]

The affinity of proton donors for SmI_2 plays an important role in the rate of reductions in bond-forming reactions. In this regard, some proton donors behave analogously to Lewis bases such as HMPA. This feature of SmI_2–proton donor combinations was first recognized by Curran and Hasegawa showing that water increased the rate of several SmI_2 reductions. Based on the color change that occurred during the course of the reaction, they proposed that the Sm reductant contained bound water.[91] Mechanistic studies by Flowers showed that the acidity of the proton donor and its affinity for Sm(II) played an important role in the mechanism of the reduction.[62] In these studies, water was shown to have a higher affinity for SmI_2 than other alcohols and generated a more powerful reductant.[62,92] The consequences of this enhanced reactivity have been demonstrated by Procter who showed that lactones and cyclic diesters are readily reduced by SmI_2–water (**Scheme 55**, Section 1.09.3.2.1.1.4).[93,94] Given the importance of proton donor coordination to SmI_2 in the production of a potent reductant, it is not surprising that multidentate alcohols such as glycols accelerate the rate of reactions. Hilmersson has shown that coordinating alcohols enhance the rate of substrate reduction by SmI_2 with the rate being proportional to the number of ethereal oxygens in the glycol.[39] Rate and mechanistic studies by Flowers showed that the mechanistic role of glycols is complex. At low concentrations the rate of electron transfer is enhanced, whereas at higher concentrations the glycol ligands saturate the coordination sphere of Sm(II) producing a less reactive reductant.[85] Combinations of water and Lewis bases also provide access to powerful reductants. This is best exemplified by the work of Hilmersson and also by the more recent work of Procter who showed that the combination of water and amines provides a method for reducing a wide range of substrates typically recalcitrant to reduction by SmI_2.[95–101]

Inorganic salts can also be used to accelerate SmI_2-mediated reactions. The addition of inorganic bases including lithium amide, lithium methoxide, lithium bromide, lithium chloride, and potassium hydroxide have been used as additives to carry out a range of reductions. In these reactions, it is likely that the anion displaces iodide on Sm to produce a new reductant in solution. Catalytic amounts of transition metal salts, such as NiI_2, $FeCl_3$, $CuCl_2$, have also been shown to increase the efficiency of SmI_2-mediated reactions and Kagan has shown that in most instances, NiI_2 is superior to other transition metal salts.[102] As a consequence of these early studies, NiI_2 has become the additive of choice in reactions that require a transition metal to catalyze a bond-forming reaction. Although NiI_2 has proven useful as an additive, its role in reactions was unknown until recently. Through a series of kinetic and mechanistic studies, Flowers and coworkers have shown that SmI_2 reduces Ni(II) to Ni(0) and that Ni(0) intermediates are responsible for the chemistry initiated by the addition of Ni(II) to SmI_2.[103] The mechanistic details for NiI_2 are described in the next section.

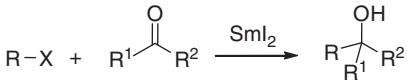
1.09.3.2.1.1.2 Grignard and Barbier reactions

The Grignard reaction is a staple in organic synthesis, coupling an alkyl halide and carbonyl containing species, traditionally through an organomagnesium species (RMgX). Procedurally the Grignard reaction is a two-step reaction. First, activated magnesium is reacted with the alkyl halide, forming the Grignard reagent *in situ*. Addition of the carbonyl substrate follows, which couples to form the desired substituted alcohol. The Barbier reaction is an identical coupling reaction; however, procedurally the substrates are added to the reaction concurrently which sometimes affects the product distribution.

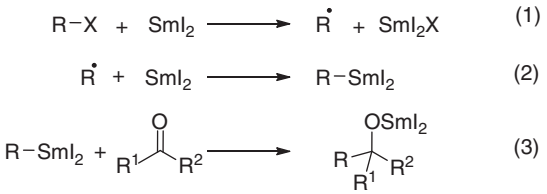
The organomagnesium species in the traditional Grignard reaction is similar to the organosamarium intermediate which is formed in Sm(II)-mediated reactions (Section 1.09.4.2.2.1), and for this reason the Barbier and Grignard reactions were among some of the first C–C bond forming reactions attempted with SmI_2 (**Scheme 21**). Using both the Grignard and Barbier procedure, SmI_2 is able to form the desired alcohol species in nearly quantitative yields.[60,67]

Owing to the order of addition for the Grignard procedure, the mechanism is straightforward: SmI_2 reduces the alkyl halide to a radical species, and through a second electron-transfer an organosamarium species is formed.[104–106] The carbonyl substrate is then added to the reaction mixture, allowing the organosamarium to nucleophilically add to the carbonyl, and on workup the alcohol species is formed. In the Barbier procedure, both substrates are reacted with SmI_2 at the same time, and for this reason a

variety of possible mechanisms could be envisioned. Kagan proposed four possible mechanisms for the Sm-Barbier reaction in 1981,[104] and through the research of Kagan, Curran, Flowers, and others, a great deal of mechanistic insight between the Barbier and Grignard procedure has been gained. However, an overall general mechanism for the Barbier reaction has not been indisputably established. Although both substrates are susceptible to Sm(II) reduction, the reduction of the alkyl halide to a radical has been shown to be the initial step.[107] It has also been demonstrated that the radical species produced from the reduction of alkyl halide does not go through a radical addition to the carbonyl. Instead, the radical species is subjected to a second single-electron transfer to form a stable organosamarium species. The organosamarium then adds to the electrophilic carbonyl to form the final coupled species (Scheme 22).

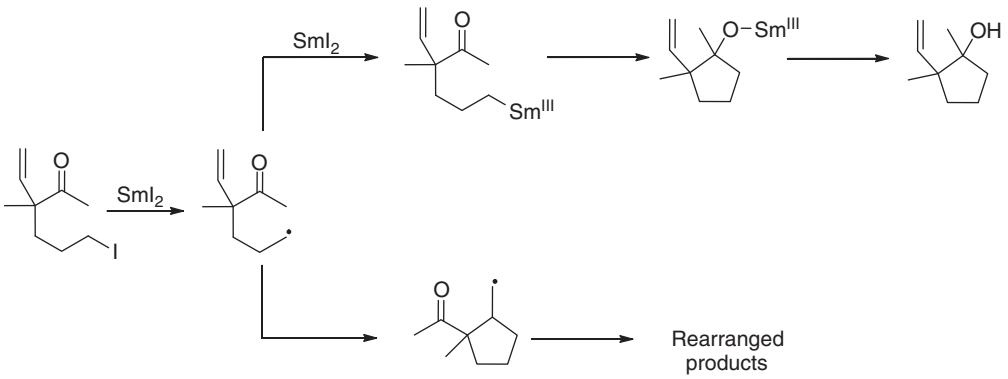


Scheme 21



Scheme 22 Reproduced from Curran, D. P.; Feving, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943, with permission from Thieme Publisher.

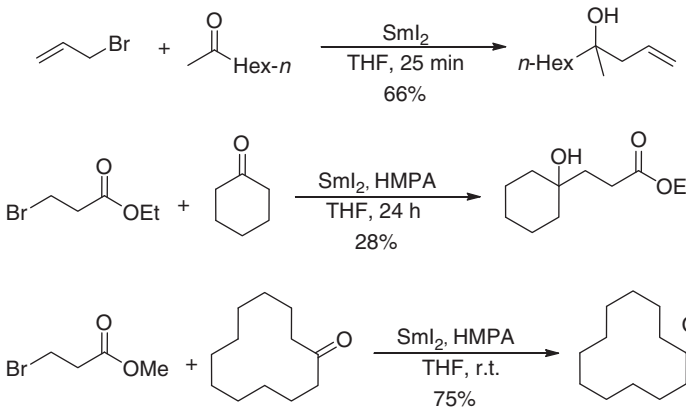
Curran used a 'radical clock' (Scheme 23) to gain information regarding the formation of an organosamarium intermediate as compared to a radical cyclization pathway.[108] Based on known rates for the cyclization of the radical species onto the alkene,[109,110] it was suspected that some radical cyclization products would be obtained along with the alcohol product from the anionic pathway. Surprisingly, it was found that when the radical clock was subjected to SmI_2 reduction, the tertiary alcohol was recovered as the only product. This result indicated that within the intramolecular Sm-Barbier reaction, the sequential single-electron transfers to form the organosamarium intermediate are faster than radical cyclization onto the olefin.



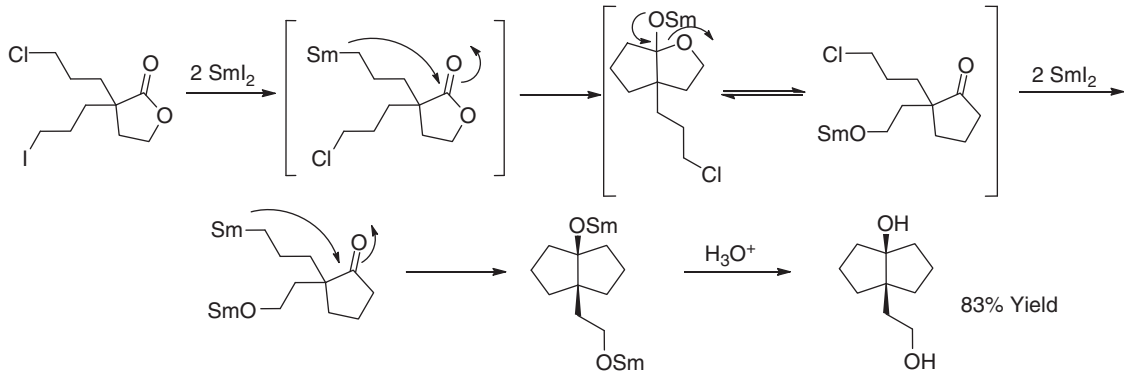
Scheme 23 Reproduced from Curran, D. P.; Gu., X.; Zhang, W.; Dowd, P. *Tetrahedron* **1997**, *53*, 9023.

Intermolecular Barbier reactions have been completed with allylic, benzylic, and propargylic halides, which successfully couple with ketones (Scheme 24).[60] In the absence of either substrate, homocoupled species are obtained, demonstrating the ability of Sm(II) to independently react with both substrates.

Intramolecular C–C bond forming reactions of the Sm-Barbier type have been used to produce a variety of compounds, especially complex ring systems. Owing to the ability of SmI_2 to selectively reduce the alkyl halide over the carbonyl, sequential cyclization processes are effectively directed. Molander explored this area with sequential intramolecular cyclizations with two pendant alkyl halide chains susceptible to SmI_2 reduction.[111] SmI_2 preferentially reduces the iodide over the chloride, forming an organosamarium capable of nucleophilic attack into the carbonyl (Scheme 25). The formation of a wide range of bicylic[*m.n.*0] and tricyclic[*m.n.*0] products was possible through SmI_2 reduction both in the presence and absence of HMPA.

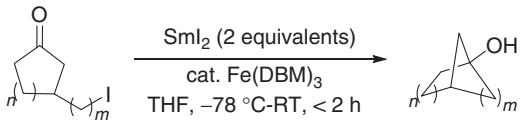


Scheme 24 Reproduced from Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693, with permission from ACS.



Scheme 25 Reproduced from Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705, with permission from ACS.

The intramolecular Sm-Barbier reaction has also been used to construct bridgehead bicyclic alcohols,[112] often integral in the carbon skeleton in complex pharmaceutical compounds and natural products. The Barbier procedure was found to be successful over a broad range of compounds; cyclopentanone through cyclooctanone rings with halo alkyl side chains 1–4 carbon units long, all with above average yields (Scheme 26). Optimization of the reaction conditions identified that the inclusion of an iron catalyst ($FeCl_3$, $FeCl_2$, $Fe(acac)_3$, and $Fe(DBM)_3$) provided the highest yields.

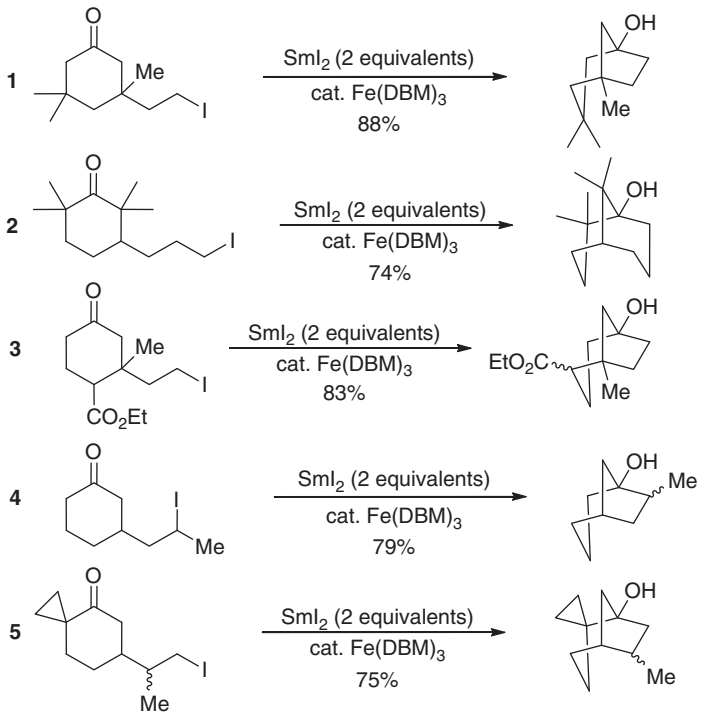


Entry	*n*	*m*	Yield (%)[a]
1	1	1	66
2	1	2	71
3	1	3	54
4	1	4	22
5	2	1	77
6	2	2	69
7	2	3	73
8	2	4	15
9	3	2	73
10	3	3	76
11	4	2	86
12	4	3	87

[a]Isolated yield.

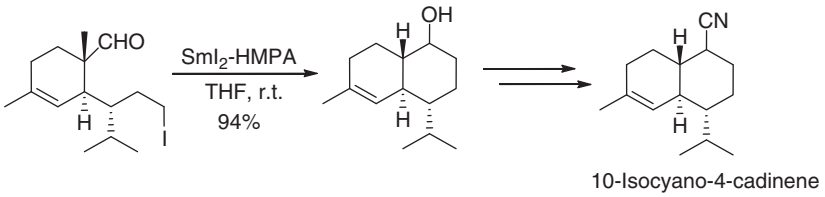
Scheme 26 Reproduced from Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112, with permission from ACS.

These reactions were expanded using starting materials containing substitutions on the cycloalkanone ring (Scheme 27), all of which were still capable of proceeding through the Barbier reaction with high yields. Highly strained ring structures were synthesized (entries 1 and 2). Secondary halides were also successful (entry 4). It is important to note that this particular cyclization cannot be achieved with other typical reductants, such as butyl lithium compounds or activated magnesium, identifying the great benefit of SmI_2 as a mild but powerful reductant.



Scheme 27 Reproduced from Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112, with permission from ACS.

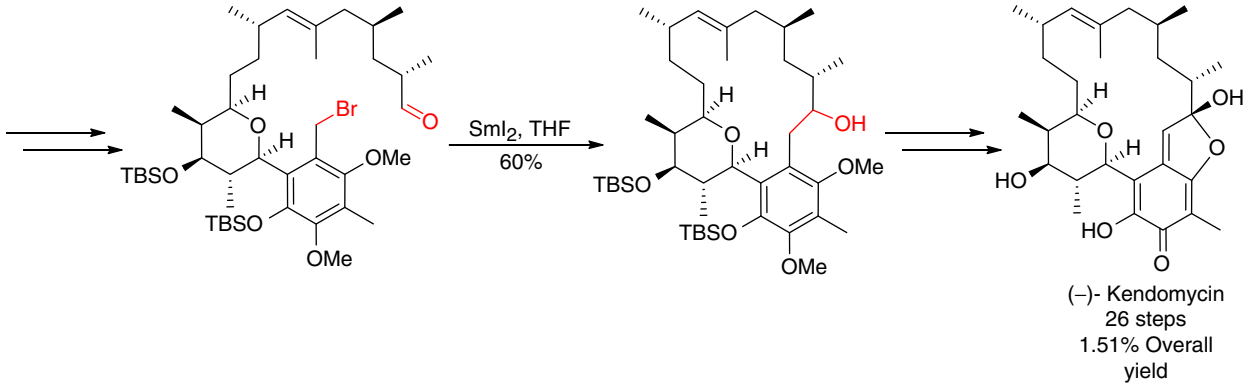
The Sm-Barbier reaction was used in the total enantioselective synthesis of 10-isocyano-4-cadinene,[113] a marine sesquiterpene which is a lead compound for a nontoxic antifouling agent. The Barbier reaction was used to form the trans-decalin framework, closing the ring in high yield (Scheme 28). This was the first example of 10-isocyano-4-cadinene synthesized in its correct natural absolute configuration (1S, 6S, 7R, 10S).



Scheme 28 Reproduced from Nishikawa, K.; Nakahara, H.; Shirokura, Y.; *et al. Org. Lett.* **2010**, *5*, 904, with permission from ACS.

An intramolecular Sm-Barbier reaction was used for the macrocyclization of the natural product kendomycin.[114] (–)-Kendomycin is a natural product originally isolated from *streptomyces violaceuber*. It is a potent antiosteoporotic agent, exhibits effective antibacterial activity against gram-positive and gram-negative strains and has enhanced cytotoxic activity toward several human tumor cell lines.[115,116] An intramolecular Sm-Barbier reaction is performed in the final stages of the synthesis, forming the strained 16-membered ring of the macrocycle in a single stereochemical configuration (Scheme 29). The macrocyclization step was completed in a 60% yield, and the final natural product was obtained in a 1.5% overall yield in 26 steps.

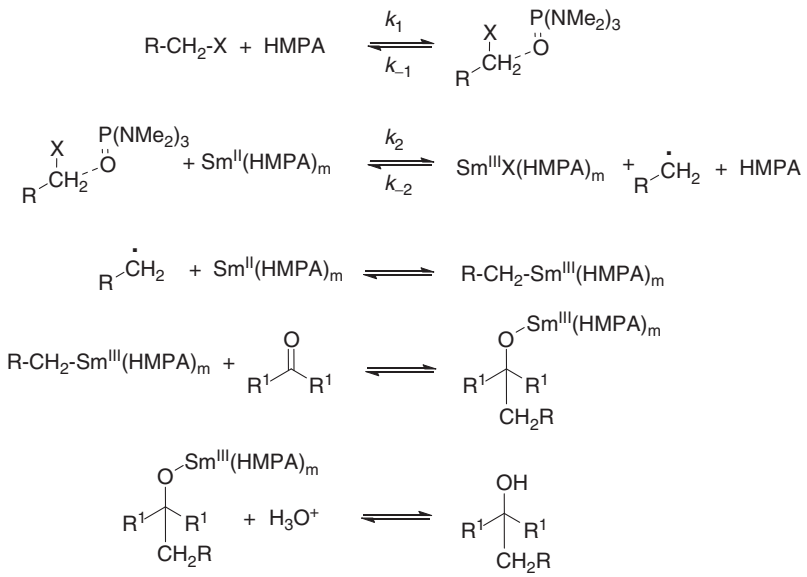
As mentioned previously, the use of HMPA in Sm-mediated reductions has taken on different roles depending on the substrates involved. When HMPA is introduced to the Sm-Barbier reaction the reaction is completed within minutes instead of hours, and the product is obtained in a higher yield with no side product formation.[67] Initially it was presumed that the reaction improvement was due to HMPA coordination with Sm, forming the more powerful reductant, allowing the reaction to be



Scheme 29 Reproduced from Lowe, J. T.; Panek, J. S. *Org. Lett.* **2008**, *17*, 3813, with permission from ACS.

completed more efficiently. However, a recent kinetic investigation of HMPA in the Sm-Barbier reaction identified a surprising result.

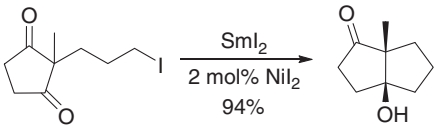
When the concentration of HMPA was increased in the Barbier reaction, the rate of the reaction continued to increase linearly well past the point where the effect could be due to HMPA coordination to the Sm-metal reductant (4–10 equivalents). The rate study also indicated a first order dependence of HMPA in the reaction, a role that seemed to be occurring before or during the initial electron transfer. Following these observations the potential for HMPA interaction with either of the substrates was investigated. Through NMR experiments as well as computational analysis it was determined that HMPA has an affinity for the alkyl halide, forming a complex through the nucleophilic oxygen of HMPA and the carbon bearing the halide on the substrate. In a pre-equilibrium step, the complex is formed between alkyl halide and HMPA, elongating the carbon–halide bond (as identified through computational analysis) and producing an intermediate more susceptible to SmI_2/HMPA reduction in the rate limiting step (Scheme 30).[69] This study was continued to secondary and tertiary species, and similar kinetics and complexes were observed.[117]



Scheme 30 Reproduced from Choquette, K. A.; Sadasivam, D. V.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2010**, *132*, 17396, with permission from ACS.

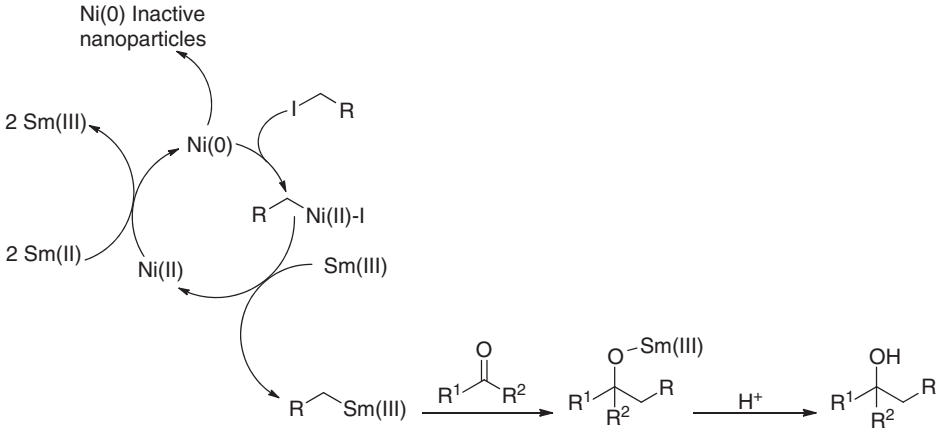
In 1996, Namy and Kagan described the use of catalytic amounts of various transition metal salts to improve the reaction time and product yield of the Sm-Barbier reaction.[102] With the addition of these salts ($FeCl_3$, $CuCl_2$, NiI_2, AgBr, among others) the reaction was completed within 10 min, with above average yields. In this report NiI_2 provided the greatest improvement. Since then the use of catalytic amounts of NiI_2 has been frequently included with Sm-Barbier reactions.[118,119] Molander included catalytic NiI_2 in intramolecular Barbier reactions[120] to form bicyclic hydroxyl ketones (Scheme 31). When NiI_2 was not added, undesired side products were obtained.

Although it is unmistakable that the transition metal catalyst enhances the reaction, it was unclear what role Ni(II) was playing in the mechanism. A careful study revealed that the Ni(II) species (NiI_2 and $Ni(acac)_2$) are being reduced by SmI_2 to form



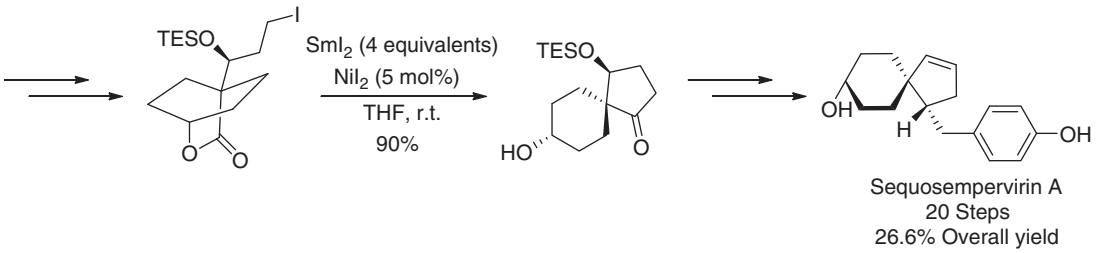
Scheme 31 Reproduced from Molander, G. A., Huérou, V. L.; Brown, G. A. *J. Org. Chem.* **2001**, *66*, 4511, with permission from ACS.

Ni(0).[103] A rate constant for the reduction identified that SmI_2 reduces NiI_2 five orders of magnitude faster than it would go through an electron transfer with either the alkyl halide or the ketone. In other words, even with the substrates in solution SmI_2 preferentially reduces Ni(II) to Ni(0). UV–Vis and transmission electron microscopy (TEM) data obtained indicated that the reduction of Ni(II) by SmI_2 produces Ni nanoparticles as well as soluble Ni(0) species. It was proposed that the soluble Ni(0) inserts into the alkyl–halide bond forming an organonickel species, which then trasmetallates with the Sm(III) present in solution (Scheme 32). Following the transmetallation, the organosamarium proceeds through the typical Sm-Barbier mechanism, coupling to the ketone. The Sm alkoxide is easily protonated through acidic workup, to form the final alcohol product (Scheme 32). The combination of facile Ni(II) reduction and insertion, along with the transmetallation step which regenerates the catalyst and forms the organosamarium intermediate are the key features that make the reaction so successful. Although Ni(0) nanoparticles are produced through the reduction, it was found that the nanoparticle formation is a deactivation pathway in the reaction and the soluble Ni(0) intermediates propagate the Barbier reaction.



Scheme 32 Reproduced from Choquette, K. A.; Sadasivam, D. V.; Flowers, R. A. II. *J. Am. Chem. Soc.* **2011**, *133*, 10655, with permission from ACS.

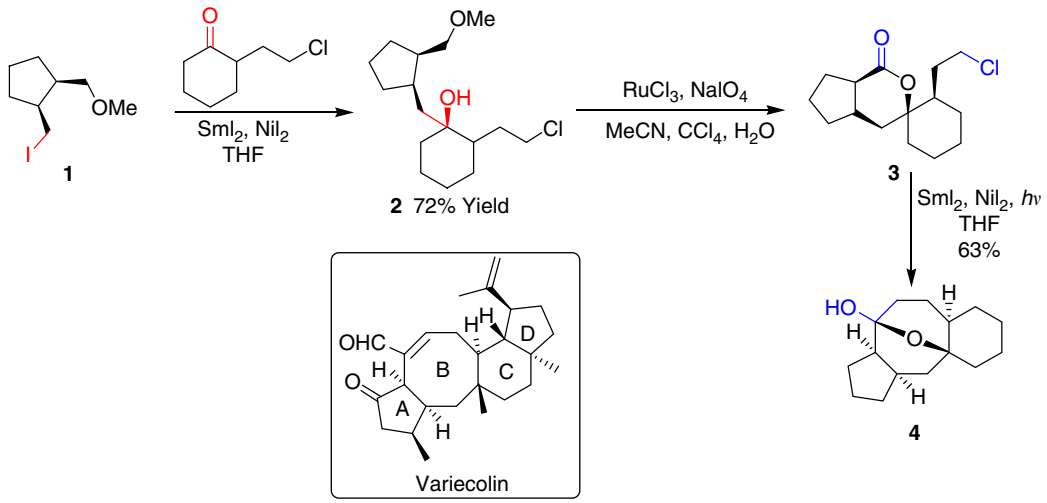
The use of NiI_2 in the Sm-Barbier reaction was crucial in the synthesis of natural product Sequosempervirin A ((4R)-4-(4-hydroxybenzyl)spiro[4.5]dec-1-en-8-ol) (Scheme 33).[121] A total synthesis of this compound was first presented in 2007 by Maity and Ghosh,[122] however a mixture of regio- and stereoisomeric compounds were obtained due to reduction of ketone moieties in intermediate steps. Recently Honda and coworkers[121] circumvented this issue by using the Sm-Barbier reaction in an intramolecular cyclization step, which they found to be most successful with the addition of 5 mol% NiI_2. This new stereocontrolled route for the synthesis was achieved in 20 steps with a 26.6% overall yield, improved from the 2% yield employing the 2007 method.



Scheme 33 Reproduced from Ito, Y.; Takahashi, K.; Nagase, H.; Honda, T. *Org. Lett.* **2011**, *13*, 4640, with permission from ACS.

Control over the Sm-Barbier reaction was exhibited in the synthesis of a variecolin model (Scheme 34, 4). The sesterterpenoid, variecolin, is a natural product with known biological activities, such as immunosuppressant activity as well as being an antagonist of the angiotensin-II receptor. In the retrosynthetic analysis for the formation of variecolin model 4, it was envisioned to proceed through two separate Sm-Barbier reactions. These reactions highlight the interesting characteristic of the Sm-reaction to

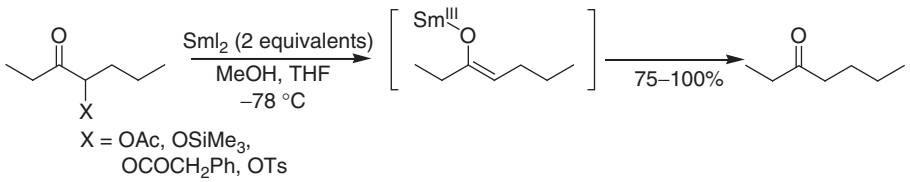
selectively interact with I over Cl, and was achieved with the addition of catalytic NiI_2 (Scheme 34).[123] The first intermolecular Barbier reaction proceeded with complete recovery of the chloride on the molecule, eliminating the need for a protecting group. This reaction was then followed by Sharpless oxidation of **2** to its corresponding lactone in a high yield. The remaining pendant chloride was then cyclized through a second intramolecular Barbier reaction under photochemical Sm/Ni conditions to form the final intramolecular cyclooctane and complex four-ring system. Again based on the finding of Flowers described above, it is presumed that the Barbier reactions are actually proceeding through Ni(0) chemistry and not direct SmI_2 reduction.



Scheme 34 Reproduced from Molander, G. A.; Quirmbach, M. S.; Silva, L. F. J.; Spencer, K. C.; Balsells, J. *Org. Lett.* **2001**, *3*, 2257, with permission from ACS.

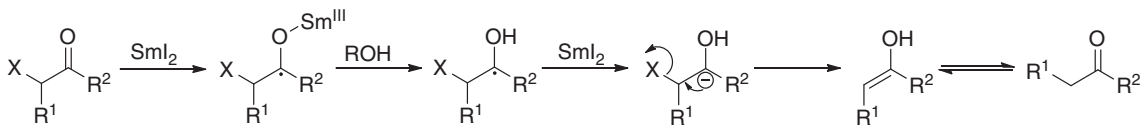
1.09.3.2.1.1.3 Reformatsky-type reactions

SmI_2 has the ability to reduce α-heteroatom-substituted carbonyl compounds without overreducing the carbonyl functionality (Scheme 35).[46] These reductions are believed to proceed through an intermediate Sm(III) enolate which when generated can be used either as a nucleophile in coupling reactions, or could simply be protonated in solution.[46] An excellent review by Procter on Sm(III) enolates is available.[124]

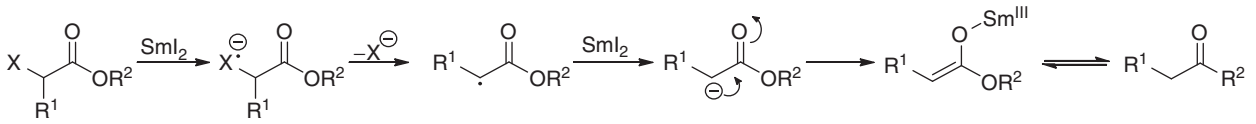


Scheme 35 Reproduced from Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1986**, *51*, 1778, with permission from ACS.

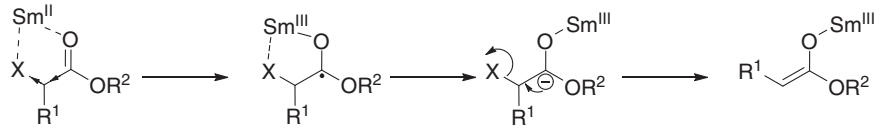
Two possible mechanisms for the formation of Sm-enolates have been proposed. In the first mechanism, Molander suggested that following single-electron transfer by SmI_2 a ketyl radical is formed, which is quenched by a cosolvent.[46] A subsequent reduction produces a carbanion which undergoes β-elimination to produce the enol tautomer of the final product ketone (Scheme 36). An alternative mechanism was proposed taking into account that esters are not typically reduced to radicals by SmI_2. When esters are used as substrates, Molander proposed electron transfer to the α-position generates a radical-anion, which undergoes fragmentation to produce a radical intermediate. A second reduction by SmI_2 produces the Sm-enolate, which can be protonated to form the final ester (Scheme 37). Another possible mechanism for ester reduction takes Sm coordination into consideration. The electron-withdrawing character of the α-heteroatom can facilitate the reduction of the ester carbonyl group to form the ketyl radical (Scheme 38). Once the activating heteroatom has been removed, no further ester reduction is possible.



Scheme 36 Reproduced from Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1986**, *51*, 1778, with permission from ACS.



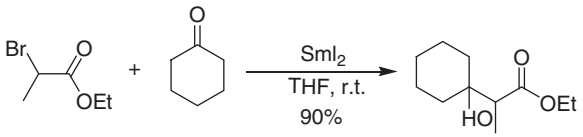
Scheme 37 Reproduced from Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1986**, *51*, 1778, with permission from ACS.



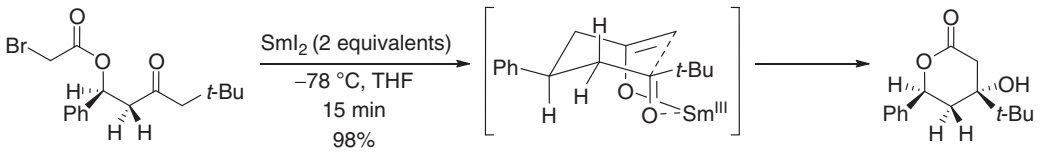
Scheme 38 Reproduced from Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1986**, *51*, 1778, with permission from ACS.

When Sm-enolates are in solution with aldehydes or ketones they readily undergo an aldol reaction. More specifically, when an aldol condensation occurs with a Sm-enolate that was generated through the reduction of an α–halo carbonyl, the transformation is classified as a Reformatsky reaction. The reaction is carried out under 'Barbier conditions,' which simply means that a 1:1 mixture of the α–halo carbonyl and coupling partner are reacted with SmI_2 at the same time.

The first intermolecular Reformatsky reaction was carried out in Kagan's seminal report, coupling an ethyl bromopropionate and cyclohexanone, achieving heterocoupling in a high yield under mild conditions (Scheme 39).[60] Soon thereafter, Molander performed intramolecular cyclizations utilizing the Reformatsky transformation[125] achieving complete stereochemical control over a range of substituted starting materials (Scheme 40).

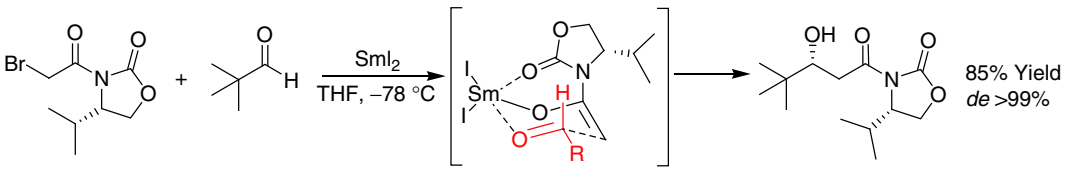


Scheme 39 Reproduced from Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693, with permission from ACS.



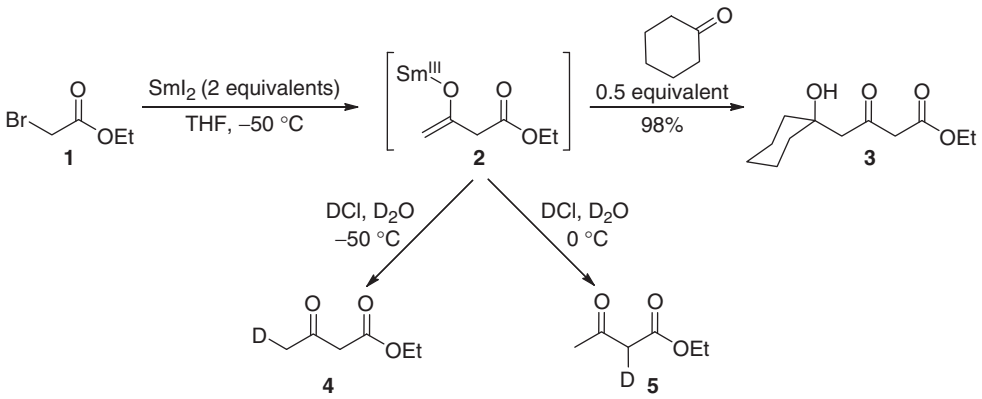
Scheme 40 Reproduced from Molander, G. A.; Etter, J. B. *J. Am. Chem. Soc.* **1986**, *109*, 6556, with permission from ACS.

Intermolecular Reformatsky reactions can also proceed with control over the stereochemistry.[126] Coordination of the incoming carbonyl species with the Sm-enolate positions the electrophile in a manner that the addition takes place in one orientation, producing a single diastereomer (Scheme 41). High diastereoisomeric excess is difficult to achieve with other aldol reactions, once again highlighting the impact of Sm-reactions on synthetic chemistry.



Scheme 41 Reproduced from Fukuzawa, S.; Matsuzawa, H.; Yoshimitsu, S. *J. Org. Chem.* **2000**, *65*, 1702, with permission from ACS.

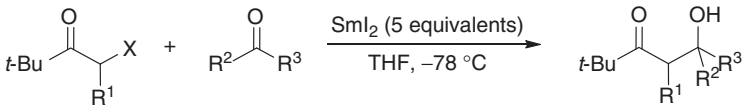
Although there is still a lot to be learned about the reactivity of Sm-enolates, their ability to direct the Reformatsky reaction is apparent and the results of these reactions have provided some insight that has been useful. Utimoto and Matsubara were able to produce Sm-enolates (Scheme 42, 2) from α-bromo esters, which could successfully couple with cyclohexanone in high yields (Scheme 42, 3).[127] However, when the enolate formed *in situ* was quenched with D_2O at the reaction temperature (− 50 °C), the expected deuterated species was isolated (Scheme 42, 4). When the temperature was raised to 0 °C after reduction, followed by quenching with D_2O, a rearranged product was obtained (Scheme 42, 5). This experiment identified that the intermediate enolate



Scheme 42 Reproduced from Utimoto, K.; Matsui, T.; Takai, T.; Matsubara, S. *Chem. Lett.* **1995**, *24*, 197, with permission from The Chemical Society of Japan.

is stable at $-50\,^{\circ}C$, but goes through a thermal isomerization when the temperature is raised. Furthermore, the isomerized enolate could not couple with aldehydes or ketones to produce a Reformatsky product.

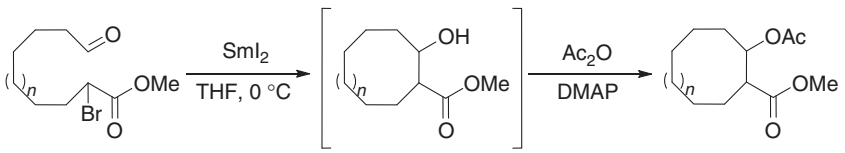
Jamison explored a range of species in intermolecular Reformatsky reactions[128] and found that primary and secondary α-bromo and α-chloroketones can be used to form the enolates. The enolates were also able to attack simple and hindered aldehydes and ketones (Scheme 43).



Entry	X	R^1	R^2	R^3	Yield (%)
1	Br	H	H	Cy	94
2	Br	Me	H	Cy	80
3	Cl	H	H	Cy	>99
4	Cl	Me	H	Cy	94
5	Br	H	t-Bu	Me	98
6	Cl	H	t-Bu	Me	93

Scheme 43 Reproduced from Sparling, B. A.; Moslin, R. M.; Jamison, T. F. *Org. Lett.* **2008**, *10*, 1291, with permission from ACS.

Inanaga used an intramolecular Reformatsky reaction to produce large carbocycles,[129] a moiety common in many natural products. These large ring structures are often difficult to construct, but the SmI_2-mediated method proceeded with a simple, mild procedure obtaining high yields (Scheme 44).

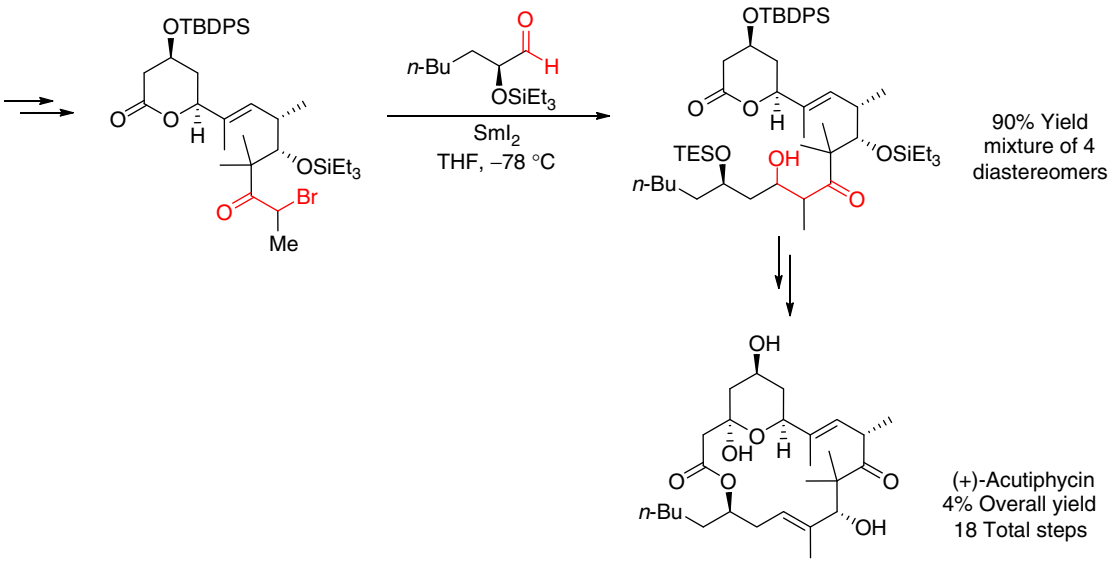


Entry	n	Final ring size	Yield (%)
1	1	8	68
2	2	9	70
3	4	11	74
4	7	14	82
5	8	15	82

Scheme 44 Reproduced from Inanaga, J.; Yokoyama, Y.; Handa, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 6371.

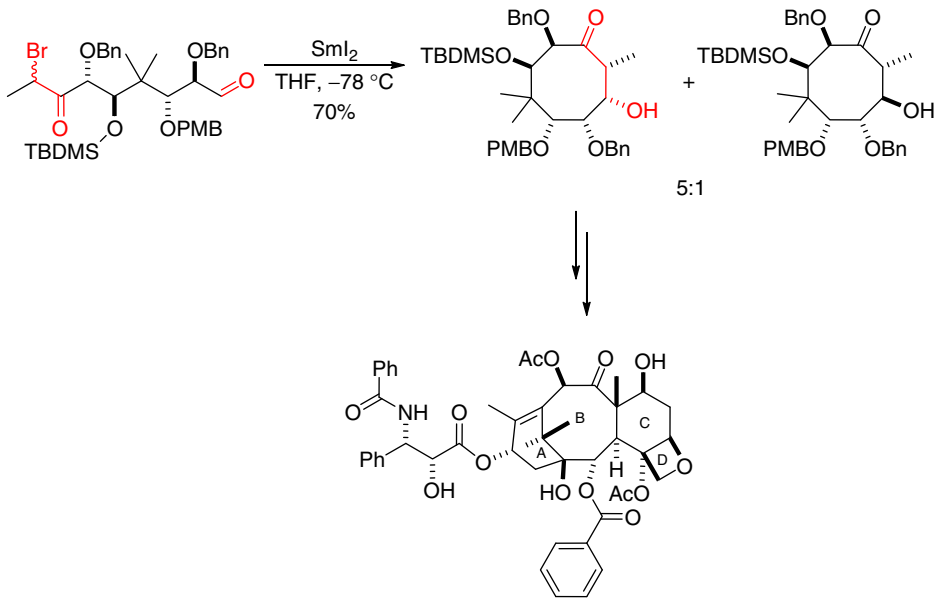
A very impressive use of SmI_2-mediated Reformatsky coupling was demonstrated by Jamison for the synthesis of (+)-acutiphycin.[130] This natural product, isolated in 1984, has potent activity against murine Lewis lung carcinoma. The naturally occurring source of acutiphycin is harvested from blue-green algae (*Oscillatoria acutissima*); however, it has been determined that

the algae no longer produce this metabolite in nature. The scarcity of this important therapeutic put a high demand on the development of a total synthesis of acutiphycin in its active configuration. After over 20 years, only one successful total synthesis had been reported.[131,132] In 2006, Jamison reported a convergent total synthesis of the natural product, with an integral coupling step utilizing an intermolecular Reformatsky reaction. In his studies many typical coupling reactions including the Mukaiyama aldol, Horner–Wadsworth–Emmons, and cross-metathesis were attempted and failed. The Reformatsky reaction was attempted and failed using activated zinc to produce the enolate. However when SmI_2 was used, the desired product was obtained in an unexpected 90% yield (Scheme 45). The reaction did produce a mixture of diastereomers, however when the mixture was subjected to subsequent dehydration, a single isomer of the product was obtained.



Scheme 45 Reproduced from Maslin, R. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 15106, with permission from ACS.

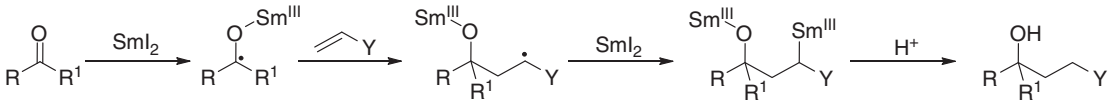
In 1999, Mukaiyama published a total synthesis of the natural product paclitaxel, which is an anticancer drug marketed as Taxol®.[133] The Sm-mediated Reformatsky reaction was used to construct the highly functionalized 8-membered ring, which becomes the interior ring B in the final product (Scheme 46). The Reformatsky reaction allowed the cyclization to proceed with high diastereoselectivity and a 70% isolated yield.



Scheme 46 Reproduced from Mukaiyama, T.; Shiina, I.; Iwadare, H.; *et al. Chem. Eur. J.* **1999**, *5*, 121, with permission from Wiley.

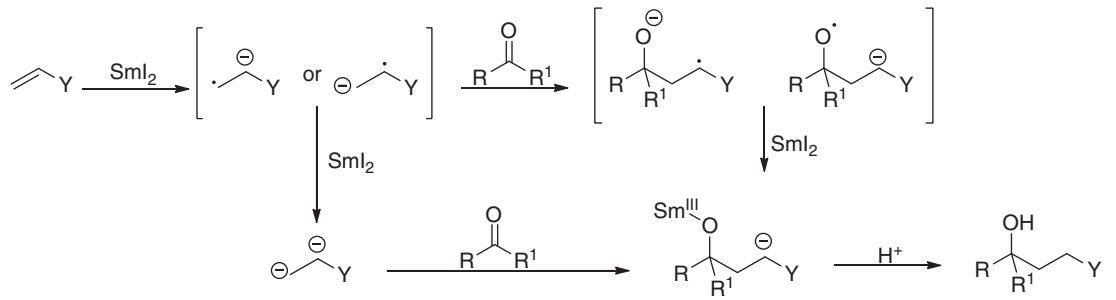
1.09.3.2.1.1.4 Carbonyl-alkene coupling

The single electron reduction of a carbonyl species followed by an inter- or intramolecular radical addition to an alkene is fundamentally one of the most important bond-forming reactions in organic synthesis. Intramolecular reactions lead to the formation of a variety of carbo- and heterocyclic ring systems of various sizes. Traditionally, the mechanism for the carbonyl-alkene coupling is thought to proceed through a 'carbonyl first' order (Scheme 47), in which the carbonyl goes through a single electron reduction to form a ketyl radical anion, which adds to a carbon–carbon unsaturation site. Further reduction by SmI_2 forms an organosamarium intermediate, which can be protonated on acidic work up, or by a proton source in solution.



Scheme 47 Reproduced from Procter, D. J.; Flowers, R. A., II.; Skrydstrup, T. In *Organic Synthesis Using Samarium Diiodide: A Practical Guide*; Royal Society of Chemistry Publishing: UK, **2010**, with permission from Royal Society of Chemistry.

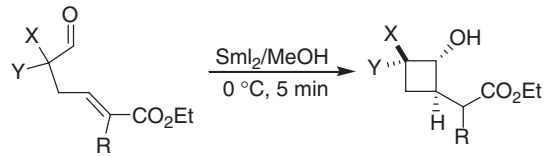
It has also been suggested that when electron-deficient alkenes are involved, an 'alkene-first' mechanism could occur (Scheme 48). Within this scheme SmI_2 preferentially reduces the alkene, followed by anionic (or radical) addition to the carbonyl functionality.



Scheme 48 Reproduced from Procter, D. J.; Flowers, R. A., II.; Skrydstrup, T. In *Organic Synthesis Using Samarium Diiodide: A Practical Guide*; Royal Society of Chemistry Publishing: UK, **2010**, with permission from Royal Society of Chemistry.

Procter has carried out a series of studies to differentiate between these two mechanisms, and as described below, the reaction conditions and cosolvents play a role in which pathway the reaction proceeds through. Within these reactions, the outcome of intramolecular ketyl-olefin cyclizations could be altered depending on the carbonyl species, stereochemistry of the alkene, as well as the proton source involved in the reaction.

First, functionalized cyclobutanols were formed through a 4-*exo-trig* mechanism.[134] The reaction proceeded with moderate yields and in all cases anticyclobutanol products were obtained, with no trace of *syn*-products when MeOH was used as a cosolvent (Scheme 49). It was reasoned that the observed selectivity was an effect of the cosolvent, which has been shown to coordinate to the Sm metal center. With the Sm-coordination sites taken up by cosolvent interaction, the ability of oxophilic Sm to interact with both oxygen-containing functional groups on the substrate is disrupted, leading to an intermediate species which favors the anticonfiguration on protonation. This supposition was verified by attempting the reaction in the presence of other coordinating solvents such as HMPA (Scheme 49, entry 3) and H_2O (Scheme 49, entry 4) forming the predicted species. When a noncoordinating proton source was used, such as EtOH, a 1:1 mixture of *anti*:*syn* diastereomers was obtained.

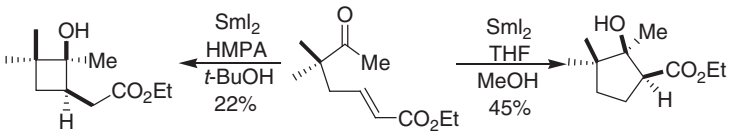


Entry	Additive	X	Y	R	Yield (%)
1	MeOH	CH_3	CH_3	H	65
2	MeOH	CH_3	CH_3	CH_3	66
3	HMPA	OBn	CH_3	H	57
4	H_2O	CH_3	CH_3	CH_3	44

Scheme 49 Reproduced from Johnston, D.; McCusker, C. F.; Muir, K.; Procter, D. J. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 681, with permission from Royal Society of Chemistry.

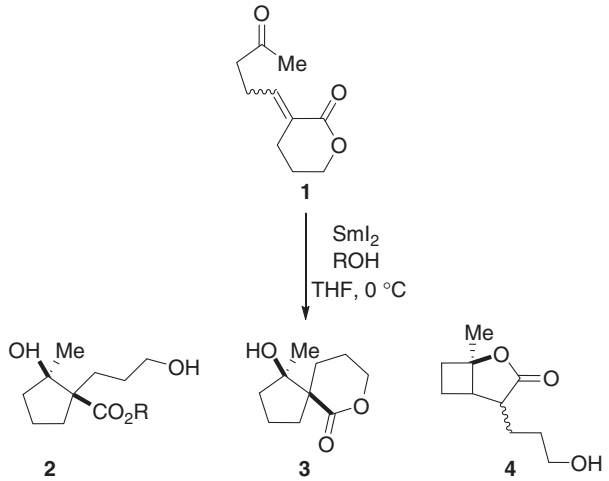
The study was then extended to ketones.[135] Instead of obtaining the cyclobutanol products through a 4-*exo-trig* cyclization, cyclopentanol products were obtained with MeOH as a cosolvent. However, when HMPA and noncoordinating *t*-BuOH were

employed, cyclobutanols were isolated through 4-*exo-trig* cyclization (Scheme 50). It was suggested through mechanistic studies that SmI_2 reduction in the presence of MeOH proceeds through a sequential reduction/intermolecular aldol process, to form the functionalized *syn*-cyclopentanols.



Scheme 50 Reproduced from Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett.* **2002**, *4*, 2347, with permission from ACS.

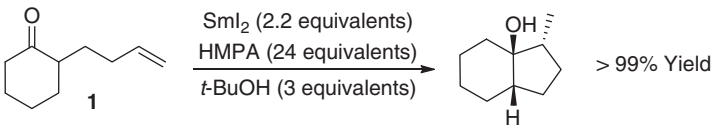
The drastic effect in reactivity seen from the change in cosolvent was extended to other alcohols (Scheme 51), and an interesting conclusion was surmised.[136] It was proposed that the ability of the cyclization to go through a 4-*exo-trig* or aldol spirocyclization is controlled by the ability of the cosolvent to protonate the intermediate species. Because *t*-BuOH has a slower protonation time, radical anion cyclization occurs first, forming the cyclobutanols (Scheme 51, 4). MeOH efficiently protonates the intermediate anion species, causing the radical to proceed through an aldol cyclization to form *syn*-cyclopentanols (Scheme 51, 2). These results identify that the use of proton donors as additives in SmI_2-mediated reactions can play an integral role in the process, changing the outcome of the reaction.



	2	3	4
MeOH	100%	–	–
EtOH	41%	12%	10%
i-PrOH	–	10%	75%
t-BuOH	–	–	66%

Scheme 51 Reproduced from Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett.* **2002**, *4*, 2347, with permission from ACS.

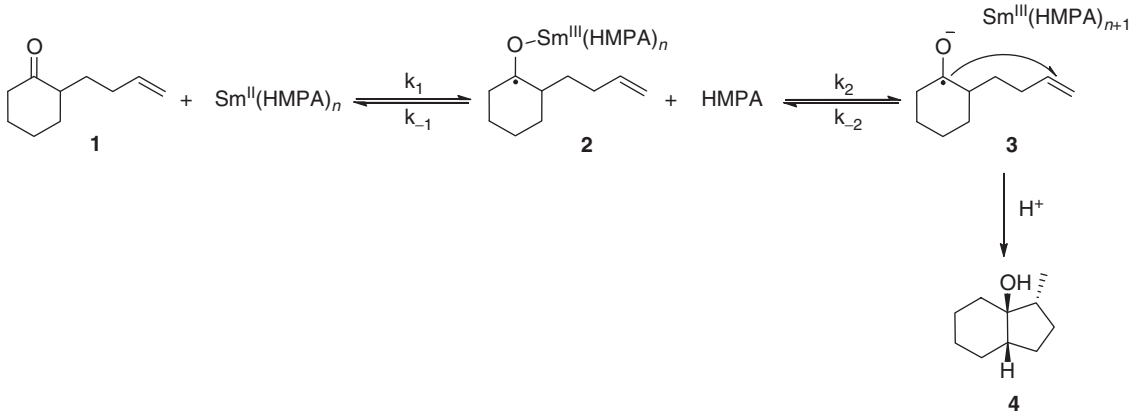
The critical role of cosolvents in carbonyl-alkene additions are best exemplified by the elegant work of Molander.[137] Through a series of reactions containing increasing amounts of HMPA, Molander proposed that the sterically encumbered SmI_2-HMPA complex was responsible for the observed products and diastereoselectivities of 5- and 6-*exo*-ketyl-olefin cyclizations. He ascribed the success of the reaction to protection of the intermediate ketyl radical formed after initial electron transfer being shielded from solvent by proximal coordinated Sm(III)-HMPA. More recent studies have shown that the addition of HMPA in the Sm-mediated coupling of carbonyls and alkenes plays an important mechanistic role beyond coordinating to the Sm-metal center. The rate of the intramolecular carbonyl-olefin cyclization of substrate **1** (Scheme 52) was monitored over a range of HMPA concentrations.



Scheme 52 Reproduced from Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132, with permission from ACS.

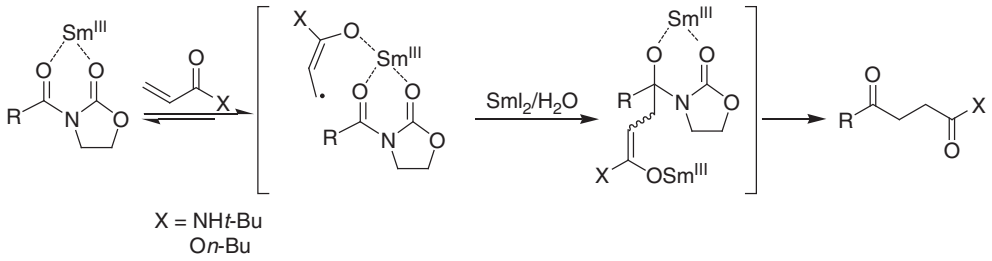
If HMPA was not included in the reaction, the desired cyclization did not occur. Kinetic and mechanistic studies showed a postelectron transfer role for HMPA beyond to coordination to the Sm-metal.[138]

Owing to its oxophilic nature, Sm(III)/HMPA coordinates and stabilizes the ketyl intermediate. However, the sterically encumbered Sm-HMPA-ketyl complex hinders radical addition to the pendent olefin. When HMPA is present in solution (>10 equivalents), an additional equivalent of HMPA can coordinate to the Sm-metal center, releasing it from the ketyl intermediate (Scheme 53). The loss of Sm from the anion intermediate leads to a solvent-separated ion pair (**3**), which is now free to undergo the 5-*exo-trig* cyclization.[138] This mechanistic insight on the role of HMPA was unexpected, and could not have been predicted through observations of product formation alone. This example highlights the significant information that can be gained through detailed kinetic and mechanistic studies, especially in reference to the complex role of additives in Sm-mediated reactions.



Scheme 53 Reproduced from Sadasivam, D. V.; Antharjanam, P. K. S.; Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2008**, *130*, 7728, with permission from ACS.

Another additive that has been used to promote Sm coupling reactions is water. Water was initially used as a proton source in some Sm reactions, but it also has the ability to coordinate to the metal center and displace I^- to the outer sphere.[139] Work done by Skrydstrup reported the ability of the Sm/H_2O system to couple N-acyl oxazolidinones with acrylates and acrylamides to produce γ-carbonyl esters and amides (Scheme 54).[140] The results of these reactions led to a mechanistic study by Skydstrup and Flowers to determine if the coupling proceeded through a ketyl radical anion intermediate or a radical pathway. In the case of this coupling reaction, mechanistic evidence identified that the reductive coupling of an activated ester or amide with an N-acyloxazolidinone proceed through the reduction of the activated ester or amide to produce a radical which then added to the carbonyl of the N-acyloxazolidinone.[141] Within this pathway, it is suspected that a chelated intermediate with Sm(III) forms (Scheme 54), which helps facilitate the otherwise slow intermolecular radical addition onto carbonyls. The hard Lewis acid character of Sm(III) lowers the π^* C=O orbital to allow radical addition to become more favorable. The Sm(III) coordination also tethers the molecules together and positions them in an orientation that promotes the intermolecular addition.

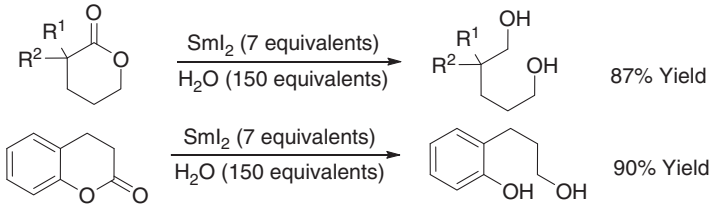


Scheme 54 Reproduced from Jensen, C. M.; Lindsay, K. B.; Taaning, R. H.; *et al. J. Am. Chem. Soc.* **2005**, *127*, 6544, with permission from ACS.

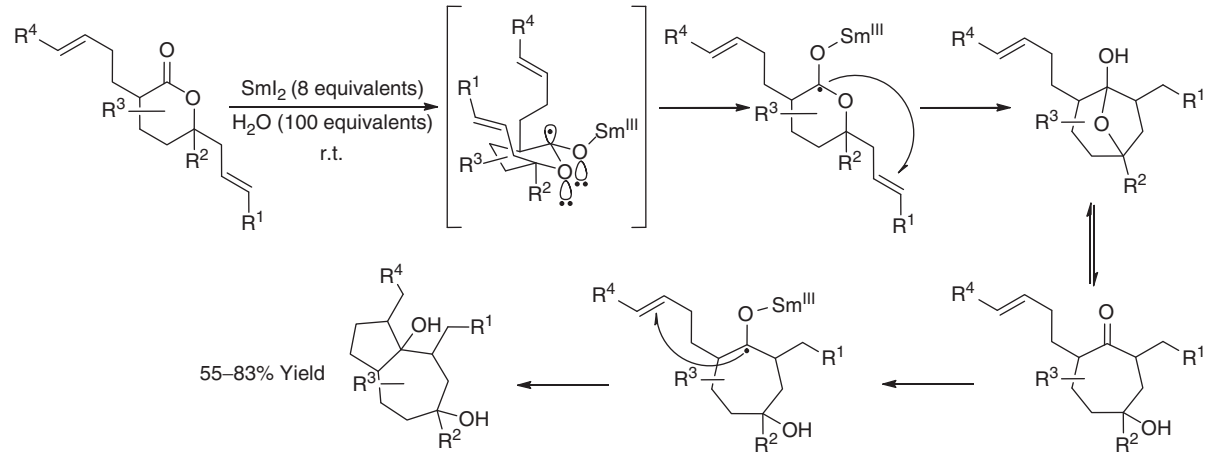
Procter found that the addition of water as a cosolvent allows the selective reductive ring-opening of lactones to form diols (Scheme 55), whereas in the absence of H_2O no reaction occurs.[93] It was proposed that the ring-opening proceeds through four successive electron transfers and protonations facilitated by H_2O coordinating and producing a more powerful reductant, as well as acting as a proton source.

The reduction was expanded to radical cascade reactions that proceeded through the radical anion formed after the first electron transfer. It was suggested that the radical anion produced from the initial electron transfer is stabilized by the anomeric effect,[94] preferentially producing an axial radical which facilitates the cyclization selectivity observed (Scheme 56). The radical cyclizes onto the pendant olefin, followed by organosamarium protonation from the excess water in solution. A second electron

transfer by SmI_2 produces another radical anion which can intramolecularly cyclize with the remaining olefin to form the final bicyclic product on protonation.[142]

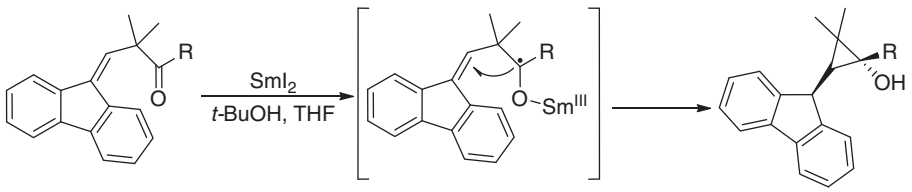


Scheme 55 Reproduced from Duffy, L. A.; Matsubara, H.; Procter, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 1136, with permission from ACS.



Scheme 56 Reproduced from Guazzelli, G.; De Grazia, S.; Collins, K. D.; *et al. J. Am. Chem. Soc.* **2009**, *131*, 7214, with permission from ACS.

3-*Exo-trig* cyclizations of β,γ-unsaturated carbonyl compounds were carried out to produce cyclopropanols (Scheme 57).[143,144] Although various cyclizations have been carried out using the Sm-mediated ketyl-olefin method, this was the first report in which a 3-membered ring was formed with aldehydes and ketones without the aid of ester-activated alkenes.

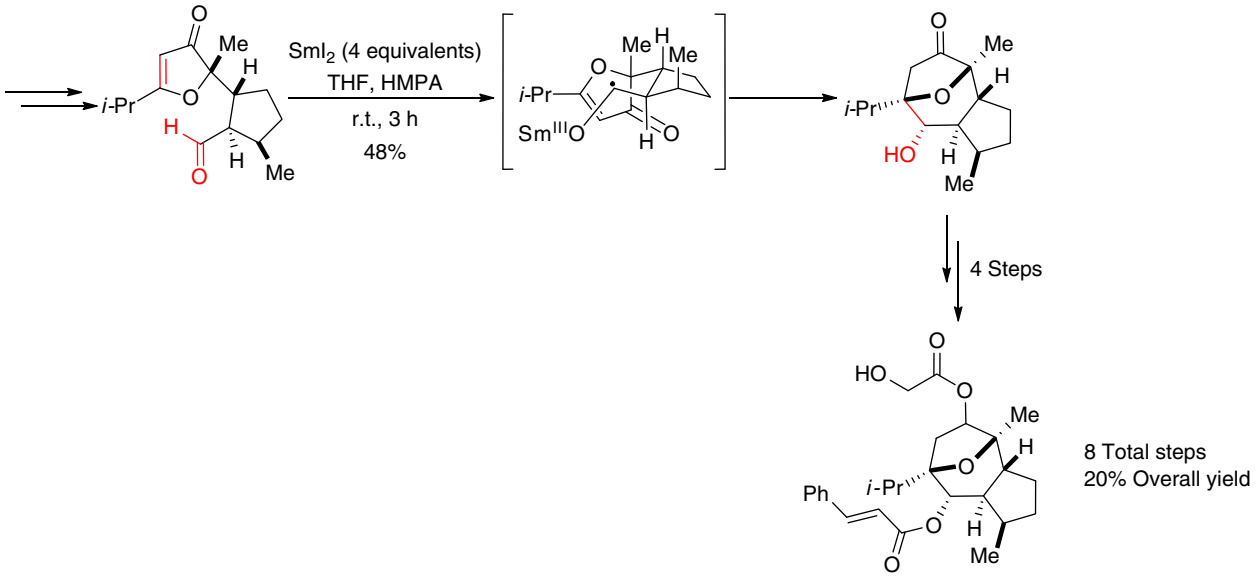


Entry	R	Yield (%)
1	H	61
2	CH_3	29
3	Ph	48

Scheme 57 Reproduced from Martin-Fontecha, M.; Agarrabeitia, A. R.; Ortiz, M. J.; Armesto, D. *Org. Lett.* **2010**, *12*, 4082, with permission from ACS.

SmI_2-mediated ketyl-olefin cyclization cascade reactions often proceed with excellent control of structure and stereochemistry. This is eloquently demonstrated when reductive cascades are used in integral C–C bond forming reactions which close large skeletons of natural products. An excellent example is the use of SmI_2 in the synthesis of englerin A, a guaiane sesquiterpene natural product. Englerin A has only recently been isolated,[145,146] and has already exhibited a range of biological activities, including selective growth inhibition against six renal cancer cell lines, which is two- to threefold more potent than current pharmaceutical treatments as well as exceptionally low toxicity in mouse models. These unique properties suggest this species has a high medicinal potential and is a hot target for synthetic chemists. The structure of Englerin A contains a highly functionalized 5-6-5 oxatricyclic framework and two ester-bearing stereogenic centers (Scheme 58). Chain and coworkers[147] established a short synthesis of this complex natural product using SmI_2 in a key C–C bond forming step to produce the strained cyclic interior, while

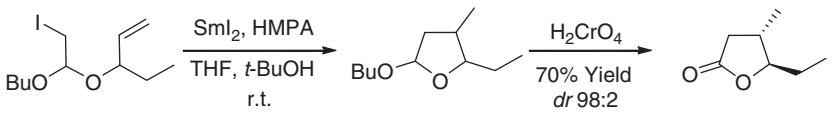
maintaining the absolute stereochemistry of the natural product. The second synthetic step calls for a Michael addition, in which a diastereomeric mixture of aldehydes (2:1 *dr* desired: Σ others) cannot be avoided. Even with this caveat, Sm/HMPA-mediated ketyl-radical cyclization onto an alkene forms the desired structure in 43% yield, with the correct stereochemistry and oxidation level needed to perform the subsequent reactions (Scheme 58). This critical C–C bond forming reaction was not successful using any other single electron reductant such as titanium(III), vanadium(I) or lithium napthalenide. The use of HMPA was necessary to achieve the desired chemical transformation. This synthetic approach produces a 20% overall yield in an 8-step synthesis of the natural product Englerin A.



Scheme 58 Reproduced from Li, Z.; Nakashige, M.; Chain, W. J. *J. Am. Chem. Soc.* **2011**, *133*, 6553, with permission from ACS.

1.09.3.2.1.1.5 Halide-alkene

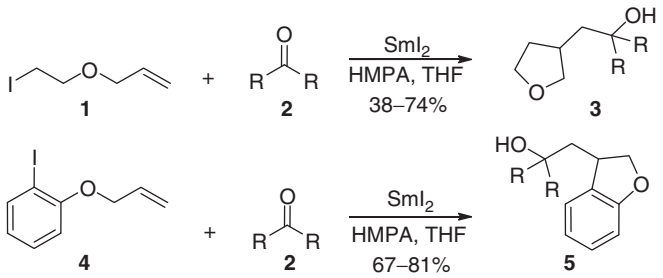
Another method of carbon–carbon bond formation utilizing SmI_2 is carbon-centered radicals adding or cyclizing onto unsaturated regions. Before SmI_2, these transformations were commonly initiated through halide reduction by tributyltin hydride. Although this method is successful to promote radical formation and successive cyclization, the experimental procedure for the removal of the tin-containing byproducts after the reaction is extensive. Also, the radical species produced were often quenched through hydrogen atom transfer by the tin hydride in solution, leading to a diminished amount of desired cyclized product. Utilizing SmI_2 in these reactions to produce the radical species has greatly improved the conditions and scope of these reactions. The most successful and most commonly reported halide-alkene reactions are intramolecular. Fukuzawa used an intramolecular cyclization with SmI_2/HMPA to form a substituted lactone in a simple two-step procedure (Scheme 59).[148]



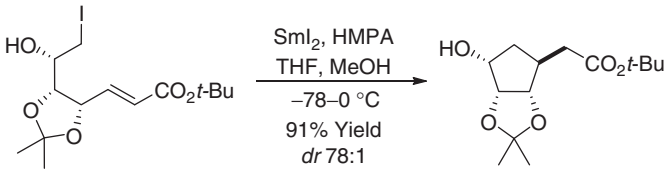
Scheme 59 Reproduced from Fukuzawa, S.; Tsuchimoto, T. *Synlett* **1993**, 803, with permission from Thieme Publisher.

Molander has shown that SmI_2-mediated halide-alkene couplings proceed through tandem intramolecular cyclization followed by intermolecular coupling (Scheme 60).[149] Within this process it was concluded that the alkyl halide was reduced to a radical followed by radical cyclization onto the pendant olefin forming a terminal carbon radical. An intermediate organosamarium is produced through a second single-electron transfer to the radical, which then adds to the carbonyl electrophile. It is important to note that the radical cyclization is faster than the reduction of the radical intermediate, which would lead to β-elimination of one of the two alkoxy groups.

Bennett used a Sm-mediated cyclization to form functionalized cyclopentanes from sugar-derived substrates.[150,151] The cyclization proceeded with a high degree of diastereoselectivity and high yields (Scheme 61). The addition of HMPA as well as a proton source was required to avoid competing 1,4-reductions of the α,β-unsaturated ester and cleavage of the allylic C–O bond.

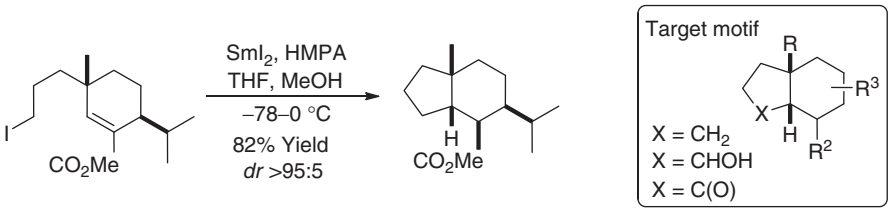


Scheme 60 Reproduced from Molander, G. A.; Harrnig, L. S. *J. Org. Chem.* **1990**, *55*, 6171, with permission from ACS.



Scheme 61 Reproduced from Salari, B. S. F.; Biboutou, R. K.; Bennett, S. M. *Tetrahedron* **2000**, *56*, 6385.

In a study aimed to develop stereoselective syntheses of compounds with *cis*-hydrindane cores,[152] the Sm-mediated halide-alkene cyclization proved successful. The desired bicyclic product was obtained in high yield and a single diastereomer was isolated (Scheme 62).



Scheme 62 Reproduced from Findley, T. J. K.; Sucunza, D.; Miller, L. C.; Davies, D. T.; Procter, D. J. *Chem. Eur. J.* **2008**, *14*, 6862, with permission from Wiley.

Molander found that the addition of NiI_2 in catalytic amounts is critical for the intramolecular cyclization of halides onto activated olefins (Scheme 63).[153,154] The cyclizations were successful with primary and secondary halides with α,β-unsaturated esters and amides, and was later expanded to cyclization with α,β-unsaturated lactones to form bicyclic products.

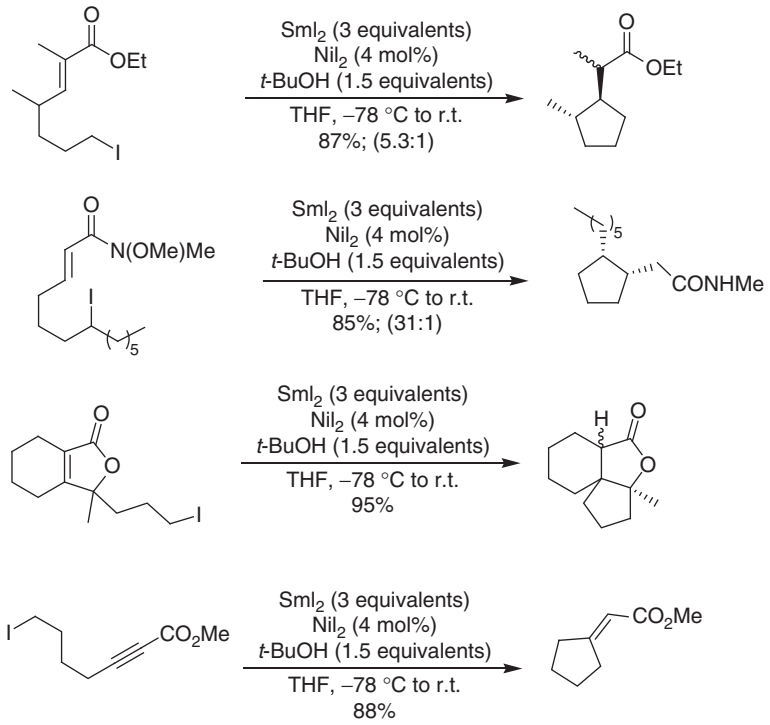
In the original publications, Molander proposed a radical pathway in which SmI_2 reduced the halide to a radical, which cyclized to the olefin. In light of the recent mechanistic studies identifying that SmI_2 reduces the Ni(II) species five orders of magnitude faster than SmI_2 reduces a primary alkyl iodide, it is likely that the reaction proceeds through a Ni(0) initiated process (similar to that described in Barbier, Section 1.09.3.2.1.1.2) and not a radical pathway (Scheme 64).

1.09.3.2.1.1.6 Pinacol coupling

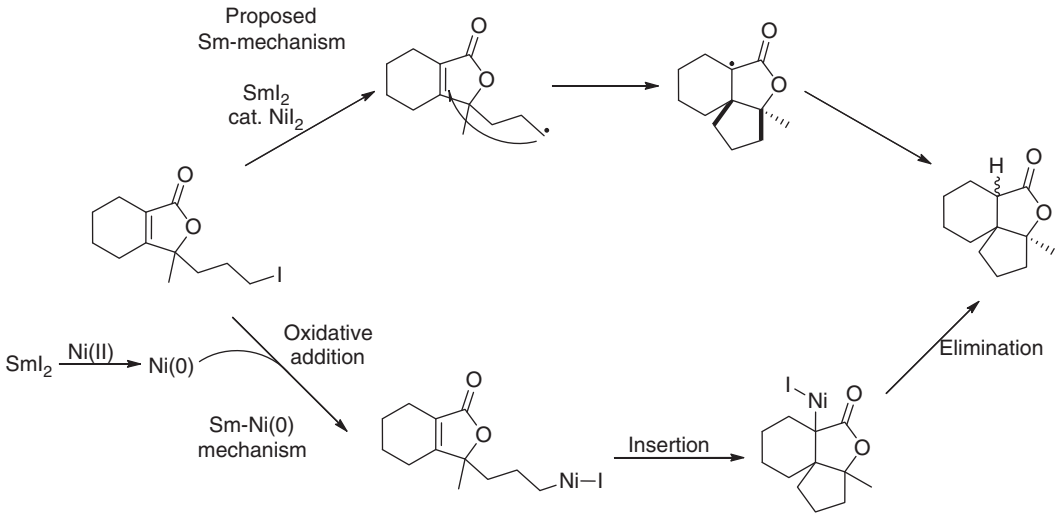
Traditional pinacol reactions are the reductive coupling of carbonyl groups to form 1,2-diols (Scheme 65). Using SmI_2 is a straightforward, mild method for achieving this important moiety with high yield. The path the reaction follows depends on the carbonyl functionality being reduced (aldehyde, ketone, or conjugated carbonyl) as well as whether it is intra- or intermolecular. After the initial electron transfer to reduce the carbonyl, the radical anion produced could proceed through three different pathways (Scheme 66). In Path A, the ketyl radical is reduced by a second electron transfer forming a dianionic or metallaoxirane species, which can add to another carbonyl species, forming the coupled product. Path B assumes after the initial electron transfer to form the ketyl radical, a radical-radical coupling occurs. In Path C, the radical formed from the reduction couples with an unreacted carbonyl species.

When the pinacol coupling is an intramolecular reaction there is strong evidence[155] that the mechanism follows through a pathway similar to Path C (Scheme 66), where an oxophilic Sm(II) species is coordinated to both of the carbonyl oxygens (Scheme 67). The bridged structure stabilizes the ketyl intermediate and facilitates inner-sphere single-electron transfer, promoting bond formation.

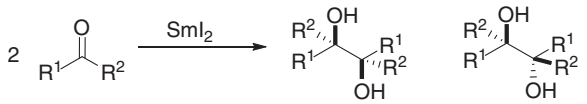
In most cases of intermolecular pinacol reactions there is low stereocontrol and both *threo* and *erythro* stereoisomers are formed. There are reported cases in which coupling sterically hindered substrates promoted some control over the stereoselectivity. Skrydstrup showed a marked increase in the *threo* isomer when a bulky 2,2-dimethylpropanal substrate was used over



Scheme 63 Reproduced from Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 7418 and Molander, G. A.; Jean, D. J. S., Jr. *J. Org. Chem.* **2002**, *67*, 3861, with permission from ACS.



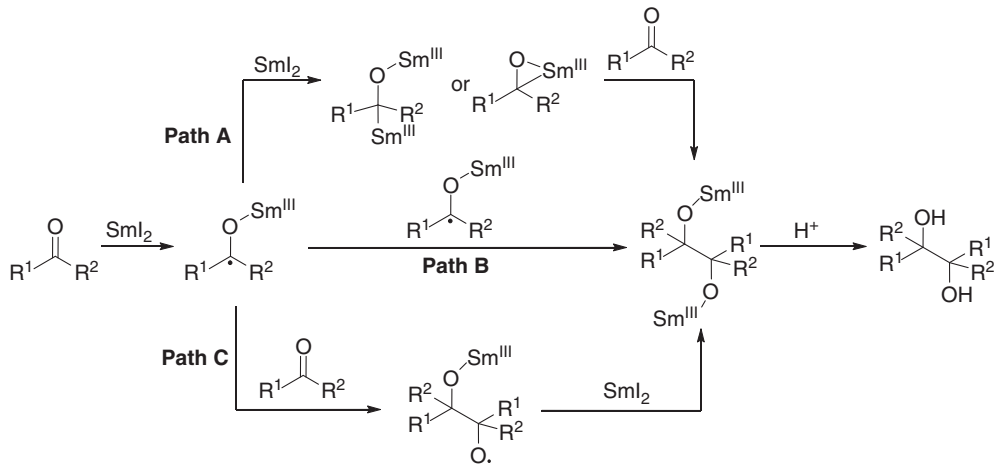
Scheme 64



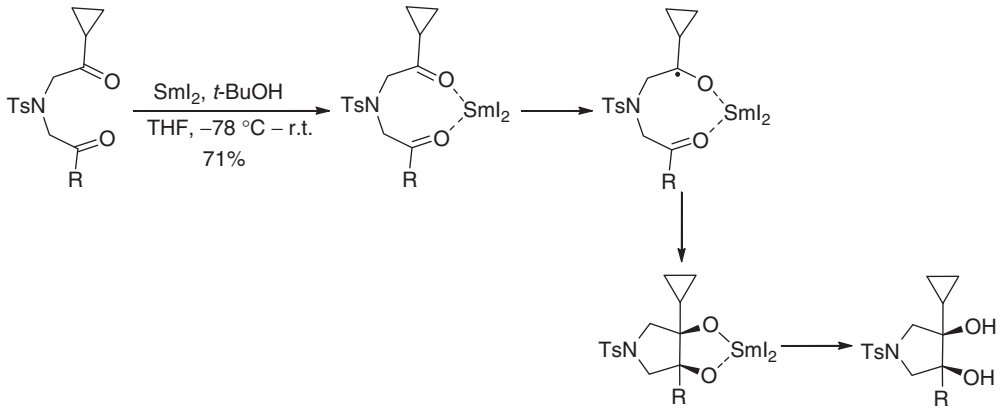
Scheme 65

2-methylbutanal (Scheme 68).[156] They also showed that with the addition of tetraglyme as a complexing agent with Sm,[157] the stereocontrol over the less hindered 2-methylbutanol was improved (Scheme 68, 3).

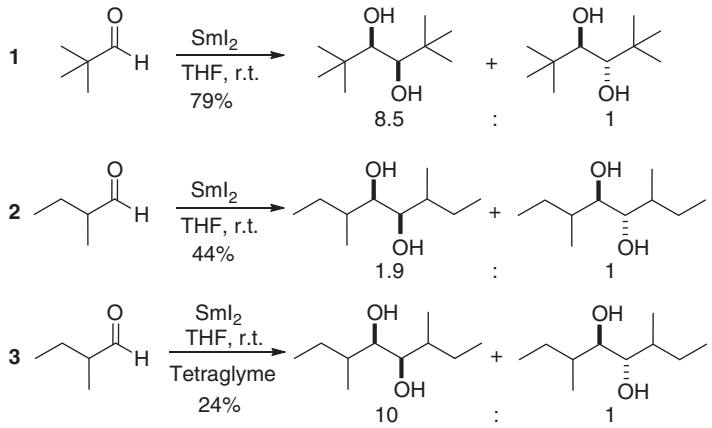
As compared to intermolecular pinacol reactions, intramolecular cyclizations tend to have a greater degree of diastereoselectivity. In the synthesis of the monosaccharide, caryose, a Sm-mediated pinacol coupling was used to construct *cis*-1,2-diols



Scheme 66 Reproduced from Procter, D. J.; Flowers, R. A., II; Skrydstrup, T. In *Organic Synthesis Using Samarium Diiodide: A Practical Guide*; Royal Society of Chemistry Publishing: UK, **2010**, with permission from Royal Society of Chemistry.



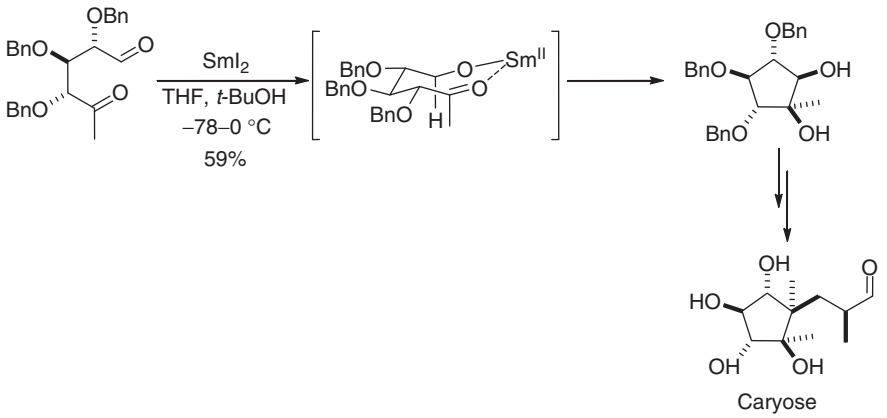
Scheme 67 Reproduced from Foster, S. L.; Handa, S.; Krafft, M.; Rowling, D. *Chem. Commun.* **2007**, 4791, with permission from Royal Society of Chemistry.



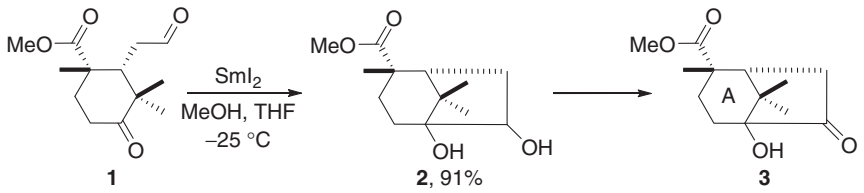
Scheme 68 Reproduced from Christensen, T. B.; Riber, D.; Daasbjerg, K.; Strydstrup, T. *Chem. Commun.* **1999**, 2051, with permission from Royal Society of Chemistry.

from 1,5- and 1,6-dicarbonyl precursors.[158] The cyclization produced the *cis* stereoisomer almost exclusively. The selectivity stems from the polar substituent group α to the reacting carbonyl, which will orient *anti* to the newly formed *cis*-1,2-diol (Scheme 69).

Intramolecular pinacolization is used for the synthesis of the bicyclic ring system of Taxol®. Intramolecular reductive coupling of the aldehyde and ketone by SmI_2/MeOH in THF provides bicyclic diol **2** in a 91% yield. Subsequent Swern oxidation provides key intermediate **3** in an 85% yield (Scheme 70).[159]

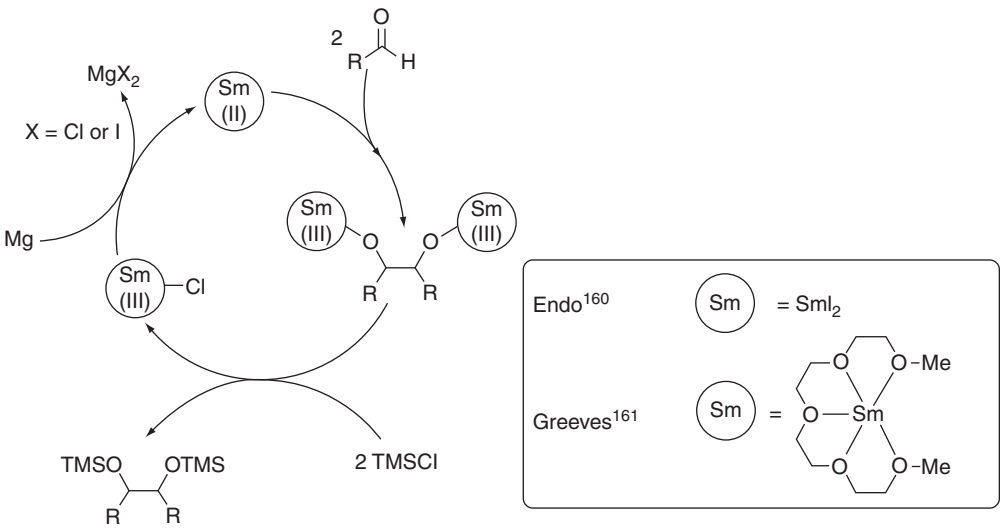


Scheme 69 Reproduced from Adinolfi, M.; Barone, G.; Iadonisi, A.; Mangoni, L.; Manna, R. *Tetrahedron* **1997**, *53*, 11767.



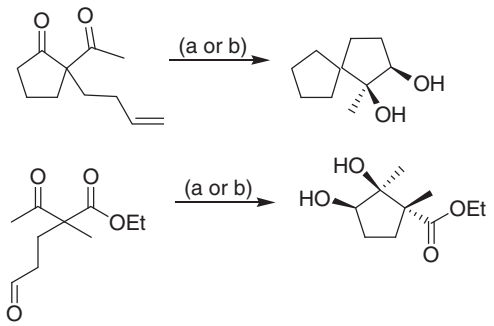
Scheme 70 Reproduced from Arseiyadis, S.; Yashunsky, D. V.; Pereira de Freitas, R.; *et al. Tetrahedron Lett.* **1993**, *34*, 1137.

In typical Sm-mediated reactions a stoichiometric amount of Sm is needed in order to carry out the single-electron transfers to all of the substrates involved. This poses a problem when reactions need to be scaled up, especially on an industrial scale since a very large volume of the relatively expensive reagent needs to be used. For this reason, developing a simple method which utilizes a catalytic amount of SmI_2 is on the forefront of current Sm-research. In order for a catalytic system to function, a species would need to be included which is able to reduce Sm(III) back to Sm(II). Endo and coworkers developed a catalytic system for pinacol coupling using Mg as a coreductant. Magnesium has a reduction potential similar to Sm, and should have the capacity to reduce Sm(III) (Sm = −2.41 V, Mg = −2.37 V). When SmI_3 was treated with activated Mg, the color changed from yellow to dark-blue, indicating the formation of SmI_2.[160] Pinacol coupling of aliphatic and aromatic ketones and aldehydes were achieved using only 10 mol% of SmI_2 and excess Mg. TMSCl was added to break the Sm–O bond after the coupling occurred, and release Sm(III) back into the cycle (Scheme 71). The reaction proceeded with good to excellent yields (28–82%), but with no diastereoselectivity. No reaction took place in the absence of SmI_2, providing evidence that the active reducing agent is Sm and not the Mg/TMSCl system.



Scheme 71 Reproduced from Nomura, R.; Matsuno, T.; Endo, T. *J. Am. Chem. Soc.* **1996**, *118*, 11666, with permission from ACS.

Greeves further developed the catalytic reaction to effectively promote diastereoselectivity[161] by adding ligands around the Sm metal. An important aspect of this system was to find a ligand which would chelate to both the Sm^{II} reductant as well as Sm^{III} after the reduction occurred. Out of a variety of ligands tested, tetraglyme was the only ligand which supported the catalytic system (Scheme 71) and exhibited control over diastereoselectivity. The pinacol coupling of aromatic and aliphatic aldehydes was successful for both inter- and intramolecular reactions. Intramolecular cyclizations were performed with substrates previously reported by Molander under stoichiometric conditions,[162] and the impact of the new conditions on the yield and diastereomeric excess were observed. As shown in Scheme 72, the catalytic Sm/tetraglyme system provided improved yields and comparable diastereoselectivities to the traditional Sm method (more discussion on catalytic Sm(II) system in Misc. Reactions, Section 1.09.3.2.1.1.8).

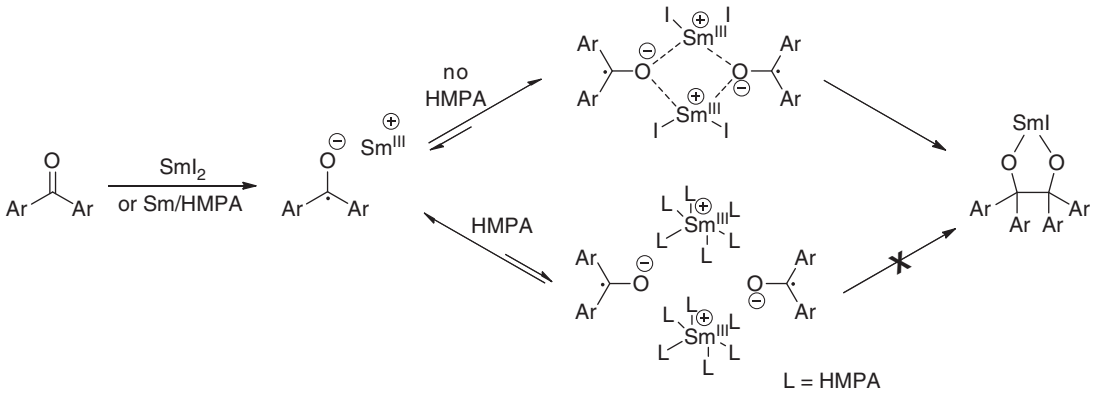


(a) Stoichiometric	(b) Catalytic
44% Yield, 99% *de*	81% Yield, 84% *de*
77% Yield, 99% *de*	86% Yield, 99% *de*

(a) 2 equivalents SmI_2, 2 equivalents MeOH, THF, –78 °C.[162]
(b) 10 mol% SmI_2/tetraglyme, 16 equivalents Mg, 2 equivalents Me_2SiCl_2, THF, r.t.[161]

Scheme 72 Data taken from the following references; however the figure is not reprinted as shown. Nomura, R.; Matsuno, T.; Endo, T. *J. Am. Chem. Soc.* **1996**, *118*, 11666 and Aspinall, H. C.; Greeves, N.; Valla, C. *Org. Lett.* **2005**, *7*, 1919, with permission from ACS.

The effect of HMPA on pinacol coupling was explored. It was assumed that the addition of HMPA would increase the speed and efficiency of the reaction since it produces a more powerful single-electron reductant. Through a kinetic study observing the rates of *p*,*p*′-dichlorobenzophenone pinacolization (Scheme 73), it was shown that HMPA addition actually hindered the rate of coupling.[163] As HMPA was added (3–20 equivalents) the rate of the coupling steadily decreased until rates steadied at 20 equivalents. It is known that HMPA complexes very tightly to Sm, and has the ability to displace other ligands such as THF and alcohols.[35,82,164,165] In addition, Sm(II) and Sm(III) species have been shown to coordinate with the carbonyl species and help promote coupling (Scheme 67). However, in some cases, Hoz has shown that HMPA can hinder pinacol coupling. He proposed that HMPA competes for Sm-coordinated ketyl after the reduction, obstructing the lanthanide from fulfilling a postelectron transfer bridging role.[163]

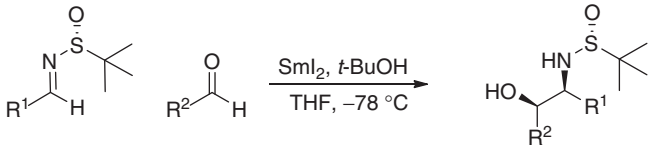


Scheme 73 Reproduced from Data taken from the following reference; however the figure is not reprinted as shown. Farran, H.; Hoz, S. *Org. Lett.* **2008**, *10*, 865, with permission from ACS.

Coupling of a carbonyl species with imine derivatives (such as oximes and hydrazones) is commonly referred to as a hetero-pinacolization, and has found utility in the formation of heterocycles and both vicinal and *β*-amino alcohols. It has been proposed that the reaction proceeds through formation of a ketyl radical which adds to the C=N bond.

Although hetero-pinacolization is the most direct route for constructing *β*-amino alcohols, achieving control over the stereoselectivity has been an issue in the reactions reported. Xu and Lin devised a system which couples N-sulfinyl imine with an aldehyde to obtain the desired *β*-amino alcohol with high yields and excellent control over the stereo- and chemoselectivity

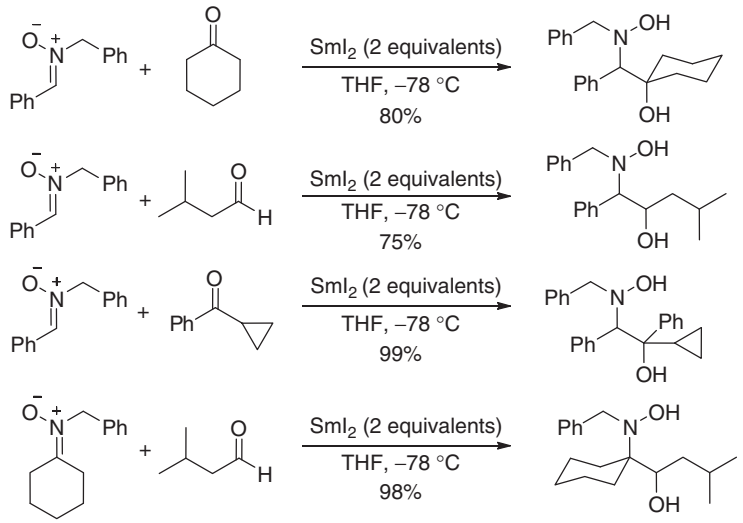
(Scheme 74).[166] The diastereoselectivity was proposed to proceed through a chelation controlled pathway where the final stereochemistry was directed by the N-sulfinyl group and the steric bulk of the aldehyde.



Entry	R^1	R^2	Yield (%)	dr	ee
1	4-$CH_3C_6H_4$	*i*-Pr	92	>99:1	98
2	4-$CH_3C_6H_4$	C_6H_{11}	90	99:1	>99
3	4-$CH_3C_6H_4$	PhC_2H_4	95	88:12	95
4	Ph	*i*-Pr	86	99:1	97
5	$BnOCH_2$	*i*-Pr	82	>99:1	97

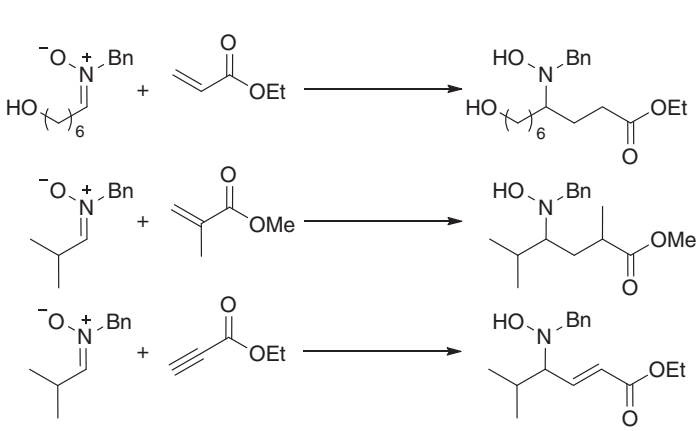
Scheme 74 Reproduced from Zhong, Y.; Dong, Y.; Fang, K.; *et al. J. Am. Chem. Soc.* **2005**, *127*, 11956, with permission from ACS.

Nitrones have also been identified as successful hetero-pinacol coupling partners with both aldehydes and ketones to form α-*N*-hydroxyamino alcohols (Scheme 75).[167]



Scheme 75 Reproduced from Masson, G.; Py, S.; Vallée, Y. *Angew. Chem. Int. Ed.* **2002**, *41*, 1772, with permission from Wiley.

Py and Vallée utilized a Sm/H_2O system to achieve a reductive conjugate addition of nitrones into α,β-unsaturated esters.[167] In the absence of water product was obtained, but at decreased yields (Scheme 76). For all the reactions only heterocoupling was

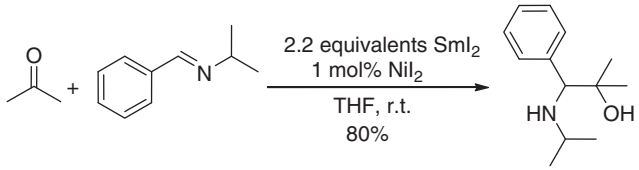


SmI_2, –78 °C	SmI_2/H_2O, –78 °C
60% Yield	73% Yield
29% Yield (>95:5)	74% Yield (>95:5)
<10% Yield	71% Yield

Scheme 76 Reproduced from Masson, G.; Py, S.; Vallée, Y. *Angew. Chem. Int. Ed.* **2002**, *41*, 1772, with permission from Wiley.

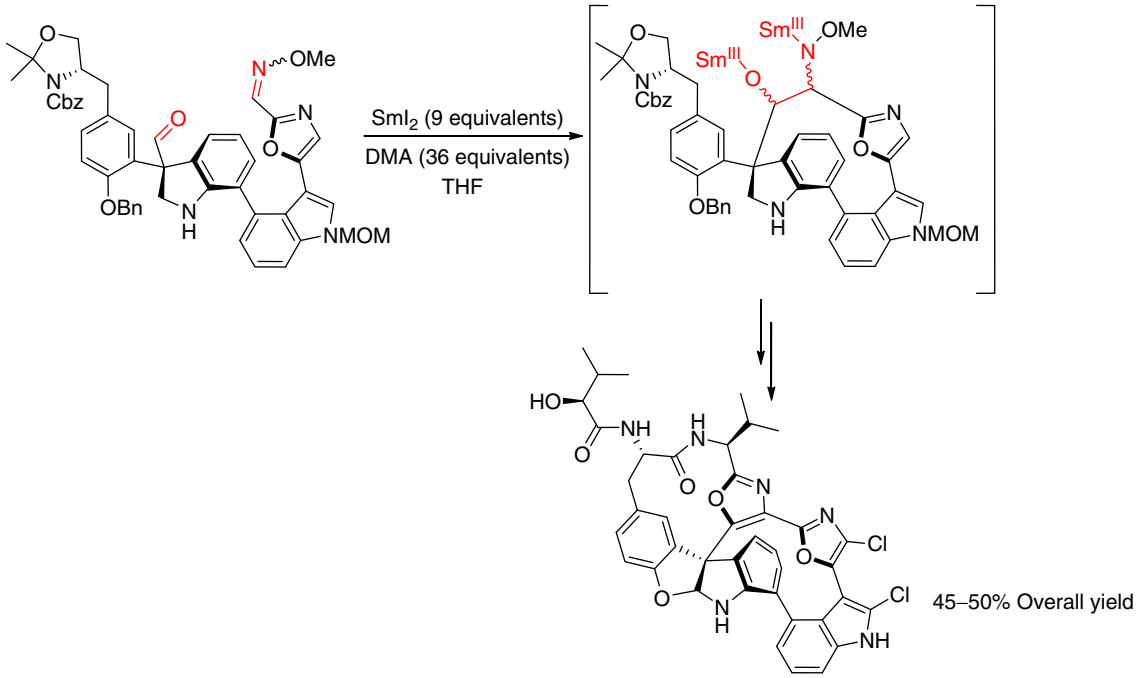
observed. It was suggested that the reaction proceeded through nitrone reduction followed by conjugate addition onto the α,β-unsaturated ester.

Heterocoupling of an imine to a variety of ketones was accelerated with the addition of catalytic NiI_2 (Scheme 77).[168] The use of this additive is common in Sm reactions even though the role of the Ni was unclear (*see* Sm-Barbier in Section 1.09.3.2.1.1.2 and halide-alkene in Section 1.09.3.2.1.1.5). Owing to more recent mechanistic findings,[103] it is presumed that this reaction could be proceeding through Ni(0) chemistry, although an investigation of its role in this system has not been explored.



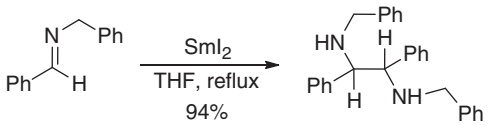
Scheme 77 Reproduced from Machrouchi, F.; Namy, J.-L. *Tetrahedron Lett.* **1999**, *40*, 1315.

An excellent example of the use of hetero-pinacolization was used to form the macrocycle of diazonamide A.[169,170] The aldehyde-oxime pinacol reaction closed a 14-membered ring (Scheme 78), the largest ring reported through this mechanism, and was the first to trap the intermediate organosamarium with a species other than a simple acylating agent (step not shown).



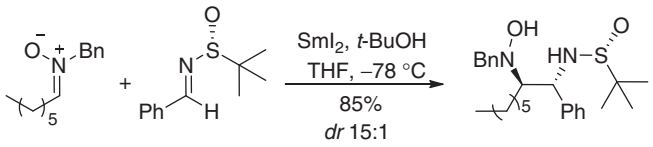
Scheme 78 Reproduced from Nicolaou, K. C.; Snyder, S. A.; Giuseppone, N.; *et al. J. Am. Chem. Soc.* **2004**, *126*, 10174, with permission from ACS.

Pinacol-type reactions are also used to describe homocoupling reactions of imines to form diamine species or asymmetric coupling of imines with nitrones or other imine derivatives. One of the first reports of SmI_2-mediated imine coupling was done by Enholm[171] (Scheme 79), and the mechanism was assumed to proceed through a similar radical coupling or radical attack as was invisioned for pinacol homocoupling (Scheme 66). The formation of vicinal diamines was achieved with high yields, but an undetermined mixture of meso- and D-, L-diastereomers was obtained.



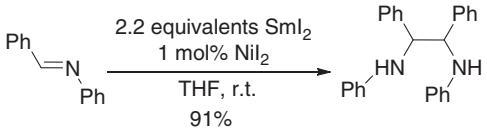
Scheme 79 Reproduced from Enholm, E. J.; Forbes, D. C.; Holub, D. P. *Synthetic Commun.* **1990**, *20*, 981, with permission from Tayolr & Francis.

Xu used an (*R*)-*N*-*tert*-butanesulfinyl imine coupled with nitroester in order to maintain control over the stereoselectivity for the synthesis of functionalized asymmetric vicinal diamines (Scheme 80).[172] The reaction proceeded with high yields and selectivity with a range of substituted coupling partners.



Scheme 80 Reproduced from Zhong, Y.; Xu, M.; Lin, G. *Org. Lett.* **2004**, *6*, 3953, with permission from ACS.

Namy determined that the addition of catalytic amounts of NiI_2 also increased the efficiency of the coupling reaction of imines to form diamines (Scheme 81). In the absence of NiI_2, the reaction needed to be carried out at reflux for 6–16 h for the reaction to come to completion.

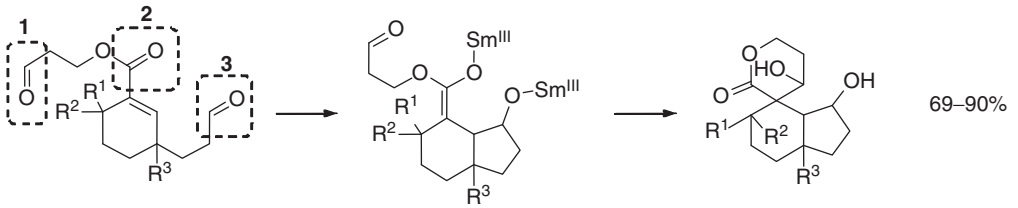


Scheme 81

1.09.3.2.1.1.7 Cascade reactions

Cascade or sequential reactions carry out a sequence of multiple bond-forming transformations in a one-pot reaction. The reaction proceeds without isolation or purification of any intermediate species. As the reaction progresses, the product from an initial transformation becomes the reactive species to initiate another bond formation and this cascade of reactions allows for the formation of complex multifunctional and polycyclic compounds. However, for sequential reactions to be useful, they should be extremely efficient and specific to minimize formation of unwanted side products and proceed with high yields. Cascade reactions are particularly successful through Sm reduction since SmI_2 reduces various functional groups at such different rates; the driving force behind the success of the Sm-Barbier reaction, Reformatsky, and heteropinacolizations. In cascade reactions this property is exploited, and molecules are designed in a way that the sequential reductions take place in an order which properly assembles the molecule desired. Examples of cascade reactions can be found in the previous sections, specifically Schemes 25 and 56. There are four main types of Sm-mediated cascade reactions, depending on the types of reactions involved in the transformations: (1) radical–radical, (2) radical–anionic, (3) anionic–radical or (4) anionic–anionic.

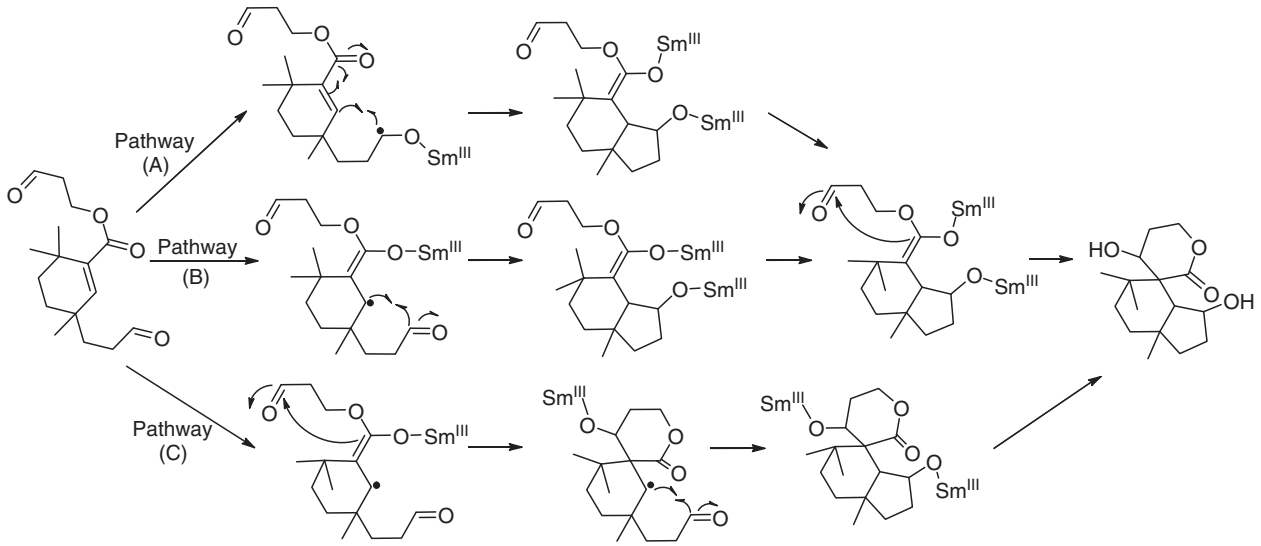
Often when cascade reactions are performed with a substrate which contains multiple reductive functionalities it is difficult to determine the pathway the cascade proceeds through. In a recent cyclization cascade developed by Procter, a tricyclic system with four stereocenters with high diastereoselectivity is produced (Scheme 82).[173] The driving force behind the desired cyclization is that SmI_2 selectively reduces the carbonyl species 'one at a time'. In the starting molecule, there are three accessible carbonyl groups available for reduction by SmI_2, two pendant aldehydes (Scheme 82, carbonyls **1** and **3**), and an intramolecular α,β-unsaturated ester (Scheme 82, carbonyl **3**). Rate constants for the reduction of these individual functional groups by SmI_2 have not been determined, so it is uncertain which functionality would be preferentially reduced. However, due to the selective nature of the reaction it is presumed the mechanism follows a discrete pathway.



Scheme 82 Reproduced from Helm, M. D.; Sucunza, D.; Silva, M. D.; Helliwell, M.; Procter, D. J. *Tetrahedron Lett.* **2009**, *50*, 3224.

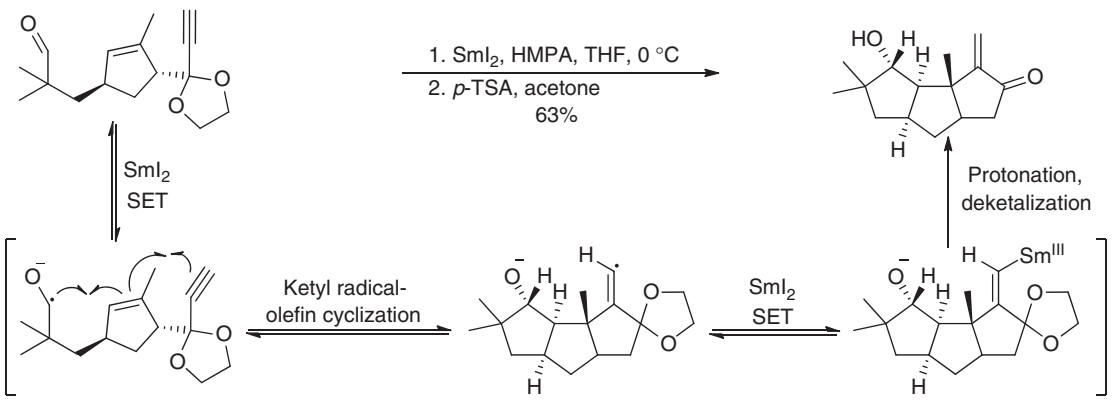
Based on the product isolated from the reaction a few mechanistic pathways could be envisioned (Scheme 83). Pathway A assumes the reduction and subsequent cyclization of aldehyde **3** occurs at a rate faster than a similar reduction and cyclization can take place at aldehyde **1**, causing the initial step to predominate through the radical cyclization proposed. In both pathways B and

C, the α,β-unsaturated ester is reduced preferentially over the aldehydes, forming a Sm-enolate which either goes through a radical addition to the aldehyde within close proximity (Pathway B) or cyclization of the enolate into aldehyde **1** (Pathway C). Without more kinetic data it is difficult to elucidate which pathway it proceeds through, but by gaining this information this cyclization could be applied more efficiently to other syntheses. Even without the mechanism, the information at hand conveys that the reaction maintains control over the diastereoselectivity, which could be attributed to the strong chelation of Sm(III) and oxygen in the intermediate organosamarium species, possibly through bridging.



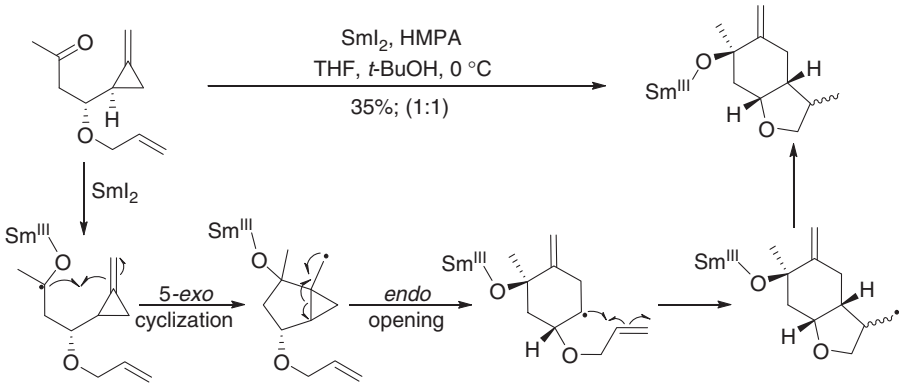
Scheme 83

In a more predictable pathway, *radical–radical cyclization* was used in a critical step for the synthesis of (±)-hypnophilin (Scheme 84).[174] A ketyl radical is formed through reduction by SmI_2, which goes through a tandem 5-exo-trig cyclization of the radical onto the alkene followed by a 5-endo-dig cyclization of the newly formed tertiary radical onto the alkyne to form the radical-bearing tricyclic system. The final product is obtained following a second SET from SmI_2 and proton abstraction. Radical–radical sequential reactions are favored in the presence of stable radicals that are relatively inert to reduction by SmI_2 to the anion, such as tertiary, aryl and allylic radicals.



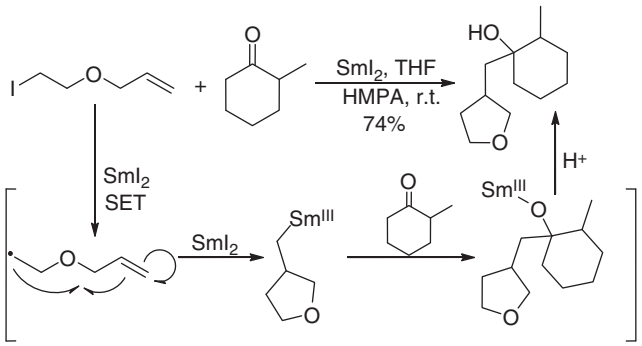
Scheme 84 Reproduced from Fevig, T. L.; Elliot, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064, with permission from ACS.

Radical–radical cascades were used in the SmI_2-cyclization of methylenecyclopropyl ketones (Scheme 85), which were used in the short synthesis of (±)-paeonilactone B and (±)-6-*epi*-paeonilactone A.[175] Within the cascade, a ketyl radical is formed through reduction by SmI_2. The radical cyclizes onto the pendant alkene through a 5-*exo* mechanism, forming a bicyclic system with the pendant primary radical. Facile 'endo' opening affords the substituted cyclohexanone. The radical on the ring is in proximity to cyclize and form the 5-membered ring. This step is nonselective, forming a 1:1 mixture of diastereoisomeric bicyclic compounds, which on protonation yields a 1:1 ratio of products.



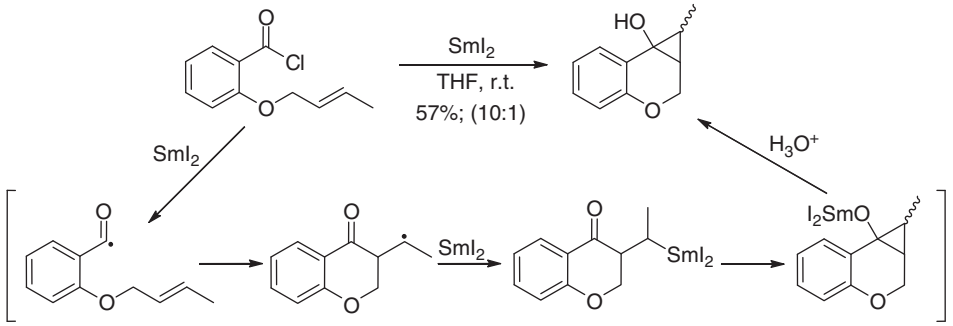
Scheme 85 Reproduced from Boffey, R. J.; Whittingham, W. G.; Kilburn, J. D. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 487, with permission from Royal Society of Chemistry.

Sm-mediated *radical-anion cascade* reactions are the most commonly employed and usually proceed through an initial radical-alkene cyclization, as shown below (Scheme 86).[176] The initial single-electron transfer to the carbon-iodide forms a primary radical, which readily proceeds through an intramolecular 5-*exo-trig* cyclization to form a cyclopentane containing a pendant primary radical. The radical can be reduced to an organosamarium after a second electron transfer. The organosamarium then proceeds through an intermolecular Sm-Barbier reaction, which on protonation forms the final coupled alcohol in a 74% yield.



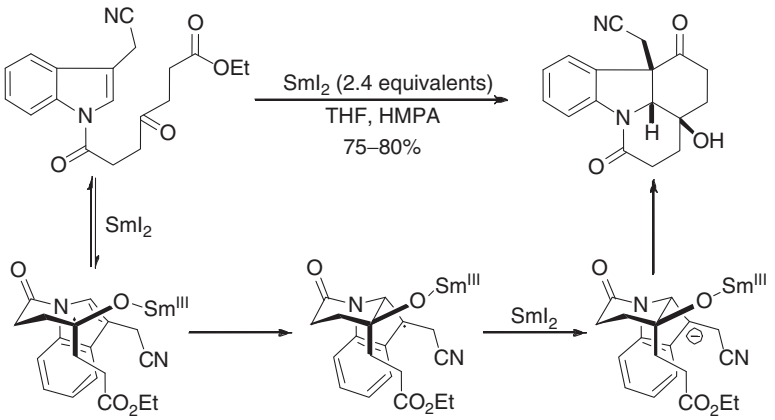
Scheme 86 Reproduced from Molander, G. A.; Kenny, C. *J. Org. Chem.* **1991**, *62*, 4511, with permission from ACS.

Kagan used a radical–anion cyclization cascade reaction for the formation of tricyclic alcohols.[177] The proposed mechanism goes through a radical cyclization onto an alkene, followed by radical reduction to an organosamarium which can then proceed through a Barbier reaction (Scheme 87).



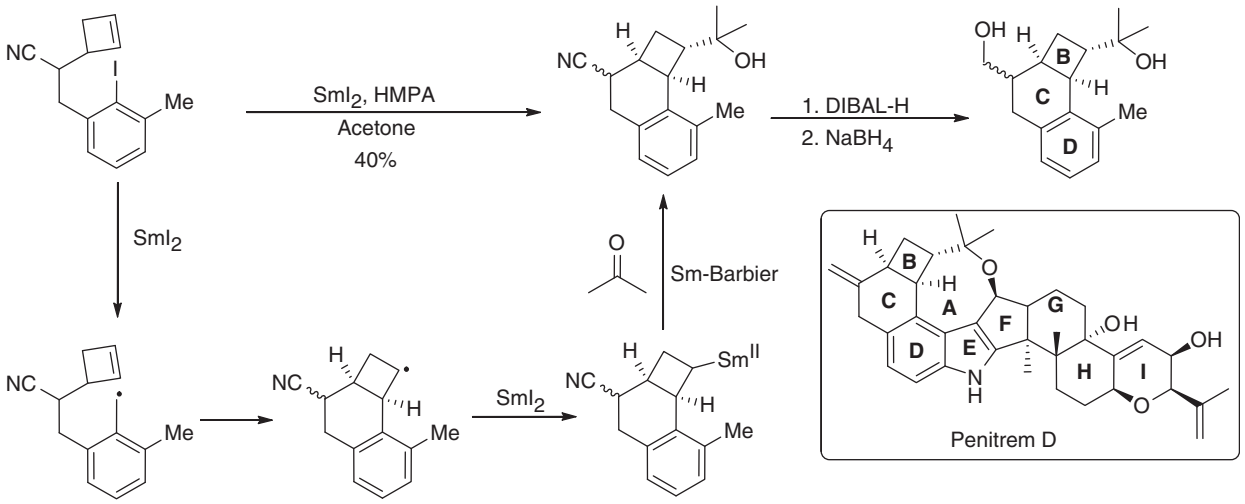
Scheme 87 Reproduced from Sasaki, M.; Collin, J.; Kagan, H. B. *Tetrahedron Lett.* **1988**, *29*, 6105.

A radical–anionic cascade reaction was utilized in the synthesis of a *Strychnos* alkaloid, strychnine,[43] forming three stereogenic centers in the polycyclic system (Scheme 88). The mechanism proposed for the reaction initiates with the reduction of the internal ketone forming a tertiary radical, which adds to the unsaturation on the pentane ring. After a second electron transfer by SmI_2, addition into the carbonyl completes the transformation.



Scheme 88 Reproduced from Beemelmanns, C.; Reissig, H. U. *Angew. Chem. Int. Ed.* **2010**, *49*, 8021, with permission from Wiley.

For the synthesis of the BCD ring structure of penitrem D, a radical-anionic cascade was employed, following a radical–alkene, Barbier mechanism.[178] The starting material was designed to promote radical–alkene cyclization (Scheme 89) to form a stable six-membered ring on reduction with SmI_2. The pendant radical was then reduced to an organosamarium, which is followed up with an intermolecular Barbier reaction with acetone. The product of the cascade is reacted to reduce the nitrile to a primary alcohol – an intermediate construct for the synthesis of penitrem D.



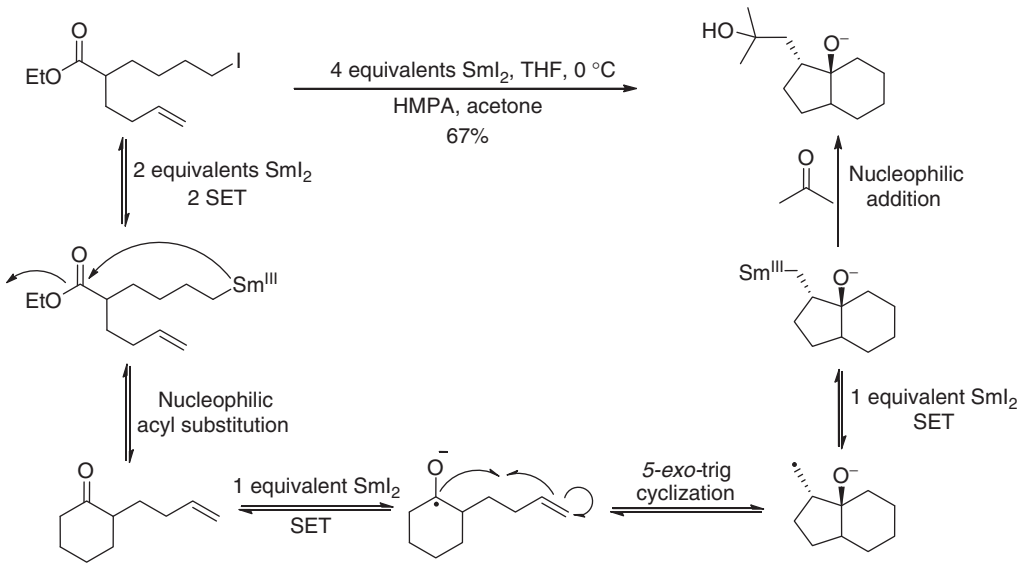
Scheme 89 Reproduced from Rivkin, A.; Gonzalez-Lopez he Turiso, F.; Nagashima, T.; Curran, D. P. *J. Org. Chem.* **2004**, *69*, 3719, with permission from ACS.

Casacade reactions which lead with an anionic transformation usually begin with alkyl halide reduction by SmI_2, which when in the absence of an electrophile for a favorable cyclization, readily forms an organosamarium species. An example of an anionic–radical cascade is shown in Scheme 90.[179] After two successive single-electron transfers, the primary organosamarium species is formed, which goes through a nucleophilic acyl substitution to form the substituted cyclohexanone. An additional single-electron transfer by SmI_2 produces a ketyl radical which undergoes a 5-*exo-trig* cyclization with the pendant olefin, forming a primary radical. A fourth single-electron transfer from SmI_2 produces an organosamarium which attacks the electrophilic acetone to produce the final product in a 67% yield.

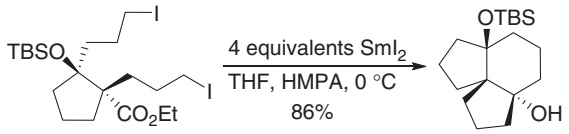
Anionic-anionic transitions take place through combinations of Barbier-type reactions and nucleophilic acyl substitutions; such as tandem Barbier–Barbier cyclizations (Scheme 25, Section 1.09.3.2.1.1.2). Scheme 91[111] and Scheme 92, and SmI_2-mediated nucleophilic acyl substitution-Barbier addition, seen in Scheme 93.

Ring expansion can be achieved through a Barbier-fragmentation cascade,[180,181] and was used to construct the seven-membered ring of sarcodonin G (Scheme 94).[182] The halide goes through two successive single-electron reductions by SmI_2 to form an organosamarium, which proceeds through a Barbier cyclization to form a cyclopropane. Subsequent ring expansion through fragmentation produces the seven-membered ring.

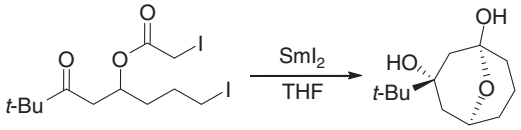
Epoxide ring-opening reactions can also be initiated by SmI_2, but follow a slightly different mechanism from the cascade reactions seen (Scheme 95). The ketyl radical anion is formed through reduction of the ketone and triggers ring opening of the



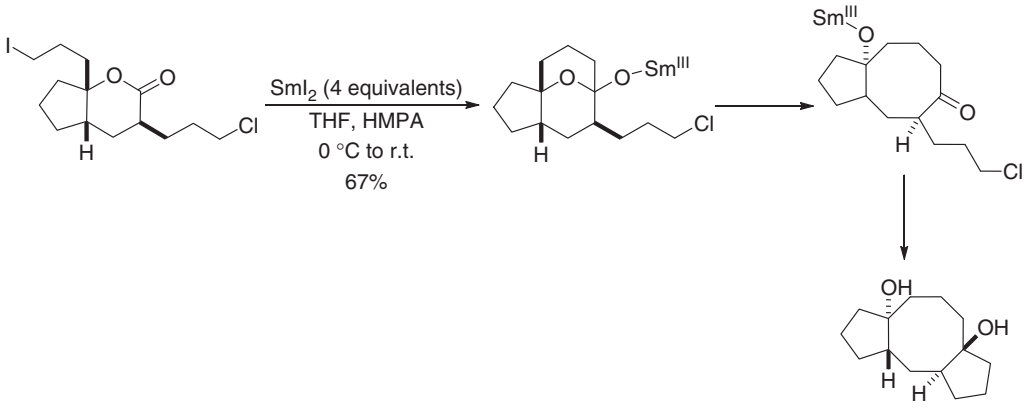
Scheme 90 Reproduced from Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 2944, with permission from ACS.



Scheme 91 Reproduced from Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705, with permission from ACS.

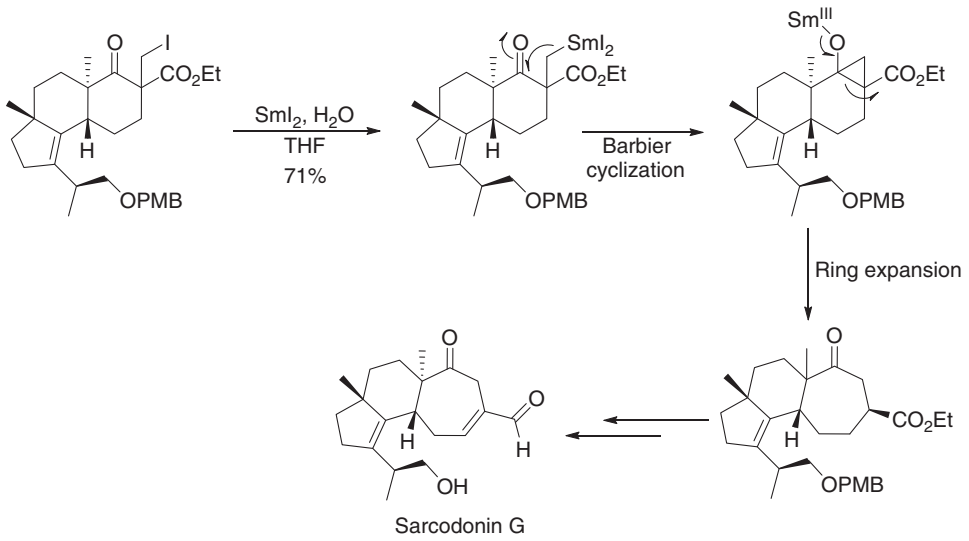


Scheme 92 Reproduced from Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705, with permission from ACS.

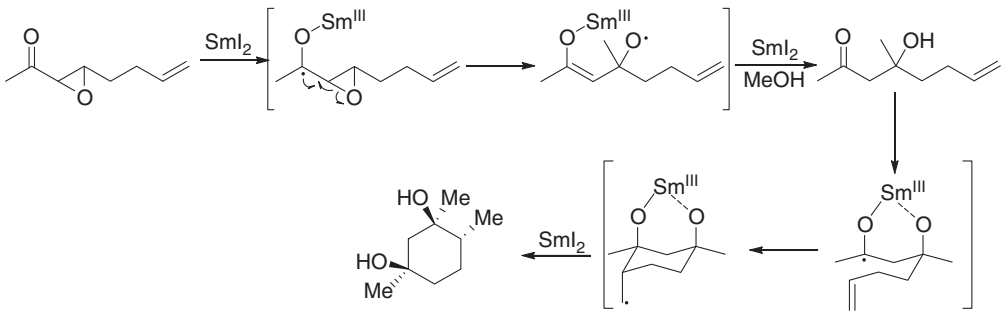


Scheme 93 Reproduced from Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705, with permission from ACS.

epoxide to form an oxygen radical. The oxygen radical is reduced by a second single-electron transfer to form an oxygen anion which abstracts a proton from the proton donor in solution (alcohol, in this case MeOH). The resultant β-hydroxyketone is reduced further to a ketyl radical that undergoes ketyl-olefin coupling. The primary radical formed as the result of the coupling is reduced to an organosamarium species that finally abstracts another proton to form a cyclic diol in excellent yields and stereochemical control.[183]



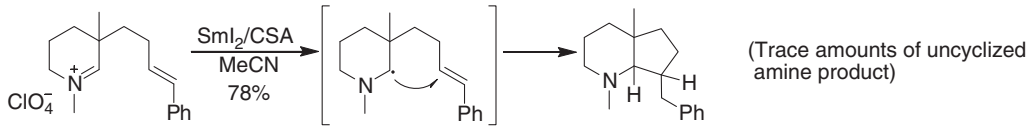
Scheme 94 Reproduced from Piers, E.; Gilbert, M.; Cook, K. L. *Org. Lett.* **2000**, *2*, 1407, with permission from ACS.



Scheme 95 Reproduced from Molander, G. A.; de Pozo Losada, C. *J. Org. Chem.* **1997**, *62*, 2935, with permission from ACS.

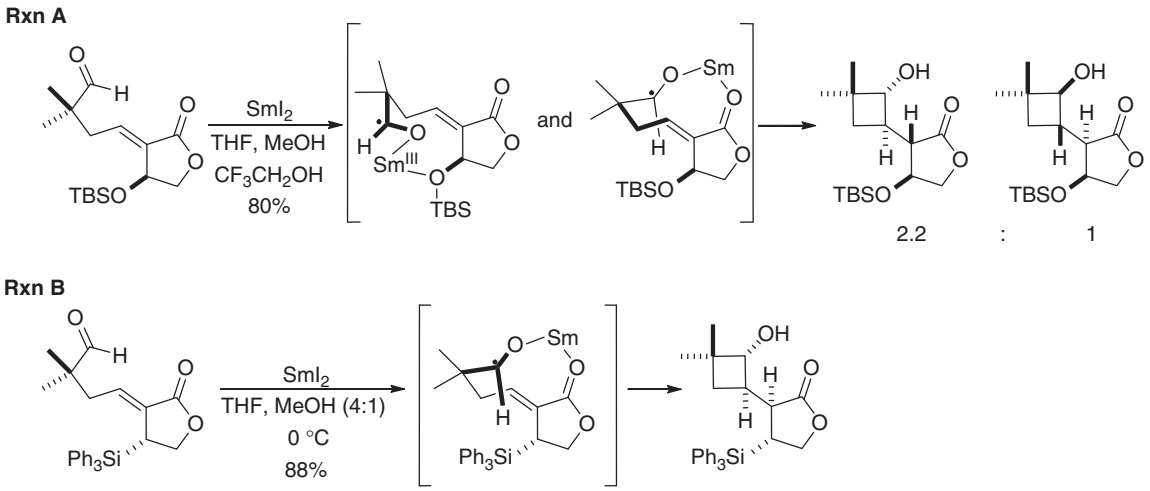
1.09.3.2.1.1.8 Misc. reactions

In 1988, Martin explored the area of radical cyclizations generated from γ-unsaturated iminium salts.[184] The formation of the heterocycles was believed to proceed through 5-*exo-trig* cyclization, producing the bicyclic product in high yields with only trace amounts of the reduced amine detected (Scheme 96). The reaction was run with at least one equivalent of camphorsulfonic acid (CSA). In the absence of CSA a larger amount of the amine along with dimerized products were obtained. These results led to the conclusion that the protonated form of the unsaturated α-amino radicals undergoes cyclization more readily than the unprotonated form.



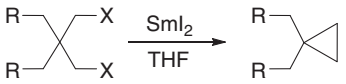
Scheme 96 Reproduced from Martin, S. F.; Yang, C.; Laswell, W. L.; Rüeger, H. *Tetrahedron Lett.* **1988**, *29*, 6685.

As a method for effectively directing Sm-mediated reactions, Procter has developed a method which utilizes a silyl group to control the outcome of a cyclization.[185] As has been discussed in earlier examples, the coordination of Sm(III) to intermediate ketyls can sometimes have a deleterious effect on cyclizations if the coordination blocks a cyclization pathway, or if the Sm(III) coordinates at an unwanted position. This was the case when TBSO was used as a 'blocking group' to control the diastereoselectivity in the cyclization to form cyclobutanol species (Scheme 97, rxn A). Two intermediate species can be envisioned based on the mixture of diastereomers obtained, in which Sm(III) chelates between the ketyl and the carbonyl on the lactone as well as the oxygen on the silylether. Using a bulky silyl group avoided the unwanted secondary interaction with the blocking group, and produced the product with complete diastereocontrol (Scheme 97, rxn B).



Scheme 97 Reproduced from Harb, H. Y.; Collins, K. D.; Garcia Altur, J. V.; *et al. Org. Lett.* **2010**, *12*, 5446, with permission from ACS.

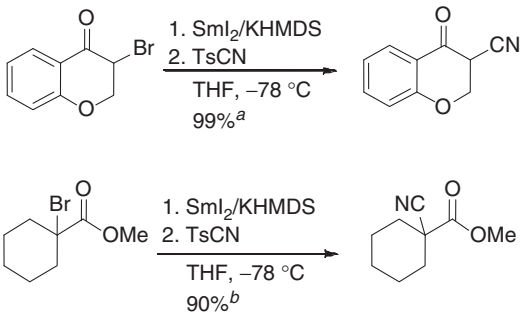
Cyclopropanation was carried out under SmI_2 conditions proceeding through a 3-*exo-tet* mechanism with 1,3-dihalopropanes.[186] These reactions were extremely successful with iodo and bromo halides, and acceptable yields were obtained for chloro species (Scheme 98). A variety of substitutions were also tolerated.



Entry	R	X	Conditions	Yield (%)
1	Ph	I	r.t., 3 h	99
2	4-$MeOC_6H_4$	I	r.t., 3 h	98
3	$CH_3(CH_2)_9CH_2$	I	r.t., 3 h	57
4	Ph	Br	70 °C, 3 h	87
5	4-$MeOC_6H_4$	Br	70 °C, 3 h	82
6	$CH_3(CH_2)_9CH_2$	Br	70 °C, 3 h	82
7	Ph	Cl	70 °C, 48 h	69
8	4-$MeOC_6H_4$	Cl	70 °C, 48 h	23

Scheme 98 Reproduced from Ohkita, T.; Tsuchiya, Y.; Togo, H. *Tetrahedron* **2008**, *64*, 7247.

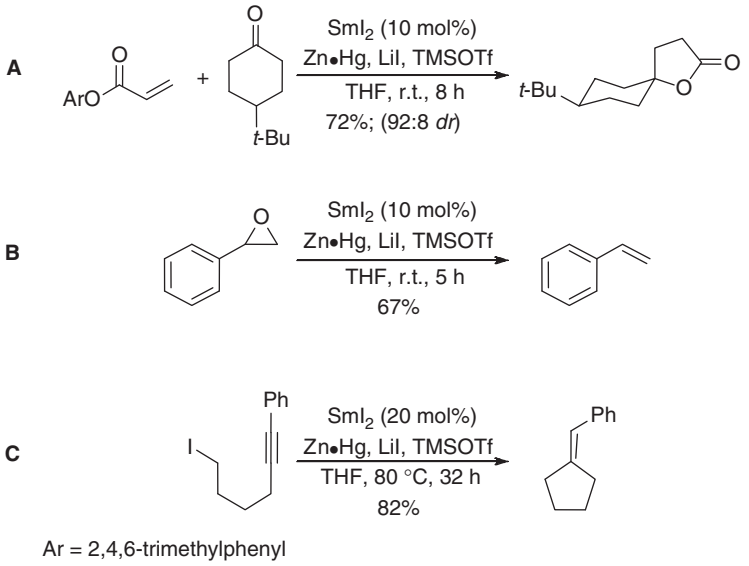
Hilmersson devised a method for α-cyanation of ketones and esters using potassium hexamethyldisilazane (KHMDS) as an additive through a Reformatsky-type transformation.[99] Sm(II) species with KHDMS ($Sm(HDMS)_2$) were attempted, but with very little success in this reaction. When the concentration of KDMS was decreased to one equivalent, the desired α-cyano product was obtained (Scheme 99).



[a]GC yield. [b]Isolated yield.

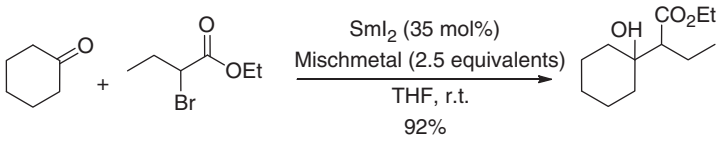
Scheme 99 Reproduced from Ankner, T.; Fridén-Saxin, M.; Pemberton, N.; *et al. Org. Lett.* **2010**, *12*, 2210, with permission from ACS.

Catalytic Sm(II): The goal of creating a system in which Sm(II) can be used catalytically was introduced in the discussion of pinacol reactions (Section 1.09.3.2.1.1.6). Although practical and general approaches to using SmI_2 as a substoichiometric reagent remains elusive, other approaches toward this goal will be discussed here. After Endo reported the use of catalytic SmI_2 with Mg as a coreductant for pinacol reactions, Corey initiated a study to determine the best coreductant for regenerating Sm(II) from Sm(III) *in situ*. It was determined that the order of reactivity of reduction was Mg > Al > Zn.[187] Examining the other conditions needed for the catalytic reaction to be successful, he showed that a combination of SmI_2, LiI, and $Me_3SiOSO_2CF_3$ (TMSOTf) with Zn-Hg gave excellent results in the reductive coupling of ketones with acrylates to produce γ-butyrolactones (Scheme 100, **A**). This catalytic SmI_2 reagent system was also effective for the reduction of an epoxide (Scheme 100, **B**) and cyclization of the haloalkyne (Scheme 100, **C**). The latter reaction required 20 mol% SmI_2 and elevated temperature for successful conversion to product.



Scheme 100 Reproduced from Corey, E. J.; Zheng, G. Z. *Tetrahedron Lett.* **1997**, *38*, 2045.

One of the main issues with using zinc or magnesium as a coreductant is that they are reactive toward many organic substrates, such as alkyl halides. Also, in Corey's system TMSOTf is critical for the success of the catalytic reaction, used to cleave the Sm(III)–O bond. It is, however, an expensive reagent. Ideally, the species used in the catalytic Sm-reactions should be less expensive than using a stoichiometric amount of Sm. To circumvent these issues, Namy devised a catalytic-Sm system using mischmetal as the coreductant (Scheme 101). Mischmetal is an alloy of light lanthanides (La 33%, Ce 50%, Nd 12%, Pr 4% Sm and other lanthanides 1%) which has the redox capabilities to break to Ln–O bond but at a low cost. Using mischmetal as the coreductant, Barbier, Reformatsky reactions, halide reductions, and pinacol coupling were successfully carried out.[188,189]



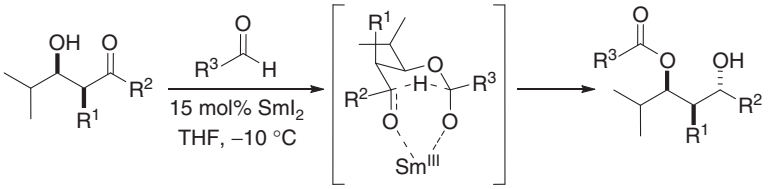
Scheme 101 Reproduced from Helion, F.; Namy, J.-L. *J. Org. Chem.* **1999**, *64*, 2944, with permission from ACS.

Orsini has also reported the use of a 10 mol% SmI_2-Mg reagent system in the Reformatsky reactions of α-halocarbonyl compounds, nitriles, and phosphonates with ketones, aldehydes, and imines.[190] Although progress has been made in the field of catalytic Sm-mediated reactions, the scope of these reactions is still limited.

Sm(II) as a precatalyst: In some reactions, catalytic amounts of SmI_2 are used for the *in situ* formation of a catalytic Sm(III) species. In these cases, a catalytic amount of SmI_2 was used in the synthesis, however it was determined that the trivalent state of Sm was the active Lewis acid catalyst. In these reactions, a coreductant to regenerate Sm(II) is not needed, and the reaction mixture changes immediately from blue to yellow, also indicating the loss of SmI_2 and the presence of the trivalent species.

Evans and coworkers established a SmI_2-catalyzed intramolecular Tishchenko reaction in which SmI_2 acts as a precatalyst for the Sm(III)-catalyzed system.[191] In this transformation, excess aldehyde is used with a substoichiometric amount of SmI_2 to convert β-hydroxy ketones into *anti*-diol monoesters in high yield and high diastereomeric excess (Scheme 102). The reaction is proposed to proceed through a six-membered Sm(III) chelate between the ketone carbonyl and the hemiacetal oxygen. Deuterium

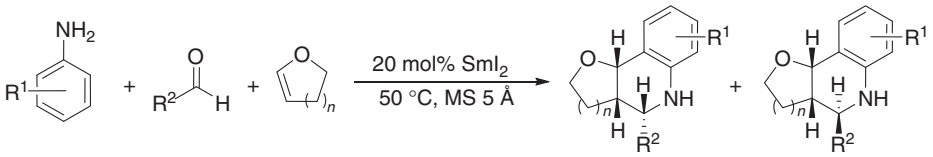
labeling studies with CD_3CDO resulted in the complete deuterium incorporation at the newly generated carbinol center. Since aldehydes are readily reduced to pinacols by SmI_2, it is likely that the active catalyst is an Sm(III) species with a pinacolonate ligand derived from aldehydes in solution.



Entry	R^1	R^2	R^3	Yield (%)	*anti:syn*
1	H	*n*-Hexyl	Me	96	>99:1
2	H	*n*-Hexyl	Me_2CH	95	>99:1
3	H	*n*-Hexyl	Ph	94	>99:1
4	H	Me_2CH	Me	85	>99:1
5	H	Me_2CH	Ph	99	>99:1
6	Me	Me_2CH	Me	85	>99:1
7	Me	Et	Me_2CH	95	>99:1

Scheme 102 Reproduced from Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447, with permission from ACS.

Three-component Aza–Diels–Alder reactions were completed with catalytic amounts of SmI_2, forming pyrano- and furano[3,2-*c*]quinoline derivatives (**Scheme 103**).[192] The synthesis was found to be stereoselective based on the temperature and concentration of the substrate used. Under elevated temperatures (50 °C) and in THF solvent the *trans* isomer predominated with high yields and selectivity. To promote formation of the *cis* isomer, the reaction temperature was lowered to −20 °C, and the reaction was run neat. The synthesis utilized catalytic Sm(II), without a coreductant, suggesting that Sm(II) acted as a precursor to the active catalytic species, Sm(III).



a **b**

Entry	R^1	R^2	*n*	a/b Ratio	Yield (%)
1[a]	H	Ph	2	4:96	93
2[b]	H	Ph	2	77:23	70
3	H	1-Napthyl	2	0:100	89
4	H	4-Me-C_6H_4	2	5:95	93
5	H	4-MeO-C_6H_4	2	4:96	88
6	H	4-Cl-C_6H_4	2	0:100	94
7	4-Me	Ph	2	4:96	93
8	2-Me	Ph	2	0:100	90
9	4-MeO	Ph	2	2:98	95
10	H	Ph	1	4:96	86

[a]*Trans*-reaction conditions: aldehyde/amine/dihydropyran 1:1.1:1.4, 0.3 M, 50 °C, 5 h (Entries 1, 3–10).
[b]*Cis*-reaction conditions: aldehyde/amine/dihydropyran 1:1.1:1.4, solvent free, –20 °C, 24 h (Entry 2).

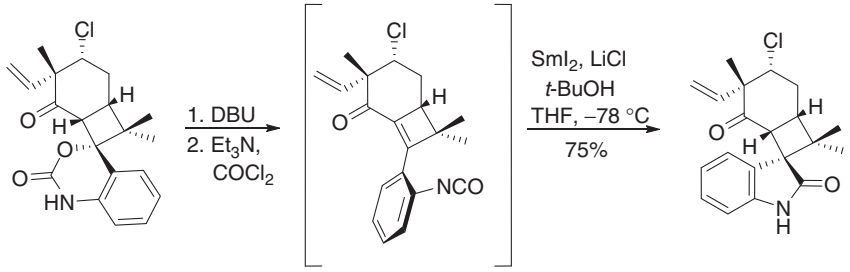
Scheme 103 Reproduced from Zhou, Z. H.; Xu, F.; Han, X.; Zhou, J.; Shen, Q. *Eur. J. Org. Chem.* **2007**, 5265, with permission from ACS.

1.09.3.2.1.2 $SmBr_2$ and $SmCl_2$

Although it is recognized that SmI_2 is the most commonly used reductant among the Sm(II) halides, samarium dibromide ($SmBr_2$), and samarium dichloride ($SmCl_2$) have also been employed in several synthetic applications. The main shortcoming of these reductants is their limited solubility in organic solvents. The first reported synthesis of $SmBr_2$ was carried out through the

reduction of $SmBr_3$ by H_2 at 740 °C.[193] A more straightforward preparation of $SmBr_2$ was carried out by the conversion of Sm_2O_3 to a $SmBr_3$ hydrate followed by drying and reduction with metallic lithium.[194] Two other preparations that are straightforward employ the reaction of LiBr with SmI_2 to produce $SmBr_2$ *in situ*,[67,195] or reaction of excess Sm metal with 1,1,2,2-tetrabromoethane in THF.[196] Microwave heating greatly facilitates the latter process.[197] The synthesis of $SmCl_2$ was first reported by Rossmanith in 1979[198] and was carried out by the reduction of $SmCl_3$ by lithium naphthalenide in THF. $SmCl_2$ can be generated *in situ* by the addition of LiCl to SmI_2 in THF. More recently, $SmCl_2$ has been prepared in water by combining Sm metal and $SmCl_3$.[199]

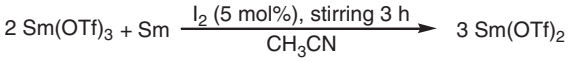
Both $SmBr_2$ and $SmCl_2$ are strong reductants. The $E_{1/2}$ of $SmBr_2$ is -1.55 ± 0.07 V and the potential of $SmCl_2$ is -1.8 ± 0.1 V versus SCE.[67] Although the reductants do not have the broad applicability of SmI_2, they do have advantages in some instances. Kagan and coworkers have shown that $SmBr_2$ is an effective reductant for the cross coupling of benzophenone with dialkyl and cyclic ketones providing good yields of products.[194] More recently Namy and coworkers have developed a procedure that allows the use of a catalytic amount of $SmBr_2$ in pinacol coupling reactions when mischmetal is employed as a sacrificial stoichiometric reductant.[200] $SmCl_2$ has also been applied to optimize the reaction conditions for the cyclization of an isocyanine to form spirooxindoles in the total synthesis of (±)-Welwitindolinone (**Scheme 104**).[201] With SmI_2 alone only 5% of the desired product was recovered, and with the addition of HMPA the yield only increased to 32%. When 8.4 equiv. of LiCl was included the desired product was obtained in a 75% yield as shown below.[201]



Scheme 104 Reproduced from Reisman, S. E.; Ready, J. M.; Weiss, M. M.; *et al. J. Am. Chem. Soc.* **2008**, *130*, 2087, with permission from ACS.

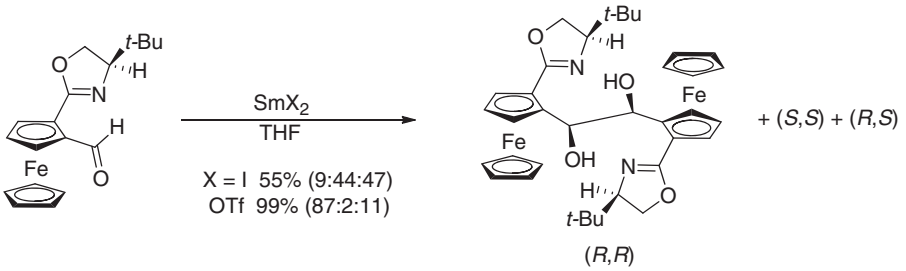
1.09.3.2.2 Samarium(II) triflate

In several instances, samarium(II) triflate ($Sm(OTf)_2$) has been employed in place of SmI_2. The reductant is typically prepared by the reaction of $Sm(OTf)_3$ with 1 equivalent of an organolithium or organomagnesium reagent in THF.[202] Although, the role of the Li or Mg counterion containing salts in follow-up reactions of $Sm(OTf)_2$ is not known, *s*-BuLi is generally more effective than *s*-BuMgCl in reductive coupling reactions.[203] Over the ensuing years a number of other approaches have been developed for the synthesis of $Sm(OTf)_2$,[204–206] but these protocols often times require the use of reagents that are difficult to prepare or require extended periods of time. As a consequence, most synthetic examples utilizing $Sm(OTf)_2$ employ the preparation originally described by Fukuzawa.[202,203] The UV–vis spectra of $Sm(OTf)_2$ in THF obtained from reduction of $Sm(OTf)_3$ by Grignard reagents are different from that produced through reduction by an organolithium reagent.[203] To address these issues and provide approaches to well defined reagents, Flowers has shown that $Sm(OTf)_2$ can be generated by reacting SmI_2 in THF with 2 equiv. of potassium triflate and removing the potassium iodide side product through filtration.[207] $Sm(OTf)_2$ can also be prepared in acetonitrile as shown below in **Scheme 105**. Employing this approach, the reductant was produced in nearly quantitative yield and the reagent was obtained with concentrations up to 0.09 M (as determined by iodometric titration).[208]



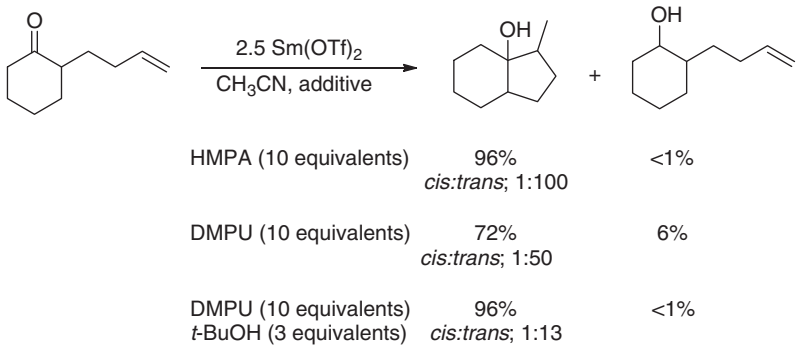
Scheme 105

Although the use of $Sm(OTf)_2$ has been limited, in some cases it has been shown to be a more effective reagent than SmI_2.[202,203] For example, using Sm-Grignard conditions, $Sm(OTf)_2$ demonstrated better diastereoselectivity than SmI_2 for the addition of alkyl iodides to 2-methylcyclohexanone, 4-*tert*-butylcyclohexanone, and 2-phenylpropanal.[209] Fukuzawa has demonstrated that $Sm(OTf)_2$ is superior to SmI_2 in the pinacol coupling of chiral formylferrocenes (**Scheme 106**). Interestingly, $Sm(OTf)_2$ provided the (*R*,*R*) stereoisomer predominantly whereas use of SmI_2 gave the (*R*,*S*) isomer with significantly reduced selectivity and yield.[209] In this work, a range of organolithium and Grignard reagents were examined for the preparation of $Sm(OTf)_2$ from the trivalent precursor and follow-up pinacol coupling. Interestingly, the use of *n*-BuLi in place of *s*-BuLi led to a decrease in the (*R*,*R*) selectivity of the reduction and the use of Grignard reagents led to higher yields of unwanted side-products. These experiments show that even modest changes of the organometallic reagent have an impact on the stereoselectivity of the coupling.



Scheme 106 Reproduced from Fukuzawa, S.; Yahara, Y.; Kamiyama, A.; Hara, M.; Kikuchi, S. *Org. Lett.* **2005**, *7*, 5809, with permission from ACS.

More recently Flowers has shown that $Sm(OTf)_2$ in acetonitrile provides a viable alternative to SmI_2-THF in carbonyl-alkene coupling reactions.[208] The cyclization of 2-but-3-enyl-cyclohexane-1-one was examined in the presence and absence of the additives HMPA and DMPU (Scheme 107). Reduction employing 10 equiv. of HMPA gave an instantaneous reaction and provided a nearly quantitative yield of cyclized product. The diastereoselectivity of the reaction was relatively high and consistent with reactions employing SmI_2-HMPA in THF. Reactions utilizing DMPU provided reasonable yields and diastereoselectivity of cyclized product but the reactions were considerably slower than those employing HMPA. Interestingly, addition of *t*-BuOH to reactions containing HMPA and DMPU had no impact on the yield, diastereoselectivity, or rate of the reaction, but had a significant impact on the yield and selectivity of the reaction containing DMPU.[208] Taken together, the work employing $Sm(OTF)_2$ shows that changes to the organometallic reagents used to generate the reductant as well as additives employed have a large impact on reaction outcomes. As a consequence, it is important to screen conditions carefully when using this reagent in a bond-forming reaction.

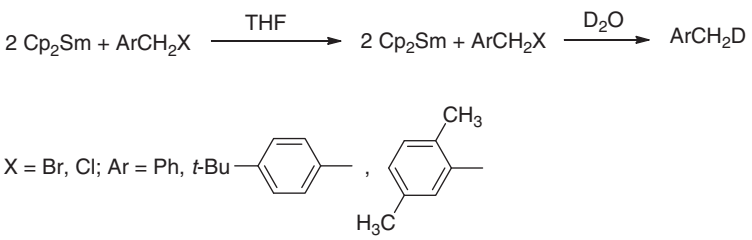


Scheme 107 Reproduced from Maisano, T.; Tempest, K. E.; Sadasivam, D. V.; Flowers, R. A., II. *Org. Biomol. Chem.* **2011**, *9*, 1714, with permission from Royal Society of Chemistry.

1.09.3.2.3 Sm(II) cyclopentadienyl reductants

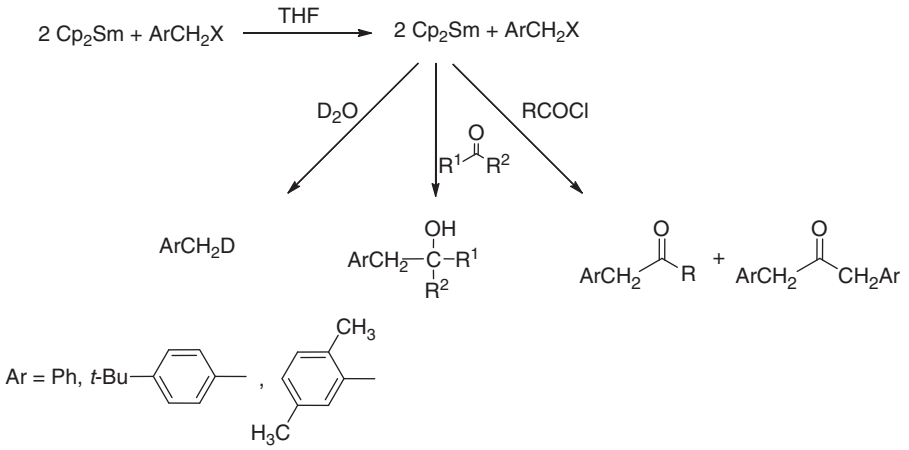
Ligands based on the cyclopentadienyl unit have played an important role in the development of Sm(II) chemistry. Although there are a range of cyclopentadienyl ligands, two of them, C_5H_5 (Cp), and C_5Me_5 (Cp^*), are the most prevalent in reactions. The synthesis of $SmCp_2$ and $SmCp^*_2$ is straightforward and most readily performed through the reaction of an equivalent of SmI_2 with two equivalents of the appropriate cyclopentadienylide salt in THF.[210,211]

The insolubility of $SmCp_2$ in THF and other commonly used organic solvents has limited its use in synthesis. However, there are a few examples where this reagent is reported to have benefits over the use of SmI_2. The addition of benzylic halides to a suspension of $SmCp_2$ in THF resulted in the formation of a solution in which the precipitate disappeared.[211] Formation of an organometallic species was proposed based on the fact that addition of D_2O resulted in the formation of monodeuterated toluene derivatives (Scheme 108). The intermediate benzylsamarium complex was found to be stable up to 24 h at room temperature without any evidence of decomposition.



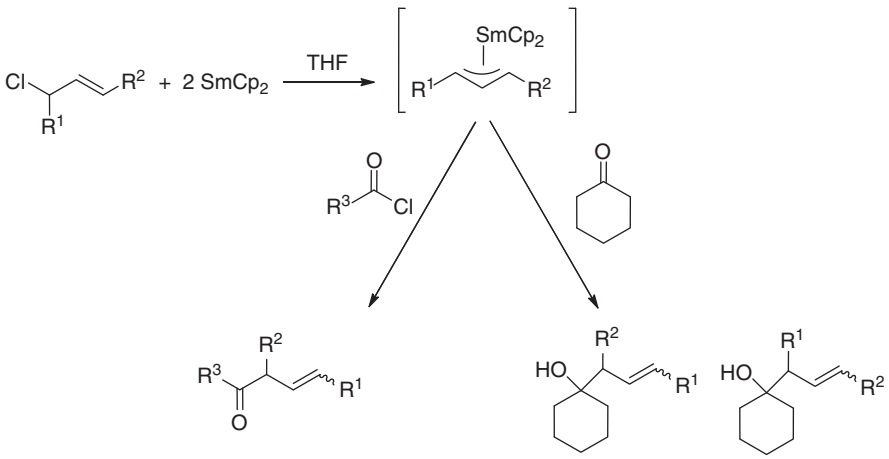
Scheme 108 Reproduced from Namy, J.-L.; Collin, J.; Zhang, J.; Kagan, H. B. *J. Organomet. Chem.* **1987**, *328*, 81.

Benzylsamarium complexes show a range of reactivity. Reaction with benzyl halides produces 1,2-diphenylethanes in good yields. Addition of benzylsamariums to a wide variety of ketones and aldehydes leads to good yields of alcohols. Reactions of benzylsamarium derived from $SmCp_2$ with acid chlorides produce a mixture of alcohols and ketones (Scheme 109).[212]



Scheme 109 Reproduced from Kagan, H. B.; Collin, J.; Namy, J.-L.; *et al. J. Alloy Compd.* **1993**, *192*, 191.

In related studies it was discovered that allyl chlorides react with $SmCp_2$ to give allylsamarium intermediates (Scheme 110). The allylsamarium intermediates are proposed to have a η^3 structure based on the reactivity of the intermediate with ketones. These reagents can also be reacted with acid chlorides to provide β,γ-unsaturated ketones.[213,214]



Scheme 110 Reproduced from Bied, C.; Collin, J.; Kagan, H. B. *Tetrahedron* **1992**, 3877.

In seminal work Evans and coworkers reported the synthesis of $SmCp^*_2$.[215] This reagent is soluble in a wide range of organic solvents including benzene, THF, and hexanes enabling the chemistry of Sm(II) to be investigated over a broad range of conditions. This synthesis and the work that followed from this seminal report has had a profound impact on the use of Sm(II) reductants in a number of diverse areas including, but not limited to, organic and inorganic synthesis, catalysis, and polymerization reactions. Although these studies are beyond the scope of this work, comprehensive reviews are available.[12,216,217]

1.09.3.2.4 Sm(II) amide reductants

Sterically bulky monoanionic nitrogen ligands have also played an important role in the development of Sm(II) chemistry. Among nitrogen-based ligands, the *bis*-(trimethylsilyl)amide ligand ($N(SiCH_3)_2$) has been the most commonly exploited due to its ability to form monomeric Sm(II)-based reductants. Relatively little synthetic chemistry has been exploited using $SmN(SiCH_3)_2$, but there are a few examples. Flowers and coworkers showed that this reductant is useful in the reductive coupling of aldimines.[218,219] Reduction of the N-butyl and N-benzyl imines of benzaldehyde by $SmN(SiCH_3)_2$ in THF provide the coupled diamine with good *anti* selectivity, whereas $SmBr_2$ and $SmI_2/H_2O/NEt_3$ give little diastereoselectivity in the coupling reaction.

More recently, $N(SiCH_3)_2$ has been used as a mixed ligand system with SmI_2 in the cyanation of α-halocarbonyls as shown in (Scheme 99).

The use and application of divalent Sm, and to a lesser extent Yb, as reagents in organic synthesis have grown substantially in the past 30 years since their introduction by Kagan. Their use as stoichiometric reductants has grown unabated with over 100 publications a year. In fact, SmI_2 is still employed in the development of cascade and tandem reactions that are an integral part of multistep syntheses. Although the use of stoichiometric Sm(II) continues to grow, there are several challenges. Methods that employ an inexpensive sacrificial coreductant are relatively scarce and HMPA is still the additive of choice in many reactions, although some progress is being made. The recent work of Procter employing H_2O as an additive has created new reaction space for novel reductions. Additionally, the work of Hilmersson and more recent work of Procter on the use of SmI_2/H_2O/amine in bond-forming reactions will help lead to protocols that mimic the beneficial behavior of HMPA, but provide safer alternatives.

1.09.4 Trivalent Sm and Yb

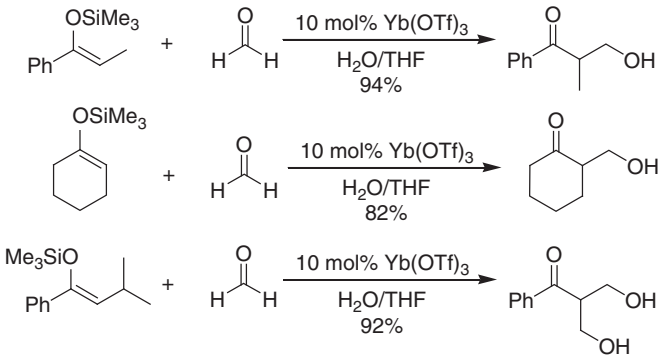
Sm and Yb reagents are most stable in the +3 oxidation state, and salts of these lanthanides, as well as other organolanthanide variants, successfully facilitate many bond-forming reactions. They act as strong Lewis acids as well as organometallic intermediates. The strong Lewis acid character is a consequence of the oxophilicity of the lanthanides, providing them with a strong affinity toward oxygen-containing functional groups. Often times, the hard nature of the metal center is complimented by soft ligands, and most commonly utilized reagents contain halide counter ions (LnI_3, $LnCl_3$) or the electron-withdrawing trifluoromethanesulfonate (triflate), $Ln(OTf)_3$. In particular, the triflate ligand has found important synthetic usefulness in Sm(III) and Yb(III)-based reagents. The utility of $Sm(OTf)_3$ and $Yb(OTf)_3$ is a consequence of their ability to tolerate aqueous systems. An additional benefit is the ease of catalyst recovery after reaction workup. Yb(III) and Sm(III) are also utilized as organometallic intermediates which can be transmetalated with other metals such as copper or lithium to facilitate organometallic reactions. Furthermore, organo-Sm(III) and -Yb(III) species are generated as intermediates in Sm(II)- and Yb(II)-initiated reactions. Owing to their oxophilicity, these intermediates direct stereoselectivity through coordination or chelation with neighboring oxygen containing functional groups such as alcohols, esters, etc.

1.09.4.1 Yb(III)

1.09.4.1.1 Lewis acid promoted reactions

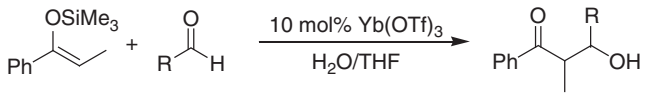
1.09.4.1.1.1 Aldol and related addition reactions

In 1991 Kobayashi and coworkers set out to find a Lewis acid that could couple commercially available formaldehyde (which contains a significant amount of water) with silylenolethers through a Mukaiyama Aldol type reaction.[220] Lewis acids typically react with even trace amounts of water, leading to deactivation of many catalysts. Kobayashi and his colleagues determined that lanthanide triflate-based Lewis acids were able to catalyze the coupling reaction with low catalyst loadings (1 mol% yielded 90% product) and remained active within aqueous media. In addition, the catalyst was recovered in nearly quantitative yield and successfully recycled without diminished reaction yields. Among the $Ln(OTf)_3$ salts tested, $Yb(OTf)_3$ was the most successful, and a wide range of silyl enol ethers were coupled with formaldehyde to produce the corresponding hydroxymethylated adducts (Scheme 111).



Scheme 111 Reproduced from Kobayashi, S. *Chem. Lett.* **1991**, 2187, with permission from The Chemical Society of Japan.

A range of substituted aldehydes were also examined (Scheme 112) which exploited the ability of $Yb(OTf)_3$ to catalyze a wide range of Mukaiyama Aldol reactions in high yields even in the presence of H_2O.[221,222] Other lanthanide(III) triflates were found to also catalyze the reaction ($Sm(OTf)_3$ 91% yield, $La(OTf)_3$ 88% yield), however subsequent studies were routinely performed with $Yb(OTf)_3$.

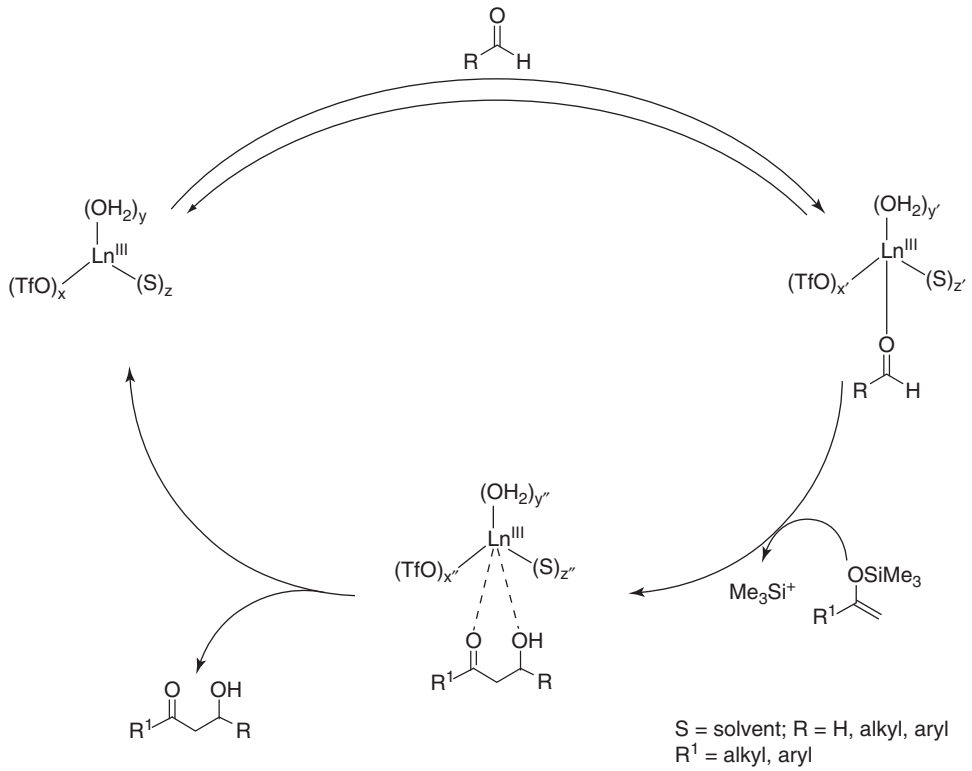


Entry	R	Yield (%)
1	CH_3	93
2	CH_2Cl	95
3	Ph	81

Scheme 112 Reproduced from Kobayashi, S. *Tetrahedron Lett.* **1992**, *33*, 1625.

The effect of water on the reaction was investigated and a delicate balance was observed. The amount of water present led to dissociation of THF ligands from $Yb(OTf)_3$, and coordination by water. The on-off equilibrium of water molecules coordinating and dissociating from the metal center allowed aldehyde coordination and activation, followed by silylenolether attack to form the aldol adduct. The ideal water conditions were determined to be 10–20 mol% water in solvent.[222] The yield slowly decreased as more water was added, finally obtaining only 18% product with a 100% aqueous system.

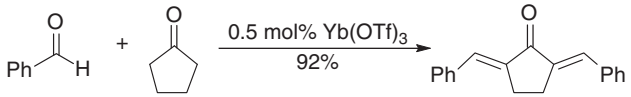
More recent elegant mechanistic work of Allen has shown that triflate dissociation from the Ln(III) center is critical in the reaction.[223] Addition of water to $Ln(OTf)_3$ in organic solvents leads to displacement of the triflate ligands from Ln(III) (a range of substituted aldehydes were also examined (Scheme 113)). As the water concentration is increased, more ligands dissociate from the Ln(III) metal. At water concentrations more than 20% all of the triflate ligands were replaced. As a consequence, metal saturation by water prevents aldehyde coordination leading to a decrease in yield. Solutions containing 20% water were the most effective due to an advantageous dynamic that leads to triflate displacement, but simultaneously provides open coordinations sites for interaction of aldehyde with the Ln(III) center as shown below.



Scheme 113 Reproduced from Dissnayake, P.; Allen, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 6342, with permission from ACS.

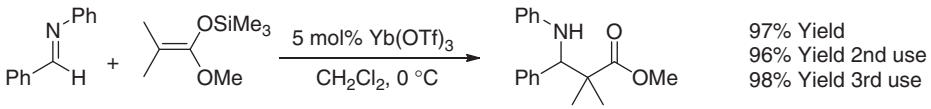
Although the examples above show the importance of water in reactions, an efficient approach to the Mukaiyama Aldol reaction was used in the synthesis of α,α'-bis(substituted benzylidene) cycloalkanes, in which a solvent-free system was used to obtain excellent yields (Scheme 114). The substrates and catalyst were refluxed at 90 °C under solvent free conditions, and after the reaction was complete (6 h) the Yb catalyst was removed through aqueous extraction and could be reused in up to 5 additional reactions.[224]

Use of $Yb(OTf)_3$ as a Lewis acid was also found to be efficient in the activation of imines.[225] As a consequence, formation of β-amino ketones or β-amino esters was accomplished through the coupling of imines and enolates in the presence of catalytic



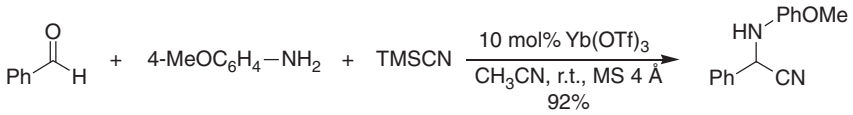
Scheme 114 Reproduced from Wang, L.; Sheng, J.; Tian, H.; *et al. Synthesis* **2004**, *18*, 3060, with permission from Thieme Publisher.

$Yb(OTf)_3$ (Scheme 115). Similar to the previous examples, Yb(III) was easily recovered from the aqueous phase of the reaction after work-up, and could be used successfully to catalyze additional reactions.



Scheme 115 Reproduced from Kobayashi, S.; Araki, M.; Ishitani, H.; Satoshi, N.; Hachiya, I. *Synlett* **1995**, 233, with permission from Thieme Publisher.

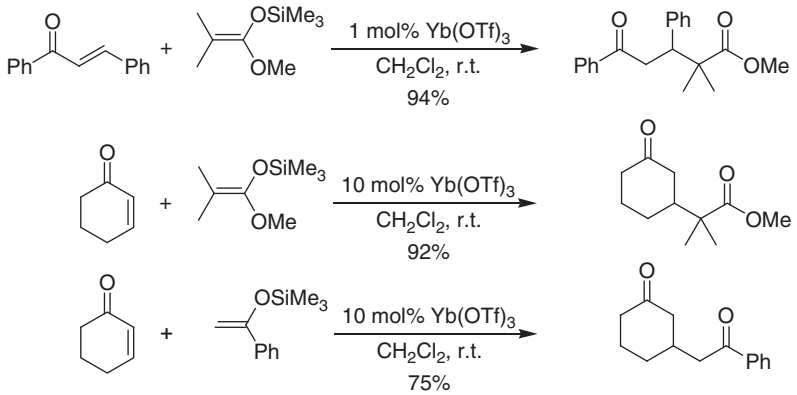
In a related reaction, *in situ* formation of imines catalyzed by Yb(III) was employed to form α-amino nitriles, important intermediates for the synthesis of amino acids. $Yb(OTf)_3$ was successfully used to couple an aldehyde and amine in the presence of cyanotrimethylsilane (TMSCN), a safe cyano anion source (Scheme 116).[226] During the formation of the imine intermediate, water was produced as a byproduct. Although most Lewis acid catalysts would deactivate under these conditions, $Yb(OTf)_3$ remains active. This reaction was run efficiently with 4 Å molecular sieves to sequester the excess water; however good yields were achieved even in their absence.



Scheme 116 Reproduced from Kobayashi, S.; Ishitani, H.; Ueno, M. *Synlett* **1997**, 115, with permission from Thieme Publisher.

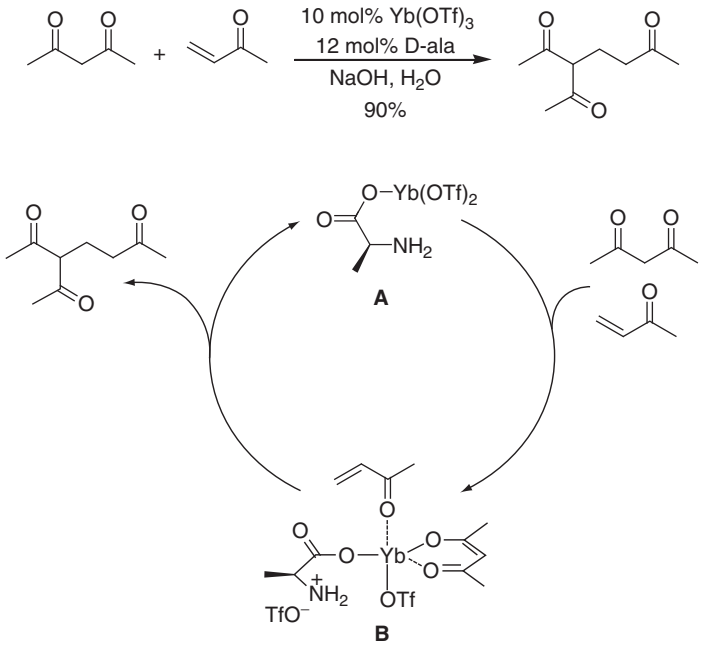
1.09.4.1.1.2 Michael additions

The use of $Yb(OTf)_3$ Lewis acid catalyst can also be extended to Michael reactions of silyl enolates with α,β-unsaturated ketones[227] (Scheme 117). These reactions were carried out with various silyl enol ethers and unsaturated ketones, all of which obtained high yields in both the first and second runs with the catalyst.



Scheme 117 Reproduced from Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, *33*, 6818.

Subsequent studies showed that the addition of catalytic D-alanine drastically increased the rate of the reaction.[228] Successful reactions were performed in a biphasic aqueous system, in which the substrates and catalysts were added to water. After reaction stirring was stopped, the mixture separated into two distinct phases. The product was recovered from the organic phase, and the regenerated catalyst in the aqueous phase was subjected to another batch of reagents. In the absence of the Yb catalyst no reaction occurred, and with the addition of the amino acid the reaction time decreased from 5 days to 16 h. It was proposed that alanine accelerates the reaction by acting as a ligand, displacing a triflate from $Yb(OTf)_3$ to give **A** (Scheme 118). With the addition of the substrates another triflate ligand is displaced from the lanthanide by the bidentate β-ketoenolate (**B**, Scheme 118), which bring

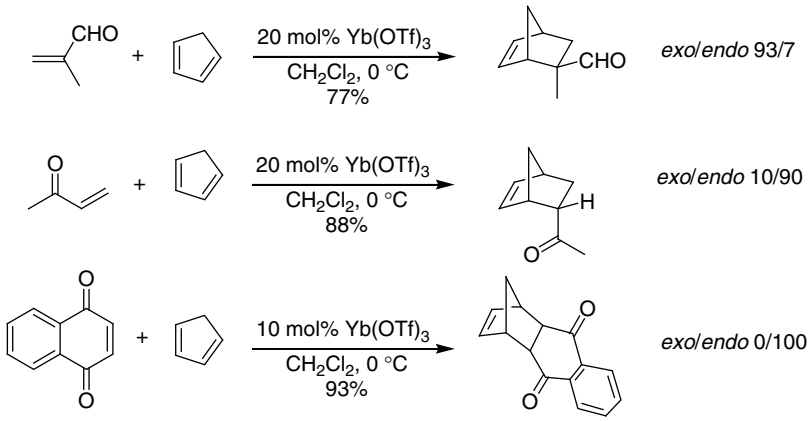


Scheme 118 Reproduced from Aplander, K.; Ding, R.; Lindström, M.; Wennerberg, J.; Schultz, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 4543, with permission from Wiley.

the substrates in close proximity for addition. This intermediate complex was suggested based on the work by Christoffers, which showed that the coordination of negatively changed ligands can significantly enhance the reactivity of the β-ketoenoate toward an electrophile, presumably weakening the covalent character of the M–O bond.[229]

1.09.4.1.1.3 Diels–Alder reactions

The scope of $Yb(OTf)_3$ as a catalyst was expanded by employing it in a variety of Diels–Alder reactions (Scheme 119).[227] Coupling of α,β-unsaturated carbonyl compounds or quinones with conjugated dienes produced the desired bi- and tetracyclic adducts in high yield and provided complete control over the stereoselectivity of the reaction.

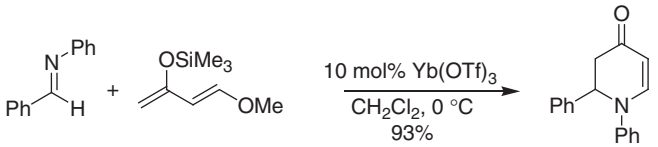


Scheme 119 Reproduced from Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, *33*, 6818.

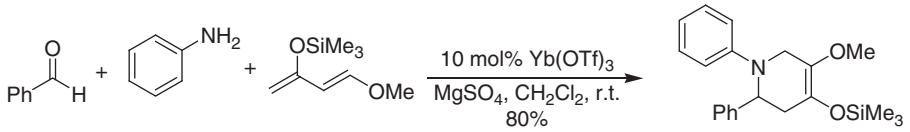
Imino Diels–Alder reactions are a useful synthetic tool, but often require a stoichiometric amount of Lewis acid to drive the reaction to completion. Kobayashi and coworkers found that the use of 10 mol% $Yb(OTf)_3$ catalyzed additions of imines with Danishefsky's diene to form cycloaddition adducts in high yield (Scheme 120).[225]

Owing to the instability of isolated imines, creative three component coupling reactions were designed to exploit the ability of $Yb(OTf)_3$ to form imines *in situ* through the reaction of aniline derivatives and aldehydes.[230] The intermediate imine reacts with Danishefsky's diene to produce pyridine derivatives in good yields (Scheme 121).

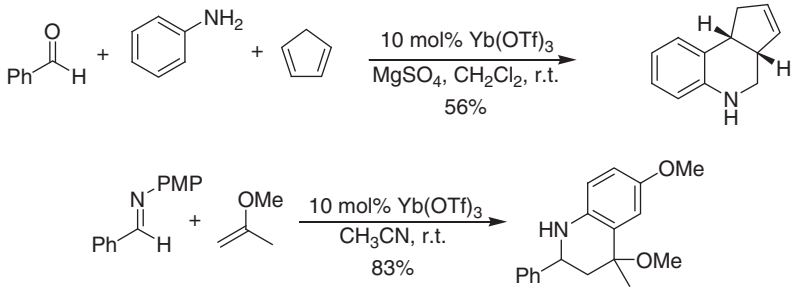
Interestingly, imines formed from the reaction of anilines, aldehydes, and alkenes form quinolines in good to excellent yields. In these cases, the imine formed *in situ* acts as an azadiene with cyclopentadiene and other alkenes acting as dienophiles (Scheme 122).[230]



Scheme 120 Reproduced from Kobayashi, S.; Araki, M.; Ishitani, H.; Satoshi, N.; Hachiya, I. *Synlett* **1995**, 233, with permission from Thieme Publisher.

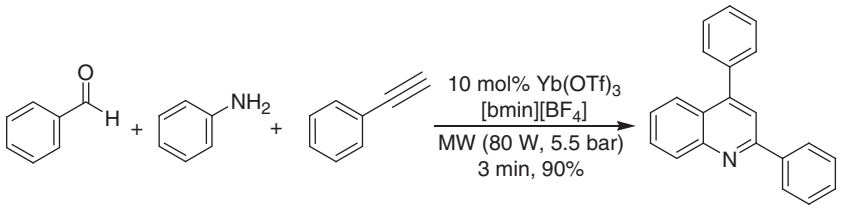


Scheme 121 Reproduced from Kobayashi, S.; Ishitani, H.; Satoshi, N. *Chem. Lett.* **1995**, 423.



Scheme 122 Reproduced from Kobayashi, S.; Ishitani, H.; Satoshi, N. *Chem. Lett.* **1995**, 423.

The synthesis of substituted quinolines using the *in situ* imine formation has been adapted to a highly efficient one-pot, Yb-catalyzed microwave reaction in ionic liquids (**Scheme 123**).[231] This reaction exemplifies the versatility and stability of the $Yb(OTf)_3$ catalyst.



Scheme 123 Reproduced from Kumar, A.; Rao, V. K. *Synlett* **2011**, *15*, 2157, with permission from Thieme Publisher.

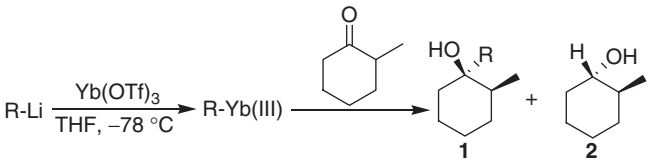
Given the generality and scope of $Yb(OTf)_3$ as a Lewis acid catalyst for a range of important bond-forming reactions in different solvent milieu, it is likely that new applications of this reagent will be identified.

1.09.4.1.2 Organometallic reactions

1.09.4.1.2.1 Transmetallation and organoytterbium intermediates

The addition of Yb(III) salts to organolithium, Grignard, and related reagents has been shown to provide important selectivity in carbonyl additions not available in the absence of the lanthanide salt. In many traditional carbonyl addition reactions there is little control over the diastereoselectivity of the final product. In descriptions of reactions employing Yb(III) in conjunction with an organolithium or Grignard reagent, the addition of the lanthanide salt is proposed to produce an organoytterbium intermediate. Given the oxophilic nature of Yb(III), it is not always clear if an organoytterbium is being produced, or if Yb(III) is acting as a Lewis acid that activates the carbonyl for addition. Furthermore, addition of organolithium and Grignard reagents to $Sm(OTf)_3$, has been shown to produce $Sm(OTf)_2$.[202] Since Yb(III) is easier to reduce through single-electron transfer it is also possible that under some conditions, Yb(II) intermediates are generated that lead to reactions proceeding through one-electron processes instead of the traditional two-electron organometallic nucleophilic addition to carbonyls. Given the lack of characterization of intermediates in these reactions, all examples will be referred to as organoytterbium reactions, but it is important to recognize the reactions may be more complex than expected for traditional organometallic addition to a carbonyl.

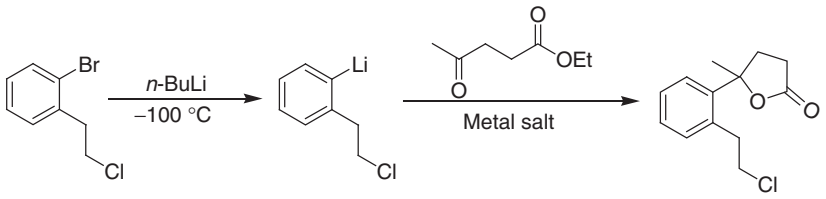
The seminal work using Yb(III) in conjunction with organolithium and Grignard reagents was carried out by Molander and coworkers.[232] They discovered that the addition of $Yb(OTf)_3$ to organolithium and Grignard reagents produced an intermediate that reacted with substituted ketones and aldehydes leading to very high diastereoselectivities. The intermediate organoytterbium produced reacts with ketones and aldehydes through preferential equatorial attack onto the carbonyl.[232] In all cases reported, the diastereoselectivities were superior to those carried out in the absence of $Yb(OTf)_3$. Several examples for additions to 2-methyl cyclohexanone are shown below (Scheme 124). The success of this process deemed $Yb(OTf)_3$ an attractive option for a mild, selective organometallic reagent.



Entry	R-Li (equivalent)	Ketone equivalent	Ratio 1:2	Yield (%)
1	Methyllithium (1)	0.81	98.1:1.9	91
2	*n*-Butyllithium (2)	1.0	99:1	91
3	Phenyllithium (1.1)	0.84	>99:<1	73
4	*Trans*-1-hexenyllithium (2)	1.0	96.7:3.3	75
5	*Cis*-1-hexenyllithium (2)	1.0	97.4:2.6	78
6	*Tert*-butyllithium (2)	1.0	200:1	53
7	Vinylmagnesium bromide (1)	0.9	97.5:2.5	89

Scheme 124 Reproduced from Molander, G. A.; Burkhardt, E. R.; Weinig, P. *J. Org. Chem.* **1990**, *55*, 4990, with permission from ACS.

The approach described above was expanded for the synthesis of lactones containing a pendant halide. In the coupling of aryl dihalide and ketone esters to produce substituted lactones, both organolithium and organomagnesium nucleophiles produced unsatisfactory yields. The best yields of the desired lactone were obtained with the addition of $Yb(OTf)_3$ to the organolithium intermediate to produce the desired product.[119] The initial organolithium forms nearly quantitatively in the first step, but only 28% of the lactone was formed with Li salts alone (Scheme 125). Transmetallation with Mg was attempted, however, the organomagnesium nucleophile produced only a 5% yield of the desired lactone. Use of $Yb(OTf)_3$ for transmetallation of the organolithium species led to an improved 70% isolated yield. Using this approach, lactones were formed from a wide range of dihalide and keto ester partners, further displaying the versatility of $Yb(OTf)_3$ (Scheme 126).

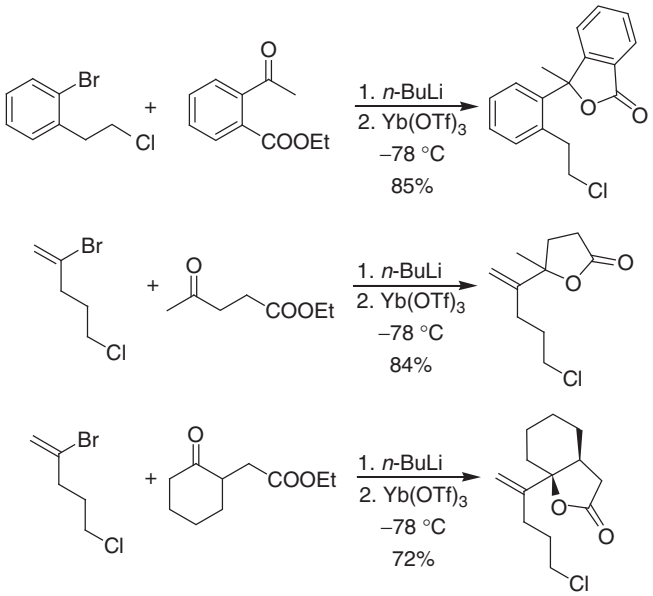


Metal salt	Yield (%)
n-BuLi	28
$MgBr_2$	5
$Yb(OTF)_3$	70

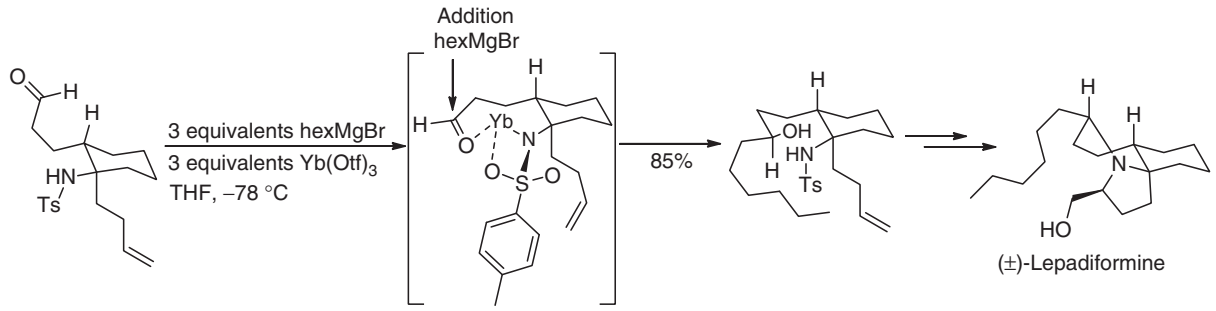
Scheme 125 Reproduced from Molander, G. A.; Köllner, C. *J. Org. Chem.* **2000**, *65*, 8333, with permission from ACS.

The use of intermediate organoytterbium nucleophiles have been found to improve the addition to carbonyls in the key step of the synthesis of natural products. The total synthesis of (±)-Lepadiformine employed $Yb(OTf)_3$ with a Grignard reagent to dramatically improve the stereoselectivity of the fully substituted *trans*-perhydroquinoline ring system stereoselectivity (Scheme 127), through the introduction of the hexyl group before ring closure.[233]

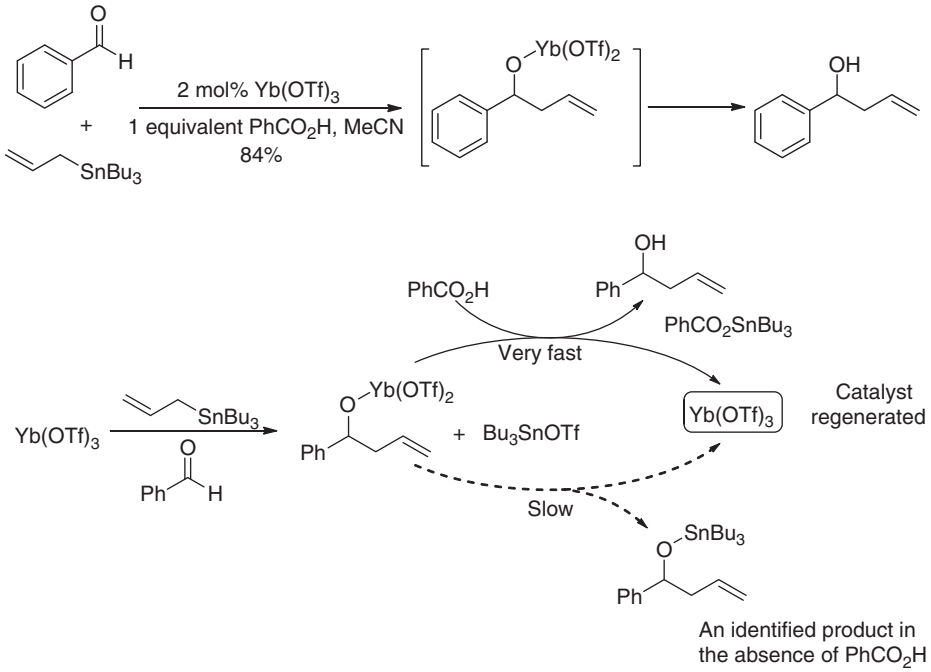
In related work on carbonyl additions, Greeves and coworkers used catalytic $Yb(OTf)_3$ in the allylation of aldehydes by allyltributyltin in acetonitrile.[234] The use of a substoichiometric amount of benzoic acid accelerated the reaction and allowed a low loading of Yb catalyst (Scheme 128).[235] It was proposed that the addition of benzoic acid facilitates the regeneration of the lanthanide catalyst, increasing the reaction rate. In this case, it is likely $Yb(OTf)_3$ is acting as a Lewis acid to activate the aldehyde for attack by the allyltributyltin. The lanthanide catalyst is coordinated with the alkoxide intermediate, greatly reducing the Lewis acidity and subsequent release of the catalyst. Addition of the Brønsted acid disrupts the alkoxide restoring the Lewis acid catalyst and releasing the product.



Scheme 126 Reproduced from Molander, G. A.; Köllner, C. *J. Org. Chem.* **2000**, *65*, 8333, with permission from ACS.



Scheme 127 Reproduced from Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511, with permission from ACS.



Scheme 128 Reproduced from Aspinall, H. C.; Greeves, N.; McIver, E. *Tetrahedron Lett.* **1998**, *39*, 9283.

In addition to transmetallation reactions, Yb(II)-initiated reactions produce an organoytterbium(III) intermediate after initial electron transfer. Few studies have intimately examined these intermediates as compared to the extensive degree of work on Sm(III) intermediates, generated after substrate reduction and subsequent coordination by Sm(III). Nonetheless, when using Yb(II) reductants, it should be recognized that Yb(III) intermediates are produced and likely have an important impact on the selectivity of reactions.

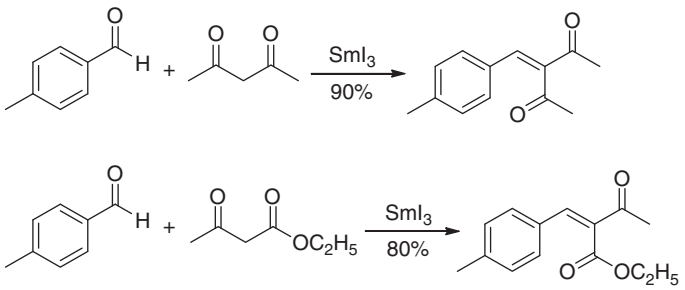
1.09.4.2 Sm(III)

1.09.4.2.1 Lewis acid promoted reactions

1.09.4.2.1.1 Aldol and related addition reactions

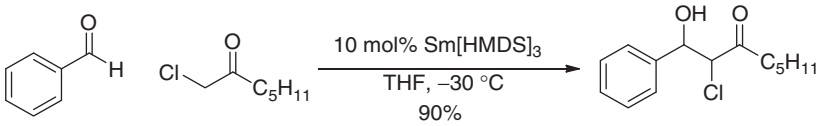
Lewis acids of Sm(III) often contain halide or triflate ligands with SmI_3 and $Sm(OTf)_3$ being employed extensively. Although both are good Lewis acids, $Sm(OTf)_3$ exhibits the same positive attributes as $Yb(OTf)_3$, namely tolerance to water, high recoverability and recyclability as a catalyst.[221,222] In the following sections, examples are chosen where Sm(III) provides important advantages over Yb(III).

SmI_3 has been employed effectively in the condensation of aldehydes with β-diketones or β-ketoesters to give benzylidene-substituted β-diketones and ketoesters (Scheme 129).[236] This procedure allowed the Aldol reaction to take place in neutral, mild reaction conditions, and all reactions were complete within 3 h. This is a distinct advantage to base-catalyzed approaches using piperdine which take several days to complete.



Scheme 129 Reproduced from Bao, W.; Zhang, Y.; Wang, J. *Synthetic Comm.* **1996**, *16*, 3025, with permission from Tayolr & Francis.

Another Sm(III)-based reagent that has been employed as a Lewis acid is Sm(III) hexamethyl disilazide ($Sm(HMDS)_3$).[237] Since the HMDS ligand is sterically encumbered, $Sm(HMDS)_3$ is proposed to exist as a monomer. This catalyst was used for the aldol coupling of α-chloro ketones with aldehydes to form the cross-coupled product; no homocoupled products were obtained (Scheme 130). When other Lewis acid catalysts such as $Sm(O\text{-}i\text{-}Pr)_3$ or $La(O\text{-}i\text{-}Pr)_3$ were used, the reactions were slower and achieved yields of only 47 and 56%, respectively.



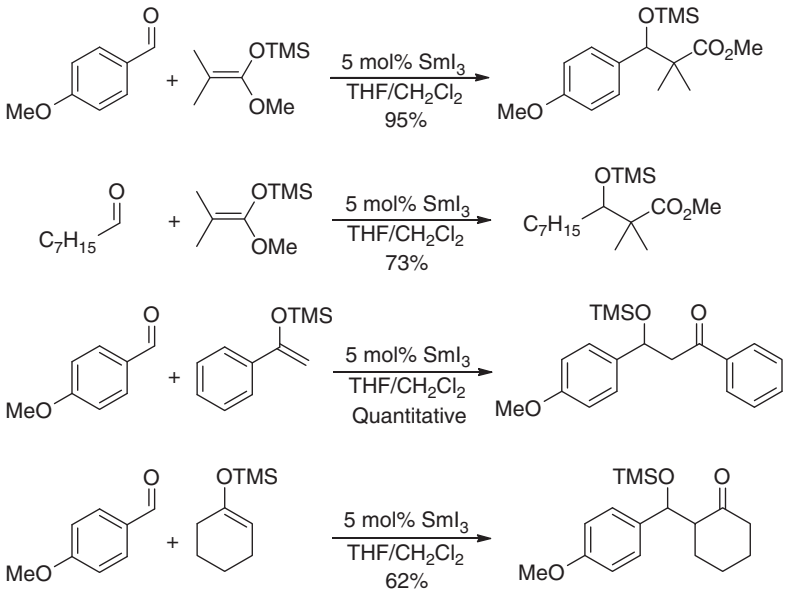
Scheme 130 Reproduced from Sasai, H.; Arai, S.; Shibasaki, M. *J. Org. Chem.* **1994**, *59*, 2661, with permission from ACS.

Catalytic amounts of SmI_3 were used in Mukaiyama-Aldol reactions with ketene silyl acetals and aldehydes to form the cross-coupled products in high yields.[238,239] The advantage of this approach is that the use of the Sm(III) catalyst allows the isolation of the silyl ether product (Scheme 131).

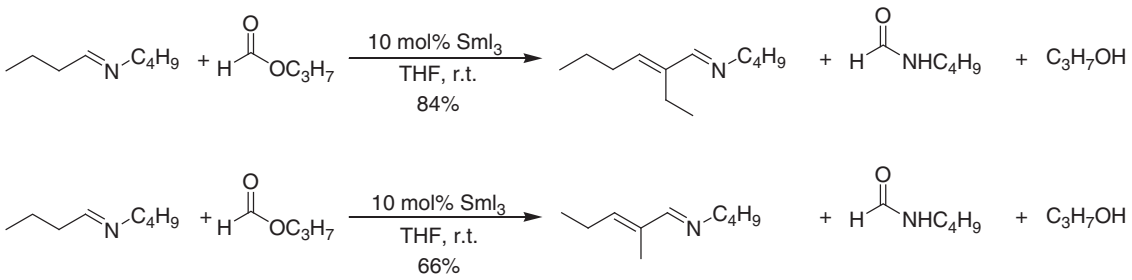
In an Aldol-type condensation of imines, catalytic Sm(III) was used to produce α,β-unsaturated imines.[240] In this reaction, the presence of formates facilitated the elimination of the intermediate amines from the aldol adducts, promoting the formation of the α,β-unsaturated imines (Scheme 132). *N*-Butylformamide and propanol were also recovered as byproducts from the reaction. In this reaction system, the addition of the formate-promoted elimination of amine, which then reacted with another molecule of the formate to reform the reactant imine (Scheme 133), which is then subjected to another condensation reaction. The reaction also provided excellent yields when aldehydes were employed in place of formates.

1.09.4.2.1.2 Michael additions

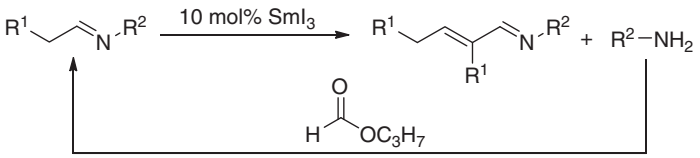
The conjugate addition of indoles to electron-deficient olefins can be significantly accelerated using $Sm(OTf)_3$. The advantage of this approach is that Michael additions are performed under mild conditions with a variety of substituted indoles and olefins



Scheme 131 Reproduced from Giuseppone, N.; Van de Weghe, P.; Mellah, M.; Collin, *J. Tetrahedron* **1998**, *54*, 13129.



Scheme 132 Reproduced from Shiraishi, H.; Kawasaki, Y.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *Tetrahedron Lett.* **1996**, *37*, 7291.

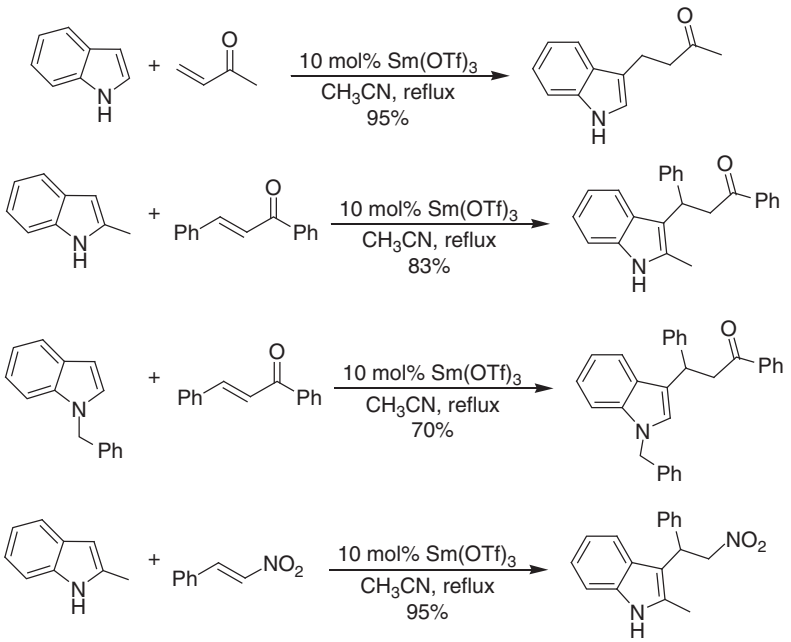


Scheme 133 Reproduced from Shiraishi, H.; Kawasaki, Y.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *Tetrahedron Lett.* **1996**, *37*, 7291.

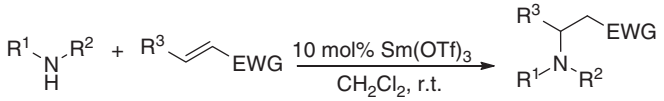
(Scheme 134).[241,242] An additional advantage of this method is that indole starting materials did not have to be protected before the coupling reaction. The mild reaction conditions allow for a wide range of functional groups to be employed in the reaction.

The aza-Michael variant is an important C–N bond forming reaction used frequently for the synthesis of β-amino ketones, building blocks for antibiotics, natural products and β-amino alcohols. Yadav and coworkers utilized $Sm(OTf)_3$ as a Lewis acid catalyst in a simple, mild procedure to obtain a wide range of these synthetically important molecules. A variety of amines and alkenes were coupled (Scheme 135), obtaining the Michael adducts in high yields.[243]

Collins established a preparation of enoxysilanes through the addition of carbonyl compounds to a ketene silyl acetal (methyl trimethylsilyl dimethylketene acetal).[244] Catalytic SmI_2 was utilized to promote the reaction, achieving high yields and good stereochemical control, predominately forming the Z isomer (Scheme 136). In a study performed to optimize the catalytic Michael Addition, it was found that the use of Sm(II) and Sm(III) catalysts yielded nearly identical yields and isomeric ratios (Scheme 136, entries 1 and 2). This result identified that the catalytically active species in this reaction is likely Sm(III) and that the Lewis acid trivalent Sm is responsible for the activity and selectivity observed (Scheme 136).



Scheme 134 Reproduced from Zou, X.; Wang, X.; Cheng, C.; Kong, L.; Mao, H. *Tetrahedron Lett.* **2006**, *47*, 3767.



	(Amine)		(Olefin)		
Entry	R^1	R^2	R^3	EWG	Yield (%)
1	Bn	H	H	CO_2Et	96
2	4-Pyridylmethyl	Et	H	CO_2Et	92
3	$-(CH_2)_2O(CH_2)_2-$		H	CN	90
4	4-Pyridylmethyl	Et	H	CN	90
5	$-(CH_2)_2O(CH_2)_2-$		H	$CONH_2$	90
6	$-(CH_2)_4-$		Ph	NO_2	89

Scheme 135 Reproduced from Zou, X.; Wang, X.; Cheng, C.; Kong, L.; Mao, H. *Tetrahedron Lett.* **2006**, *47*, 3767.

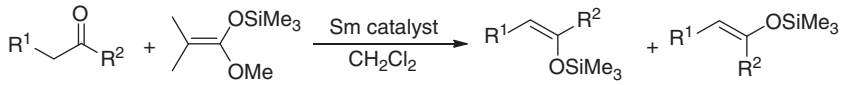
1.09.4.2.1.3 Diels–Alder reactions

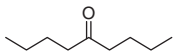
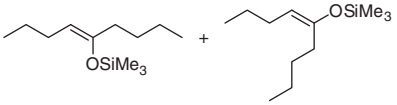
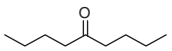
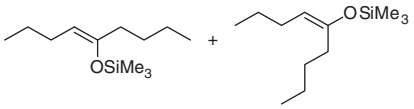
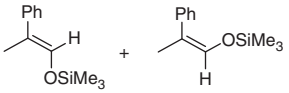
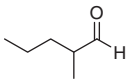
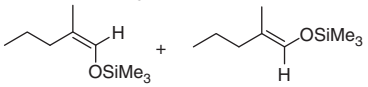
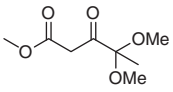
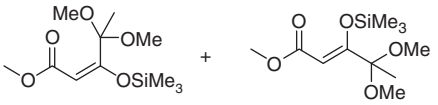
Colin and coworkers employed catalytic SmI_2 as a precursor for Sm(III) in imino-Diels–Alder reactions.[245] As shown in Scheme 137, entries 1 and 2, when SmI_3 is used as the catalyst in place of SmI_2 nearly identical results were obtained. The color of the reaction also indicated that it proceeded through an Sm(III)-catalyzed mechanism; after addition of the substrates to the SmI_2 solution the reaction turned from dark blue to yellow/orange, and retained the yellow color until the end of the reaction. The loss of the blue color of SmI_2 is consistent with oxidation of the metal. The addition of imines to cyclopentadiene were also carried with catalytic SmI_2 (SmI_3 catalytic system), obtaining a mixture of isomers (Scheme 138).

More complex and sterically encumbered catalysts based on Sm(III) have been designed to control the enantioselectivity of cycloaddition reactions. Trivalent lanthanide Lewis acid catalysts derived from pyridyl-bis(oxazoline) (pybox) ligands have been synthesized and used in quinone Diels–Alder reactions,[246] achieving excellent yields and near complete control over the *ee* (Scheme 139). Solvent was found to play an important role in the reaction, affecting the enantioselectivity of the final product. The best synthetic results were obtained with a 1:1 mixture of THF:toluene at $-78\ ^{\circ}C$ with the Sm catalyst. These results suggested that THF is most likely acting as a ligand for Sm and imparting additional control on the selectivity of the reaction.

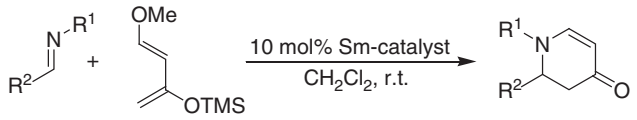
1.09.4.2.1.4 Miscellaneous

Traditionally, β-amino alcohols can be synthesized by simply mixing an epoxide in the presence of a nucleophilic amine at elevated temperatures. However, the high temperature damages sensitive functional groups, limiting the procedure to substrates able to tolerate these conditions. To address this shortcoming, Yadav and coworkers developed a $Sm(OTf)_3$ catalyzed addition that allowed for a regioselective ring-opening by preferential attack of the nucleophile on a substituted epoxide (Scheme 140).[247] The



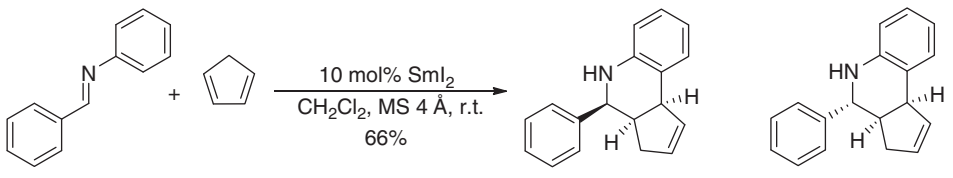
Entry	Carbonyl	Products	Catalyst	Yield (%)	Ratio (Z/E)
1			10 mol% SmI_2	90	82:18
2			10 mol% SmI_3	88	78:22
3			5 mol% SmI_2	72	90:10
4			5 mol% SmI_2	78	70:30
5			5 mol% SmI_2	75	78:22

Scheme 136 Reproduced from Hydrio, J.; Van de Weghe, P.; Collin, J. *Synthesis* **1997**, 68, with permission from Thieme Publisher.



Entry	R^1	R^2	Catalyst (10 mol%)	Yield (%)
1	Ph	*o*-$CH_3OC_6H_4$	SmI_2	72
2	Ph	*o*-$CH_3OC_6H_4$	SmI_3	71
3	Ph	Ph	SmI_2	61
4	Ph	*p*-$CH_3OC_6H_4$	SmI_2	82
5	*o*-$CH_3OC_6H_4$	Ph	SmI_2	86
6	*p*-$CH_3OC_6H_4$	Ph	SmI_2	86
7	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	SmI_2	87
8	*p*-$CH_3C_6H_4$	Ph	SmI_2	63
9	$CH_2C_6H_4$	*o*-$CH_3OC_6H_4$	SmI_2	79

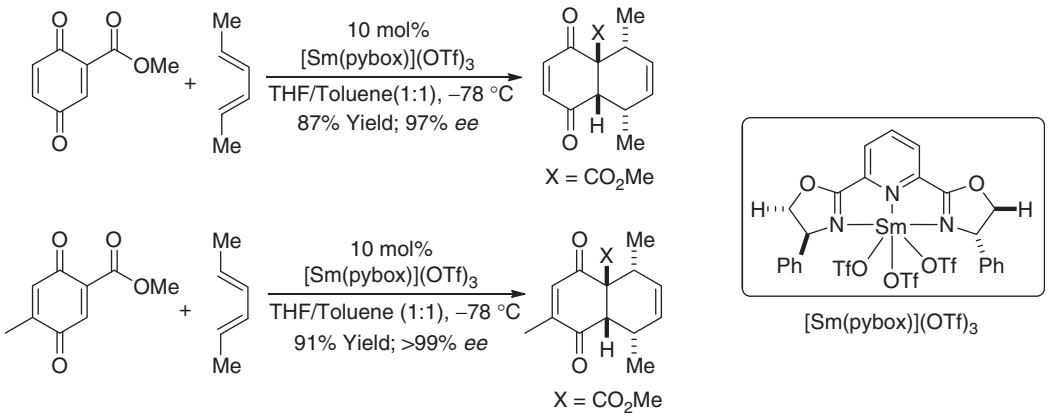
Scheme 137 Reproduced from Collin, J.; Jaber, N.; Lannou, M. I. *Tetrahedron Lett.* **2001**, *42*, 7405.



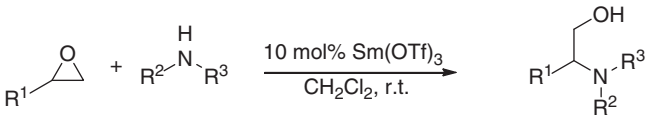
Scheme 138 Reproduced from Collin, J.; Jaber, N.; Lannou, M. I. *Tetrahedron Lett.* **2001**, *42*, 7405.

utility of this procedure was shown by applying this ring-opening step to the synthesis of various commercially available *β*-blockers, such as propranolol, atenolol and RO363 (Scheme 141), all of which were synthesized with enhanced yields, milder reaction conditions devoid of side-products.

An enantioselective version of this reaction was reported by Collin et al. In this approach, Sm iodo-(*S*)-binaphthoxide was employed for the enantioselective catalytic ring opening of epoxides by aromatic amines (Scheme 142).[248] Optimization of the

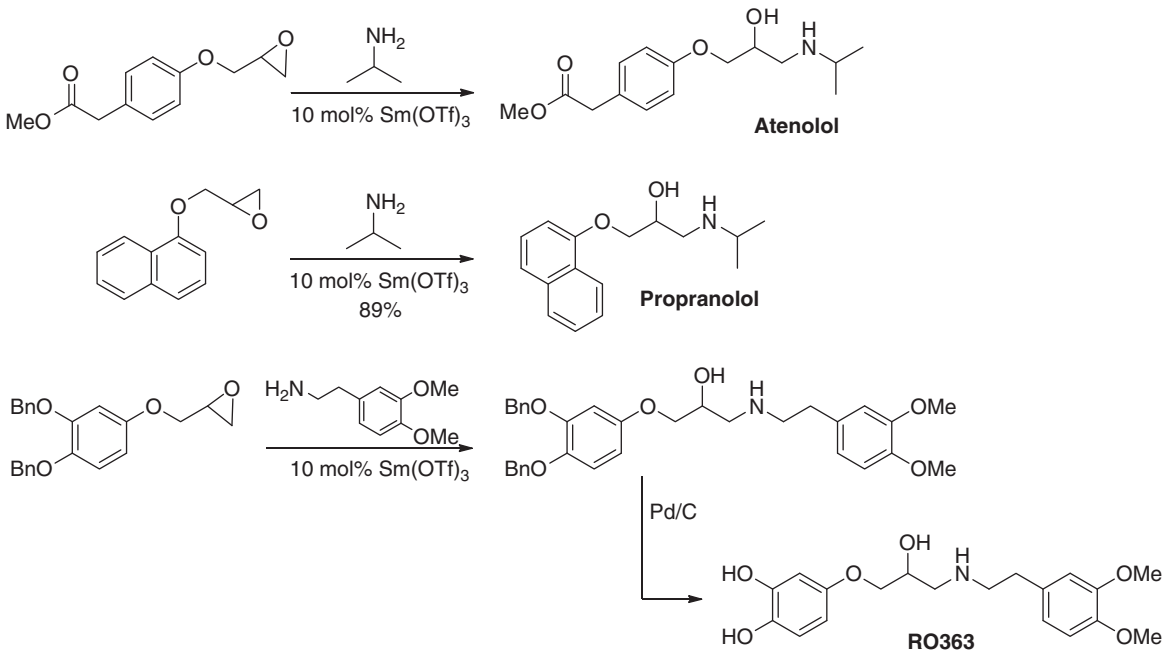


Scheme 139 Reproduced from Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10162, with permission from ACS.

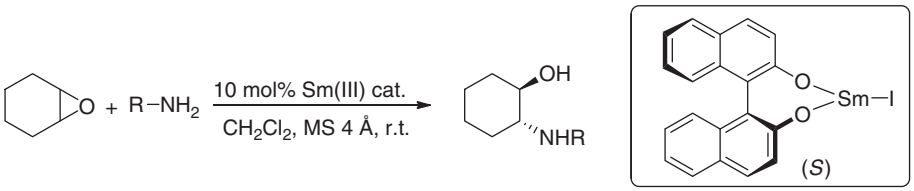


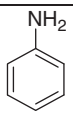
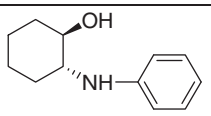
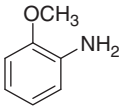
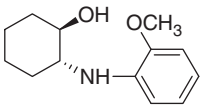
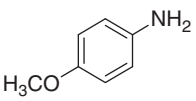
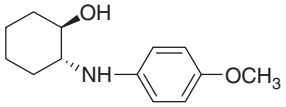
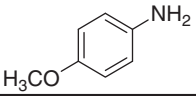
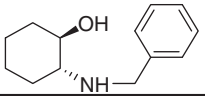
Entry	Epoxide R^1	Amine R^2	Amine R^3	Reaction Time (h)	Yield (%)
1	Ph	Ph	H	1	96
2	C_4H_9	Ph	H	3	90
3	Ph	Ph	CH_3	1.5	93
4	Ph	—$CH_2CH_2N(Ph)CH_2CH_2$—		2	92
5	Ph	*i*-Pr	H	1.5	90
6	–CH_2O-*o*-NO_2–Ph	Ph	H	2.5	90

Scheme 140 Reproduced from Yadav, J. S.; Reddy, A. R.; Rao, Y. G.; Narsaish, A. V.; Reddy, B. V. S. *J. Mol. Cat. A: Chem.* **2007**, *261*, 207, with permission from ACS.



Scheme 141 Reproduced from Yadav, J. S.; Reddy, A. R.; Rao, Y. G.; Narsaish, A. V.; Reddy, B. V. S. *J. Mol. Cat. A: Chem.* **2007**, *261*, 207, with permission from ACS.



Entry	Amine	Product	Temp (°C)	Yield (%)	ee (%)
1			r.t.	55	20
2			–40	79	91
3			r.t.	70	52
4			–40	85	91
5			r.t.	55	58
6			–40	82	85
7			r.t.	60	6

Scheme 142 Reproduced from Carrée, F.; Gil, R.; Collin, J. *Org. Lett.* **2005**, *7*, 1023, with permission from Thieme Publisher.

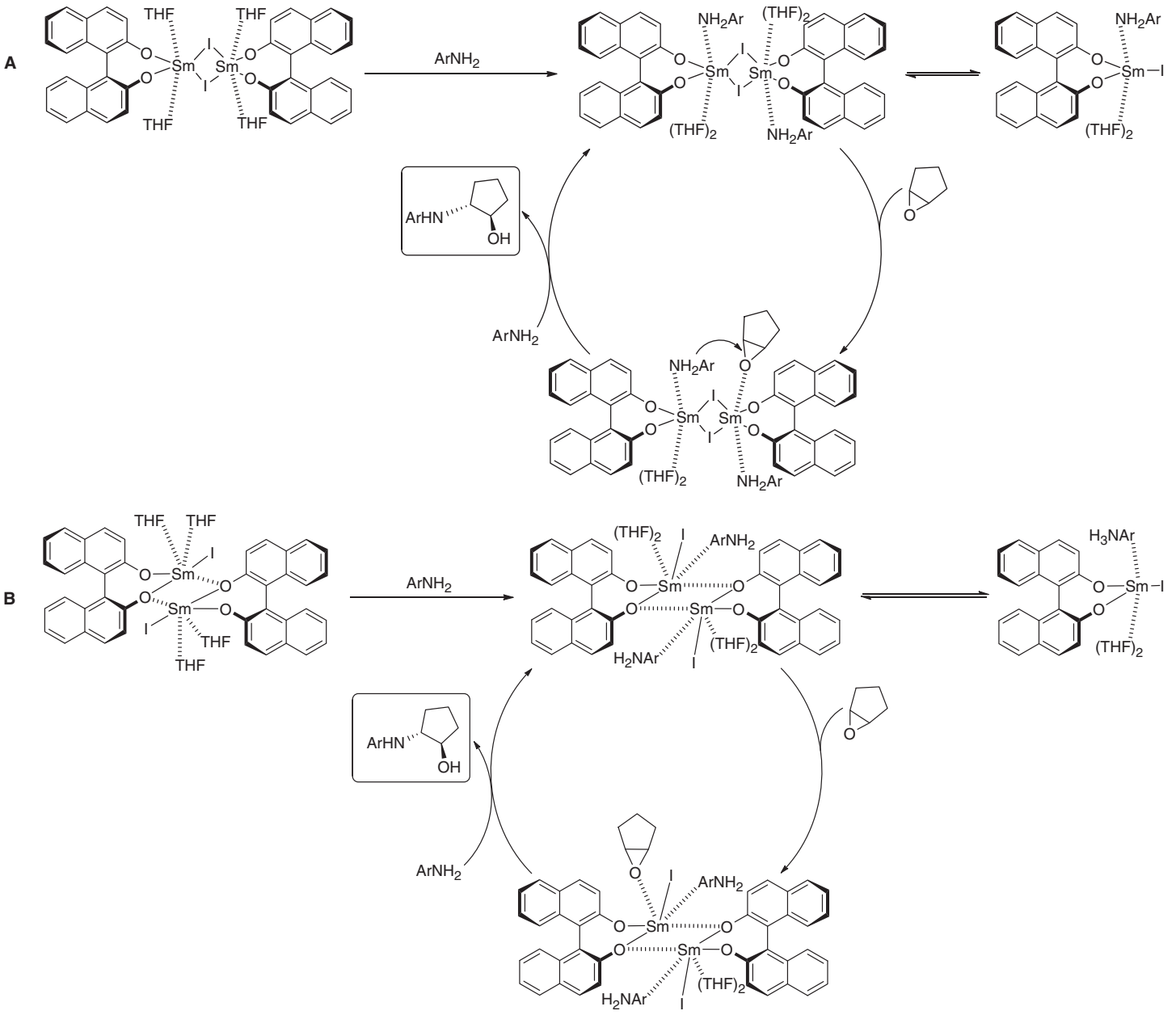
reaction conditions determined that a drop in the reaction temperature (− 40 °C) achieved the best *ee* and yields of the *β*-amino alcohols.

Follow-up mechanistic studies were initiated to probe the intermediates responsible for stereoselectivity. The reaction was postulated to proceed through a monomer-dimer equilibrium of the catalyst.[249] Two possible dimer-aggregate systems were proposed: In mechanism A the dimer forms through bridging of the iodines, whereas in mechanism B the dimer forms through the oxygens of the binaphthols (Scheme 143). Given the use of halogenated solvents and the high oxophilicity of Sm(III), it is likely that mechanism B is operating. Regardless of the discreet details of the mechanism, the reactions proceed in good yield and high enantioselectivities.

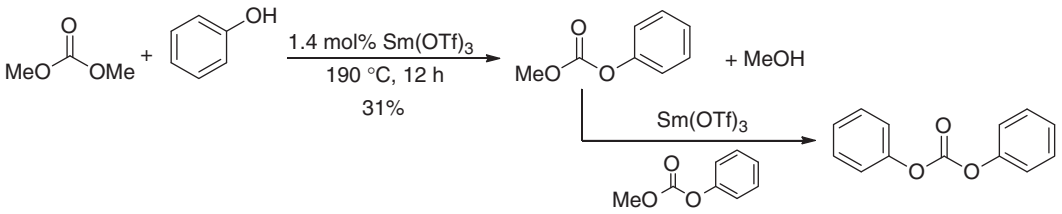
$Sm(OTf)_3$ has also been shown to be an excellent catalyst for the synthesis of diphenyl carbonate (Scheme 144),[250] an important intermediate in the production of many industrial products such as polycarbonate. The transesterification of dimethyl carbonate to form diphenyl carbonate is typically catalyzed by titanium, aluminium, or tin containing compounds or by Lewis acids such as aluminium chloride or zinc chloride. All of these reagents mentioned are highly sensitive to water and air and the catalysts are not easily recovered from the reaction mixture. $Sm(OTf)_3$ is a powerful Lewis acid able to tolerate aqueous systems with high recoverability and recyclability.[222] This Sm(III) reagent was shown to catalyze the transesterification of dimethyl carbonate with phenol to produce diphenyl carbonate in a 31% yield (Scheme 144). Although this yield is typical when compared to the traditional yields of organometallic catalysts y (11–33% yields), it has the added benefit that the catalyst can be recovered (95% recovery) and reused in subsequent reactions without diminished yields.

1.09.4.2.2 Organometallic reactions

As described above, SmI_2 and other Sm(II) (or Sm(0)) reductants form Sm(III) intermediates after electron transfer. In addition, reduction of an organohalide or an intermediate radical by SmI_2 leads to the formation of an intermediate species that is often referred to as an organosamarium compound. Although the intermediates produced during organic reactions have not been isolated and characterized, their reactivity is similar to organometallic reagents. These intermediates behave as nucleophiles with carbonyls, can be protonated, and can also undergo transmetallation with other metals.



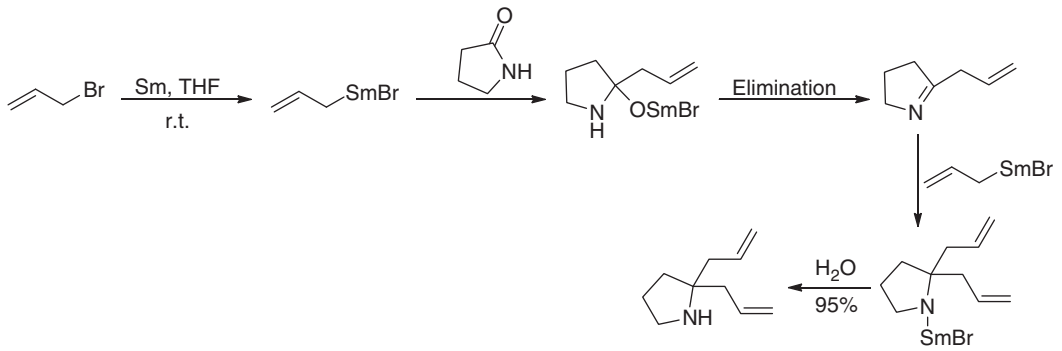
Scheme 143 Reproduced from Martin, M.; Bezzenine, S.; Collin, J. *Tetrahedron: Asymmetry* **2010**, *21*, 1722.



Scheme 144 Reproduced from Fuming, M.; Guangxing, L.; Jin, N.; Huibi, X. *J. Mol. Cat.* **2002**, *184*, 465.

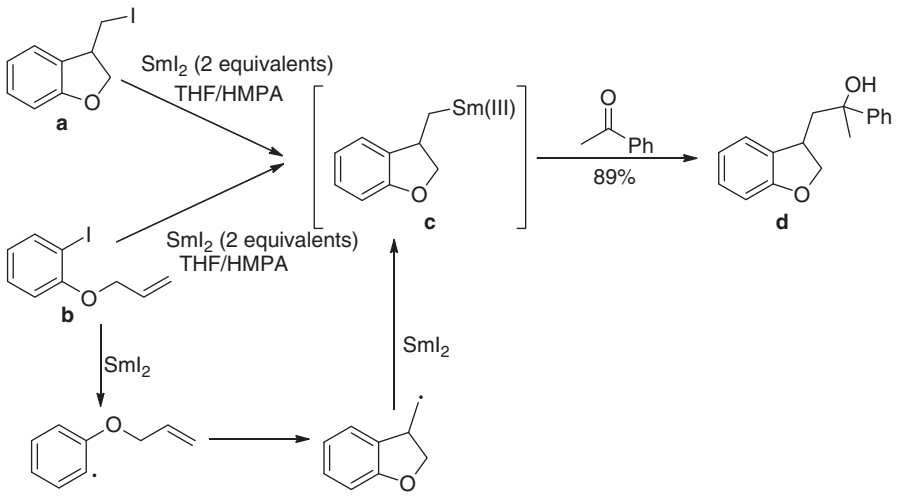
1.09.4.2.2.1 Transmetallation and organosamarium intermediates

Similar to the typical Grignard reaction where Mg inserts into the R–X bond to form the RMgX organometallic intermediate, Sm metal can be added to alkyl and aryl halides to form intermediates that behave as RSmX organometallics. In most cases described in the literature, reaction of Sm metal with allyl bromide produces intermediates that behave as organosamarium bromides. This approach can be used to efficiently form diallylated quaternary nitrogen heterocycles in good yields (Scheme 145).[251] The mechanism is proposed to proceed through an anionic organosamarium addition onto the carbonyl, simiar to that seen in the Sm-Barbier reaction (Section 1.09.3.2.1.1.2). The intermediate species proceeds through an elimination of HOSmBr to form an imine, which undergoes an alkylation by attack of a second organosamarium. On protonation the final quaternary diallyl pyrrolidine is formed in high yield.



Scheme 145 Reproduced from Li, A.; Zhang, Y. *Tetrahedron Lett.* **2001**, *42*, 8507.

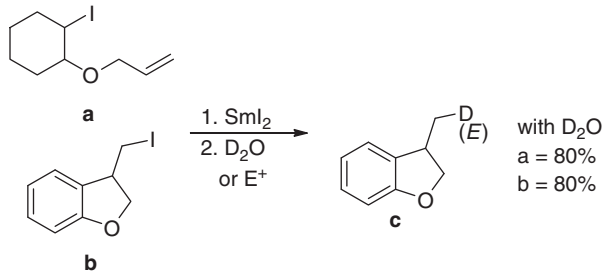
Intermediate organosamarium(III) compounds are likely the reactive intermediate in many coupling reactions labeled as 'Sm(II)-mediated'. Curran has examined the role of the organosamarium species by distinguishing between pathways of radical or organosamarium intermediates in the Sm(II)-mediated coupling reaction of aryl halides and ketones (Scheme 146).[107] In these reactions, it was noted that both starting halides (a or b) produced the same product in almost identical yields in the presence of SmI_2-HMPA in THF.[105] Through this and follow-up studies,[203,209] Curran and coworkers proposed that an organosamarium



Scheme 146 Reproduced from Curran, D. P.; Feving, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943, with permission from Thieme Publisher.

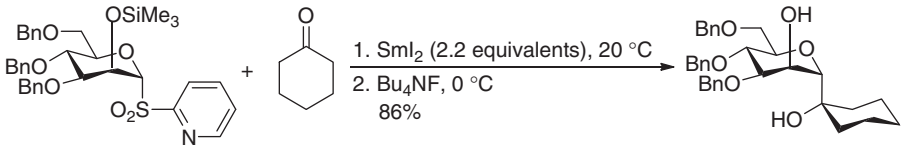
intermediate (**c**) and not a radical intermediate was responsible for bond formation. No radical–radical coupling products were recovered, further implying the formation of organosamarium species occurs more rapidly than homocoupling of the radical species.

The presence of an organosamarium species in reactions was also tested by withholding the ketone from the system and simply quenching the reduction of the alkyl halide species with D_2O. The expected cyclic product (**c**) was obtained with both the unsaturated and cyclic starting materials (Scheme 147). Following this experiment, electrophiles were added, and coupled products were obtained. These were the first examples that electrophiles could react after prereduction of the alkyl halide by SmI_2, providing evidence for the existence of the stable organometallic intermediate. The results described in these studies were further supported by rate and mechanistic studies of Flowers who showed that alkyl halides are reduced by SmI_2-HMPA several orders of magnitude faster than dialkyl ketones.[61]



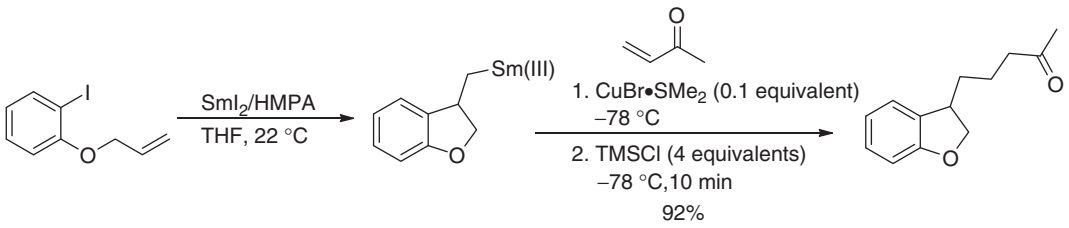
Scheme 147 Reproduced from Curran, D. P.; Feving, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943, with permission from Thieme Publisher.

The mechanistic underpinning of these reactions enabled the use of organosamarium intermediates in complex syntheses. An example of this approach is the synthesis of 1,2-*trans*-C-glycosides under Sm-Barbier conditions.[252] Glycosyl pyridyl sulfones were reduced by Sm(II), forming a glycosyl C1-organosamarium intermediate which then couples with a carbonyl compound to form the C-glycoside (Scheme 148). The intermediate organosamarium displays considerable stability against β-elimination, suppressing the formation of the undesirable glucal side product.



Scheme 148 Reproduced from Skrydstrup, T.; Jarreton, O.; Mazéas, D.; Urban, D.; Beau, J. M. *Chem. Eur. J.* **1998**, *4*, 655, with permission from Wiley.

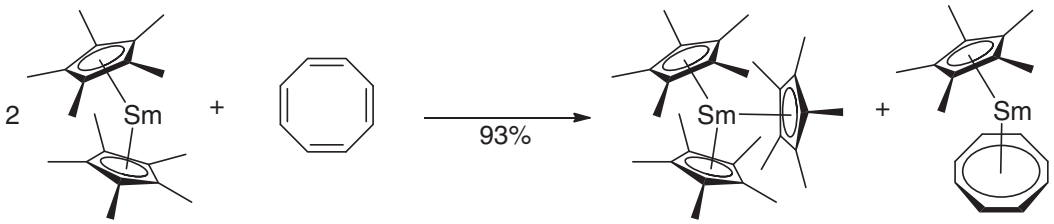
Sm(III) organosamarium transmetallation with catalytic Cu(I) has been employed in the synthesis of β-alkylated ketones from α,β-unsaturated carbonyl compounds.[253,254] The initial single-electron transfer from SmI_2 forms an intermediate Sm(III) alkylsamarium via 5-*exo*-*trig* radical cyclization. Transmetallation with copper(I) salt ($CuBr \cdot SMe_2$) produces an organocuprate that carries out conjugate addition in accordance with the general reactivity of organocuprates (Scheme 149). In the absence of Cu(I) salts, 1,2-additions of organosamarium reagents to carbonyl groups prevail.



Scheme 149 Reproduced from Totleben, M. J.; Curran, D. P.; Wipf, P. *J. Org. Chem.* **1992**, *57*, 1740, with permission from ACS.

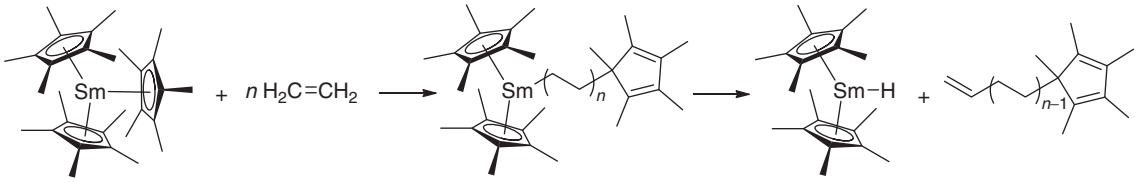
1.09.4.2.2.2 Samarocene-based reactions

Cyclopentadienyl (C_5H_5, Cp), and tris(pentamethylcyclopentadienyl) (C_5Me_5, Cp*) ligands act as excellent stabilizing ligands for Sm and other lanthanides.[255,256] Owing to the propensity of Sm to fill its coordination sphere, the large Cp and Cp* ligands provide steric stabilization, while only taking up one valence of the metal. Owing to the bulky nature of Cp*, it was long



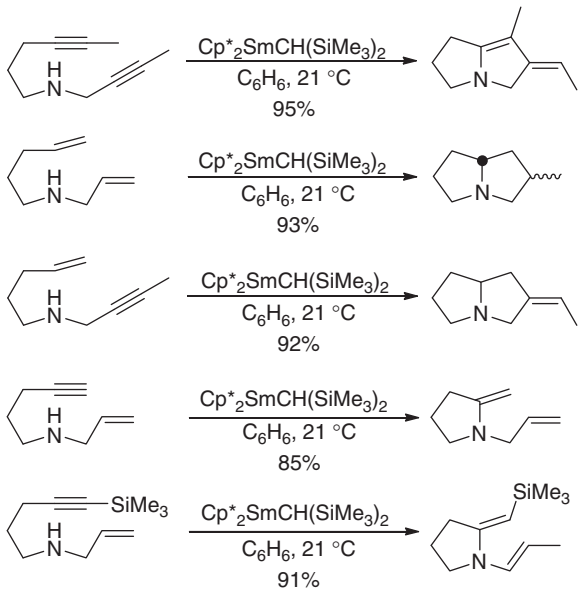
Scheme 150 Reproduced from Evans, W. J.; Gonzales, S. G.; Ziller, J. W. *J. Am. Chem. Soc.* **1991**, *113*, 7423, with permission from ACS.

speculated if synthesizing a stable $SmCp^*_3$ was possible. Seminal work by Evans and coworkers solved this problem. They showed that the combination $SmCp^*_2$ with C_8H_8 forms $(C_5Me_5)Sm(C_8H_8)$ and $Sm(C_5Me_5)_3$ in high yield (**Scheme 150**).[257] Given the imposing steric bulk of the Cp^* ligands, it was not known if substrates would be able to approach and react with the organometallic complex. The long Sm–Cp^* bond distances prevent both the ligands and the metal from having their normal electrostatic stabilization, allowing the Cp^* rings to be displaced from the electrophilic metal center. Small substrates, such as CO, ethylene, nitriles, azobenzene and even triphenyl phosphines, are able to access the Sm(III) metal center through an open channel down the three fold access in order to react.[258,259] Additionally, this sterically encumbered $SmCp^*_3$ is able to perform polymerizations, insertions, and ring openings with small molecules. Most notably, it has been shown to initiate the polymerization of ethylene[260] (**Scheme 151**) as well as ring-opening polymerization of lactones.[261]



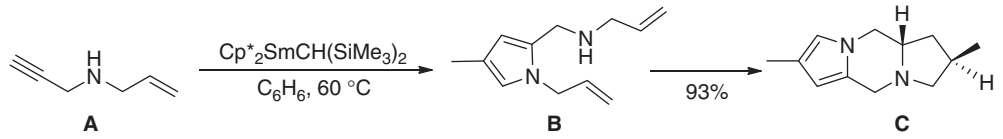
Scheme 151 Reproduced from Evans, W. J.; DeCoster, D. M.; Greaves, J. *Macromolecules* **1995**, *28*, 7929, with permission from ACS.

Samarocene-based complexes have been employed extensively as catalysts in hydroamination reactions. Seminal work of Marks and coworkers employed the samarocene complex, $Cp^*_2SmCH(SiMe_3)_2$ for intramolecular hydroamination-bicyclization of aminodialkenes and aminoalkenes (**Scheme 152**).[262] In most cases the assembly of bicyclic products predominated over monocyclization. In instances where terminal alkynes or silyl alkynes were present, protonolysis occurred leading to monocyclization.

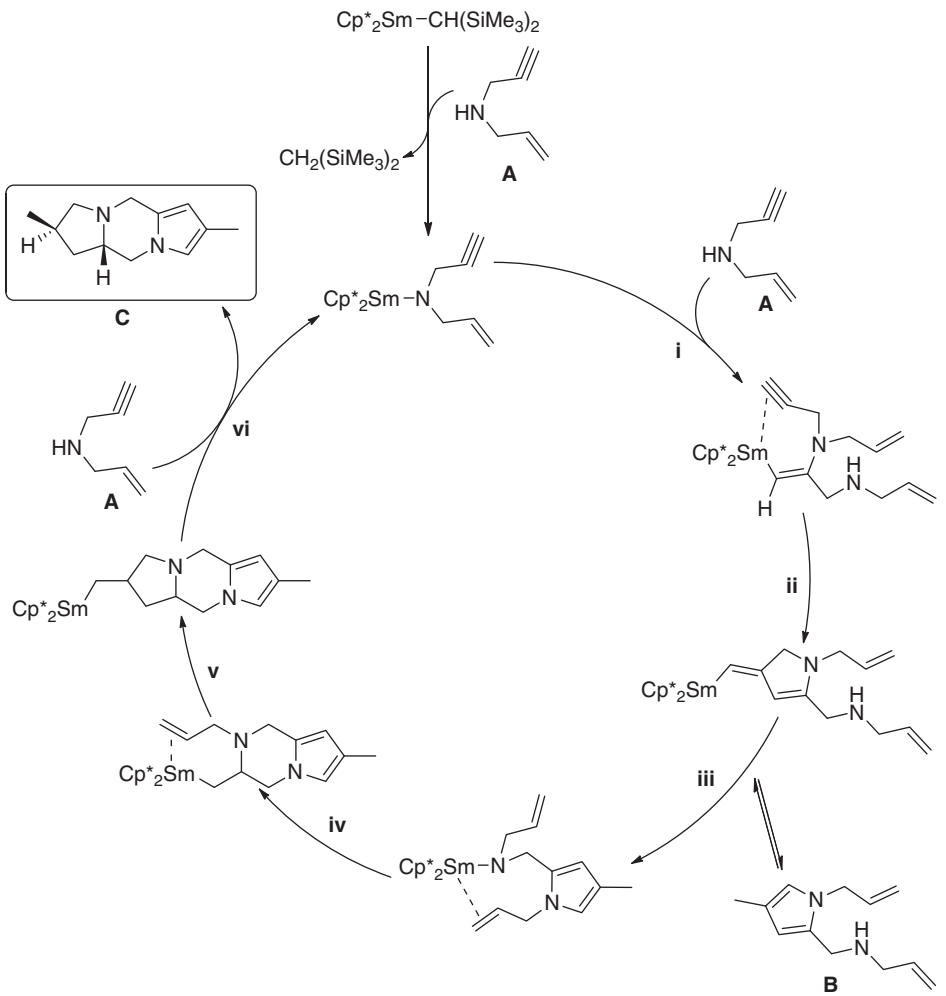


Scheme 152 Reproduced from Li, Y. W.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757, with permission from ACS.

An interesting inter-, intramolecular hydroamination-tricyclization variant of the reaction was developed by reacting *N*-allylpropargylamine with $Cp^*_2YbCH(SiMe_3)_2$ (**Scheme 153**). The catalytic cycle for this reaction is presented in (**Scheme 154**). Tandem C–N and C–C coupling of two substrates provides the stable intermediate **B**. With longer reaction times, **B** is activated to



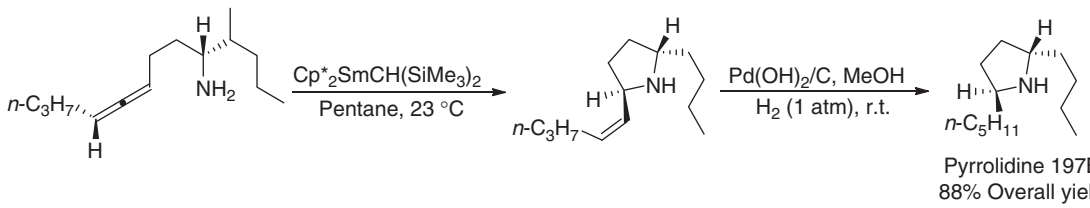
Scheme 153 Reproduced from Li, Y. W.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757, with permission from ACS.



Scheme 154 Reproduced from Li, Y. W.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757, with permission from ACS.

undergo intramolecular hydroamination-bicyclzation-tricyclization and finally protonolysis to generate the tricyclic polyheterocycle **C** in high yield.

The organosamarium catalyst and cyclohydroamination approach was used for the synthesis of naturally occurring alkaloids, such as pyrrolidine 197B [(2*S*, 5*S*,)-*trans*-2-butyl-5-pentylpyrrolidine].[263] The catalytic ring-closure produced the desired *trans*-pyrrolidine, with a pendant olefin with excellect *Z* selectivity (**Scheme 155**). After hydrogenation with Pd on carbon, the natural product pyrrolidine 197B was isolated with an overall 88% yield.



Scheme 155 Reproduced from Arrendo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633, with permission from ACS.

These examples show the utility of samarocene-based catalysts in organic synthesis. The advantage of this approach is that samarocenes can mediate tandem sequences of C–C and C–N bond-forming processes in intra- and intermolecular hydroaminations and cyclizations. Of particular importance is the ability to form a wide range of nitrogen containing heterocycles with varying degrees of appended groups and unsaturation for further functionalization in a single catalytic cycle.

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1.10 Lewis Acid Promoted Addition Reactions of Organometallic Compounds

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1.10.1 Introduction

The nucleophilic addition of an organometallic reagent to multiple bonds is one of the most important strategies to obtain new bonds. The additions to π C═X bonds (X=heteroatom) are an important family of carbon–carbon (C–C) bond-forming reactions. In particular, the usefulness of the addition of organometallic reagents is of marked importance not only for organometallic chemists but also in organic chemistry and in the synthesis of complex organic molecules. Although to date the precise mechanisms are still not known in many cases, there is intensive development of new synthetic methodologies. New organometallic reagents are being constantly introduced, and these should have some desirable properties such as excellent selectivity and reactivity, combined with low cost, environmental friendliness, and a high functional group tolerance.[1]

This chapter focuses on the addition of carbon nucleophiles such as organometallic compounds to electrophiles as an important method of formation of C–C bonds. Such reactions are extremely important in organic synthesis, and with respect to the character of the metal–carbon bond there is a wide spectrum of reactivity.[2] Unfortunately, very often the applicability of such reactions in synthesis depends on other factors such as availability of the organometallic reagent, and toxicity and of their byproduct. Furthermore, for C–C bond formation process where electrophiles with C═X bonds which carbonyl compounds and imines have used, side reactions such as enolization, self-condensation, and reduction can not only compete but also prevail over the expected addition process in certain situations. In this scenario, the combination of a nucleophilic organometallic reagent (RM) and an appropriate Lewis acid (LA) allows straightforward formation of C–C bonds by organometallic addition reactions in complex molecules possessing other sensitive functional groups. The development and application of LAs as catalysts and promoters of additions of organometallic reagents to C═X have dramatically increased in recent years in organic synthesis.

The LA plays the key role in determining the overall reaction path by controlling the generation of more reactive species. Recent insights into LA-promoted/catalyzed organometallic additions to C═X have indicated that the nature of the reactive species can depend on the manner in which LA is added to the reaction mixture (**Figure 1**). In the reaction path (1) the C═X bond electrophiles activation takes place, whereas in the reaction path (2) the modification of the organometallic nucleophiles via ate complexes takes place, which increases the selectivity and reactivity of RM.[3] For example, the organocerium ate-complex $[PhCeCl_3]MgX$ selectively reacts with aldehyde **1** in the presence of ketone **2** in contrast to when the same reaction is carried out with only PhMgX (equation 1).[4]

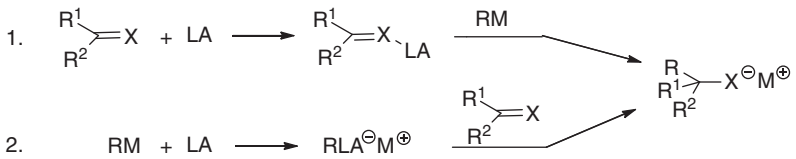
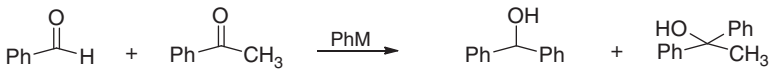


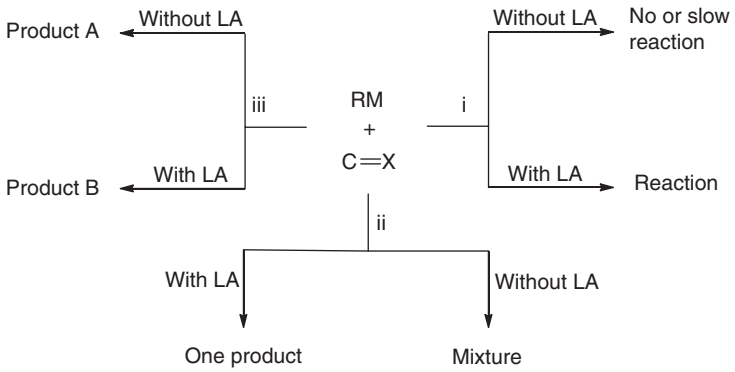
Figure 1 General reactivity of C═X systems towards organometallic reagents in the presence of Lewis acids.



	PhMgX	Yield = 64%	80	20
	$[PhCeCl_3]MgX$	Yield = 81%	99	1

(1)

It should be noted that in this type of addition the LA, which normally does not change its oxidation state, could also offer the advantage of changing the nature of the C═X bonds through its complexation and dramatically increasing the rate of addition of RM. Thus, in most organic reactions, LAs may play three different roles in the organometallic addition reactions to C═X bonds (Scheme 1), that is, the presence of LAs in inclusion to promoting the reactivity of RM (i) is able to increase the selectivity of the reaction (ii), change the reaction outcome (iii) from Product A (without LA) to Product B (with LA).



Scheme 1

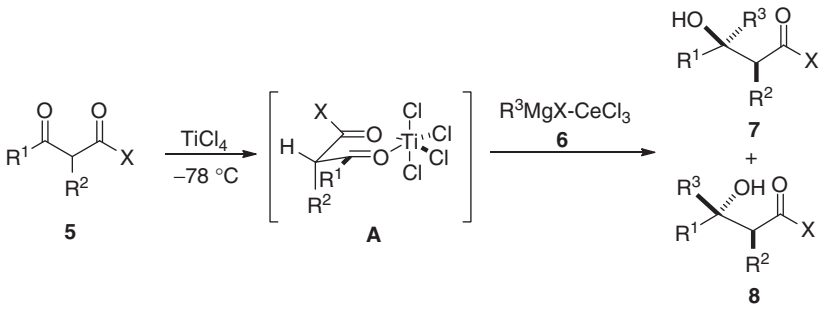
Before review of synthetic aspects of the addition of alkyl, vinyl, aryl, and alkynyl metal reagents to electrophiles with C═X bonds (the chemistry of stabilized carbanions and of other electrophiles is described in other volumes), it should be stressed that sometimes stoichiometric or excess amounts of the LA are necessary. This is due to catalyst inhibition by the product via formation of a stable LA–heteroderivate complex. Therefore, more generally, one may refer to the LA used in these protocols as a promoter.[5] However, it is well talked about that LA-catalyzed additions of organometallic compounds, with the LA used in very small quantities, are not consumed by the reaction, and may be used over and over again. This means that there is just as much catalyst at the end of the reaction as it was at the beginning. This chapter deals with both of these categories.

1.10.2 LAs Addition to Aldehydes and Ketones

The nucleophilic addition of organometallic reagents to a carbon–oxygen double bond has found wide use in the synthesis of secondary or tertiary alcohols, even in the face of competitive pathways.[6] These drawbacks have been overcome by adding a LA, and various aldehydes and ketones are converted to corresponding alcohols in high yields.[7] The activation of the carbonyl substrate by a LA occurs when the metal M of the organometallic reagent RM does not compete with the LA in the coordination of the carbonyl. This σ-coordination (or via formation of adduct) may be able to exert the differentiation of the two faces of the π C═O bond by the carbonyl partner as well as by the organometallic. Even if no facial differentiation is available, the LA will be *syn* or *anti* to particular substituents on a prochiral carbonyl compound, and the addition of a chiral organometallic occurs with a certain degree of enantioselection.

The attack of RM reagents to β-keto ester units is frequently found among the syntheses of complex molecules, for example in the recent preparation of Periplanone C, a sex pheromone of the American cockroach, *Periplaneta americana*, which has proven to be of considerable interest to synthetic chemists.[8] In general, β-functionalized tertiary alcohols represent valuable building blocks and very interesting procedures for the synthesis of these targets with high diastereomeric purity.[9] A wide variety of carbon frameworks have been introduced by $TiCl_4$-promoted addition of organocerium reagents to α-substituted-β-functionalized ketones **5** (Scheme 2).[10] The results shown in Table 1 suggest a high degree of compatibility between $TiCl_4$ and organocerium reagents. These two species are able to exert their assigned roles without undesired interactions, that is, reduction and enolization of the substrate with the use of less basic organocerium reagents. Every attempt at attacking the carbonyl group with the parent Grignard or lithium compounds led to unsatisfactory results. These nucleophilic reagents are basic enough to promptly deprotonate the active methylene hydrogen atom in **5**. The resulting enolate anion has an extremely stable cyclic structure with pseudoaromatic character, and hence it is completely inert toward nucleophilic attack. The high nucleophilicity of the organocerium species is crucial for the success of the reaction since it allows the addition to be carried out at low temperature.[11] In these conditions the formation of a stable rigid cyclic intermediate **A** by interaction between $TiCl_4$ and the β-functionalized ketone is workable. The stereochemical issue of this reaction provides strong circumstantial evidence of the mode of carbonyl activation by LA. Such substrates exhibit the potential for chelate control according to Cram's studies on the LA-promoted stereoselective addition of RM reagents to chiral acyclic substrates bearing vicinal alkyl and heteroatom substituents.[12]

The possibility of chelation of the carbonyl function C═O with a LA occurs similarly in α-keto esters. The diastereoselective addition of organometallic reagents to α-keto esters by means of a chiral auxiliary is a methodology to obtain chiral α-hydroxy

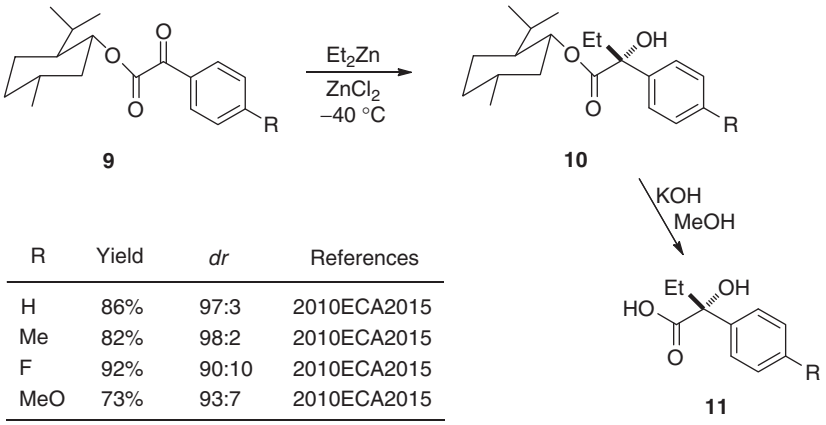


Scheme 2

Table 1 Addition of organocerium reagents to ketones 5 in the presence of $TiCl_4$ (Scheme 2)

No.	R^1	R^2	R^3	*X*	***7:8***	*Yield (%)*	*References*
1.	Ph	Me	Me	OEt	98:2	88	2006A49
2.	Ph	Me	$PhCH_2$	OBu^t	98:2	95	2006A49
3.	Ph	Me	$PhCH_2$	OPh	98:2	70	2006A49
4.	Et	Me	$PhCH_2$	NMe_2	>99:1	97	2004S3092
5.	Ph	Me	*n*-Bu	NMe_2	>99:1	85	2004S3092
6.	Et	Me	Ph	NMe_2	>99:1	85	2004S3092

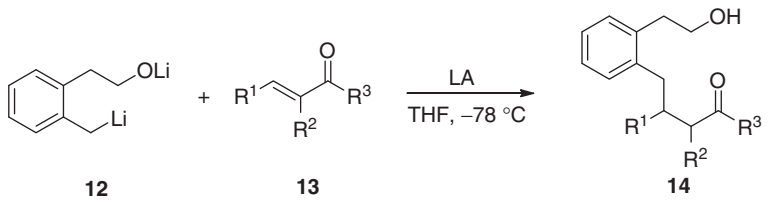
carboxylic acids, useful starting compounds for the synthesis of pharmaceuticals and natural products.[13] Given that α-keto esters react spontaneously and often uncontrollably with RM reagents, and that the reduction pathway may compete with the alkylation when RM contains a β-H atom,[14] premixing a stoichiometric amount of LA with the α-keto ester before adding the RM reagent is the preferred protocol. Through this strategy, Li et al. prepared the (–)-menthyl arylglyoxylates **9**, which for addition of Et_2Zn in the presence of $ZnCl_2$ obtain a highly stereoselective synthesis of the corresponding chiral tertiary alcohols **10**. The esters are then saponified to afford the chiral tertiary α-hydroxy carboxylic acids **11** (Scheme 3).[15]



R	Yield	*dr*	References
H	86%	97:3	2010ECA2015
Me	82%	98:2	2010ECA2015
F	92%	90:10	2010ECA2015
MeO	73%	93:7	2010ECA2015

Scheme 3

The preparation and synthetic applications of functionalized organolithium reagents (RM with M = Li) have been used extensively for their ability to generate polyfunctionalized molecules in only one reaction step.[16] It is known that organolithium compounds add to the carbonyl group of α,β-unsaturated carbonyl compounds, rather than giving 1,4-addition. From their study on the chemistry of organolithium reagents, Yus and coworkers found that the presence of a LA promotes last reaction type (1,4-addition) of some functionalized organolithium reagents to α,β-unsaturated carbonyl compounds (equation 2).[17] The functionalized organolithium compound **12** is easily prepared by arene-catalyzed lithiation of isochroman, and the reaction with α,β-unsaturated esters (Table 2, entries 2 and 3) affords lower yields than with α,β-unsaturated ketones (Table 2, entries 1 and 4). Further, the yields are moderate for the formation in some extension of the reduced product (from a metal–hydrogen exchange), and in the case of $FeCl_3$ as Lewis acid, the yields are more lowered for the occurrence of reactions of dimerization. It should be noted that when LA is a redox active species, it could catalyze the generation of highly reactive radicals, and often a complex blend of the reaction mixture is observed.

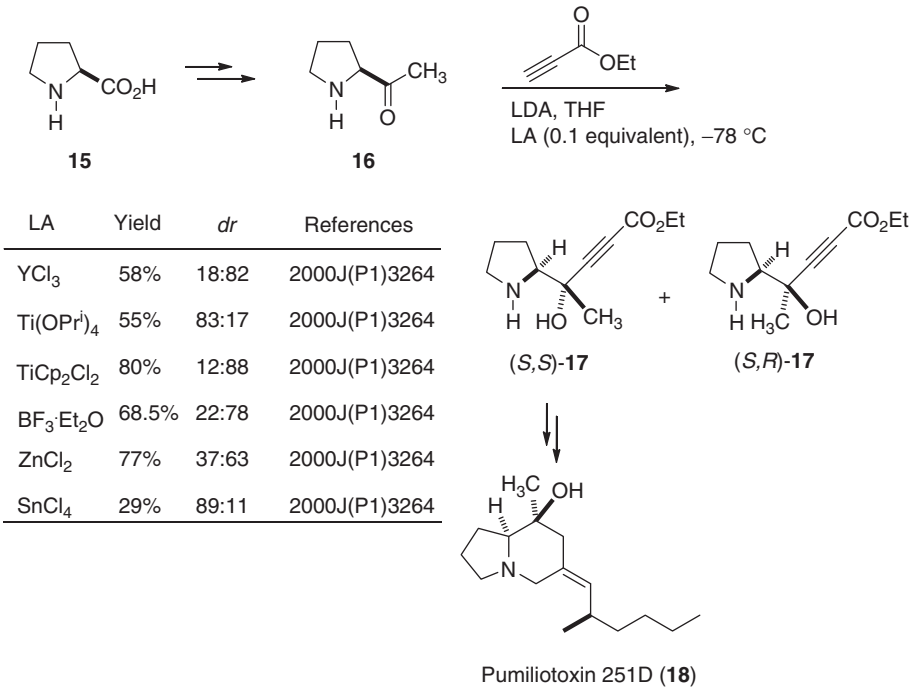


(2)

Table 2 LA-promoted conjugated addition of organolithium to carbonyl compounds (equation 2)

No.	R^1	R^2	R^3	*LA*	*Yield (%)*	*References*
1.	Ph	H	Me	$ZnBr_2$	56	2001T5799
				$FeCl_3$	42	
				BF_3	44	
2.	H	H	OEt	$ZnBr_2$	46	2001T5799
				$FeCl_3$	29	
				BF_3	35	
3.	Me	H	OMe	$ZnBr_2$	36	2001T5799
				$FeCl_3$	29	
				BF_3	30	
4.	–(CH_2)–		H	$ZnBr_2$	72	2001T5799
				$FeCl_3$	52	
				BF_3	40	

The stereo-controlled nucleophilic addition of lithium acetylenes to the carbonyl group represents another important synthetic methodology involving the use of organolithium reagents. The diastereoselective addition of ethyl lithiopropiolate to chiral α-amino ketone **16** in the presence of a catalytic amount of LA represents a way to obtain chiral tertiary propargylic alcohols, valuable chiral synthons for the preparation of complex compounds (**Scheme 4**).[18] Haing analyzed several LAs, best diastereoselectivity for **17** was observed with $TiCp_2Cl_2$ (10 mol%).



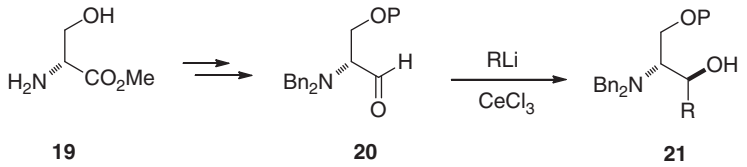
LA	Yield	*dr*	References
YCl_3	58%	18:82	2000J(P1)3264
$Ti(OPr^i)_4$	55%	83:17	2000J(P1)3264
$TiCp_2Cl_2$	80%	12:88	2000J(P1)3264
$BF_3{\cdot}Et_2O$	68.5%	22:78	2000J(P1)3264
$ZnCl_2$	77%	37:63	2000J(P1)3264
$SnCl_4$	29%	89:11	2000J(P1)3264

Scheme 4

It should be noted that the diastereoselectivity of this addition in the presence of $Ti(OPr^i)_nCl_{4-n}$ is opposite to that of $TiCp_2Cl_2$, and that two equivalents of LA reduce yield and diastereoselectivity dramatically. Chelation of a catalytic amount of LA with the

carbonyl group is proposed to promote the nucleophilic addition of alkynyl lithium reagent to the ketone **16** and improves the diastereoselectivity. The propargylic alcohol **17** with the terminal carboxylate group is a useful intermediate for a short enantioselective approach (nine steps from L-Proline) to Pumiliotoxin 251D (**18**), a significant alkaloid released onto the skin surface of Ecuadorean poisonous frog *Dendrobates tricolor*, which plays a chemical defense role.

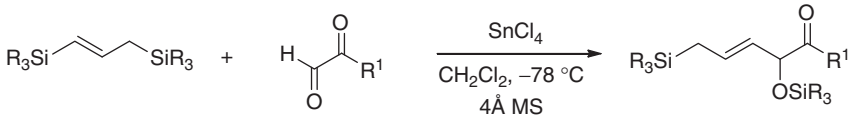
The ability of LAs to promote high-yielding addition of nonstabilized carbanionic reagents to base-sensitive carbonyl compounds has been exploited in the addition of RMs to N-protected amino aldehydes and ketones of biological relevance. In this study it was found that γ-hydroxy-β-amino alcohols, structural units in bioactive natural products, are also an important class of versatile chiral ligands. Thanks to the ability of $CeCl_3$ as LA, Zhu et al. were able to carry out the addition of an RM reagent to the carbonyl group of *N*,*N*-dibenzylserine aldehyde **20** to give protected amino alcohol **21** in good chemical yield and with excellent anti-diastereoselectivity (**Scheme 5**).[19] The usefulness of this procedure has been evaluated in the synthesis of an important β-hydroxy-α-amino acid such as (*2S,3S*)-β-hydroxyleucine.



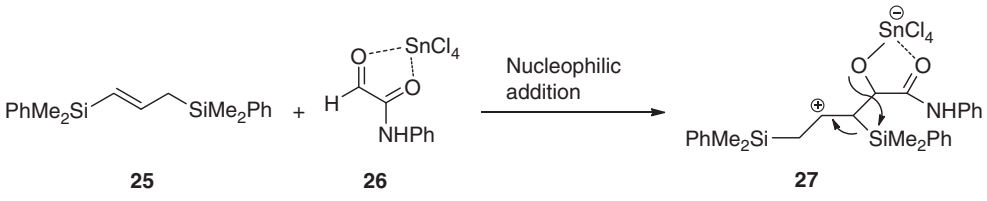
19 **20** **21**

Scheme 5

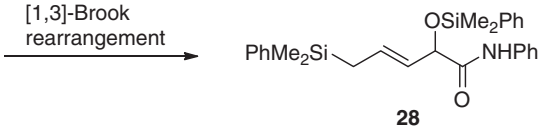
Although many kinds of LA-promoted allylic organometallics have been added to carbonyl compounds, much less developed is the addition of vinyl organometallics, presumably due to their low inherent nucleophilicity. However, recently, $SnCl_4$ has been found to be an effective LA catalyst of vinylation of glyoxylates. The addition of 4 Å molecular sieves to the reaction mixture together with a low temperature effectively suppresses protodesilylation of silane, and the addition reaction is quite effective (equation 3).[20] The nature of different silicon substituents did not show significant effects on the product distribution, and the corresponding allylsilanes are obtained in good yields. One possible mechanism involves an initial bidentate LA activation of **25** and subsequent nucleophilic addition of RM. The β-silicon-stabilized carbocation **27** adduct undergoes the [1,3]-Brook rearrangement to give allylsilane **28** (**Scheme 6**; **Table 3**).



22 **23** **24** (3)



25 **26** **27**



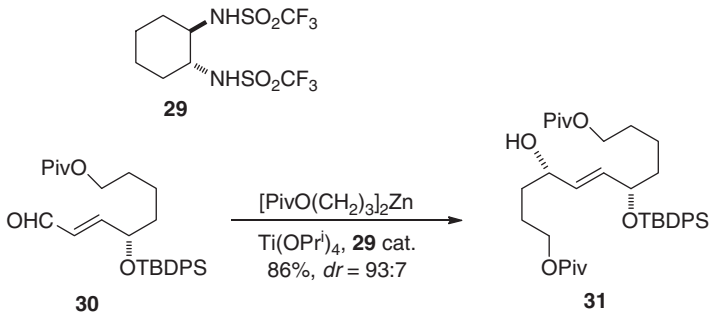
28

Scheme 6

Table 3 $SnCl_4$-catalyzed additions of vinylsilane to glyoxylates (equation 3)

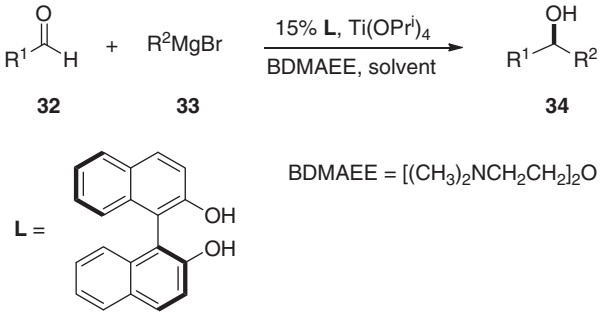
No.	*R_3Si*	*R^1*	*Equivalent $SnCl_4$*	*Yield (%)*	*References*
1.	$PhMe_2Si$	PhNH	0.15	89	2008TL6882
2.	$PhMe_2Si$	OEt	0.30	84	2008TL6882
3.	Me_3Si	OEt	0.30	71	2008TL6882
4.	Bu^tPh_2Si	OEt	0.30	85	2008TL6882

The high covalent degree of the carbon–zinc bond leads to moderate reactivity of these organometallics toward many electrophiles. In general, the reaction of organozincs with C=O electrophiles is not efficient in the absence of a LA promoter. The latter, in fact, can give rise to a transmetalation, and the new RM reagents are usually more reactive toward carbonyl compounds. Excellent results in diastereoselectivity are obtained in the presence of titanium(IV) salts as LAs, and these diastereoselective additions prove interesting if the reaction is performed by adding a ligand such as 1,2-*bis*-sufonamide **29** (Scheme 7).[21] The procedure has been exploited in the stereodefined preparation of allylic alcohols that are useful building blocks for the synthesis of prostaglandins. Replacement of $Ti(OPr^i)_4$ with sterically hindered titanium alkoxide such as $Ti(OBu^t)_4$ leads to higher diastereoselectivity.



Scheme 7

Although this procedure is very attractive for the construction of optically pure secondary alcohols, the addition of diorganozinc reagents (R_2Zn) to aldehydes has the disadvantage that only one group R can be transferred, and this makes the process less atom-economic. Thus, the direct LA catalytic asymmetric addition of Grignard reagents to aldehydes under mild reaction conditions is interesting, challenging, and highly desirable. The introduction of *bis*[2-(*N*,*N*-dimethylamino)ethyl] ether (BDMAEE) as strong basic and chelating additive, successively with $Ti(OPr^i)_4$ into the Grignard reagents, leads via transmetalation to the *in situ* generated salt $Mg(OPr^i)Br$. This efficiently deactivates RMgBr, and using a catalytic amount of the chiral ligand (S)-BINOL (**L**), a highly enantioselective addition of Grignard reagents to aldehydes is possible (Scheme 8).[22] It has been observed that long-chain alkyl Grignard reagents give higher *er* than short-chain alkyl, aryl, and vinyl Grignard reagents (Table 4).



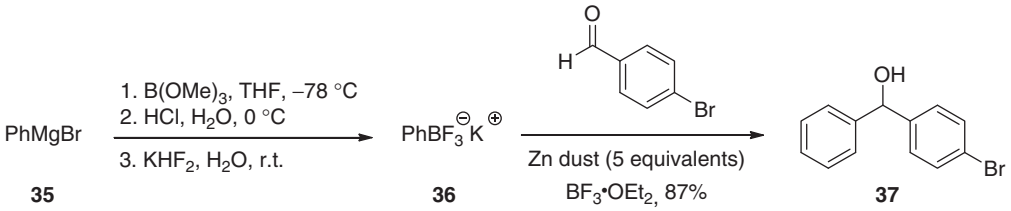
Scheme 8

Table 4 LA-catalyzed asymmetric addition of RMgBr to aldehydes (Scheme 8)

No.	R^1	R^2	*er*	*Yield (%)*	*References*
1.	2-MeO-C_6H_4	Bu^i	99:1	78	2009OL5578
2.	3-Cl-C_6H_4	Bu^i	>99:1	94	2009OL5578
3.	1-Naphth	*n*-Pentyl	95:5	51	2009OL5578
4.	1-Naphth	Bu^i	94:6	98	2009OL5578
5.	1-Naphth	Vinyl	69:31	98	2009OL5578

Organoboron compounds occupy a privileged position among organometallic compounds as nucleophilic reagents owing to their ease of synthesis, stability, and increasing commercial availability and synthetic versatility. Batey and coworkers have

reported[23] that potassium phenyltrifluoroborate salt **36**, easily achieved via the boronic acid and treatment with aqueous KHF_2, adds to aromatic aldehydes to give alcohol **37**. Zinc metal promotes the addition presumably by formation of organozinc species, and it is possible to accomplish the addition if a LA such as $BF_3 \cdot OEt_2$ is added (Scheme 9).



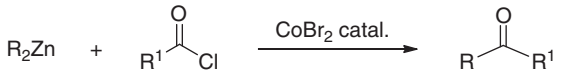
35 **36** **37**

Scheme 9

Although LA-catalyzed addition of crotylboranes to aldehydes is currently widely employed,[24] this Brown method suffers with little diastereoselection as a result of the inability to form crotylboranes in geometrically pure form. This problem has been overcome by the use of crystalline crotylsilanes, which provide enantioselectivities among the highest ever recorded for aldehydes crotylation reactions.[25]

1.10.3 LAs in Additions to Acid Derivatives

The addition of functionalized RM reagents to carboxylic acid derivatives provides the most potent procedure for the preparation of ketones starting from inexpensive substrates. Given that tetrahedral intermediate resulting from this addition rapidly decomposes to the carbonyl derivative, the reaction does not lead to ketones in high yields, because the intermediate ketones are still highly reactive toward the organometallic reagent. The importance of ketones as key intermediates for the synthesis of biologically active natural substances has suggested to Knochel and coworkers the application of $CuCN \cdot 2LiCl$ as an additive for the direct acylation of organozinc reagents.[26] Since this copper-promoted reaction needs a stoichiometric amount of copper salt, the authors found that the addition of various functionalized diorganozinc compounds to the acid chlorides in the presence of catalytic amounts (10 mol%) of $CoBr_2$ as LA affords polyfunctional ketones in good yields (equation 4).[27] The same addition is possible in the presence of $FeCl_3$ (10 mol%), but compared to the Co(II) catalysis, slightly lower yields and longer reaction times are required. This latter reaction has been successfully used in the preparation of 1,*n*-dicarbonyl compounds employing di-Grignard reagents.

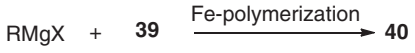


38 **39** **40** (4)

Even more recently, the catalytic activity of a supported analog of $Fe(acac)_3$, made by polymerization of the 2-(acetatoacetoxy)ethyl methacrylate, has (Table 5) been improved for the RM addition to an acyl chloride (Scheme 10).[28] The results are comparable with those obtained in the homogeneous phase; elemental analysis on the catalyst recovered by

Table 5 $CoBr_2$-catalyzed reactions of organozinc compounds with acyl chlorides (equation 4)

No.	*R*	*R^1*	*Yield (%)*	*References*
1.	$[PivO(CH_2)_5]_2Zn$	Ph	84	1996AGE108
2.	$AcO(CH_2)_5$	Ph	82	1996AGE108
3.	$AcO(CH_2)_5$	CF_3	82	1996AGE108
4.	$[PivO(CH_2)_5]_2Zn$	Hept	74	1996AGE108



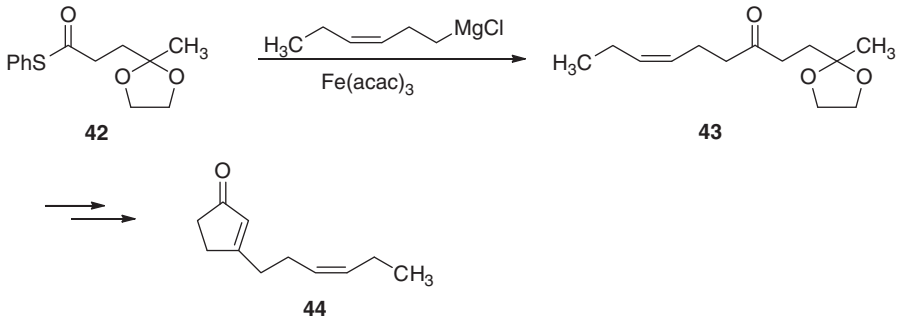
41

R	R^1	Yield	References
Et	Pent	91%	2000JMCC239
Ph	Pent	71%	2000JMCC239
Me	Ph	86%	2000JMCC239
Ph	Ph	79%	2000JMCC239

Scheme 10

centrifugation revealed a residual metal content of 91% with respect to the initially present metal loading, and good activity after each recycling has been observed.

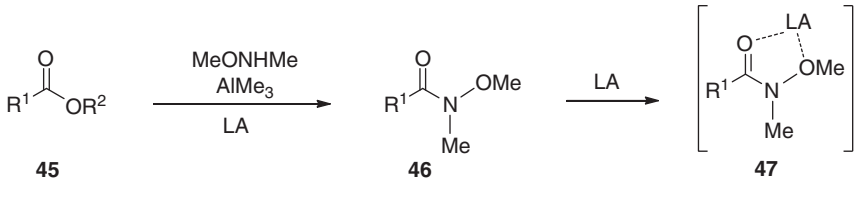
In an analogous manner, thioesters, activated by complexation with a LA, react with Grignard reagents leading to the formation of corresponding ketone in good yield. When the thioester **42** reacts with methyl Grignard reagent in the presence of catalytic amounts of $Fe(acac)_3$ yields a 1,4-diketone ethylene acetal **43**, which is a useful intermediate for the synthesis of (*Z*)-jasmone **44** (Scheme 11).[29]



42 **43** **44**

Scheme 11

The precautions mentioned above if ignored would lead to yields lower even with substiochiometric amounts of RM reagents, and the product ketones are always contaminated with difficult-to-separate tertiary alcohols.[30] An efficient new possible synthetic approach for functionalized ketones exploits a LA-promoted addition of RM reagents to amides, and the desired functionalized ketone is accompanied by only traces of tertiary alcohols. This elegant solution to the problem of overaddition to acid derivatives has been provided by Weinreb with the advent of *N*-methoxy-*N*-methylamides **46** (Scheme 12).[31] The successful single addition of nonstabilized organometallic reagents is due to the stable tetrahedral intermediate **48** formed on addition of the first equivalent of RM species to the Weinreb amide and LA complex **47**. It is this stability that precludes the collapse to a ketone under the reaction conditions and prevents the possibility of overaddition. The aqueous workup ensures in advance the quenching of all the excess organometallic species, and then the breakdown of tetrahedral intermediate **48** to furnish the ketone target **49**. The Weinreb amides **46** can be prepared by double activated amidation of esters **45**. Trialkyl aluminum is mixed with *N*,*O*-dimethylhydroxylamine (MeONHMe) to generate dialkylaluminum amide *in situ*, which increases the nucleophilicity of the nitrogen atom. The carboxylic ester is then premixed with a mild LA ($EuCl_3$) to make a carboxylic group liable to be attacked without a coordinative interaction with the aluminum activate amide.[32]

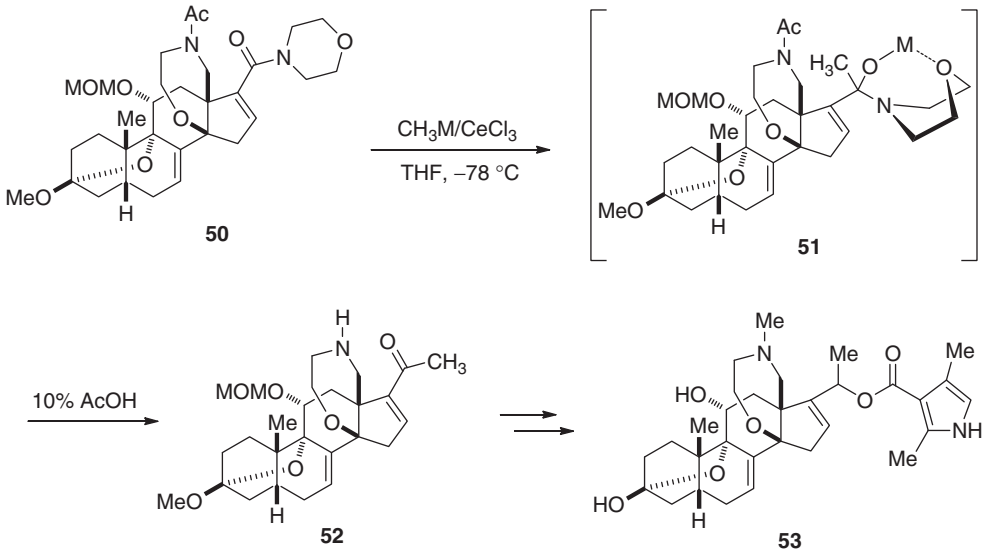


45 **46** **47** **48** **49**

Scheme 12

Despite their popularity, the Weinreb amides have several limitations, including high costs of starting materials, decreased reactivity of the carbonyl unit, and side reactions of the amine unit, excluding their use in organic synthesis on a large scale. The N-acylpyrroles and morpholine amides are useful alternatives for the synthesis of ketones by LA-promoted addition of RM reagents. In the (±)-Batrachotoxin (**53**) synthesis, a steroidal alkaloid with extremely potent neutoxin proprieties, the desired methyl ketone **52** is obtained by methyl Grignard or methyllithium addition at low temperature to morpholine amide derivative **50** (Scheme 13).[33] Under the reaction conditions the $CH_3M/CeCl_3$ complex reagent acts as a LA, coordinating with the morpholine oxygen atom, decreasing the basicity of the morpholine nitrogen, and thereby increasing the electrophilicity of the carbonyl group. Even in the presence of an excess of $CH_3M/CeCl_3$ complex no tertiary alcohol has been detected. The stable

metal-chelated tetrahedral intermediate **51**[34] precludes further addition of the organometal reagent. With the methyl ketone **52** in hand, it is possible to arrive at natural product target **53** by known chemical transformations.



Scheme 13

1.10.4 LAs in Additions to Imines and Related Derivatives

The nucleophilic addition of organometallic compounds to imines represents a powerful gateway to functionalized amino derivatives.[35] Because of the reduced electronegativity of the nitrogen atom compared to the oxygen atom, simple *N*-alkyl(aryl) imines are generally less reactive than their carbonyl analogs. The high nucleophilicity associated with the vast majority of organometallic reagents usually makes this aspect of marginal importance. However, when imines prepared from aliphatic aldehydes or ketones are used in the reaction with organometallic reagents, a competitive enolization, caused by the basic nature of the reagent, may hamper the efficiency of the addition process. This problem can be solved by employing reagents endowed with a limited basicity embedding less electropositive metals such as organoceriums.[4]

In a complementary way, the electrophilicity of the azomethine carbon can be suitably tuned by an appropriate choice of the group linked to the nitrogen atom. For this purpose, a number of versatile imino derivatives featured by the presence of tosyl-sulfonyl, alkylsulfinyl, phosphinoyl, acyl, and carbamoyl groups on the nitrogen atom have been devised.[36,37] The cited array of imino derivatives enjoys a reactivity increase through an effect of electron-withdrawing groups permanently linked to the nitrogen atom. However, this effect could also be obtained by a temporary interaction of the nitrogen lone pair with a LA, which is able to reduce its electronic density with consequent increase in the electrophilicity of the unsaturated carbon (Figure 2). In addition, the coordinating effect of the LA may also introduce a significant modification of the minimum energy conformation of the substrate, thus providing a stereochemical bias in the subsequent nucleophilic addition. In order to exert appropriate stereocontrol in these addition reactions, stereochemically pure imino derivatives should be used. Fortunately, nitrogen derivatives of aldehydes are largely obtained in their most stable *E* configuration. The same concept applies to ketimino derivatives bearing groups of pronouncedly different size at the azomethine carbon. An aspect of fundamental importance when LA are planned to be used for such purposes is their compatibility with the organomentallic reagent since their mutual stable interaction is obviously to be avoided.

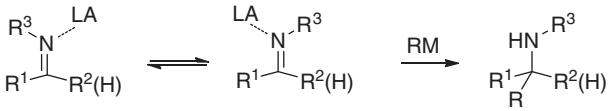
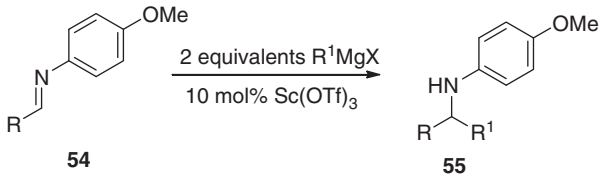


Figure 2 Proposed models for the interaction of Lewis acids with imino derivatives.

1.10.4.1 *N*-Arylimines and *N*-Alkylimines

Rate acceleration in the reaction of organolithium compounds to alkylimines is observed mostly using stoichiometric amounts of LAs such as BF_3.[38] However, in many instances this involves a preliminary reaction of the organometallic reagent with BF_3 leading

to mixed organometallic species. A true activation in the reaction of Grignard reagents with aldimines **54** is provided by $Sc(OTf)_3$, which, used in catalytic amounts, effectively promotes the nucleophilic addition leading to amines **55** (Scheme 14).[39] The same process without any catalyst is much less effective, whereas preformed solutions of Grignard reagent-$Sc(OTf)_3$ are almost completely unreactive.

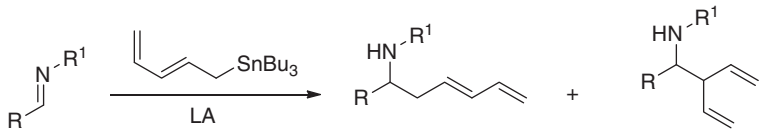


54 **55**

R	R^1	Yield	References
Ph	Me	90%	2001SL1859
Cy	Bu	95%	2001SL1859
Ph	Pr^i	99%	2001SL1859
Cy	Ph	65%	2001SL1859

Scheme14

Activation by LA becomes mandatory when the covalent nature of the carbon-metal bond increases. Reaction of pentadienyltributyltin with imines **56** may generate two distinct regioisomeric products **57** and **58** arising from an ε and γ attack, respectively (equation 5).[40] Being a nontransmetallating acid, BF_3 drives the addition toward compounds **57** through an acyclic transition state, regardless of the electronic density at the nitrogen atom of the imine (Table 6). Regiocomplementary results are observed with $InCl_3$ and also $ZnCl_2$, depending on the coordinating ability of the nitrogen atom and the reactivity of the imine. With less reactive *N*-arylimines, coordination of the LA prevails and the ε attack through an acyclic transition state is almost exclusively observed. Conversely, *N*-tosylimines are more reactive, hence transmetalation and a cyclic transition state warrant formation of adducts **58** through a γ attack.

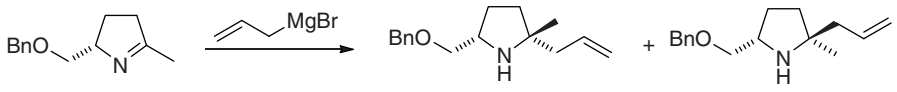


56 **57** **58** (5)

Table 6 Reaction of imines with pentadienyltributiltin promoted by LAs (equation 5)

No.	*R*	*R^1*	*LA*	***57:58***	*Yield (%)*	*References*
1.	Ph	Ph	BF_3	99:1	78	2004CL108
2.	Ph	Ts	BF_3	87:13	94	2004CL108
3.	4-NO_2Ph	Ph	$InCl_3$	99:1	51	2004CL108
4.	4-NO_2Ph	Ts	$InCl_3$	1:99	98	2004CL108

Diastereoselection in the nucleophilic addition of Grignard reagents to cyclic imines bearing stereogenic centers can be controlled with the aid of LAs. Optically pure pyrroline **59** reacts with allylmagnesium bromide leading preferentially to *cis*-**60** (equation 6).[41] In the presence of $BF_3 \cdot Et_2O$, the addition of the organomagnesium reagent occurs with reversed diastereoselectivity, thus generating *trans*-**61** as the major product. Reaction with Grignard reagent alone involves a preliminary complexation of magnesium, with the oxygen of the benzyloxy group favoring the nucleophilic attack on the same side of the substituent. Addition of the LA results in its coordination with the benzyloxy group, as well as with the imine nitrogen, providing an enhancement of the imine reactivity and directing the nucleophilic attack from the less hindered side of the pyrroline.



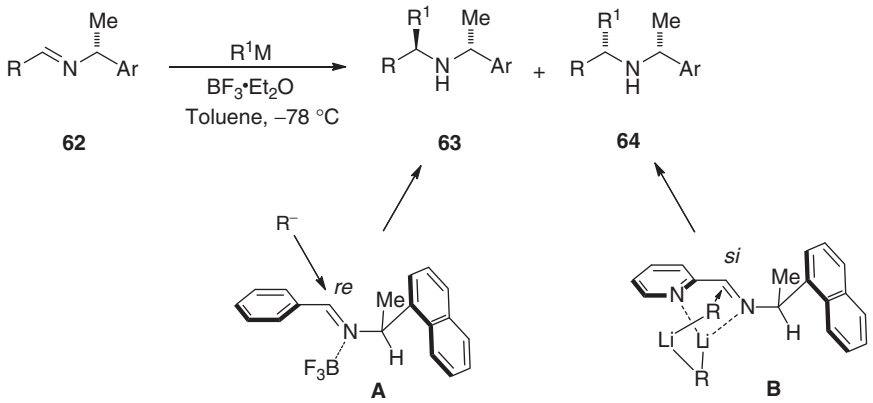
59 **60** **61** (6)

THF, 0 °C, 58% 5.8 1

BF_3•Et_2O (3 equivalents), THF, –78 °C, 73% 1 19

Open-chain chiral imines react with carbon nucleophiles with different levels of diastereoselection depending on the nature of the imine and the organometallic species employed. Organocopper and high-order cuprate reagents, in the presence of $BF_3 \cdot Et_2O$,

are the most effective for such reactions when aryl or alkyl aldimines **62** are used as substrates (Scheme 15, Table 7).[42] Conversely, organolithium reagents show unsatisfactory levels of diastereoselection when *N*-(1-phenylethyl) imines are used. A considerable increase in diastereoselectivity is evidenced by replacing the phenyl group with more sterically demanding rings such as 1-naphthyl.[43] The presence of $BF_3 \cdot Et_2O$ is mandatory in order to ensure a high diastereomeric ratio regardless of the nature of the R group of the imine. A rationale for the observed preferred formation of adduct **63** can be found in the calculated transition state A, which is preferentially attacked by the nucleophile from the *re* face of the imine. A specific behavior is displayed by the imine obtained from 2-pyridinecarbaldehyde, which in the absence of $BF_3 \cdot Et_2O$ affords adduct **64** as the major stereoisomer. In this case, it is assumed that the stereoselection is governed by a chelate complex **B** in which the alkyl group from the organolithium is released from the *si* face of the imine. Curiously, for these reactions the level of diastereoselection can also be considerably improved using TMEDA and (–)-sparteine as Lewis bases instead of $BF_3 \cdot Et_2O$.



Scheme 15

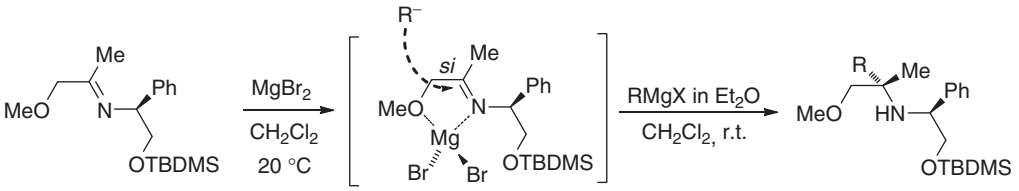
Table 7 Reaction of imines with organometallic reagents in the presence of $BF_3 \cdot Et_2O$ (Scheme 15)

No.	*R*	*R¹*	*M*	*Ar*	***63:64***	*Yield (%)*	*References*
1.	Cy	Me	CuMgCl	Ph	93:7[a]	91	1996T12571
2.	Ph	Me	CuMgCl	Ph	86:14[a]	75	1996T12571
3.	Ph	Me	Li	Ph	52:48	88	1999JOC8821
4.	Ph	Bu^n	Li	1-Naphthyl	79:21[b]	32	1999JOC8821
5.	Ph	Bu^n	Li	1-Naphthyl	92:8	88	1999JOC8821
6.	$PhCH_2CH_2$	Me	Li	1-Naphthyl	99:1	56	1999JOC8821
7.	2-Pyridyl	Me	Li	1-Naphthyl	84:16	46	1999JOC8821
8.	2-Pyridyl	Me	Li	1-Naphthyl	15:85[b]	63	1999JOC8821

[a] *(S)* enantiomer in THF.
[b] Without $BF_3 \cdot Et_2O$.

The presence of further coordinating atoms, other than the nitrogen, in the imine usually provides better levels of diastereoselection in the reaction of organometallic reagents assisted by LAs. Imine **65** features two ethereal functions, one of which is preferentially coordinated by $MgBr_2$, together with the imino nitrogen (Scheme 16).[44] The specific arrangement of the phenyl group in the chiral auxiliary of imine **65** makes the attack by the incoming nucleophile more probable from the *si* side, preferentially leading to the formation of the secondary amine (*S*,*S*)-**66**.

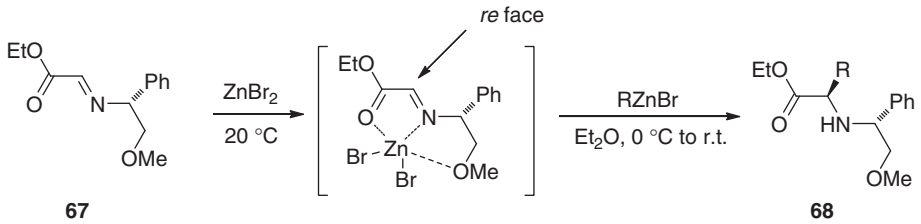
Organometallic additions to chiral α-imino esters are useful for the preparation of optically active α-amino acids. Because of the conjugated heterodiene nature of α-imino esters, nucleophilic attack may occur to three different electrophilic sites, namely, the carboxylic group, the azomethine carbon, and the imino nitrogen atom. This latter umpolung addition of an organometallic reagent to the nitrogen of α-imino esters in the presence of a LA allows to obtain *N*,*N*-disubstituted α-amino acids – a variety of pharmacologically useful compounds with a quaternary center in α-position.[45] Mechanistically, it should be noted that the regioselectivity of the process is strongly affected by the nature of the metal employed, organozinc reagents being the most effective in leading to the α-substituted amino ester derivatives. Furthermore, the occurrence of two distinct conformations of the heterodiene calls for a preliminary complexation, involving the carboxylic oxygen and imino nitrogen lone pairs, in order to lock up the imino ester in its *s-cis* arrangement. The presence of a supplementary oxygen atom in the chiral auxiliary may reinforce this complexation, giving rise to a more rigid chelate structure as in the reaction of α-imino ester **67** (Scheme 17).[46]



65 66

R	Yield	*dr*	References
Bn	87%	>99:1	1999JOC2406
Allyl	73%	98:2	1999JOC2406
Ph	50%	97:3	1999JOC2406

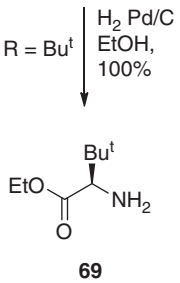
Scheme 16



67 68

R	Yield	*dr*	References
Bu^t	41%	70:30[a]	2002TA2205
Bu^t	68%	96:4	2002TA2205
Bn	62%	97:3	2002TA2205
Cy	58%	89:11[b]	2002TA2205

[a]without $ZnBr_2$
[b]CH_2Cl_2 as solvent



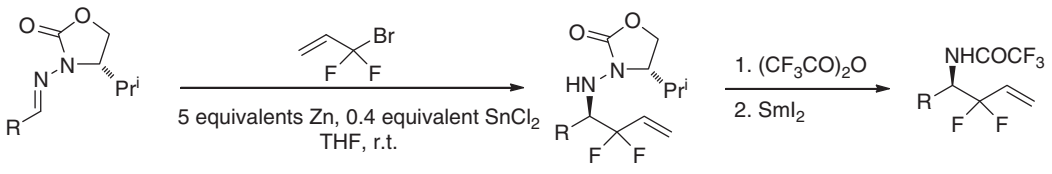
69

Scheme 17

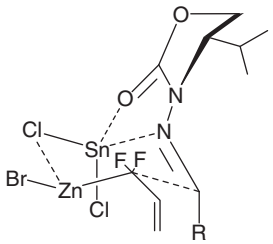
Addition of $ZnBr_2$ to compound **67** presumably leads to a bicyclic chelate structure, which enhances the electrophilicity of the azomethine carbon and favors the nucleophilic addition from the *re* face. The effect brought by the LA is evident considering the chemical yield and the diastereoselectivity obtained in the reaction of **67** with *t*-BuZnCl without any additive and in the presence of $ZnCl_2$. Easy removal of the chiral auxiliary from adduct **68** (R=Bu^t) by catalytic hydrogenation leads to the recovery of the α-amino acid ester **69**.

1.10.4.2 Hydrazones

The reactivity of hydrazones with organometallic reagents generally parallels that of imines. The introduction of chiral auxiliary groups in the hydrazine used for the preparation of hydrazones allows a subsequent diastereoselective nucleophilic addition of organometallic reagents and, after the cleavage of the N–N bond, ultimately leads to the synthesis of optically active amino derivatives. Examples of activation of the hydrazone moiety by LAs are rather scant since added salts, featured by moderate Lewis acidity such as $CeCl_3$, are often involved in transmetalation processes with organolithium or Grignard reagents, giving rise to new organometallic species. Hydrazones **70** embedding a chiral 1,3-oxazolidin-2-one moiety react with the organozinc reagent formed *in situ* from 3-bromo-3,3-difluoro propene in the presence of a catalytic amount of $SnCl_2$, leading to adducts **71** with high diastereoselectivity (Scheme 18).[47] The role of $SnCl_2$ is believed to be that of a bifunctional catalyst locking the conformation of the system, activating the hydrazone toward the nucleophilic addition, and providing formation of a tight six-membered transition state through the Lewis basicity of the chlorine atom according to the proposed model **C**. Compared to *N*-benzyl amines obtained from the corresponding imines, the cleavage of the N–N bond in hydrazines **71** is slightly more troublesome and the amino derivatives **72** are usually produced by a preliminary acylation of the secondary nitrogen atom followed by a cleavage using SmI_2.



70 71 72



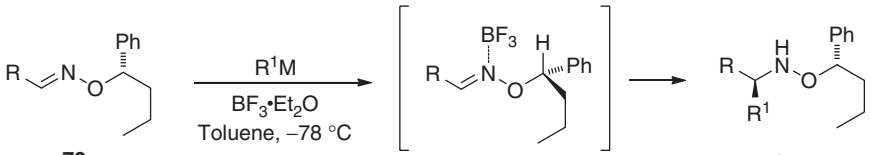
C

R	Yield	*dr*	Reference
Ph	76%	>99:1	2009OL73
4-BrPh	73%	>99:1	2009OL73
2-furyl	77%	94:6	2009OL73
Cy	73%	>99:1	2009OL73
CO_2Et	59%	96:4	2009OL73

Scheme 18

1.10.4.3 Oxime Ethers

The reaction of organometallic reagents to oxime ethers usually results in a complex mixture of products containing the expected hydroxylamine ethers together with other amino derivatives. Addition of $BF_3 \cdot Et_2O$ provides a considerable enhancement in the reactivity of the oxime ether leading to satisfactory results in terms of chemical yields. The introduction of stereodefined chiral centers in the *O*-alkyl moiety allows a diastereoselective addition of the organometallic reagents to oxime ethers **73**.[48] In this instance, the LA exerts a double effect since the increase in reactivity caused by its complexation with the nitrogen lone pair is coupled with an acquired molecular rigidity that favors a better diastereoselection in the addition process (Scheme 19). Organolithium as well as Grignard reagents can be profitably used for this reaction, which generally displays excellent diastereoselectivities in the formation of hydroxylamines **74** (Table 8).



73 74

Scheme 19

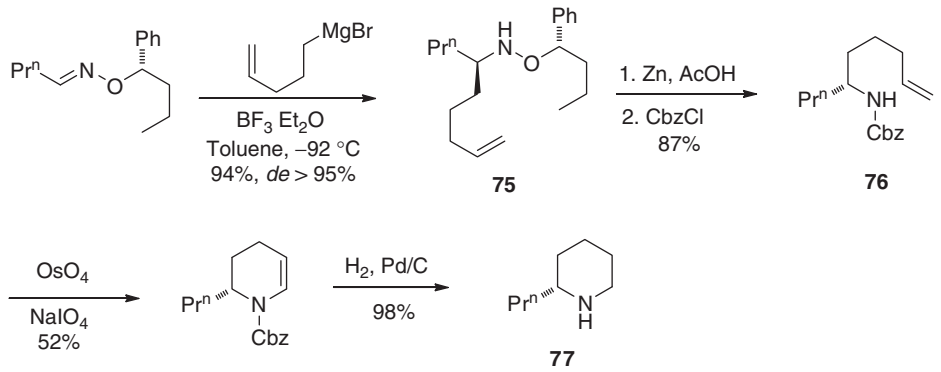
Table 8 Diastereoselective addition of organometallic reagents to chiral oxime ethers (Scheme 19)

No.	*R*	*R*[1]	*M*	*dr*	*Yield (%)*	*References*
1.	Pr^n	Pr^i	MgCl	>95:5	70	1999J(P1)3443
2.	$CHEt_2$	$CH_2{=}CHCH_2$	MgBr	98:2	100	1999J(P1)3443
3.	*c*-C_6H_{11}	Bu^n	Li	>95:5	95	1999J(P1)3443
4.	*c*-C_6H_{11}	Bu^t	Li	>95:5	68	1999J(P1)3443
5.	$PhCH_2$	Et	MgBr	90:10	62	1999J(P1)3443
6.	Ph	Bu^n	Li	>98:2	72	1999J(P1)3443

Reduction of the obtained hydroxylamines leads to amino derivatives, which can be obtained by cleavage of nitrogen-oxygen bond as illustrated for the synthesis of the alkaloid (–)-coniine **77** (Scheme 20).[49] Adduct **75** is reduced and protected at the nitrogen atom leading to carbamate **76**, which on double bond oxidative cleavage is cyclized and finally reduced to compound **77**.

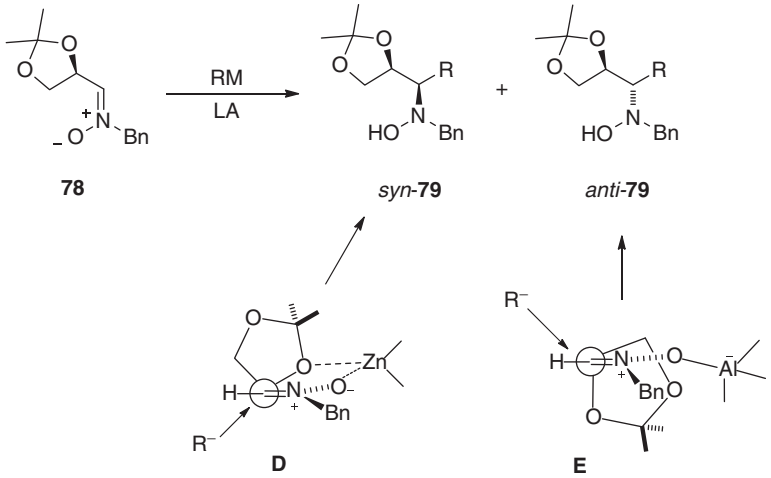
1.10.4.4 Nitrones

The 1,3-dipolar nature of nitrones permits their utilization in cycloaddition reactions as well as in nucleophilic additions to the azomethine carbon.[50] The negatively charged oxygen in nitrones is particularly prone to coordination with LAs, providing a



Scheme 20

considerable increase in their reactivity. Such complexation also has a major impact on modifying the diastereofacial preference in the nucleophilic attack of organometallic reagents to chiral nitrones. This effect is particularly strong when other coordinating atoms are located in close proximity to the reacting center. Nucleophilic additions of organometallic reagents to chiral nitrone **78** display a general preference for the hydroxylamine *syn*-**79** in the absence of any external LA (Scheme 21, Table 9).[51] A similar trend is observed with $ZnBr_2$ or TMSOTf, whereas the utilization of Et_2AlCl leads to a reversal in the diastereoselection favoring *anti*-**79**. The observed preferential formation of the *syn* stereoisomer could stem from a complexation of the O-3 of the dioxolane ring with the nitrone oxygen favoring attack of the nucleophile from the *re* side (structure **D**). When Et_2AlCl is used, a monodentate complex with the nitrone oxygen is very likely, arranging the acetal C–O bond in an orthogonal position according to the Felkin–Anh model (structure **E**), leading to a preferential attack from the *si* side. This assumption seems to be supported by the result recorded using $BF_3 \cdot Et_2O$, a known nonchelating acid, in the allylation reaction of nitrone **78**, which shows the same trend, although with higher diastereoselectivity, evidenced in the reaction with Et_2AlCl (Table 9).[52]



Scheme 21

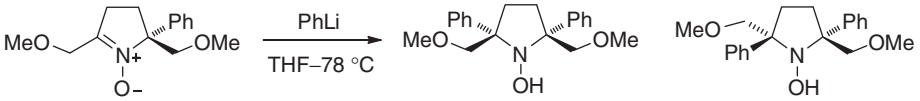
The steric constraint provided by the acetonide group in nitrone **78** is mandatory for achieving a good level of diastereoselection in the reaction with organometallic reagents. Open-chain protection, as benzyl ethers, of the hydroxy groups in a parent nitrone reveals that the stereoselectivity is largely unsatisfactory regardless of the organometallic reagent and/or the LA used.

In cyclic chiral nitrone **80** simple addition of PhLi privileges formation of *trans*-**81** indicating that the phenyl ring can be considered a more sterically demanding group than the methoxymethyl. Addition of Et_2AlCl causes a complexation between the nitrone oxygen and the methoxymethyl group linked to the stereogenic center, thus providing a shielding of the *re* face of the molecule that results in a preferential formation of *cis*-**81** resulting from the attack from the *si* side (equation 7).[53]

Table 9 Diastereoselective addition of organometallic reagents to chiral nitrone (**Scheme 21**)

No.	*R*	*M*	*LA*	*T* (°C)	*syn/anti* ***79***	*Yield (%)*	*References*
1.	CH_2OMOM	Li	–	−80	90:10	72[a]	2002TL459
2.	CH_2OMOM	Li	$ZnBr_2$	−80	80:20	77[a]	2002TL459
3.	CH_2OMOM	Li	Et_2AlCl	−80	5:95	80[a]	2002TL459
4.	Me	MgBr	$ZnBr_2$	−40	82:18	80[b]	1997TA1725
5.	Me	MgBr	Et_2AlCl	−40	18:82	76[b]	1997TA1725
6.	2-Furyl	Li	–	−80	96:4	98[a]	1994S1450
7.	2-Furyl	Li	Et_2AlCl	−80	5:95	94[b]	1994S1450
8.	Vinyl	MgBr	–	0	76:24	86[a]	1996TA1887
9.	Vinyl	Li	Et_2AlCl	0	8:92	86[b]	1996TA1887
10.	Allyl	Li	–	−80	55:45	86[a]	2008EJOC3943
11.	Allyl	Li	$ZnBr_2$	−80	90:10	75[b]	2008EJOC3943
12.	Allyl	MgBr	$ZnBr_2$	−50	>95:5	100[b]	2008EJOC3943
13.	Allyl	MgBr	Et_2AlCl	−50	35:65	90[b]	2008EJOC3943
14.	Allyl	MgBr	$BF_3 \cdot Et_2O$	−50	5:95	90[a]	2008EJOC3943

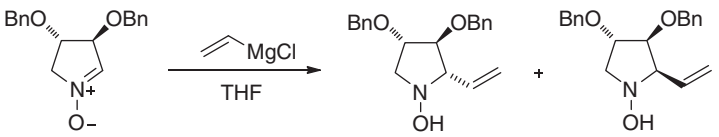
[a]THF as solvent.
[b]Et_2O as solvent.



80 *cis*-**81** *trans*-**81** (7)

	cis-**81**	*trans*-**81**
No additive	2	98
2 equivalents Et_2AlCl	90	10

A specific behavior is observed in the addition of vinylmagnesium chloride to chiral cyclic nitrone **82** (**Scheme 22**).[54] Addition of the Grignard reagent is absolutely insensitive to the reaction temperature, suggesting an entropy-controlled selectivity leading to the almost exclusive formation of *trans*-**83**. Conversely, precomplexation of nitrone **82** with Et_2AlCl results in a poor diastereoselectivity at very low temperature, whereas performing the same reaction at higher temperatures produces a marked enhancement of the selectivity that becomes identical to the one without additives at 23 °C. The nature of the substrate–LA complex system, generated at low temperature, is uncertain, but the loss of selectivity observed is rather unusual considering that a temperature decrease often has a beneficial effect on diastereoselective processes.

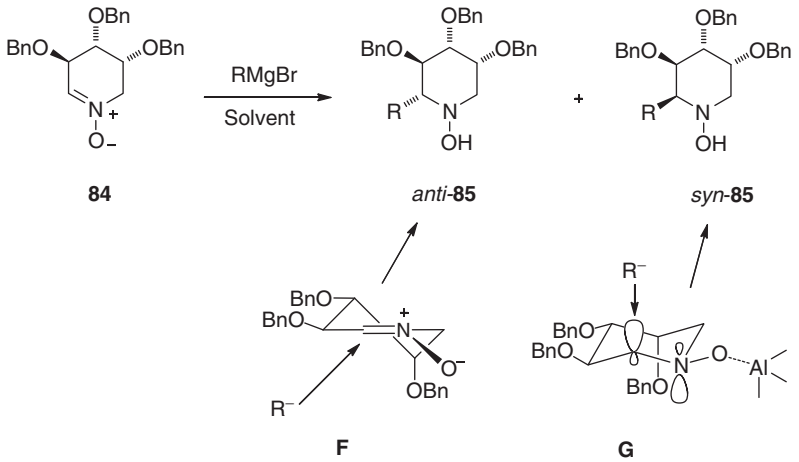


82 *trans*-**83** *cis*-**83**

	T °C		
	−80	−18	23
trans:cis - no additive	93:7	93:7	93:7
trans:cis - Et_2AlCl	63:37	87:13	93:7

Scheme 22

Diastereoselective addition of organometallic reagents to chiral six-membered cyclic nitrones provides a rapid entry to various 1-deoxyazapyranosides endowed with a powerful biological activity. The stereochemical outcome of this reaction shows a different trend compared to the five-membered analogs. The diastereomeric ratio in the reaction of chiral nitrone **84** with Grignard reagents shows a strong dependence on the nature of the added carbon framework as well as the nature of the possible LA employed (**Scheme 23**, **Table 10**).[55] The arrangement of the cyclic structure of nitrone **84** and the stereochemistry of the benzyloxy group at C-3 favor the attack of the incoming nucleophile from the *re* face as in model **F**, leading to the preferential



Scheme 23

Table 10 Diastereoselective addition of organometallic reagents to chiral nitrone (Scheme 23)

No.	*R*	*LA*	*Solvent, T (°C)*	*anti/syn*	*Yield (%)*	*References*
1.	Pr^i	–	THF, 0	95:5	79	2010EJOC5555
2.	Bn	–	THF, 0	95:5	93	2010EJOC5555
3.	Allyl	–	THF, 0	77:23	81	2010EJOC5555
4.	Vinyl	–	THF, 0	66:33	86	2010EJOC5555
5.	Vinyl	–	THF, −78	62:38	83	2010EJOC5555
6.	Vinyl	Et_2AlCl	THF, −78	19:81	85	2010EJOC5555
7.	Vinyl	Et_2AlCl	CH_2Cl_2, −78	10:90	83	2010EJOC5555
8.	Vinyl	Bu^i_2AlCl	CH_2Cl_2, −78	5:95	80	2010EJOC5555

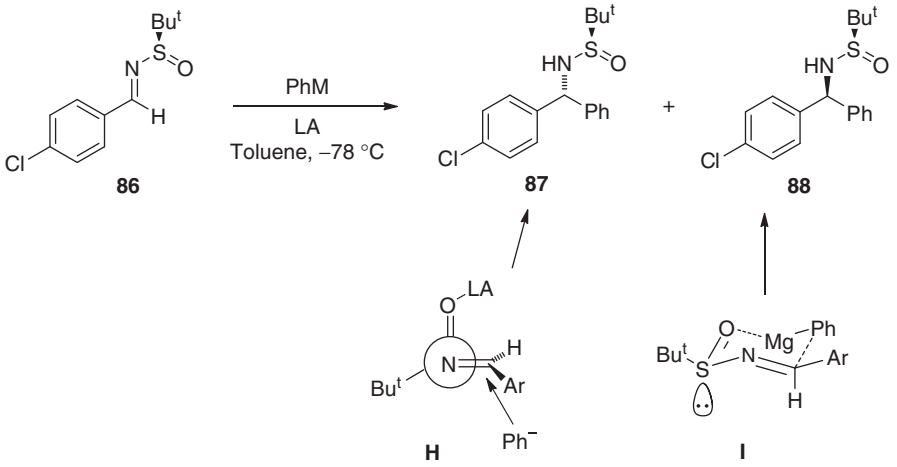
formation of *anti*-**85**. This result is observed with Grignard reagents bearing alkyl and benzyl groups, but the same preference is also observed, although with low diastereoselectivity, using allyl and vinyl reagents, regardless of the temperature of the reaction. Addition of dialkylaluminum chlorides provides a reversal of the diastereofacial preference for this reaction according to the model **G** in which coordination of the LA with the nitrone oxygen favors a chair-like transition state. On the basis of stereoelectronic effects evidenced in related systems, attack of the nucleophile becomes more probable from the *si* side giving *syn*-**85** as the major product. A poorly coordinating solvent such as dichloromethane combined with an increase in the steric bulkiness of the alkyl ligands in the LA reaches a very good level of diastereoselection.

1.10.4.5 *N*-Sulfinylimines

The stereogenic nature of the sulfur atom in *N*-sulfinylimines allows their preparation in optically pure form starting from the corresponding chiral nonracemic *N*-sulfinylamides.[36] Nucleophilic additions to *N*-sulfinylimines are therefore diastereoselective processes whose stereochemistry can be controlled by a suitable choice of the reaction conditions. The presence of a strongly polarized S–O bond makes any coordination effect of crucial importance in the addition of organometallic reagents to the azomethine carbon. These effects would also be operative in the presence of LAs, producing an increase in reactivity and a modification of the facial shielding, leading to more efficient control of the diastereoselectivity of the process.

The stereochemical outcome in the organometallic additions to *N*-*tert*-butylsulfinylaldimines depends on the nature of the metal, the solvent used, and the possible addition of LAs. In toluene, addition of PhLi to imine **86** is poorly diastereoselective when carried out without any additive (Scheme 24, Table 11).[56] An increase in stereoselectivity is observed using either Me_3Al or $BF_3 \cdot Et_2O$, indicating that interaction of the LA with the sulfinyl oxygen favors the attack from the *re* side through a Felkin–Anh model **H**, preferentially leading to isomer **87**. The utilization of PhMgBr for the same purpose leads to a reversed diastereoselection favoring amine **88** and seems to produce even worse results with the addition of LAs. These findings are consistent with a chelate model **I** that is partially disrupted by the presence of LAs. This is a general trend also observed in other reactions involving arylmetal additions to *N*-*tert*-butylsulfinylimines obtained from simple alkyl and aryl aldehydes.

Interestingly, stereoconvergent results are observed in the reaction of α-alkoxy or α-silyloxy sulfinylimines **89** with organometallic compounds both in the presence and absence of LA additives (Scheme 25, Table 12).[57] In this case, a common sense of

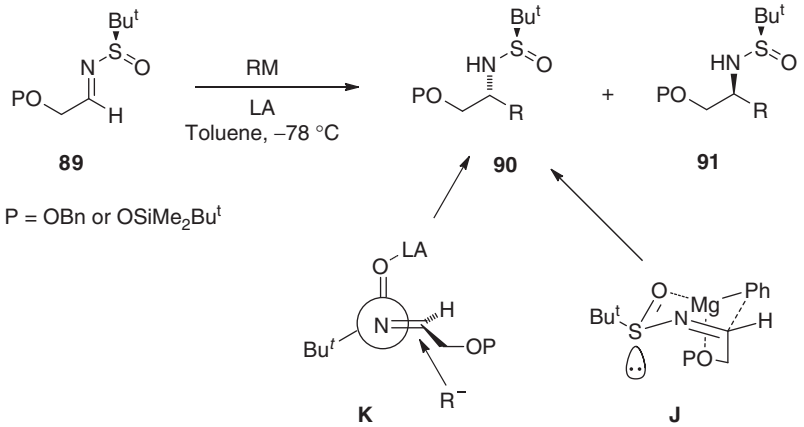


Scheme 24

Table 11 Diastereoselective addition of organometallic reagents to sulfinylimine (Scheme 24)

No.	*M*	*LA*	***87:88***	*Yield (%)*	*References*
1.	Li	–	62:38	82	2002TL923
2.	Li	Me_3Al	93:7	80	2002TL923
3.	Li	$BF_3 \cdot Et_2O$	89:11	88	2002TL923
4.	MgBr	–	9:91	78	2002TL923
5.	MgBr	Me_3Al	19:81	75	2002TL923
6.	MgBr	$BF_3 \cdot Et_2O$	72:28	78	2002TL923

stereoinduction is operative, favoring attack of the nucleophile from the *si* face in the open-chain transition state **K** but also in the alternative chelate model **J** leading preferentially to (*R,R*)-imine **90**. In the latter situation, a further chelation with the magnesium atom involving the α-oxygen is very likely, causing a reversal of the facial preference for the nucleophilic addition compared to unfunctionalized systems (*cf.* model **I**, Scheme 23). The presence of LAs again has a beneficial effect on the level of diastereoselectivity, which is particularly pronounced when organolithiums are used as reagents.

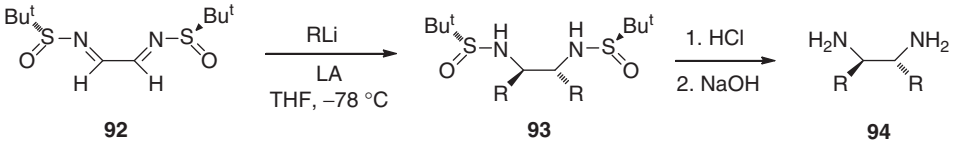


Scheme 25

Bisimine **92** derived from glyoxal is a pivotal substrate for the preparation of optically active 1,2-diamino derivatives **94** after acidic hydrolysis of the S–N bond (Scheme 26, Table 13).[58] The utilization of PhMgBr provides satisfactory results in terms of diastereoselectivity of the resulting adducts **93**, but the final 1,2-diamine is obtained with low enantiomeric ratio. PhLi alone gives respectable diastereo- and enantioselective values, which can be substantially improved using $BF_3 \cdot Et_2O$ as additive. A series of organolithium compounds can be used in this reaction with excellent results.

Table 12 Diastereoselective addition of organometallic reagents to sulfinylaldimine (P = Bn) (Scheme 25)

No.	*RM*	*LA*	***90:91***	*Yield (%)*	*References*
1.	*n*-BuMgCl	–	90:10	80	2001JOC8772
2.	*n*-BuMgCl	Me_3Al	90:10	84	2001JOC8772
3.	*n*-BuLi	–	75:25	81	2001JOC8772
4.	*n*-BuLi	Me_3Al	97:3	87	2001JOC8772
5.	PhLi	–	80:20	92	2001JOC8772
6.	PhLi	Me_3Al	96:4	96	2001JOC8772



92 **93** **94**

Scheme 26

Table 13 Diastereoselective addition of organometallic reagents to bissulfinylimine (Scheme 26)

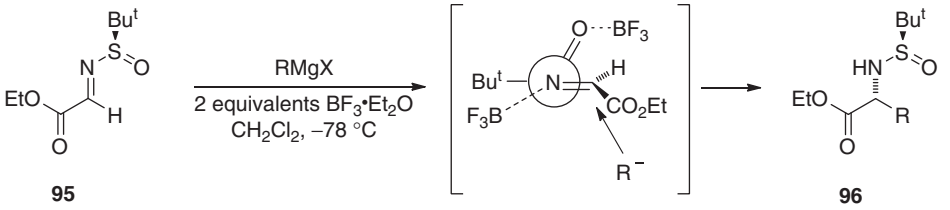
No.	*R*	*LA*	*dr* ***93***	*er* ***94***	*Yield* ***93*** *(%)*	*References*
1.	Ph	–	93:7	63:37	79[a]	2005SL2776
2.	Ph	–	91:9	96:4	78	2005SL2776
3.	Ph	Me_3Al	97:3	97:3	80	2005SL2776
4.	Ph	$BF_3 \cdot Et_2O$	95:5	99:1	88	2005SL2776
5.	4-MeOPh	$BF_3 \cdot Et_2O$	90:10	93:7	84	2005SL2776
6.	3-FPh	$BF_3 \cdot Et_2O$	86:14	98:2	81	2005SL2776
7.	4-vinylPh	$BF_3 \cdot Et_2O$	99:1	>99:1	84	2005SL2776
8.	Bu^n	$BF_3 \cdot Et_2O$	96:4	98:2	86	2005SL2776

[a]Toluene as solvent, PhMgBr as reagent.

Nucleophilic addition to α-imino esters provides access to amino acid derivatives. The utilization of $BF_3 \cdot Et_2O$ as an additive in the reaction of Grignard reagents to α-imino esters **95** gives superior results compared to other LAs in terms of both chemical yield and diastereoselectivity (Scheme 27).[59] The diastereofacial preference displayed by imino esters **95** is congruent with an open-chain transition state and better results are evidenced using two equivalents of the LA. This approach can be used for the synthesis of L-α-(1-cyclobutenyl)glycine, which involves reaction of (*S*)-imino ester **97** with 1-cyclobutenyl-magnesium bromide.[60] Adduct **98** was obtained in satisfactory yield and diastereoselectivity. The product can be easily converted into the amino acid salt **99** by acidic hydrolysis.

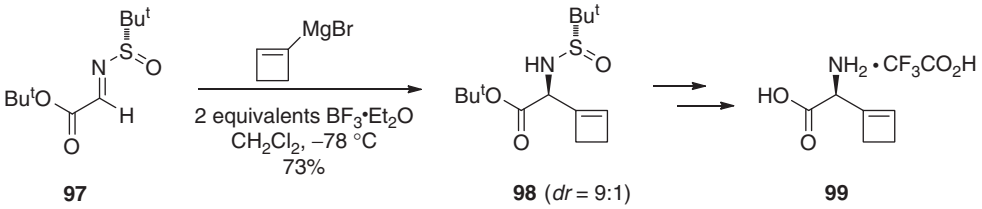
The reaction of sulfinylaldimines with allylmetal reagents shows a specific trend since, by simple tuning of the reaction solvent and additive, a remarkable reversal of diastereofacial selectivity is observed. A coordinating metal such as zinc is effectively used in the allylation of sulfinylaldimines **100**, and when the process is carried out in THF in the presence of $In(OTf)_3$ a chelate model **L** better explains the preferential formation of adduct **101** (Scheme 28, Table 14).[61] Polar aprotic media with strong solvating aptitude such as HMPA convey the transition state toward an open-chain mechanism **M**, which favours formation of adduct **102** (*dr* = 26:74). The diastereoselectivity can be strongly improved by addition of a small amount of water, the role of which is not clear but allows compound **102** to be almost exclusively formed. A similar effect is recorded in the reaction of allylmagnesium halides with a (*S*)-*N*-*p*-tolylsulfinylimine obtained from furfural, alternatively using dichloromethane alone or diethyl ether in the presence of $BF_3 \cdot Et_2O$ (Table 14, entries 7, 8).[62]

The reactivity of sulfinylketimines toward nucleophilic addition by organometallic reagents is somewhat lower compared to the parent aldimines. In the reaction of ketimines **103** with alkyl and arylorganometallic reagents satisfactory results are obtained only when lithium is the metal (Scheme 29, Table 15). Grignard and organozinc reagents give interesting results only with allyl and alkoxy frameworks, whereas organocerium and other mixed organometallic reagents are totally ineffective in providing the corresponding adducts to ketimines. As already observed for the parent sulfinylaldimines, the addition of LAs brings about a significant improvement both of the chemical yield and of the diastereoselectivity of the process (Table 15, entries 1–4). Aluminum-based acids display a particularly beneficial effect, with Me_3Al being the most effective. A remarkable difference concerning the stereochemical bias evidenced in the reaction of sulfinylketimines compared to the aldimine counterparts is the stereoconvergent character of the nucleophilic addition. In other words, a chelate transition state seems to be always operative when ketimines are used as substrates, and the role of the LA is to enhance the reactivity of the imine and the diastereoselectivity



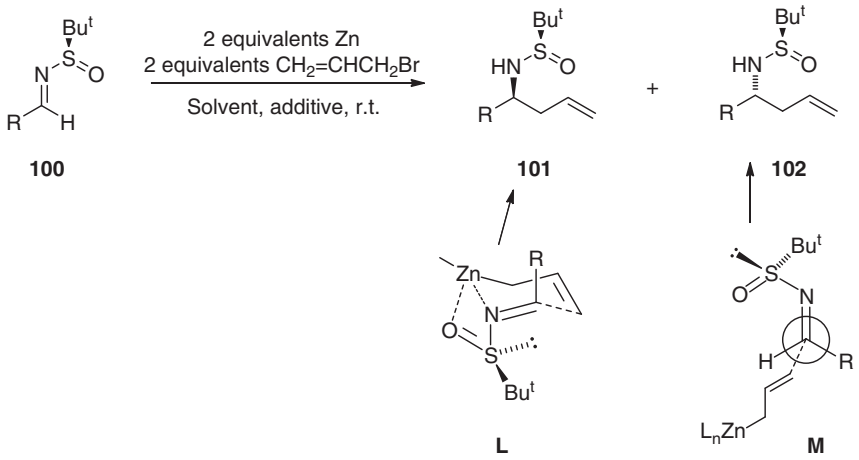
95 96

R	Yield	*dr*	References
Ph	70%	84:16	1999JOC3396
Bn	70%	94:6	1999JOC3396
Me	54%	83:17	1999JOC3396
Et	27%	>99:1	1999JOC3396



97 **98** (*dr* = 9:1) **99**

Scheme 27



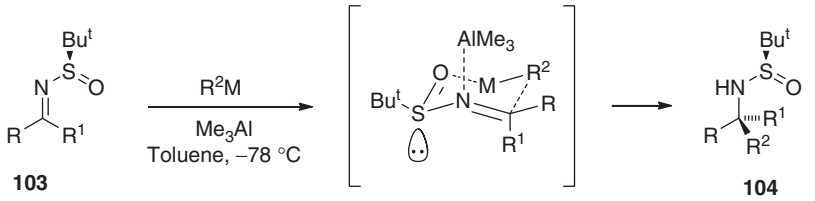
100 **101** **102** **L** **M**

Scheme 28

Table 14 Diastereoselective addition of allylzinc to sulfinylaldimines (Scheme 28)

No.	*R*	*Additive*	*Solvent*	***101:102***	*Yield (%)*	*References*
1.	Ph	$In(OTf)_3$	THF	98:2	93	2006OL4979
2.	Ph	H_2O	HMPA	1:99	97	2006OL4979
3.	4-Br-C_6H_4	$In(OTf)_3$	THF	97:3	93	2006OL4979
4.	4-Br-C_6H_4	H_2O	HMPA	2:98	99	2006OL4979
5.	Cy	$In(OTf)_3$	THF	97:3	99	2006OL4979
6.	Cy	H_2O	HMPA	3:97	94	2006OL4979
7.	2-Furyl	–	CH_2Cl_2	91:9	98[a]	2002T9621
8.	2-Furyl	$BF_3 \cdot Et_2O$	Et_2O	1:99	83[a]	2002T9621

[a]Reaction carried out on (*S*)-*N*-*p*-tolylsulfinylimine using allylMgX at −78 °C.



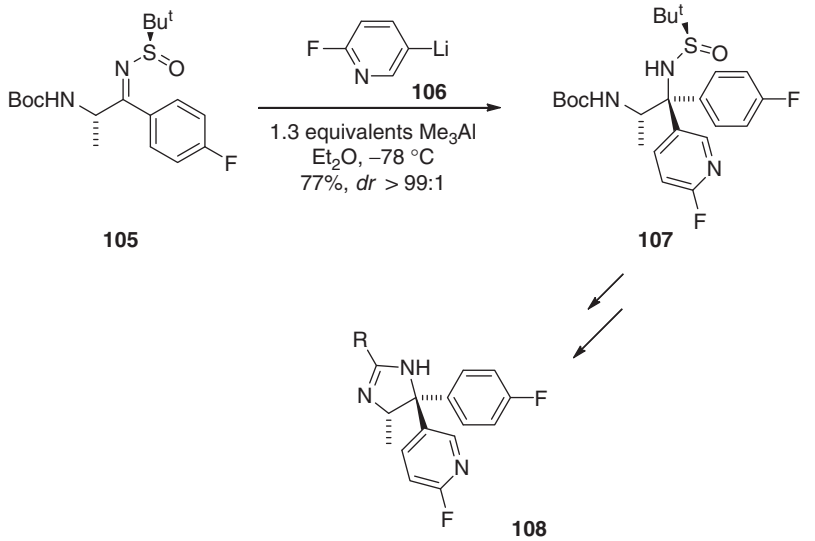
Scheme 29

Table 15 Diastereoselective addition of organometallic reagents to sulfinylketimines (**Scheme 29**)

No.	*R*	*R^1*	*R^2*	*M*	*dr* ***104***	*Yield (%)*	*References*
1.	Ph	Me	Bu^n	Li	99:1[a]	26	1999T8883
2.	Ph	Me	Bu^n	Li	98:2	86	1999T8883
3.	Pr^i	Bu^n	Ph	Li	82:12[a]	54	1999T8883
4.	Pr^i	Bu^n	Ph	Li	91:9	84	1999T8883
5.	Ph	Bu^n	Me	Li	99:1	100	1999T8883
6.	2-naphthyl	Me	Ph	Li	99:1	62	1999T8883
7.	Pr^i	Me	2-Me-5-furyl	Li	94:6[b]	97	2001TL1433
8.	$TBSOCH_2$	Me	Bu^n	MgCl	98:2	54	2001JOC8772
9.	$TBSOCH_2$	Me	Bu^n	Li	95:5	89	2001JOC8772
10.	Ph	Me	Allyl	MgBr	>99:1[a]	85	1999T8883
11.	Pr^i	Me	Allyl	MgBr	95:5[a]	93	1999T8883
12.	4-ClPh	Me	Allyl	ZnBr	97:3[c]	83	2006OL4979
13.	Bu^t	Me	TMSC≡C	Li	>99:1[d]	81	2006JOC7110
14.	Cy	Et	TMSC≡C	Li	90:10[d]	80	2006JOC7110
15.	Pr^i	Me	CF_3C≡C	Li	94:6[d]	88	2008T2301

[a]Without Me_3Al.
[b]At 0 °C.
[c]In the presence of $In(OTf)_3$ in THF at r.t.
[d]Reaction carried out on (*S*)-*N*-*tert*-butylsulfinylimine leading to *ent*-**104**.

of the process without altering the facial preference of the nucleophilic attack leading to adduct **104**. This explains why allylmagnesium reagents whose propensity to react via a chelate transition state is known do not require any activation whereas the less reactive allylzinc reagents give satisfactory results only in the presence of $In(OTf)_3$ (Table 15, entries 1–12). Finally, alkynyllithium reagents are particularly effective in leading the corresponding adducts with ketimines **103** (Table 15, entries 13–15).



Scheme 30

Diastereoselectivity in the nucleophilic addition to sulfinylketimines bearing a supplementary stereogenic center in close proximity to the imino moiety is often governed solely by the chirality of the sulfinyl group. As discussed in Scheme 29, imine **105**, obtained from L-alanine, reacts with oganolithium derivative **106** leading to adduct **107** with complete diastereoselectivity (Scheme 30).[63] Cleavage of the sulfinyl group in compound **107** provides simple access to an optically active 1,2-diamine, which is converted to a series of biologically active imidazolines **108**.

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1.11 Nucleophilic Addition of Nonstabilized Carbanions to Imines and Imine Derivatives

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Glossary

α-Chiral amine A carbon stereocenter in which one of the four substituents is an amine.

Chiral auxiliary A chiral subunit that is temporarily covalently incorporated into an organic substrate to control the stereochemical outcome of a reaction.

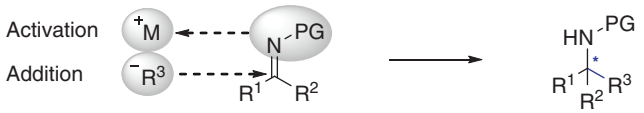
Electrophilicity The property of being able to accept both bonding electrons and reaction partner.

Nonstabilized carbon nucleophiles The carbanions in which the negative charge cannot be stabilized by resonance with electron-withdrawing substituents.

Transmetallation A type of organometallic reaction that involves the transfer of anionic ligands from one metal to another.

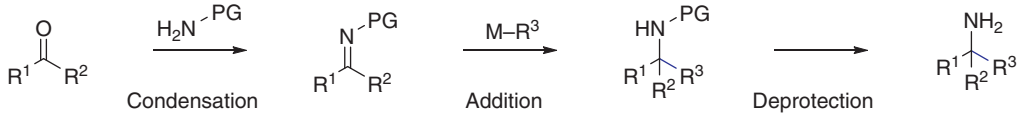
1.11.1 Introduction

The ubiquity of α-chiral amines in natural products and other biologically relevant compounds is continuously motivating chemists to develop more general and efficient methods for their formation. Over the years, the addition of nonstabilized carbanions to imines and imine derivatives (azomethines) has become one of the most powerful strategies to access these derivatives. The process usually proceeds via the *in situ* activation of the C=N bond through various means, followed by the addition of the nucleophile at C, resulting in the formation of a new carbon–carbon bond and a chiral center in the α-position of the amino group if $R^1 \neq R^2 \neq R^3$ (Scheme 1). Both steps are often considered to happen simultaneously, as the activation occurs through ligation of the *N*-PG moiety to the nucleophile counterion (M^+), either via the Lewis basic nitrogen atom of the imine or its protective group (PG). When $R^1 \neq R^2$, coordination of the imine can occur in a *syn*- or *anti*-manner depending on the nature of the substrate and M^+, an additional parameter that contributes to increase the challenge associated with the stereoselective addition of carbanions, in comparison with aldehydes which are considered to bind to the metal center in an *anti*-manner exclusively.



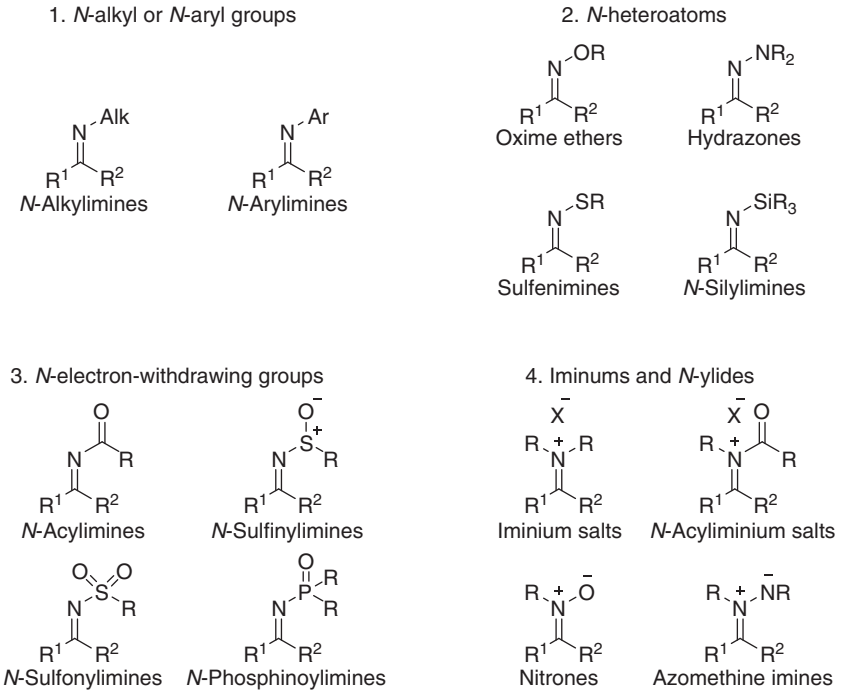
Scheme 1 General mechanism of the addition of nonstabilized nucleophiles to imines.

Recent advances in the synthesis of various imines from aldehydes has greatly contributed to enlarge the scope of accessible substrates for addition reactions. Azomethines are typically prepared by condensation of protected amines with aldehydes or ketones, leading, respectively, to aldimines and ketimines with elimination of water. Following the addition of the nucleophile, the amino protective group is removed to give access to a free amine, and the overall efficiency of these processes is often regarded as a combination of these three reactions (Scheme 2). Ideally, the imine used or its equivalent must be accessible in high yield from an aldehyde or a ketone, possessing the appropriate electrophilicity for a nucleophilic addition in mild conditions, and the *N*-PG should be easily removed afterward. Choosing the suitable *N*-PG capable of addressing these requirements while affording a general method is part of the challenge associated with these processes. While this chapter will specifically focus on the addition of nonstabilized nucleophiles to imines, it must be noted that α-chiral amines are also readily accessible via the addition of stabilized nucleophiles to imines (Mannich, Aza-Henry, or Strecker processes)[1,2] or via the reduction of the corresponding ketoimines,[1,3] including hydrogenation, reductive amination, and hydroboration methods.



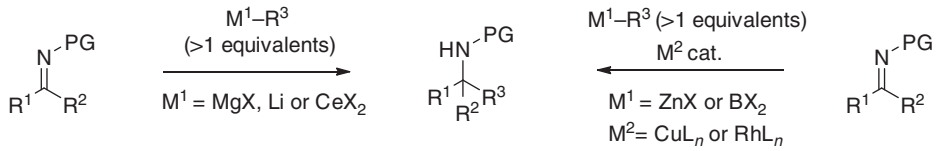
Scheme 2 Typical three-step process for the access to α-chiral amines through the addition of nonstabilized carbanions to azomethines.

The electronic properties of azomethines are highly dependent on the nature of the *N*-substituent of the substrate. Each type of *N*-substituted imines has its own reactivity profile and optimal set of conditions. These azomethines can be subdivided into four main classes depending on the type of *N*-substituent, each of which have significantly different electrophilicities, Lewis basicities, and modes of activation: (1) *N*-alkyl or *N*-aryl groups, (2) *N*-heteroatoms, (3) *N*-electron-withdrawing groups, and (4) iminums and *N*-ylides (Scheme 3).



Scheme 3 Different classes of imines and imine derivatives covered.

Regardless of the class of electrophiles used, the vast majority of examples reported in the literature for the addition of nonstabilized carbon nucleophiles employ strongly nucleophilic organometallic species such as Grignard, organolithium, or organocerium reagents, which are typically used in stoichiometric amounts (M^1–R^3, Scheme 4). More recently, the use of transition-metal catalysts (M^2) based mainly on rhodium or copper has permitted the addition of milder nucleophiles (M^1–R^3) to imines, such as organozinc or organoboron reagents, where only a catalytic amount of the active nucleophile is generated immediately through transmetallation.



Scheme 4 Different types of carbon-based nucleophiles used for the addition to imines.

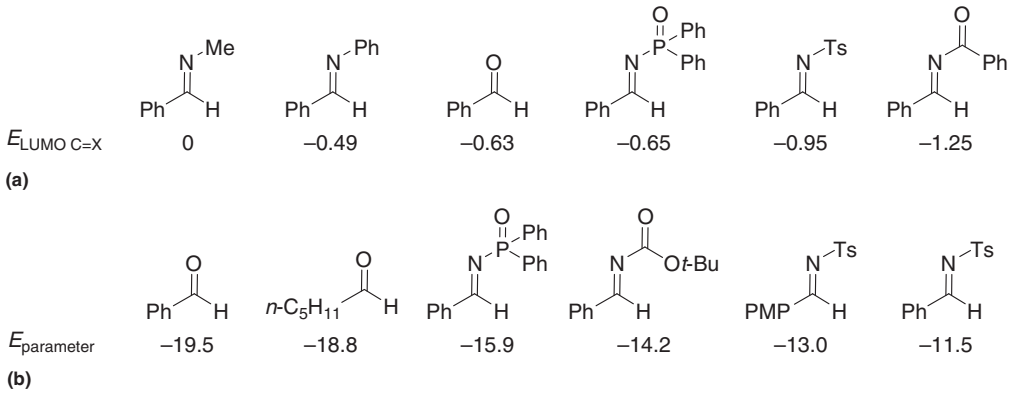
The addition of various types of organometallic reagents to lead to racemic amines has already been covered in a previous version of this chapter.[4] Since the most recent advances in this field mainly involve the formation of enantioenriched chiral amines, the focus of this chapter will remain on enantioselective processes using various strategies, employing either stoichiometric or catalytic amounts of chiral reagents.

1.11.1.1 Azomethine Reactivity

Although the process is analogous to the well-known addition of carbanions to aldehydes and ketones, significant reactivity differences are typically observed between the two electrophilic systems. Thus, the addition of nucleophiles to azomethines requires specific conditions to achieve the desired reactivity and must be treated differently. For example, the addition of organometallic reagents to azomethines, especially with the less-electrophilic *N*-alkyl imines, is sometimes hampered by various undesired side-reactions such as reduction of the C═N bond or α-deprotonation, which are typically less problematic with carbonyl derivatives. In order to circumvent these issues, it is often possible to tune the nature of the *N*-PG and/or the conditions employed to favor the addition on C═N as the major pathway.

1.11.1.2 Electrophilicity of Imines and Imine Derivatives

Compared to carbonyl derivatives, simple *N*-alkyl or *N*-aryl imines are usually more basic and less electrophilic, which means that they are sometimes more readily activated with a Lewis acid or a transition metal, whereas the addition of carbanions possessing only weakly coordinating countercations is typically more difficult. In order to increase the electrophilicity of the C═N bond, various strategies have been employed, including the use of an electron-withdrawing group (EWG) as a substituent directly linked to the imine carbon atom, such as in glyoxal derivatives. Since the presence of an α-electron-withdrawing substituent is not always desired in the final product, a more general approach consists of using *N*-EWG imines as electrophiles, where the EWG, acting as a protective and an activating group, can be cleaved after the addition to liberate a free amine. In order to quantify the effect of such *N*-substitution on the imine electrophilicity, various data issued from either experimental or theoretical studies can be used (Scheme 5).[5,6] *N*-Acylimines and *N*-tosylimines are the most electrophilic of the *N*-EWG imines, whereas *N*-alkyl- and

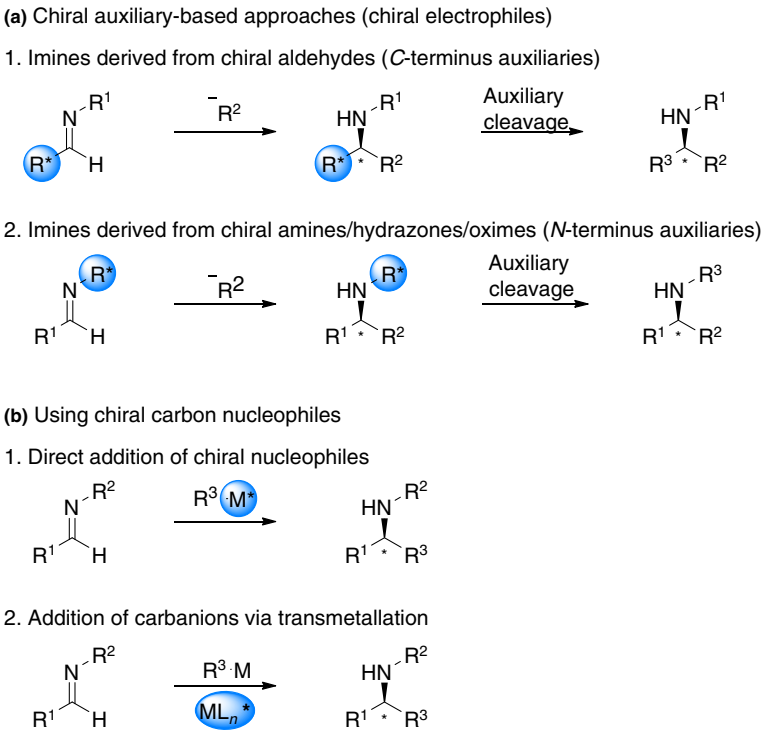


Scheme 5 Comparison of the relative electrophilicity of aldehydes and *N*-substituted imines using (a) calculation of the LUMO energies in eV (geometry optimized at B3LYP/6–31G(d))[5] and (b) Mayr's *E* parameters derived from experimental rate constants measured in aziridination/epoxidation reactions.[6]

N-aryl-substituted imines are significantly less reactive than aldehydes. Thus, strong nucleophiles such as Grignards are often needed for the addition to occur to simple *N*-alkylimines. However, the use of *N*-EWG imines as electrophiles is particularly common in catalytic asymmetric addition reactions using various transition metals such as rhodium, copper, iridium, or palladium. It should be noted that due to the purely electronic nature of these calculations, the values depicted here are independent of the different steric effects at the approach of the nucleophile and of the mode of activation employed for the addition.

1.11.1.3 Strategies for the Stereocontrol of the Addition

In order to access these compounds in their enantioenriched form through a stereocontrolled addition, various strategies have been developed. One of the most reliable ways to achieve this goal is the use of covalently bound chiral auxiliaries, which can be located either on the α-carbon (1) or on the imine *N*-substituent (2) (Scheme 6(a), chiral electrophiles). In contrast to the use of aldehydes or ketones as electrophiles where the auxiliaries can only be located on the *C*-terminus, imines permit access to a vast diversity of chiral environments around the C═N bond in order to obtain high stereoselectivities. The diastereoselective addition step is often followed by cleavage of the chiral group previously installed on the substrate, leading to an optically active α-chiral amine. Alternatively, the use of chiral nucleophiles has emerged as a powerful tool for the efficient formation of these enantioenriched moieties (Scheme 6(b)). The asymmetric induction can come directly from a chiral nucleophile added to the reaction mixture (1) or via transmetallation of an achiral nucleophile to a chiral metal complex to form an active chiral organometallic species (2).



Scheme 6 General strategies for the formation of enantioenriched α-chiral amines via the addition of carbanions to imines.

1.11.2 1,2-Additions of Unstabilized Carbanions to Imines and Imine Derivatives

Chiral auxiliary-based approaches (see Scheme 6(a) and Section 1.11.1.3), where a chiral group is covalently attached to the imine electrophile before the addition step, obviously necessitates the use of stoichiometric amounts of chiral reagents. When this chiral functional group is not desired in the final product of the sequence, the need for its installation and cleavage renders this strategy less atom-economic and retrosynthetically efficient. Nevertheless, the robust and predictable nature of such an approach still makes it to this day one of the most reliable and widespread mean for the enantioselective formation of α-branched amines.

In the past 25 years, significant advances have been made in the field of catalytic asymmetric addition of carbanions to imines in an effort to reduce the overall cost of enantioselective syntheses of chiral amines. Most of these transformations employ chiral carbanion intermediates (see Scheme 6(b) and Section 1.11.1.3) formed *in situ* from an achiral nucleophile added in

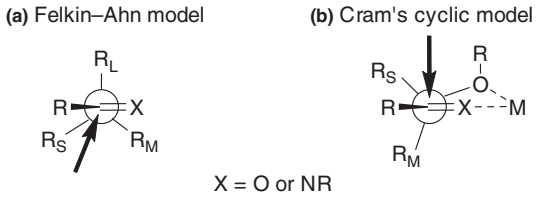
stoichiometric amount and a chiral catalyst. While this strategy can also be used with an excess of a preformed chiral nucleophile as commonly seen in the addition of allyl or crotyl groups for example, future developments in the enantioselective formation of chiral amines are expected to emerge mainly from these catalytic asymmetric processes due to their increased overall efficiency.[1,2] It is noteworthy that this approach typically offers greater functional group tolerance due to a lower concentration of the effective nucleophile in the reaction mixture. Due to the various differences of stoichiometric and catalytic systems, the following sections will be divided as follows: (1) using stoichiometric amounts of chiral reagents (including auxiliary-based approaches, Section 1.11.2.1) and (2) catalytic asymmetric methods (Section 1.11.2.2).

1.11.2.1 Using Stoichiometric Amounts of Chiral Reagents

One of the most widely studied and dependable method to access enantioenriched α-chiral amines via the addition of unstabilized carbanions to C=N electrophiles consists of using stoichiometric amounts of chiral reagents. Multiple possibilities exist for such process, where a chiral group can be located either on the *C*-terminus (Section 1.11.2.1.1) or the *N*-terminus (Section 1.11.2.1.2) of the azomethine substrate or on the attacking nucleophile (Section 1.11.2.1.3). These three strategies possess very distinct stereoinduction mechanisms and will thus be treated separately in the following Sections 1.11.2.1.1, 1.11.2.1.2, and 1.11.2.1.3.

1.11.2.1.1 Imines derived from chiral aldehydes

When the azomethine substrate is derived from a chiral aldehyde, several competing predictive models are available, where the sense of induction highly depends on the nature of the chiral group and the nucleophile employed. In analogy to the extensively studied addition of nucleophiles to carbonyl substrates, the predictive Cram, Felkin–Ahn, and Cornforth models are also applicable to azomethine chemistry. Thus, in principle, a nonchelating chiral group at the α-position of the acyclic imine will afford the Felkin–Ahn product issued from minimization of torsional strain at the transition state and subsequent attack on the most accessible face of the imine (Scheme 7(a)). Conversely, the presence of a chelating functionality at this position leads to the product issued from the addition on the least-hindered face of the chelate intermediate according to Cram's cyclic model, under the appropriate reaction conditions favoring the formation of such chelate (Scheme 7(b)). It is noteworthy that Cram's cyclic model is usually effective only with *N*-alkyl or *N*-arylimine derivatives where the most Lewis basic site of the substrate is the nitrogen atom.

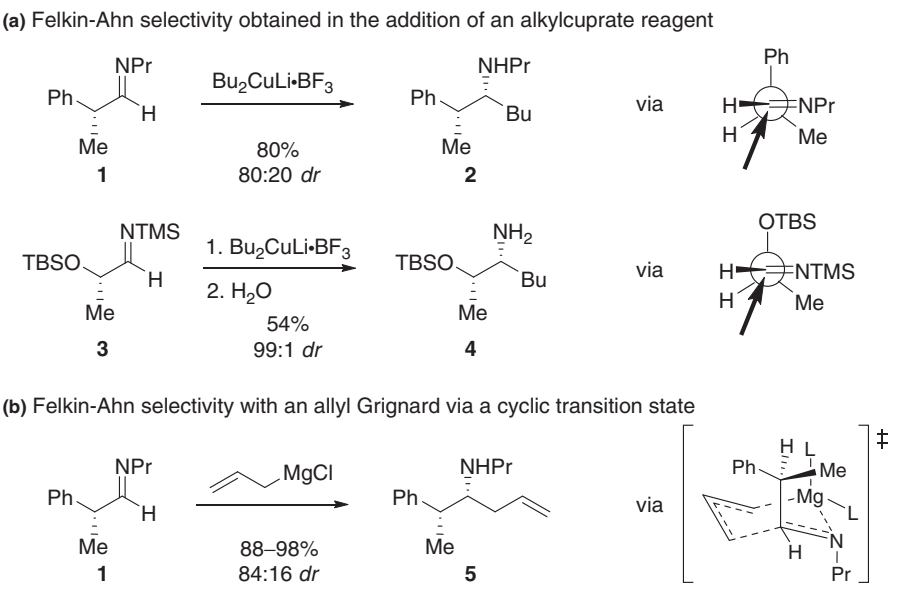


Scheme 7 Predictive models applicable to imines derived from α-chiral aldehydes.

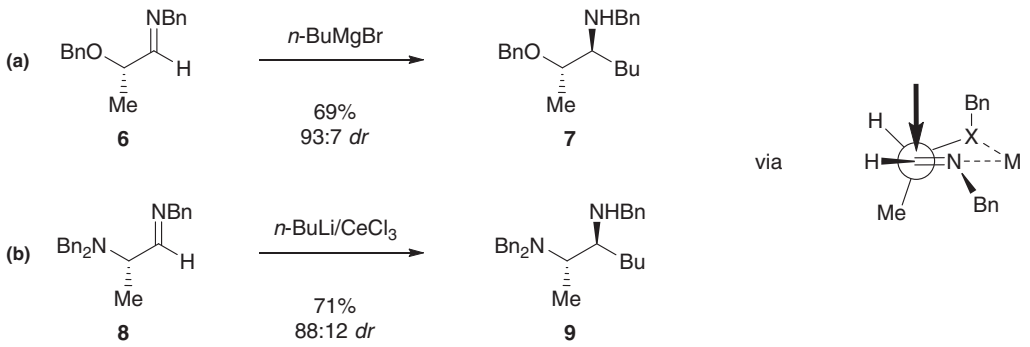
While successful examples of the Felkin–Ahn model with simple alkylmetals and imines remain scarce, the use of alkylcopper or alkylcuprate reagents complexed with BF_3 can afford a good diastereoselectivity for the Felkin product (Scheme 8(a)).[7,8] The use of allyl Grignards is more common and can provide a reasonable diastereoselectivity through a six-membered transition state (Scheme 8(b)).[7] It is noteworthy that in contrast with the corresponding carbonyl compounds, the chiral group of the imine is believed in this case to be placed in an axial conformation in the favored transition state, due to a stereoelectronic effect with the axial *N*-substituent of the imine.

The alternative use of chelation control (see Cram's cyclic model, Scheme 7(b)) is a much more general and widespread means of access to α-chiral amines from chiral aldehyde substrates. Various types of α-chiral chelating groups can be used in such processes, including α-chiral benzyl ethers (**6**) or α-chiral *N*,*N*′-dibenzylamines (**8**) (Scheme 9).[9,10] Interestingly, when the *N*-benzylimine substrate **8** was replaced with an *N*-tosylimine, the opposite diastereoselectivity from nonchelation control (Felkin–Ahn) was observed for the corresponding 1,2-diamine product. This was presumably due to the reduced Lewis basicity of such an imine which is expected to be incapable of forming a stable chelate before nucleophilic addition.[10] It is noteworthy that good diastereoselectivity can also be obtained via chelation control with hydrazones,[11] oxime ethers,[12] or nitrones[13] derived from chiral aldehydes through an analogous stereoinduction mechanism, where the size of the chelate varies depending on the nature of the imine derivative used.

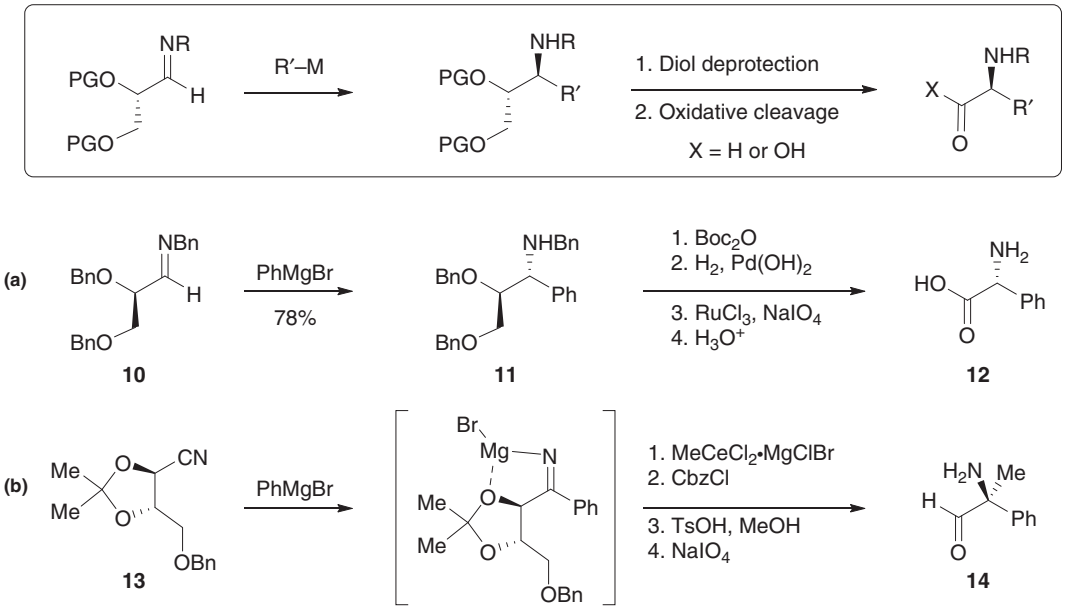
This approach for the stereocontrol of the addition of nonstabilized nucleophiles has been widely used for the synthesis of enantioenriched α-amino aldehydes, precursors of the corresponding amino acids. Two distinct strategies can be used, both involving the presence of a chiral basic group at the α-position such as a protected diol or an acetal capable of inducing a chelation-controlled addition (Schemes 10 and 11). Following the addition, the aldehyde functionality is unmasked to lead to a chiral α-aminoaldehyde. In the first case, a protected 1,2-diol such as **11** is cleaved via oxidation (Scheme 10).[14,15] In the latter case, a chiral acetal (**15**), aminal (**16**), or thioacetal (**17**) located at the α-position is hydrolyzed directly after the addition, revealing the aldehyde functionality (Scheme 11).[11g,16–18] The stereocontrol of this strategy relies on a selective chelate formation on one of the



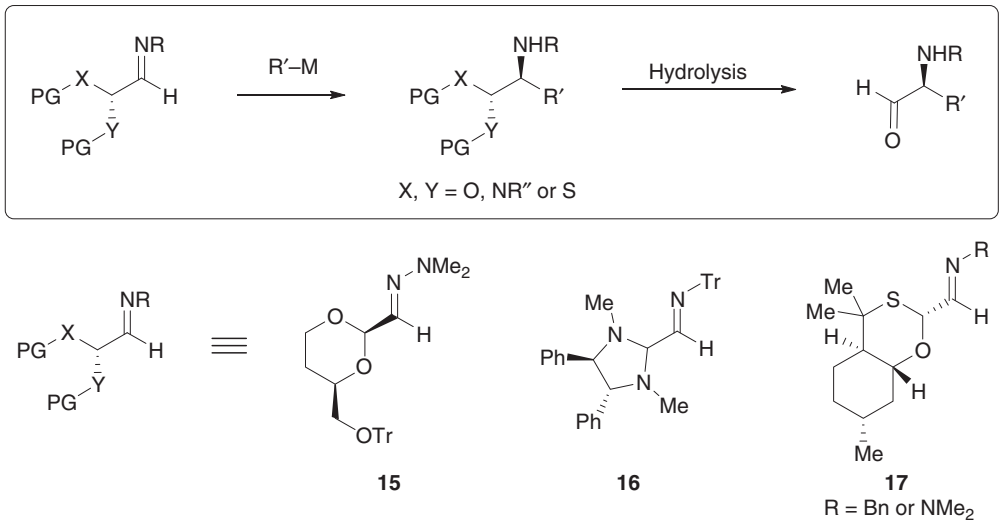
Scheme 8 Examples of Felkin–Ahn selectivity (nonchelation control) with alkyl and allyl-metal reagents.



Scheme 9 Examples of chelation control using (a) α-chiral benzyl ethers or (b) α-chiral *N,N′*-dibenzylamine chelating groups.



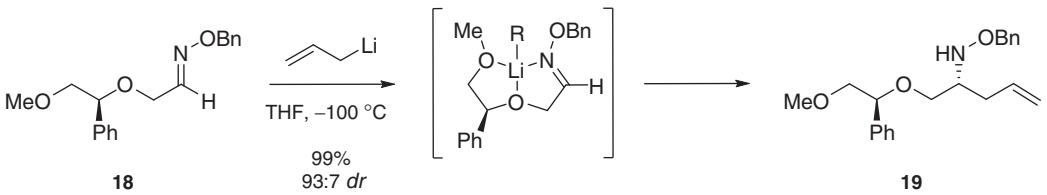
Scheme 10 Use of protected chiral diols as masked aldehyde equivalents in chelation-controlled additions.



Scheme 11 Examples of hydrolyzable chiral acetal, aminal, or thioacetal for chelate-controlled additions.

basic sites located at the α-position of the imine. Both approaches have been shown to lead to very high levels of diastereoselectivity for the addition step, with alkyl-, aryl-, or alkynyl-metal nucleophiles.

The chirality of the starting imine derivative can also be located at remote positions of the reactive addition site such as in oxime **18** (Scheme 12).[19] In this specific case, the presumed formation of a tridentate chelate before the addition ensures sufficient rigidity of the chiral moiety for the obtention of high stereocontrol for the formation of **19**.



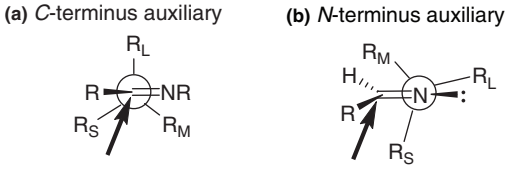
Scheme 12 Remote stereocontrol of addition achieved through a tridentate chelate.

1.11.2.1.2 Imine derivatives bearing chiral N-protective groups

1.11.2.1.2.1 Addition of organometallic reagents to chiral N-alkylimines

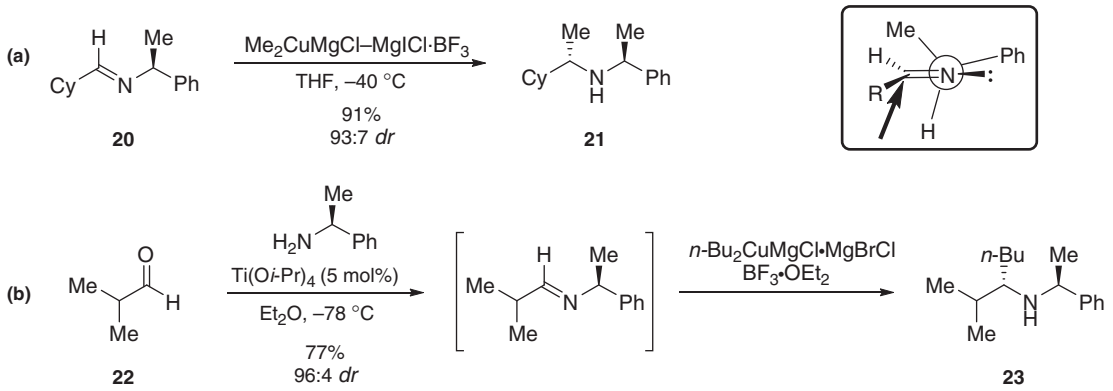
The use of chiral auxiliaries located at the *N*-terminus of the imine substrate is one of the most efficient means to access α-chiral amines via the addition of organometallic reagents to C=N bonds.

In general, auxiliaries relying solely on torsional strain for stereocontrol afford only modest stereoselectivities, not unlike what is observed in the case of imines derived from chiral aldehydes (see Section 1.11.2.1.1). In analogy to the Felkin–Ahn model for *C*-terminus auxiliaries (Scheme 13(a)), a stereochemical model has been proposed to account for the observed diastereoselectivities with *N*-terminus auxiliaries relying on nonchelation control (Scheme 13(b)).[7,20]



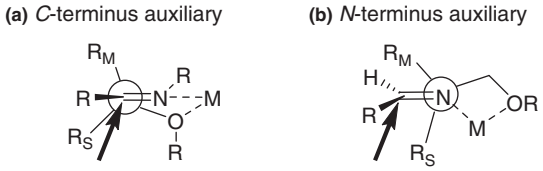
Scheme 13 Stereochemical models accounting for the observed sense of induction with nonchelating auxiliaries.

Although successful examples using these auxiliaries are quite rare,[21] the use of α-methyl benzylamine as auxiliary with cuprate/BF_3 mixtures can lead to good diastereoselectivities in certain cases (Scheme 14).[22,23]



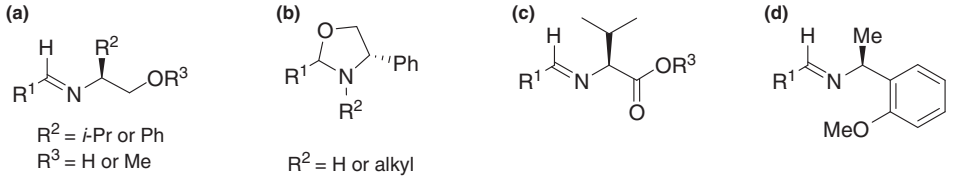
Scheme 14 Successful examples of the use of a nonchelating *N*-bound auxiliary.

N-bound auxiliaries relying on chelation control are much more widespread and structurally diverse. When the electrophile is an imine, the diastereo-outcome of the addition can be predicted via a model analogous to Cram's cyclic model for *C*-bound auxiliaries (Scheme 15).[24]



Scheme 15 Predictive models of chiral *C*- and *N*-bound auxiliaries relying on chelation control.

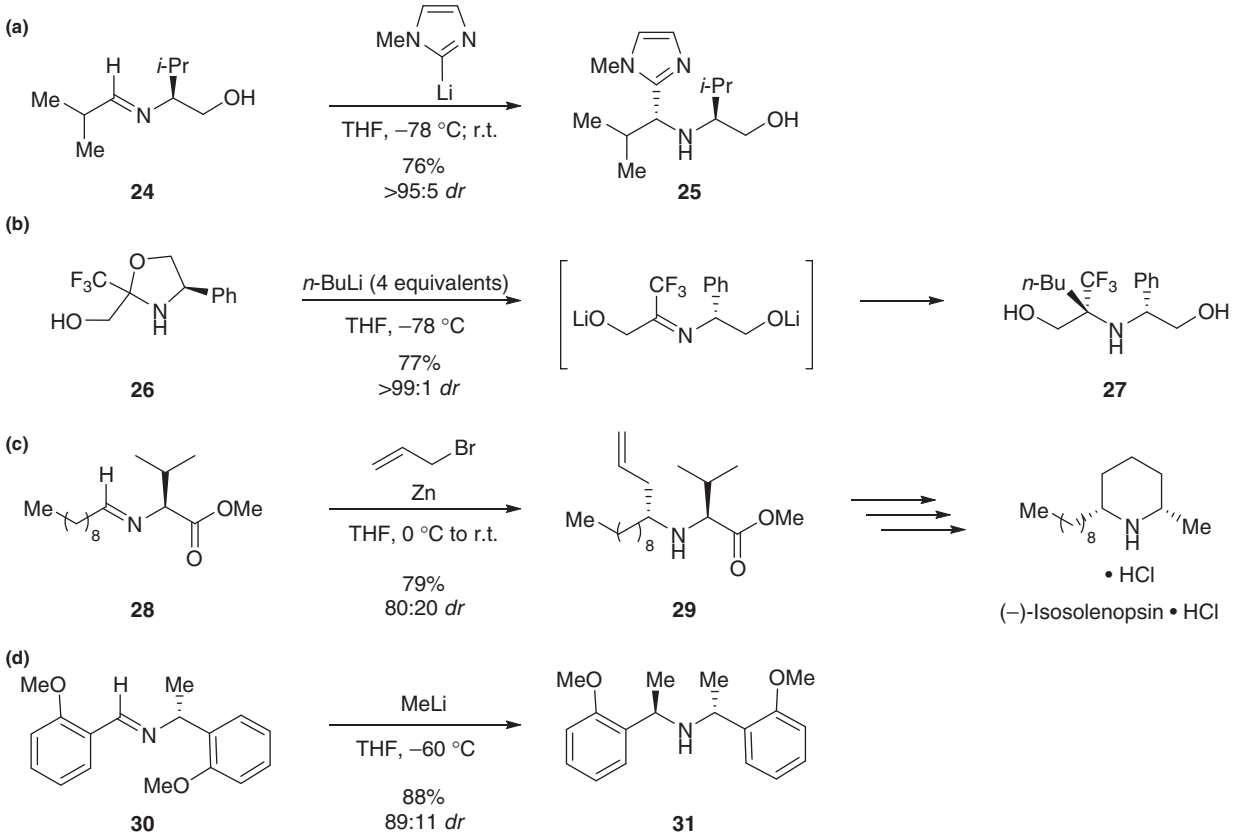
Different generic examples of these chiral chelating groups, often derived from amino acids, are illustrated in Scheme 16. While auxiliaries of types (a) and (b) are compatible with a variety of alkyl- or arylmetal reagents such as Grignards, organolithium, organozinc, organocuprates, or organocerium nucleophiles,[24,25] type (c) auxiliaries are mainly limited to allylation reactions such as Barbier-type couplings due to chemoselectivity issues with more nucleophilic carbanion equivalents.[26] The addition of a methoxy group at the *ortho*-position of α-methyl benzylamine, a nonchelation control auxiliary, leads to a distinct mechanism involving a six-membered chelate capable of high diastereoinduction with alkyl- and allyllithium reagents (see Scheme 16(d)).[27] Recent examples of the use of these auxiliaries are shown in Scheme 17.[27b,28–30]



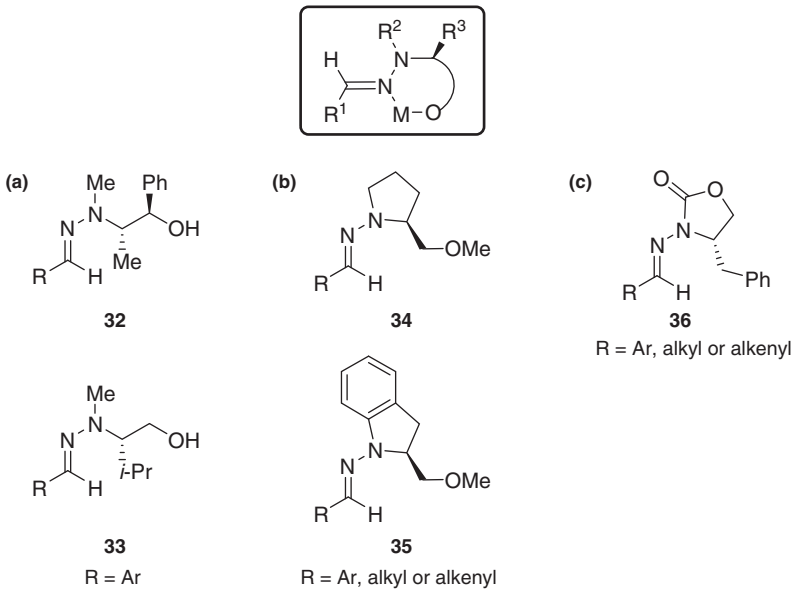
Scheme 16 Various *N*-bound chiral auxiliaries relying on chelation control for imine electrophiles.

1.11.2.1.2.2 Addition of organometallic reagents to hydrazones derived from chiral hydrazines

Chiral hydrazones, where the chirality is located at the *N*-terminus of the electrophile, have found widespread use for the synthesis of α-chiral amines via the diastereoselective nucleophilic addition of various organometallic reagents. The most successful chiral auxiliaries of this type reported to date involve a stereoinduction mechanism similar to the chelation control discussed in Section 1.11.2.1.2.1, where a five- or six-membered chelate is often invoked as a rigid controller of the diastereo-outcome of the addition (Scheme 18). The formation of this chelate activates the hydrazone toward the nucleophilic addition, which can occur either through an internal or an external delivery, depending on the conditions used. For instance, *N*-aminoephedrine- or *N*-aminovalinol-derived imines **32** and **33**, presumably forming six-membered chelates, have been shown to afford a high diastereocontrol for the addition of simple alkyl Grignard reagents (Scheme 18(a)).[31] Chiral hydrazones **34** derived from (*S*)-*N*-amino-2-methoxymethylpyrrolidine (SAMP) are particularly general electrophiles for the stereoselective addition of a variety of organometallic reagents including organolithium, Grignards, and organocerium species (Scheme 18(b)).[32] Hydrazones derived

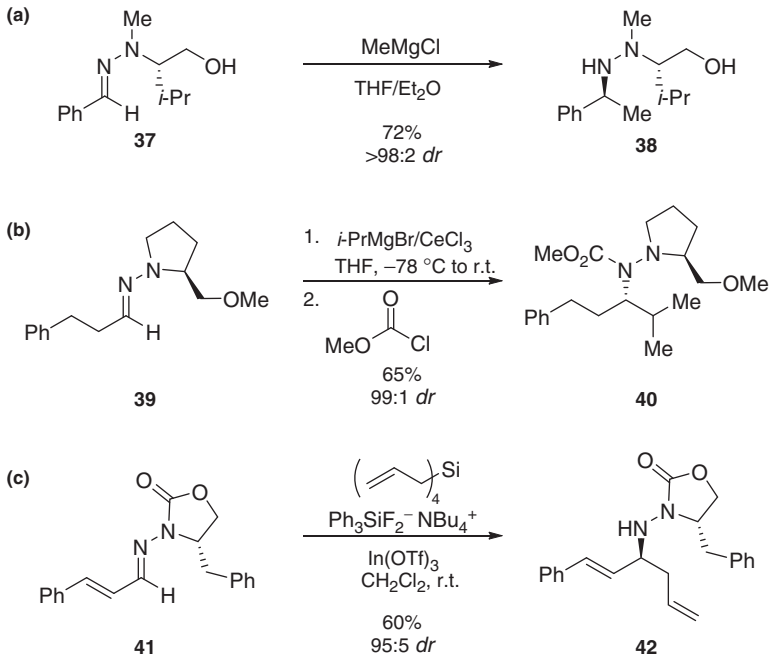


Scheme 17 Examples of the use of *N*-bound chelation-control auxiliaries.



Scheme 18 Different types of hydrazones derived from chiral hydrazines used for addition reactions.

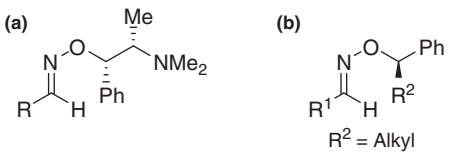
from aliphatic and aromatic aldehydes are usually tolerated and compatible with both sp^3 and sp^2 nucleophiles. More recently, the use of a chiral *N*-acylhydrazone equivalent **36** as auxiliary has been shown to be effective for the indium-mediated addition of allylsilanes to both aromatic and aliphatic electrophiles (Scheme 18(c)).[33] The scope of nucleophiles for these reactions also includes carbon radicals, usually generated from alkyl iodides.[34] Examples of the successful use of these auxiliaries is shown in Scheme 19.[31d,35,33c]



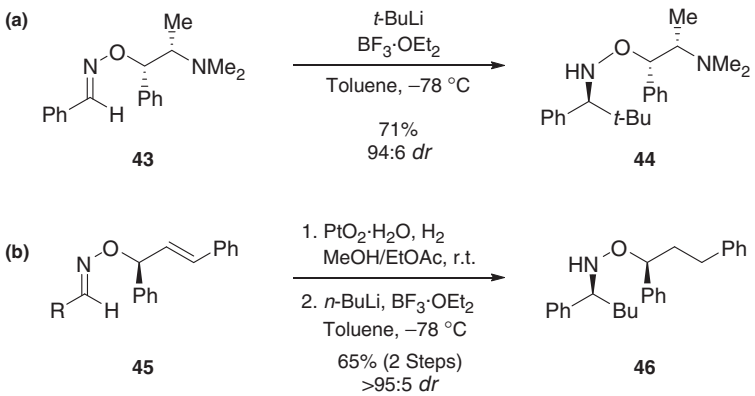
Scheme 19 Examples of the use of hydrazones derived from chiral hydrazines as electrophiles with various nonstabilized carbanion nucleophiles.

1.11.2.1.2.3 Addition of organometallic reagents to oximes and nitrones derived from chiral hydroxylamines

In analogy with hydrazones, chiral oximes derived from *O*-alkyl hydroxylamines have been used successfully as electrophiles for diastereoselective addition reactions to the C=N bond (Scheme 20).[36,37] Although these substrates are usually considered to be less general than their hydrazone counterparts, a number of successful examples of their use have been reported, some of which are depicted in Scheme 21.[36,38]

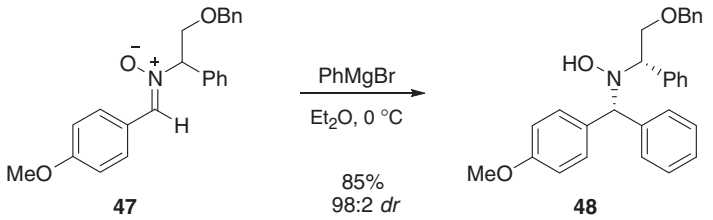


Scheme 20 Different types of oximes derived from chiral hydroxylamines used for addition reactions.



Scheme 21 Use of *O*-chiral oximes for diastereoselective additions of nonstabilized carbanions.

When the imine derivative is synthesized from a chiral *N*-alkyl hydroxylamine instead, a chiral nitrone is generated, which can act as competent electrophile for the highly diastereoselective addition of Grignard and organolithium reagents (Scheme 22).[39]

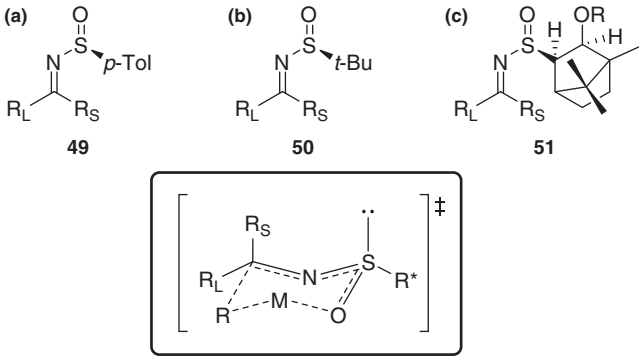


47 48

Scheme 22 Use of a *N*-chiral nitrone as electrophile for diastereoselective additions.

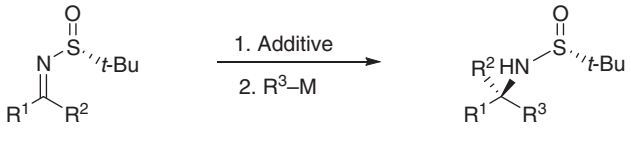
1.11.2.1.2.4 Addition of nonstabilized carbanions to chiral N-sulfinylimines

One of the most general and reliable type of *N*-bound auxiliary for the diastereoselective addition of Grignard reagents to the C═N bond consists of a sulfinyl group directly bound to nitrogen, where the sp^3-hybridized sulfur atom is chiral and enantiopure (Scheme 23). The most efficient auxiliaries of this type reported to date are **49**[40] and **50**[41] (Schemes 23(a) and (b)), while some success in diastereoselective additions has also been reported with a parent camphor-derived analog (**51**, Scheme 23(c)).[42] The less-hindered *N*-toluenesulfinylimines **49** are only compatible with allyl- and benzyl-Grignard reagents due to competitive attack on the sulfinyl group with other nucleophiles such as alkyl-, vinyl-, and arylmetals. The use of a very hindered *N*-*tert*-butanesulfinyl group instead allows a chemoselective addition on the imine functionality with these nucleophiles, generally with very high diastereocontrol (**50** and **58**, Scheme 23(b) and Table 1). A six-membered transition state, where the sulfur substituent and the large group of the imine are placed in equatorial positions, accounts for the observed relative configuration of the products observed in such reactions (Scheme 23). Some examples of the use of these auxiliaries are shown in Scheme 24.[40a,41b,42a]



Scheme 23 Different types of *N*-sulfinylimines used for addition reactions.

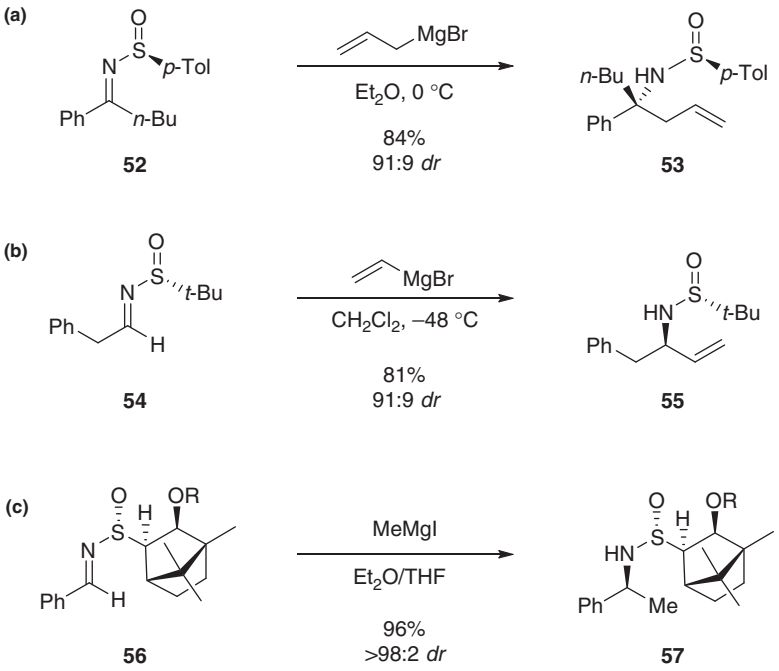
Table 1 Chiral *N*-*tert*-butanesulfinylimines as electrophiles in the stereoselective addition of Grignard and organolithium reagents



58 59

Entry	R^1	R^2	R^3–*M*	*Yield (%)*	dr	*Additive*	*References*
1[a]	Et	H	PhMgBr	>99	96:4	–	41a
2[a]	*i*-Pr	H	EtMgBr	>99	97:3	–	41a
3[a]	Ph	H	EtMgBr	98	92:8	–	41a
4[b]	*i*-Pr	Me	PhLi	93	97:3	Me_3Al	41b
5[b]	Ph	Me	*n*-BuLi	86	98:2	Me_3Al	41b
6[b]	Ph	*n*-Bu	MeLi	>99	99:1	Me_3Al	41b
7[b]	2-Naphthyl	Me	PhLi	62	99:1	Me_3Al	41b

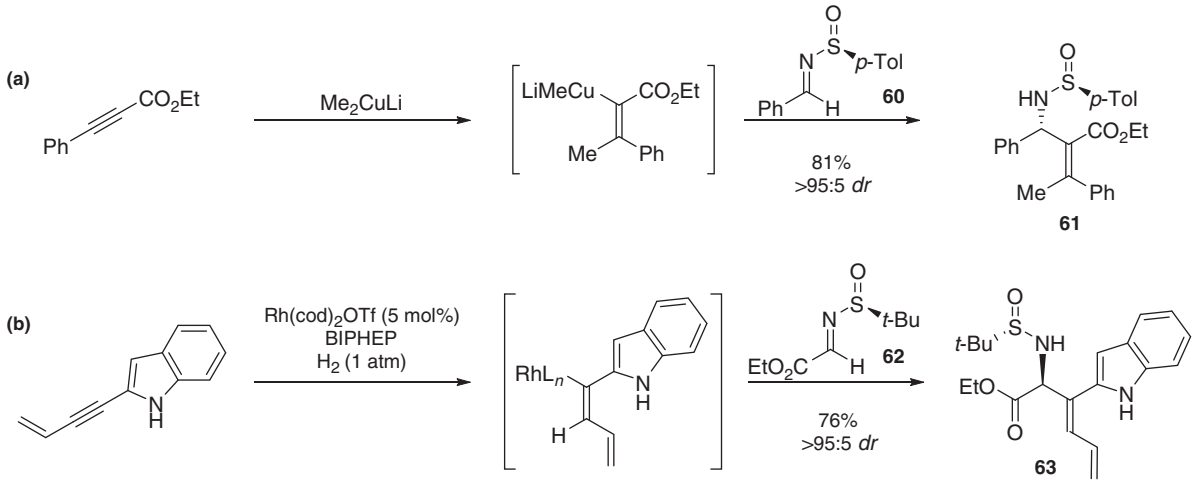
[a]CH_2Cl_2 was used as solvent.
[b]Toluene was used as solvent.



Scheme 24 Examples of the use of chiral *N*-sulfinylimines as electrophiles with Grignard reagents.

The more challenging addition to the parent ketimines is possible by using organolithium reagents instead of Grignards in the presence of trimethylaluminum as stoichiometric additive (Table 1, entries 4–7).[41b] This Lewis acid is thought to increase the electrophilicity of the imine through *N*-ligation, affording a higher yield of the addition product.

Vinyl-substituted nucleophiles can be generated *in situ* through carbo- or hydrometallation of alkynes, using organocuprates or Rh-based catalysts, respectively, and subsequently react with chiral *N*-sulfinylimines, leading to stereochemically defined polysubstituted allylamines such as **61** or **63** in high stereoselectivity (Scheme 25).[40e,41n]

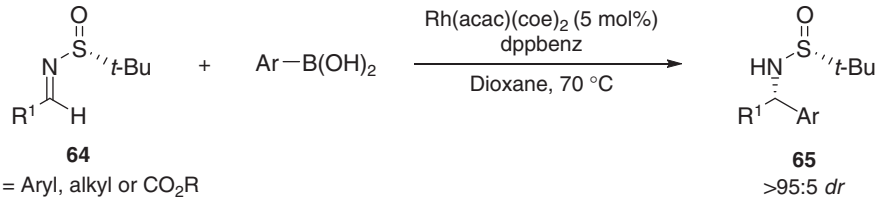


Scheme 25 Diastereoselective vinylation of chiral *N*-sulfinylimines via carbo- and hydrometallation of alkynes.

The diastereoselective addition of arylboronic acids to the same type of imine derivatives is possible through the use of Rh(I) catalysts, affording a mild alternative to aryl-Grignard reagents as stoichiometric nucleophiles (Scheme 26).[41k,l] In this type of process, only a catalytic amount of the active arylrhodium nucleophile is generated immediately through transmetallation.

1.11.2.1.3 Stoichiometric addition of chiral nucleophiles

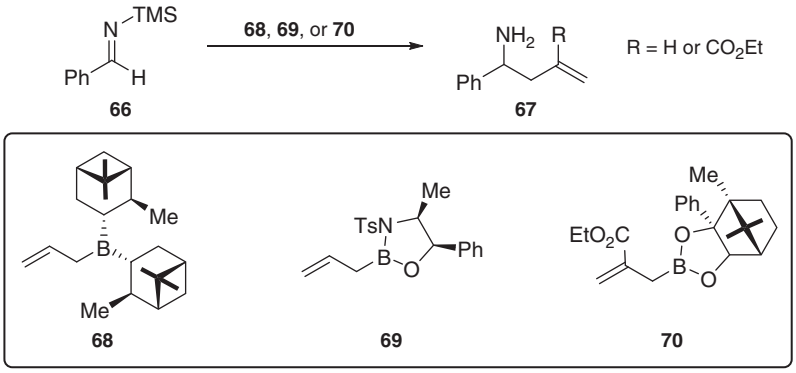
In contrast to the use of chiral imine derivatives as electrophiles, the stereocontrol of the addition may also arise from the interaction of an approaching chiral nucleophile with an achiral imine. While this concept is nowadays often employed in various



Scheme 26 Rh(I)-catalyzed diastereoselective arylation of chiral *N*-sulfinylimines.

types of catalytic asymmetric reactions (see Section 1.11.2.2), most of the successful methods reported to date using stoichiometric amounts of chiral nucleophiles are limited to allylation or crotylation chemistry. An advantage of such a strategy is the direct formation of an enantiopure α-chiral homoallylic amine, without the need for the cleavage of a chiral auxiliary. For instance, when a chiral allylboron reagent such as **68**, **69**, or **70** is used as nucleophile with *N*-trimethylsilylimine **66**, the corresponding free amine product **67** can be directly obtained in high stereoselectivity (Table 2).[43] In the case of nucleophile **68**, it was reported that the addition of a stoichiometric amount of H_2O at −78 °C is essential to achieve high yields and stereoselectivities.[43e]

Table 2 Addition of chiral allylboron reagents to achiral *N*-trimethylsilylimine **66**



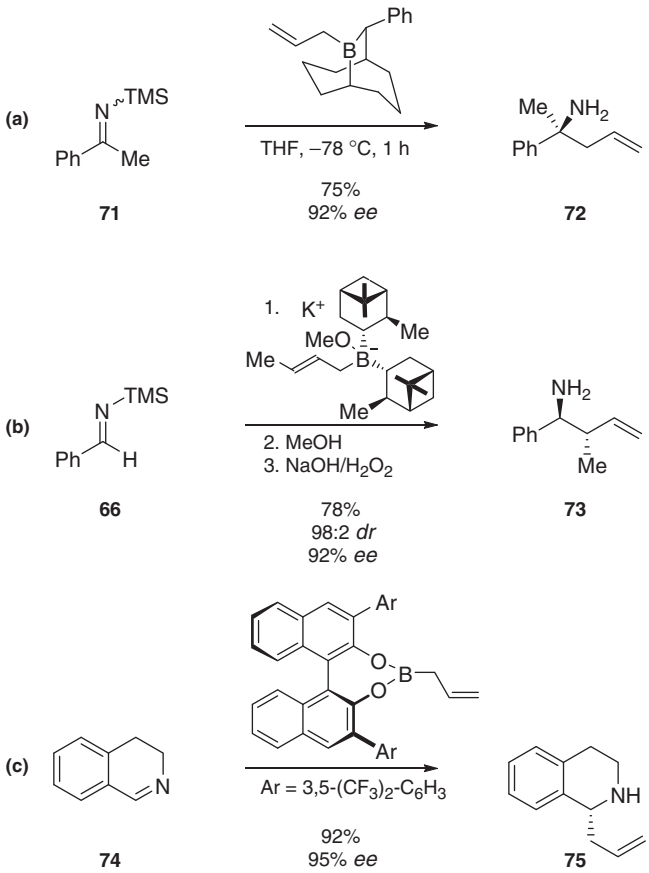
Entry	*Nucleophile*	*Conditions*	*Yield (%)*	ee *(%)*	*References*
1	**68**	THF, −78 °C, 3 h	70	73	43a
2	**68**	THF/H_2O, −78 °C, 30 min	90	92	43e
3	**69**	THF, −78 °C, 3 h	89	92	43b
4	**70**	Toluene, r.t., 2 weeks	92	>95	43j

Several other successful examples of the use of chiral allylboron reagents as stoichiometric nucleophiles have been reported (Scheme 27). The enantioselective allylation of ketoimines such as **71** is also possible through the use of an enantiopure *B*-allyl-10-phenyl-9-borabicyclo[3.3.2]-decane nucleophile, although generally with lower yields than with the parent aldimines (Scheme 27(a)).[43i] The addition of a chiral crotylboron reagent analogous to allylboron nucleophile **68** allows for the stereospecific formation of β-chiral homoallylic amines such as **73** in good yields (Scheme 27(b)).[43g] Moreover, the allylboration of cyclic *N*-alkylimine **74** was reported to be highly enantioselective when a BINOL-derived allylboron nucleophile was employed (Scheme 27(c)).[43h]

The addition of pseudoephedrine-derived chiral allylsilane reagents of type **76** to *N*-acylhydrazones has also proven to be quite general (Table 3).[44] Indeed, good yield and stereoselectivity are typically observed for hydrazones derived from both aldehydes and ketones (entries 1–4), and the analogous reaction with the parent crotylboron reagents also proceeds with high stereocontrol (entries 5–6).

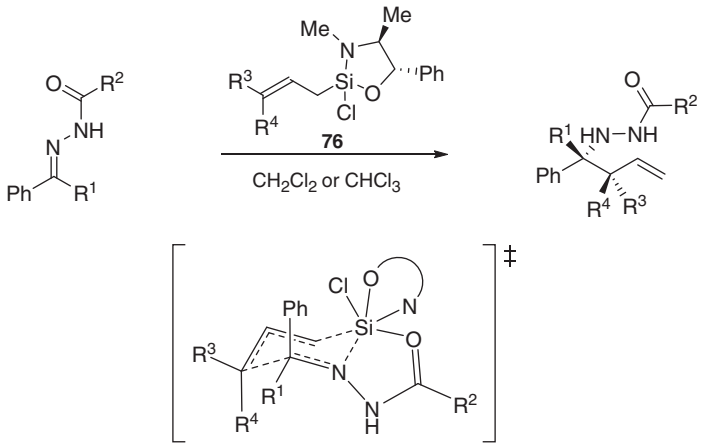
Chiral allyl- or crotylzinc reagents bound to bis(oxazoline) ligands are also competent nucleophiles in this type of process, and the stereoselectivity observed is typically high with a cyclic *N*-alkylimine such as **74** or glyoxal-derived oximes **77** (Scheme 28).[45]

N-Acylhydrazones **79** have been reported to react with a chiral allylindium species formed *in situ* in a mixture of In(0), allyl iodide, and a chiral BINOL derivative to afford *N*-acyl homoallylhydrazines **80** with good enantioselectivity (Scheme 29).[46] Although a catalytic asymmetric version of this reaction is theoretically possible, the use of a stoichiometric quantity of the BINOL derivative was found to be optimal for the enantioselectivity. The structure of the BINOL ligand was later on modified to allow a highly efficient catalytic asymmetric process, where only 10 mol% of this chiral moiety is necessary.[47]

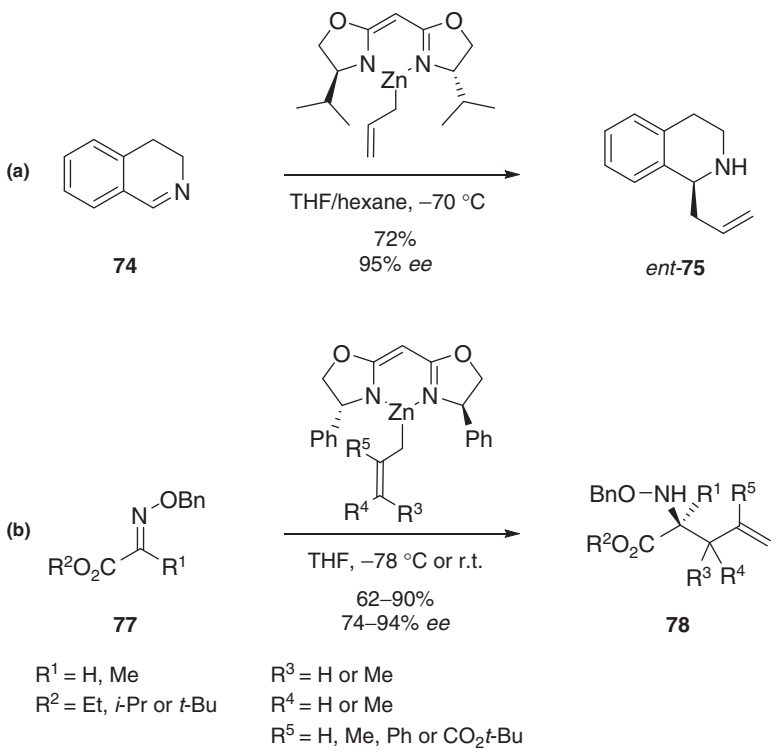


Scheme 27 Other methods for the stereoselective addition of chiral allylboron reagents to various imine derivatives.

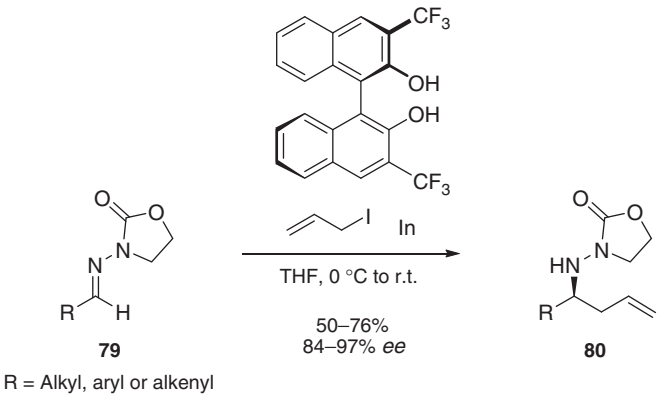
Table 3 Addition of chiral allylsilane reagents to *N*-acylhydrazones



Entry	*R*[1]	*R*[2]	*R*[3]	*R*[4]	*Yield (%)*	dr	ee *(%)*	*References*
1	H	Me	H	H	86	–	88	44c
2	Me	Ph	H	H	86	–	90	44d
3	*i*-Pr	Ph	H	H	80	–	97	44d
4	CO_2Me	Ph	H	H	76	–	93	44d
5	H	Ph	Me	H	89	95:5	97	44c
6	H	Ph	H	Me	81	96:4	95	44c



Scheme 28 Addition of chiral allylzinc-bis(oxazoline) nucleophiles to imine derivatives.



Scheme 29 Addition of chiral allylindium species to *N*-acylhydrazones.

1.11.2.2 Catalytic Asymmetric Addition of Nonstabilized Carbanions to Achiral Imines

The rise of asymmetric catalysis in the past few years in a vast array of transformations has inspired many organic chemists to develop new strategies for the synthesis of α-chiral amines in their enantioenriched forms via addition reactions. An advantage of these catalytic asymmetric transformations resides in the overall efficiency and atom economy of the process where, unlike most methods presented in Section 1.11.2.1, the chiral group employed to induce the enantioselectivity does not need to be installed on the substrate or removed from the addition product. In the past decades, this field has received considerable interest from the scientific community, from which the most efficient methods are summarized in the following Sections 1.11.2.2.1 and 1.11.2.2.2.

1.11.2.2.1 Catalytic activation of the nucleophile with chiral Lewis bases

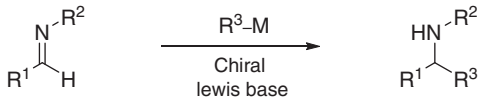
One of the first catalytic asymmetric strategies explored for the synthesis of α-chiral amines through the addition of nonstabilized nucleophiles to imine derivatives consists of using a substoichiometric amount of a chiral bidentate Lewis base capable of

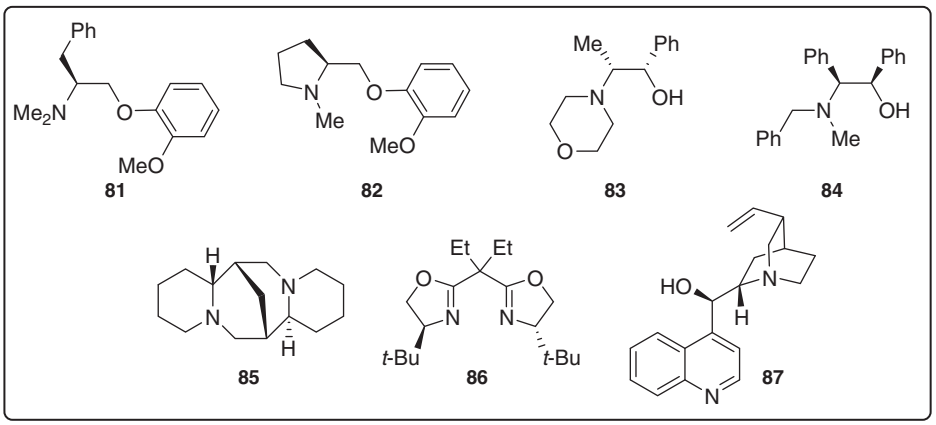
activating the organometallic nucleophile via complexation of the metal center (Scheme 30). The key for the success of such an approach mainly resides in the fact that the reagent complexed with the chiral Lewis base is more nucleophilic than the parent uncomplexed species (R–M), affording a faster addition reaction when this chiral environment is present around the nucleophile. This difference in the rates of addition, if considerable enough, can suppress a background (nonenantioselective) process between the uncomplexed nucleophile and the imine substrate, with careful optimization of the reaction conditions. In such a situation, only a catalytic amount of the chiral ligand can, in principle, be added, and the product isolated is solely issued from the addition of the more reactive complexed chiral species.

Scheme 30 Principle of catalytic activation of the nucleophile using a chiral Lewis base.

Although considerable efforts have been devoted to this area of research over the years, only a limited number of successful examples have been reported to date, mainly using organolithium and diorganozinc reagents as nucleophiles. Most of the Lewis basic ligands employed with this approach are chiral amino alcohols or diamines such as **81**–**87** (Table 4).[48–54] With these methods, it is often found that the amount of Lewis base added has an important influence on the enantioselectivity observed in the addition product even in optimized conditions, which highlights the lack of difference in reactivity between the achiral uncomplexed species and the desired chiral complexed nucleophile. As shown in Table 4, most of these methods employ a considerable amount of the chiral ligand (10–50 mol%), and the efficiency of this type of process is usually quite specific.

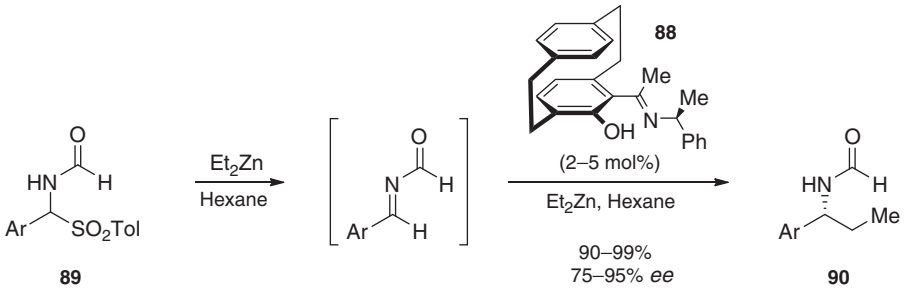
Table 4 Different chiral Lewis bases used in catalytic amounts to promote the addition of organolithium and diorganozinc reagents to imine derivatives





Entry	*Ligand (mol%)*	R^1	R^2	R^3–*M*	*Yield (%)*	ee *(%)*	*References*
1	**81** (30)	Ph	PMP	BuLi	99	60	48b
2	**82** (25)	Ph	Ph	BuLi	44	6	49a
3	**83** (50)	Ph	$P(O)Ph_2$	Et_2Zn	69	85	50
4	**84** (50)	Ph	$P(O)Ph_2$	Et_2Zn	67	90	51
5	**85** (20)	$Ph(CH_2)_2$	PMP	BuLi	91	79	52
6	**86** (10)	Ph	PMP	MeLi	97	69	53
7	**87** (50)	Ph	$P(O)Ph_2$	Et_2Zn	77	87	54

One of the rare successful examples of this type of method was reported in 2002, using *N*-formyl arylimine substrates with chiral [2.2]paracyclophane-based *N,O*-ligand **88** as catalyst (Scheme 31).[55] Due to the instability of these substrates, it is preferable to form them *in situ* from their corresponding sulfinate adduct by the addition of one extra equivalent of Et_2Zn acting as a



Scheme 31 Enantioselective addition of Et_2Zn to *N*-formyl imines catalyzed by a [2.2]Paracyclophane-based *N,O*-ligand.

base. Aromatic derivatives **90** are generally formed in high yields and enantioselectivities with Et_2Zn, using only 2–5 mol% of the Lewis basic catalyst. The same type of ligand was also used for the addition of Ph_2Zn to these substrates.[55b,56]

The seminal research work in this area has helped organic chemists considerably to understand and surpass the challenges in the catalytic asymmetric addition of nonstabilized nucleophiles to imines. This initial work has thus provided the foundation for the discovery of new catalytic asymmetric methods of addition reactions using chiral transition metal-based catalysts, which will be discussed in the following Section 1.11.2.2.2.

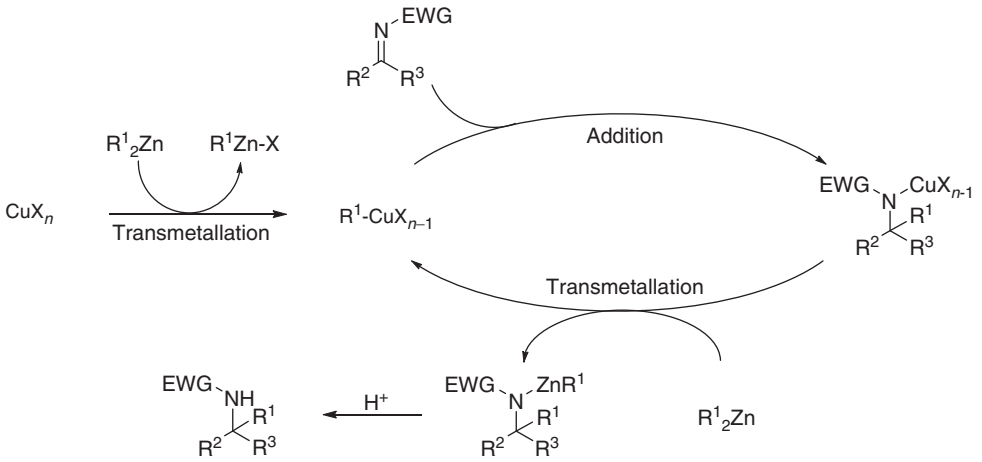
1.11.2.2.2 Use of chiral metal complexes as catalysts

In the past few decades, the success of chiral transition-metal complexes to efficiently catalyze addition reactions has been well established. In reactions involving nonstabilized nucleophiles and imine derivatives, the most successful approach is to employ a chiral catalyst capable of transmetallation with a nonstabilized nucleophilic partner added in stoichiometric amounts. This active chiral nucleophile catalytically formed is then capable of stereoselective addition reactions to the C=N bond to form enantioenriched α-chiral amine derivatives. This field of research has generated considerable interest from the scientific community, leading to the development of the most efficient methodologies for the synthesis of α-chiral amine derivatives through addition reactions. The optimal strategy employed for these processes and the synthetic applications of the products formed highly depend on the nature of the nucleophile and the catalyst used. For this reason, the following subsections are divided according to the function of the hybridization of the nonstabilized carbanion equivalent used, i.e., C-sp^3 nucleophiles (alkylation and allylation, Section 1.11.2.2.2.1), C-sp^2 nucleophiles (vinylation and arylation, Section 1.11.2.2.2.2), and C-sp nucleophiles (alkynylation, Section 1.11.2.2.2.3).

1.11.2.2.2.1 Addition of C-sp^3 nucleophiles

1.11.2.2.2.1.1 Addition of alkylmetals

A vast variety of transition metals have proven to be competent at catalyzing addition reactions to imine derivatives. One of the first systems studied in this field is the Cu-catalyzed addition of diorganozinc reagents. In this type of process, imine derivatives bearing EWGs are usually required, and the practicality of the method often relies on the ease of liberation of this group following the stereoselective addition. A possible mechanism for this reaction is shown in **Scheme 32**. A diorganozinc species added in stoichiometric amounts is capable of transmetallation with the Cu salt used as catalyst (typically $Cu(OTf)_2$), forming an active Cu-alkyl nucleophile, which adds to the imine derivative. The resulting adduct can then transmetalate with the diorganozinc species, regenerating the active nucleophilic catalyst and the zinc salt of the amine product. If a chiral ligand is complexed to the Cu center

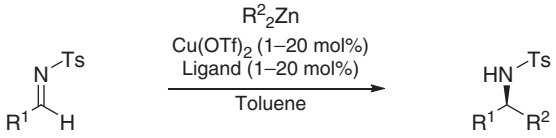


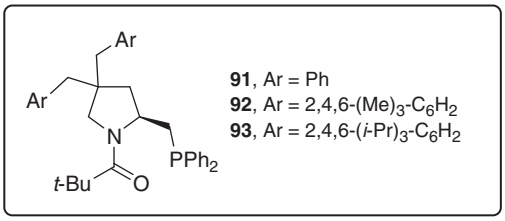
Scheme 32 Postulated mechanism for the Cu-catalyzed addition of diorganozinc reagents to imine derivatives.

throughout the process, then a catalytic enantioselective reaction can be envisioned via appropriate control of the chiral environment around the Cu center.

The first successful method of this type employed chiral amido-phosphines such as **91–93** as ligands for the $Cu(OTf)_2$-based catalyst with *N*-sulfonylimines as electrophiles (Table 5).[57] Based on previous observations made in conjugate addition chemistry using diorganozinc nucleophiles,[58] it was first determined that a Cu catalyst bound to phosphine ligands helped minimizing the amount of undesired reduction products in these reactions. Optimization of the chiral phosphine ligand led to amido-phosphines **91–93**, which afford a highly enantioselective process for aromatic as well as aliphatic aldimine derivatives with Et_2Zn, whereas the addition of Me_2Zn or $(i\text{-Pr})_2Zn$ furnishes slightly lower enantiomeric excesses.[59] While bis(oxazoline) and pybox-type ligands are commonly used in asymmetric catalysis with copper, their use as chiral ligands with these *N*-sulfonylimines electrophiles only led to poor enantioselectivity.[60]

Table 5 Cu-catalyzed enantioselective addition of diorganozinc reagents to *N*-sulfonylimines using chiral amido-phosphine ligands





Entry	*Ligand*	R^1	R^2	*Yield (%)*	ee *(%)*
1	**91**	Ph	Et	98	93
2	**92**	Ph	Et	97	96
3	**93**	Ph	Et	96	88
4	**93**	Ph	Me	97	87
5	**93**	Ph	*i*-Pr	92	78
6	**92**	*c*-C_6H_{11}	Et	84	96
7	**92**	$Ph(CH_2)_2$	Et	69	93

N-Phosphinoylimines are also reactive electrophiles in this type of reaction, and the use of a chiral bis(phosphine) monoxide such as **94**, a hemilabile ligand prepared from Me-DuPHOS, leads to excellent enantioinduction for a number of *N*-phosphinoylimine derivatives and diorganozinc reagents (Table 6).[61] Notably, it was found that the chirality around the phosphine-oxide moiety of **94** was not essential for high stereoinduction, since other ligands such as **95** or **96** also afford good enantioselectivity.[61h]

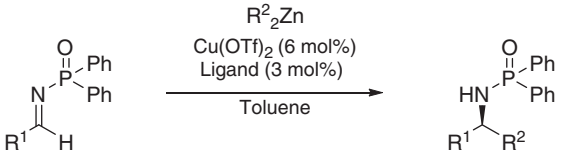
With the less-stable aliphatic *N*-phosphinoylimines as substrates, it is often preferable to use a *p*-toluenesulfinic acid adduct as bench-stable starting material, which gets converted to the corresponding imine under the reaction conditions (Scheme 33(a)).[61c] This reaction is also possible with trifluoromethylketoimines as electrophiles, leading to good enantioselectivity for the corresponding *N*-phosphinoylamines (Scheme 33(b)).[61i]

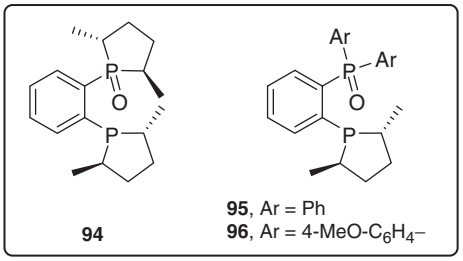
Chiral binaphthylthiophosphoramide ligand **97** also induces high enantioselectivity for this reaction with Et_2Zn and aromatic substrates (Scheme 34).[62,63] In this work, it was found that 15 mol% of the chiral ligand is necessary for good enantioinduction.

N-Formylimines formed *in situ* from their corresponding sulfinic acid adducts are also good substrates for these reactions, where 2 equivalents (relative to Cu) of a monodentate chiral phosphoramidite ligand (**98**) is optimal for the obtention of good enantiomeric excesses (Scheme 35).[64] While all imine derivatives tested afforded high yield in this reaction, aliphatic electrophiles furnished only poor enantioselectivity. It is noteworthy that in addition to diorganozinc reagents, trialkylaluminum nucleophiles were found to be reactive in this process.

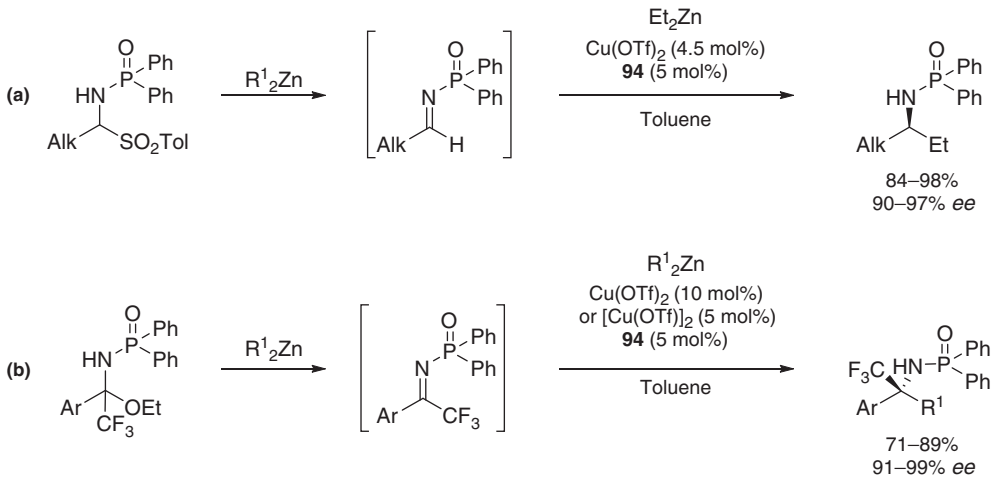
Recently, it was found that early transition metals such as zirconium and hafnium were competent catalysts for the addition of diorganozinc reagents to *N*-*o*-anisidylimines (Table 7).[65] The use of peptide-based ligands **100–102** affords a highly enantioselective reaction with $Zr(Oi\text{-Pr})_4$, where both aromatic aliphatic functionalized substrates are compatible with various diorganozinc reagents. For aliphatic substrates, the imine is formed *in situ* by condensation of the corresponding amine and aldehyde (Method B), and the yield observed is typically lower than for aromatic electrophiles (entries 6–8). The use of an analogous hafnium-based catalyst instead generally improves the yield while still affording high enantioselectivity (Scheme 36(a)).[65d] These reactions were later found to be also compatible with a variety of electron-poor ketoimine derivatives (Scheme 36(b)).[65e]

Table 6 Cu-catalyzed enantioselective addition of diorganozinc reagents to *N*-phosphinoylimines using chiral bis(phosphine) monoxide ligands





Entry	*Ligand*	R^1	R^2	*Yield (%)*	ee *(%)*
1	**94**	Ph	Et	96	98
2	**95**	Ph	Et	91	86
3	**96**	Ph	Et	84	94
4	**94**	1-Naphthyl	Et	96	97
5	**94**	2-Furyl	Et	97	96
6	**94**	*c*-C_3H_5	Et	95	94
7	**94**	Ph	Me	87	97
8	**94**	Ph	*i*-Pr	84	95
9	**94**	Ph	*n*-$C_{10}H_{21}$	73	97
10	**94**	Ph	TBSO–$(CH_2)_6$–	52	90

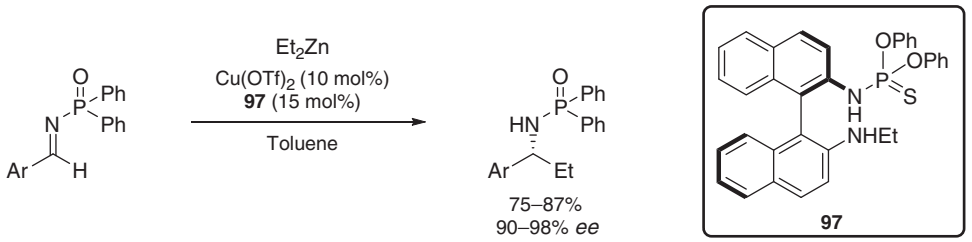


Scheme 33 Cu-catalyzed enantioselective addition of diorganozinc reagents to aliphatic *N*-phosphinoylimines and *N*-phosphinoyl trifluoromethylketoimines.

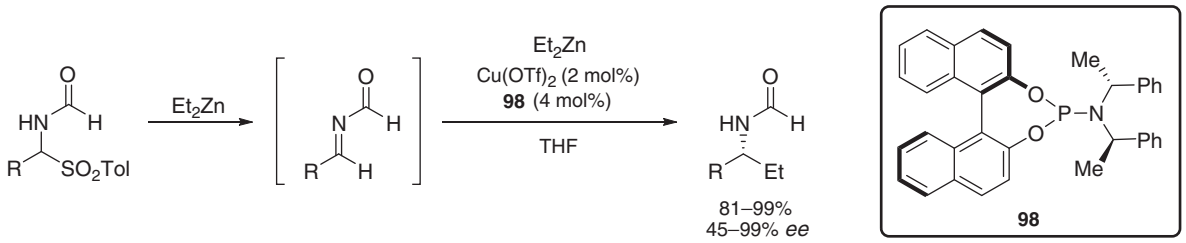
The particular case of Me_2Zn addition to imine derivatives represents a considerable challenge in this chemistry due to the low reactivity of this species in most Cu-catalyzed addition reactions. Using an Rh(I)-based catalyst bound to chiral diene **103**, it is possible to obtain the corresponding adducts in high yields and excellent enantioselectivity, regardless of the substitution on the aromatic *N*-tosylimine employed as substrate (Scheme 37).[66]

1.11.2.2.2.1.2 Addition of allylmetals

Although the enantioselective allylation of imine derivatives using stoichiometric amounts of chiral nucleophiles is well recognized as a highly effective process (see Section 1.11.2.1.3), the development of new methods using only a catalytic amount of the

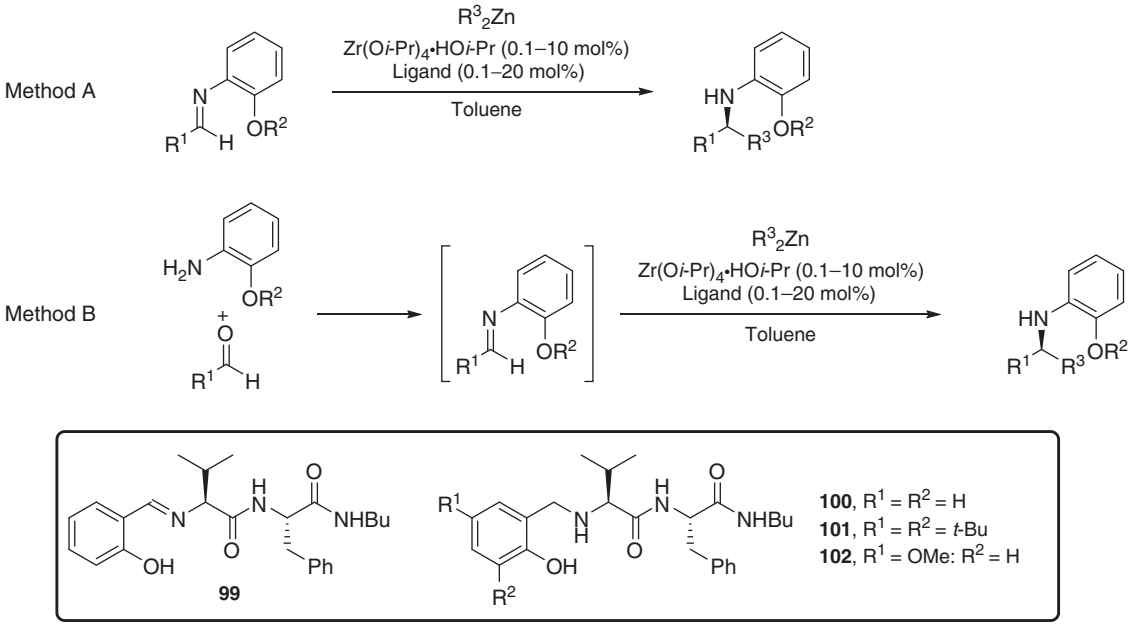


Scheme 34 Cu-catalyzed enantioselective addition of Et_2Zn to *N*-phosphinoylimines using chiral ligand **97**.

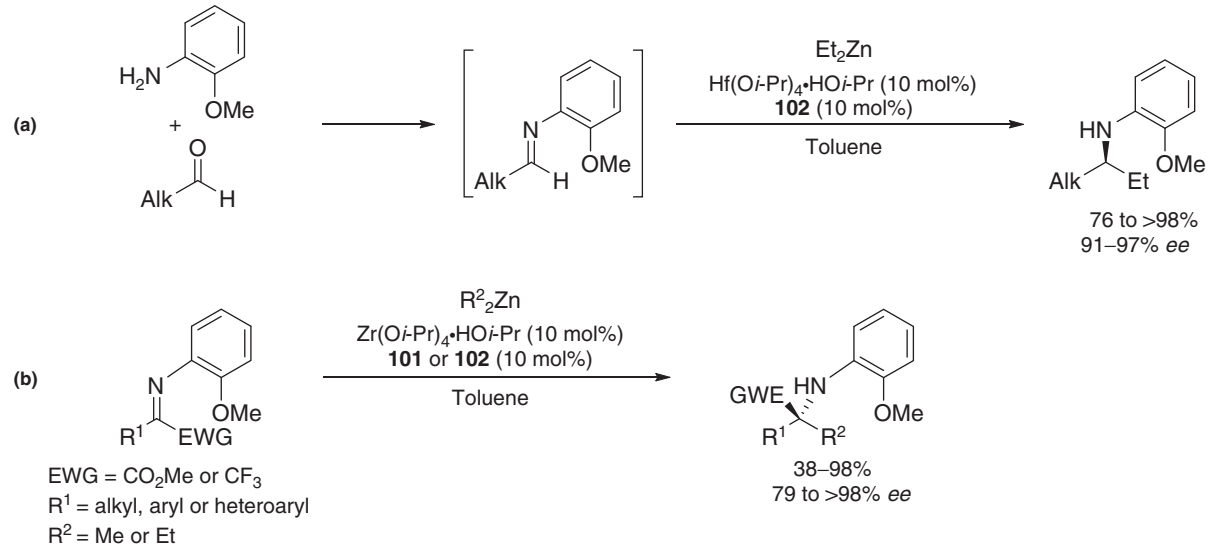


Scheme 35 Cu-catalyzed enantioselective addition of Et_2Zn to *N*-formylimines using chiral phosphoramidite **98**.

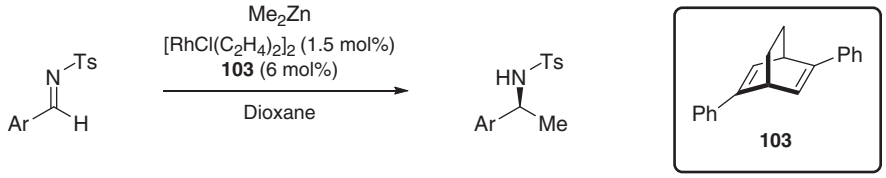
Table 7 Zr-catalyzed enantioselective addition of diorganozinc reagents to *N*-*o*-anisidylimines using peptide-based ligands



Entry	*Ligand*	*Method*	R^1	R^2	R^3	*Yield (%)*	ee *(%)*
1	**99**	A	Ph	Me	Et	82	93
2	**99**	A	2-Furyl	Me	Et	87	97
3	**100**	A	Ph	Me	Me	79	88
4	**100**	A	Ph	Me	n-C_8H_{17}	63	98
5	**99**	B	3-Pyridyl	Me	Et	>98	85
6	**102**	B	n-C_4H_9	Me	Et	69	97
7	**102**	B	Br-$(CH_2)_5$–	Me	Et	57	95
8	**101**	B	$TBSOCH_2CC$	Ph	Et	70	>98

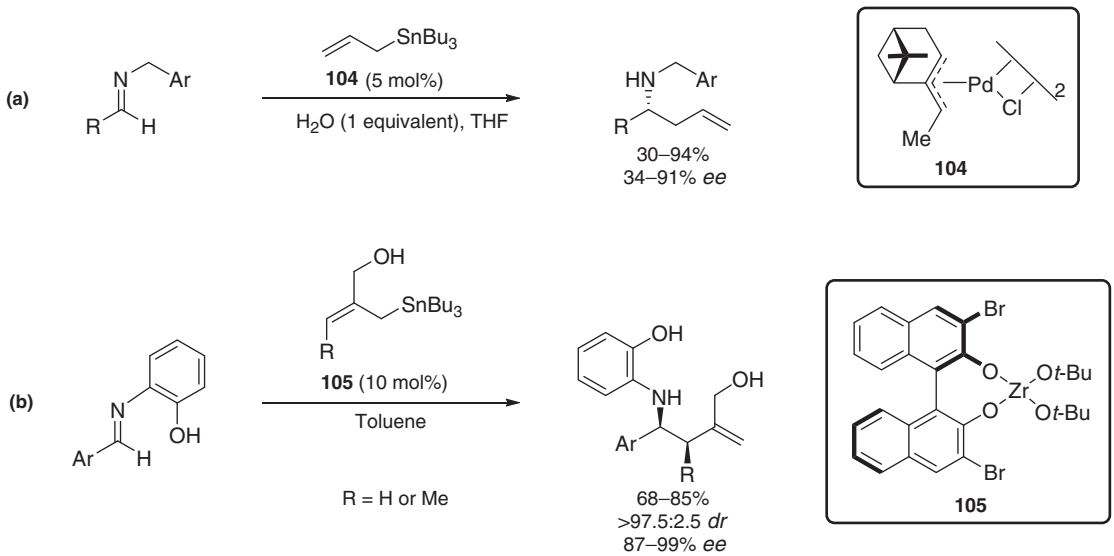


Scheme 36 Zr- and Hf-catalyzed enantioselective addition of diorganozinc reagents to *N*-*o*-anisidyl aliphatic aldimines and electron-poor ketoimines using peptide-based ligands.



Scheme 37 Rh-catalyzed addition of Me_2Zn to *N*-sulfonylimines using chiral diene **103** as ligand.

chiral agent responsible for the enantioinduction is highly desirable. In this context, chiral Pd- and Zr-based chiral complexes **104** and **105** are found to be highly efficient in catalyzing the addition of various achiral allylstannanes to *N*-benzyl- and *N*-*o*-anisidylimines, respectively, in good enantioselectivity for aromatic substrates (Scheme 38).[67,68] In the case of the Pd-catalyzed reaction (Scheme 38(a)), the addition of water to the reaction mixture is necessary for the obtention of high enantiomeric

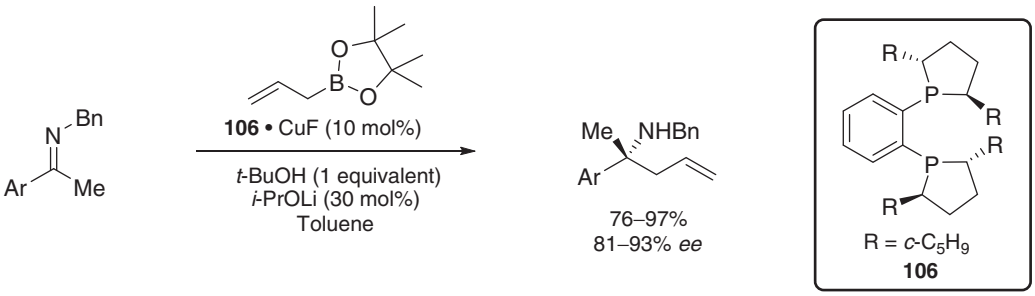


Scheme 38 Pd- and Zr-catalyzed enantioselective allylations of *N*-benzyl and *N*-arylimines using allylstannanes.

excesses.[67c] Moreover, the allylstannane can be replaced with an allylsilane reagent with similar efficiency,[67b,d] and the analogous carboethoxyallylation is also possible.[67e] In the case of palladium-based catalysts, transmetallation from the stannane to the Pd center is proposed to occur, followed by the addition of the allylpalladium intermediate to the imine. Conversely, the Zr-catalyzed reactions are proposed to proceed through a direct nucleophilic attack of the stannane reagent to the imine, after both reactants have bound to the zirconium center (Scheme 38(b)). This hypothesis is mainly based on the fact that the methylenehydroxy group at the 2-position of the allylstannane was found to be important for high enantioinduction, providing the nucleophile a binding point to the chiral Zr complex and affording a more organized transition state.

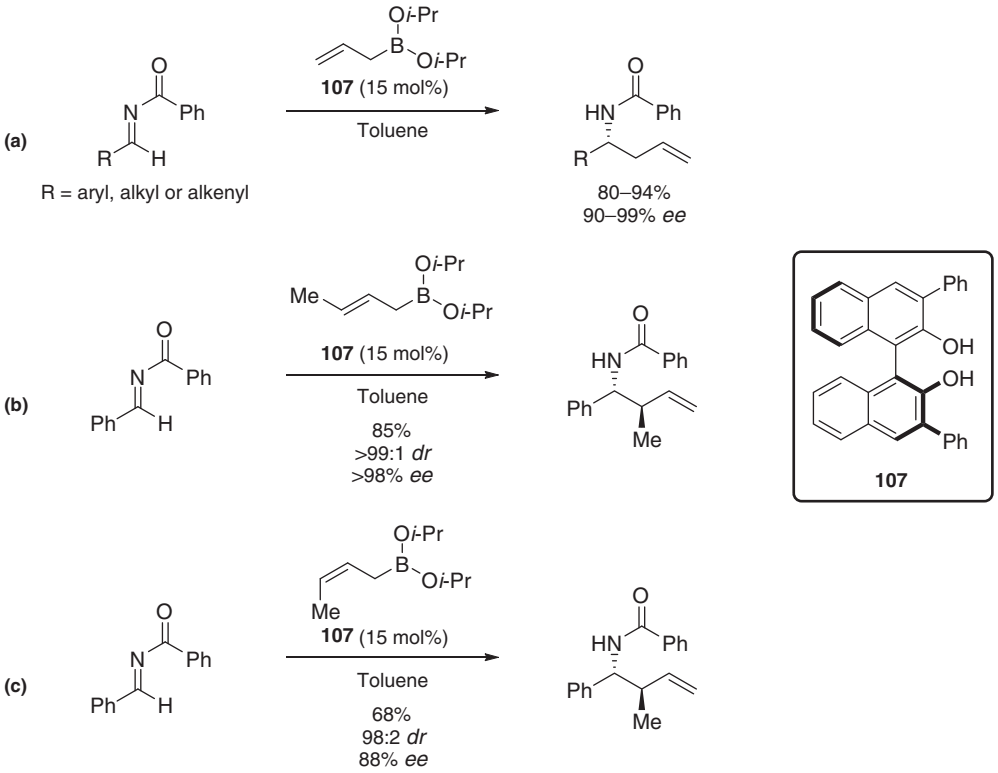
In addition to these reactions, it is noteworthy that a few other enantioselective methods involving Zn- or Cu-based catalysts were developed for the addition of allylstannane and allylsilane nucleophiles to α-iminoesters, although the stereoselectivity of these processes are usually modest.[69]

Allylboronates are found to be competent nucleophiles for the enantioselective allylation of *N*-benzylketoimines electrophiles with a Cu-based catalyst linked to DuPHOS derivative **106** (Scheme 39).[70] In this reaction, the fluoride counterion is thought to accelerate the transmetallation of the allyl group from the boronate species to the chiral Cu complex before the addition.



Scheme 39 Cu-catalyzed enantioselective allylboration of *N*-benzylketoimines.

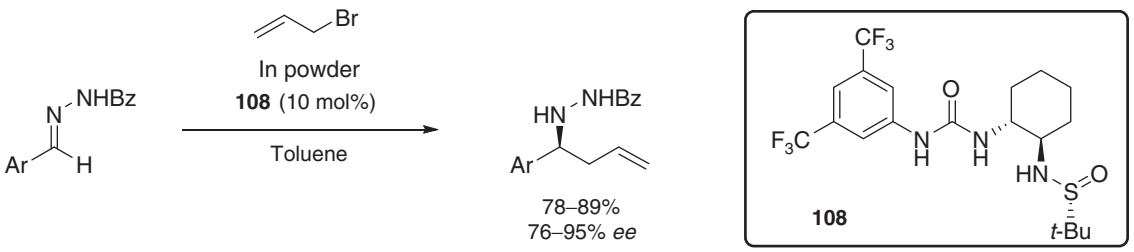
The metal-free catalytic enantioselective allylboration of *N*-acylimines is possible when BINOL derivatives such as **107** are used as organocatalysts (Scheme 40).[71] This reaction is proposed to proceed via ligation of the allylboronate to the BINOL catalyst with



Scheme 40 Organocatalyzed allyl- and crotylboration of *N*-acylimines.

loss of *i*-PrOH, followed by allylboration of the imine activated through hydrogen bonding with the remaining free hydroxyl group of the organocatalyst. The corresponding *cis*- and *trans*-crotylboronate reagents also afford a high enantioselectivity in the process, leading to the *anti*-product in both cases, which is in sharp contrast with what is usually observed in uncatalyzed processes. This result highlights the distinct stereoinduction mechanism in this case, where a boat-type transition state is proposed to be favored when the *cis*-crotylboronate is employed.

As previously discussed in Section 1.11.2.1.3, allylindium species formed *in situ* from allylbromide and In(0) are known to efficiently add to *N*-acylhydrazones. When a chiral urea such as **108** is present to activate the imine electrophile via hydrogen bonding, a highly enantioselective organocatalyzed reaction is possible (Scheme 41).[72] Although the corresponding *cis*- and *trans*-crotylindium species are also effective nucleophiles in terms of the yield of the homoallylic benzoylhydrazine product formed, the diastereoselectivity of the addition was found to be poor in this particular case.



Scheme 41 Organocatalyzed enantioselective addition of allylindium to *N*-benzoylhydrazones.

1.11.2.2.2.2 Addition of C-sp² nucleophiles

1.11.2.2.2.2.1 Addition of alkenylmetals

The catalytic asymmetric addition of alkenylmetal nucleophiles to imine derivatives, leading to enantioenriched allylic amines, is an extremely important transformation. A considerable challenge associated with these processes is the preparation of a stereodefined vinylic nucleophile that will be reactive enough for addition reactions with imines. Although the hydroboration of alkynes is well established as an effective route for the synthesis of highly substituted alkenylboranes, these reagents are typically not nucleophilic enough to react with imines in uncatalyzed processes. When a chiral Ni(0) catalyst is added to the reaction mixture containing an alkyne and an *N*-alkylimine electrophile, an enantioselective oxidative coupling can occur, leading to an enantioenriched allylic amine (Scheme 42(a)).[73] The transmetallation of the resulting alkenylnickel intermediate with BEt_3 and subsequent reductive elimination leads to the formation of a densely substituted allylic amine in good enantioselectivity. Alternatively, a chiral Ir(I) catalyst bound to ligand **110** was found to be also competent in effecting this type of enantioselective oxidative coupling reaction, and the presence of H_2 terminates the catalytic cycle to lead to the synthesis of a wide range of enantioenriched allylic amines (Scheme 42(b)).[74] When an analogous Rh(I) catalyst is used instead in the presence of acetylene, a chiral *cis*-dienylmetal equivalent is formed and is capable of highly enantioselective alkenylation of *N*-sulfonylimines (Scheme 42(c)).[75]

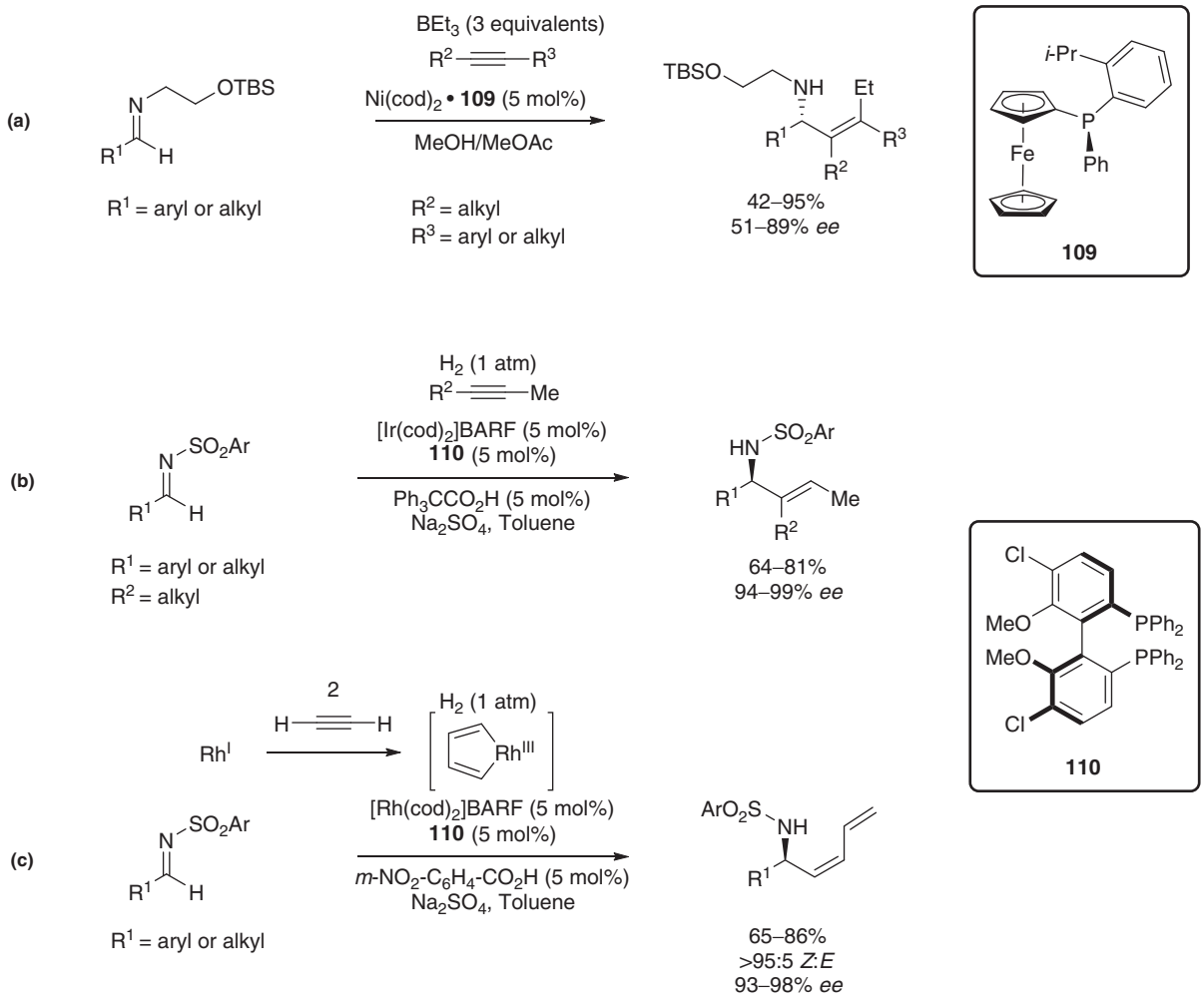
In analogy to the organocatalyzed allylboration of imine derivatives (see Scheme 40 and Section 1.11.2.2.2.1.2), vinylboronates can add to α-iminoester intermediates formed *in situ* through enantioselective organocatalysis with a chiral diol such as **111**, where a wide range of substituents on the amine or the alkenylboronate nucleophile are tolerated (Scheme 43).[76]

1.11.2.2.2.2.2 Addition of arylmetals

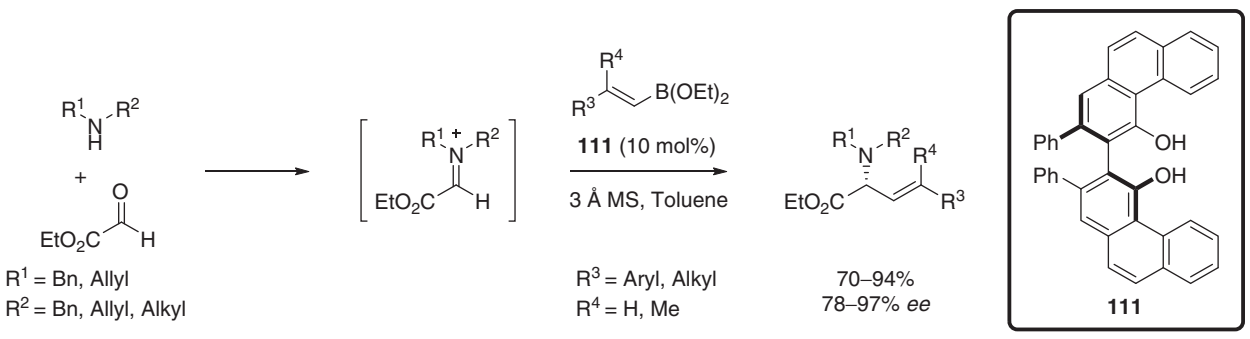
Enantioenriched diarylmethylamines are valuable intermediates in the synthesis of a variety of pharmacologically relevant compounds. The catalytic asymmetric arylation of imine derivatives has emerged as one of the most powerful tools for the synthesis of these products. Indeed, other methods for the synthesis of α-chiral amines, such as the enantioselective reduction of the corresponding diarylketoimines, are often ineffective at inducing high enantioselectivity in these cases.

The Rh(I)-catalyzed enantioselective addition of arylmetal equivalents to *N*-sulfonylimines has become one the most efficient ways to effect this process. Over the years, a wide variety of chiral phosphorus-based ligands have been evaluated for this reaction, and the most efficient methods are summarized in Table 8.[77] Aryltitaniums, arylstannanes, arylboroxines, or arylboronic acid can be used as arylmetal equivalents added in stoichiometric amounts, usually with high yields and enantioselectivities.

The Rh(I)-catalyzed enantioselective arylation of alkenylimines is also possible with ligand **112** in similar conditions, and the enantioselective arylation of aliphatic *N*-tosylimines with arylboronic acids is highly efficient using chiral bis(phosphine) **118** (Schemes 44(a) and (b)). It is noteworthy that these aforementioned processes offer a valuable alternative to the enantioselective addition of alkenylmetals and alkylmetals to aromatic imine derivatives, respectively. Provided that the sulfinate adduct is employed as substrate, *N*-Boc imines can also be used effectively as electrophiles (Scheme 44(c)).



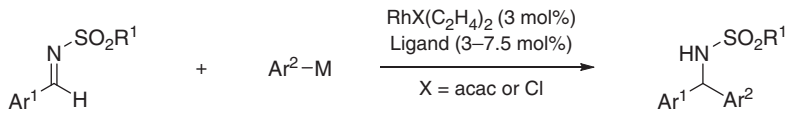
Scheme 42 Metal-catalyzed enantioselective vinylation of imine derivatives via the formal carbo- and hydrometallation of alkynes.

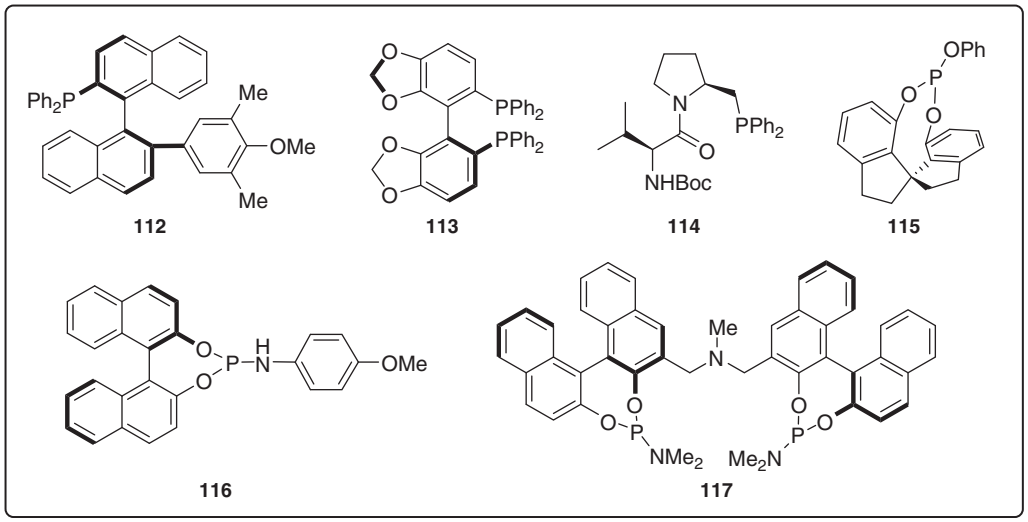


Scheme 43 Organocatalyzed enantioselective vinylboration of iminium electrophiles.

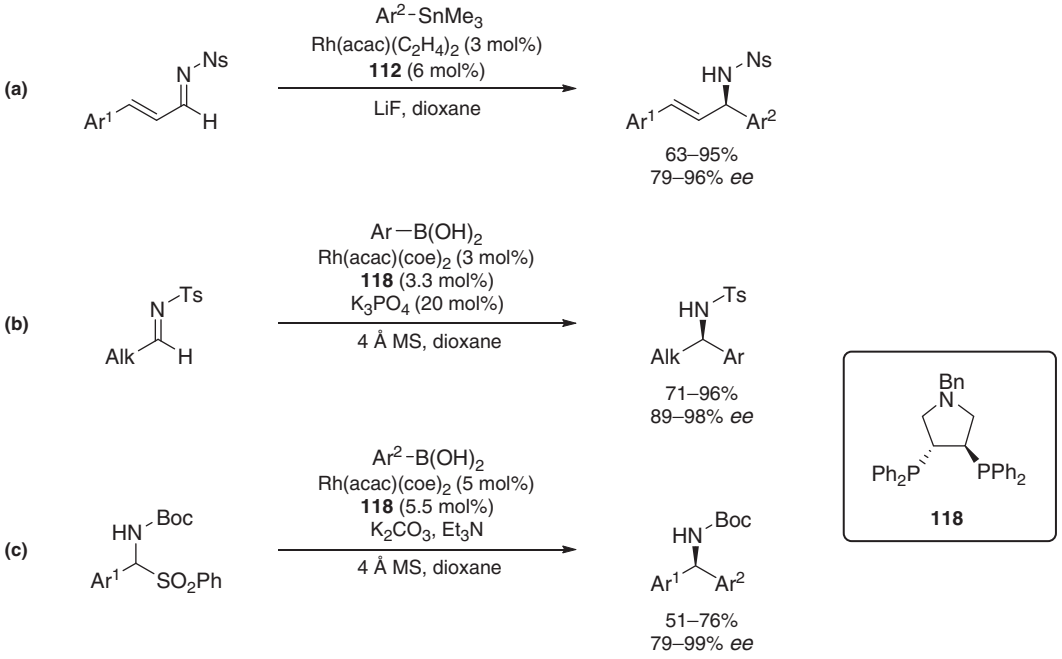
Chiral dienes such as **103** or **119** have been found to be powerful ligands in this type of transformation, affording superior yields, enantiomeric excesses, and substrate generality for the synthesis of diarylmethylamines from *N*-sulfonylimines than most chiral phosphorus-based ligands presented earlier (Table 9).[78] When using diene **119**, *N*-nosylimines can be employed as substrates, which allows for a deprotection of the resulting chiral sulfonamides in milder conditions.

Table 8 Rh(I)-catalyzed enantioselective arylation of *N*-sulfonylimines using chiral phosphine ligands



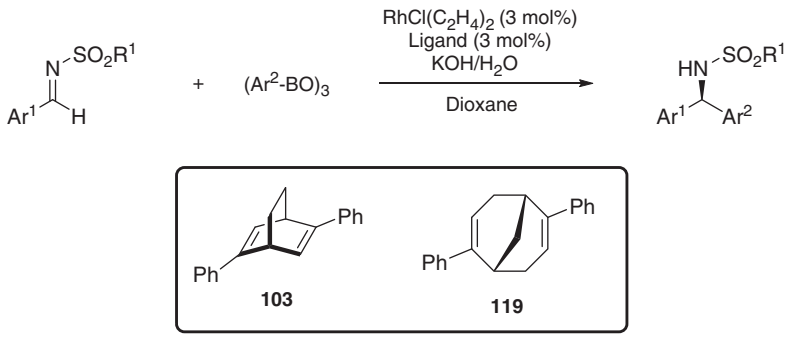


Entry	*Ligand*	*Ar^1*	*Ar^2–M*	*R^1*	*Yield (%)*	ee *(%)*
1	**112**	4-Cl–C_6H_4	Ph-$SnMe_3$	4-NO_2–C_6H_4	83	92
2	**113**	4-Cl–C_6H_4	Ph–Ti(O*i*-Pr)$_3$	2,4,6-(*i*-Pr)$_3$-C_6H_4	95	94
3	**114**	4-Me–C_6H_4	(4-Ph–C_6H_4–BO)$_3$	4-Me–C_6H_4	86	72
4	**115**	4-Cl–C_6H_4	Ph–$B(OH)_2$	4-Me–C_6H_4	85	93
5	**116**	4-Cl–C_6H_4	Ph–$B(OH)_2$	NMe_2	95	95
6	**117**	4-Cl–C_6H_4	Ph–$B(OH)_2$	4-Me–C_6H_4	98	95



Scheme 44 Rh(I)-catalyzed enantioselective arylation of various imine derivatives using chiral phosphine ligand **118.**

Table 9 Rh(I)-catalyzed enantioselective arylation of *N*-sulfonylimines using chiral diene ligands



Entry	*Ligand*	*Ar*^{1}	*Ar*^{2}	*R*^{1}	*Yield (%)*	ee *(%)*
1	**103**	4-Cl–C_6H_4	Ph	4-Me–C_6H_4	96	98
2	**119**	4-Cl–C_6H_4	Ph	4-NO_2–C_6H_4	96	98
3	**103**	4-CF_3–C_6H_4	Ph	4-Me–C_6H_4	97	95
4	**119**	4-CO_2Me–C_6H_4	Ph	4-NO_2–C_6H_4	95	95
5	**103**	4-MeO–C_6H_4	Ph	4-Me–C_6H_4	96	99
6	**119**	4-MeO–C_6H_4	Ph	4-NO_2–C_6H_4	98	99
7	**103**	1-Naphthyl	Ph	4-Me–C_6H_4	95	98
8	**119**	1-Naphthyl	Ph	4-NO_2–C_6H_4	94	96
9	**103**	Ph	4-Cl–C_6H_4	4-Me–C_6H_4	99	99
10	**119**	Ph	4-Cl–C_6H_4	4-NO_2–C_6H_4	96	99
11	**103**	Ph	4-MeO–C_6H_4	4-Me–C_6H_4	97	96
12	**119**	Ph	4-MeO–C_6H_4	4-NO_2–C_6H_4	94	98

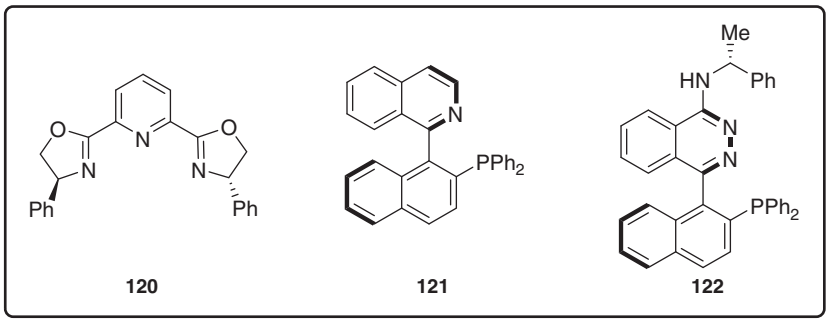
1.11.2.2.2.3 Addition of C-sp nucleophiles

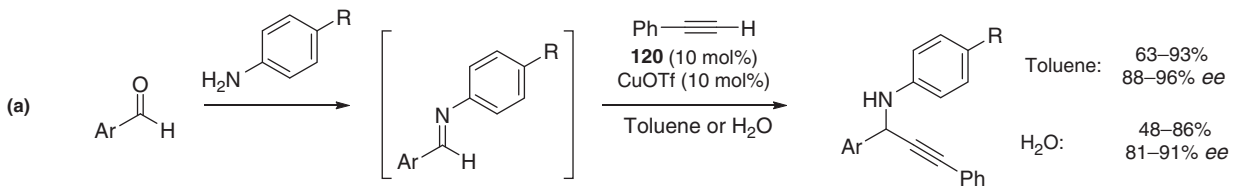
The vast array of transformations applicable to alkyne functionalities makes propargylamines versatile intermediates for the synthesis of complex molecules. Until recently, the enantioselective addition of alkynylmetal equivalents to imine derivatives to form these products in enantioenriched form was only possible using stoichiometric amounts of chiral reagents.[79] A major breakthrough for the synthesis of enantioenriched propargylamines was the development of an enantioselective version of the A^3-coupling, involving the reaction of an amine, an aldehyde, and a terminal alkyne with a chiral Cu catalyst (Scheme 45). Using chiral ligand **120** with *N*-arylimines formed *in situ* leads to an efficient process for the addition to aromatic substrates, with good enantioinduction (Scheme 45(a)).[80,81] It is noteworthy that this transformation can be done in water with similar efficiency, and the reaction is also possible with preformed α-iminoesters as electrophiles. Secondary amines, leading to iminium intermediates instead as active electrophiles, can also be used with copper catalysts derived from CuBr and **121** or **122**, affording excellent enantioselectivity for aromatic as well as aliphatic substrates, with a wide range of substitution tolerated on the alkyne nucleophile (Schemes 45(b) and (c)).[82,83]

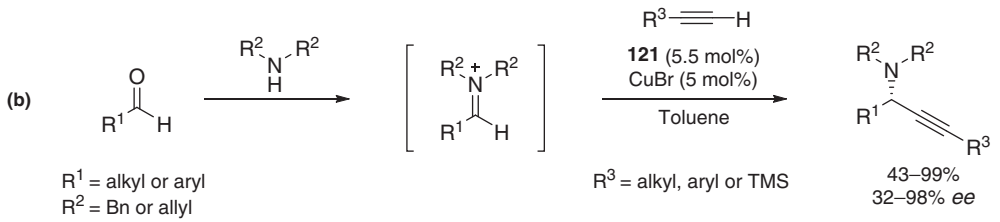
Chiral Zr-catalysts based on peptides such as **102** can be used with mixed alkynylzinc reagents and *N*-anisidylimines to produce propargyl amines in good yields and enantioselectivities (Scheme 46).[84] The alkynylzinc nucleophile can be substituted with an aryl, alkyl, or a trimethylsilyl (TMS) group with reasonable stereoselectivities.

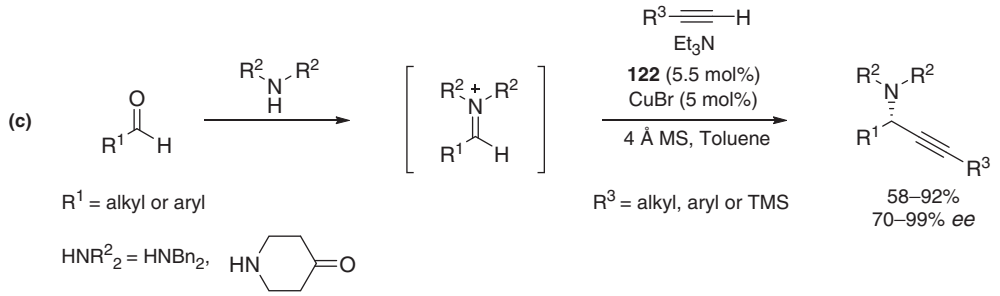
1.11.3 Summary and Outlook

The ubiquity of α-chiral amines in pharmaceutically relevant compounds has long motivated researchers to develop new methods for their synthesis. The addition of nonstabilized nucleophiles to imine derivatives has become one of the most reliable ways to form these compounds, and the development of a vast variety of strategies for their production in enantioenriched form has provided chemists with an array of available tools to achieve their goals. Although less atom-economic, chiral auxiliary-based approaches, where the chirality can be located at either terminus of the C=N bond, still constitute some of the most reliable and predictable methods for the synthesis of a variety of enantioenriched α-chiral amines. In the past two decades, tremendous progress has been achieved in the field of asymmetric catalysis, in general, and the knowledge acquired during that time is partly due to the continuous efforts devoted to the development of more efficient asymmetric addition reactions to imine derivatives. The catalytic enantioselective addition of sp^3, sp^2, or sp carbon-centered nonstabilized nucleophiles is now available with a variety of substrates, although addition reactions to ketoimine derivatives still represent a considerable challenge in certain cases.

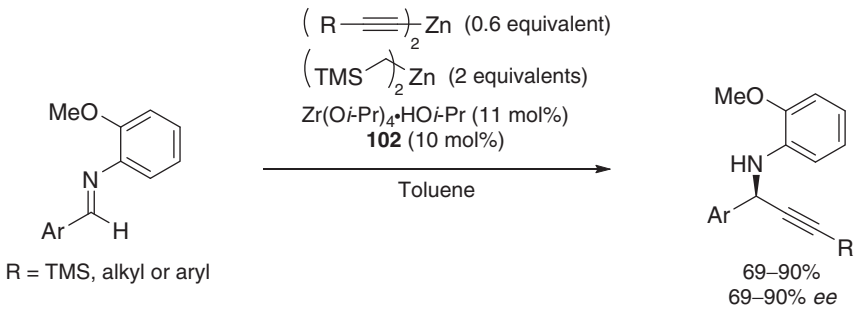








Scheme 45 Cu(I)-catalyzed enantioselective alkynylation of imine derivatives formed *in situ* from aldehydes and amines.



Scheme 46 Zr-catalyzed enantioselective alkynylation of *N*-anisidylimines using dialkynylzinc reagents.

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1.12 Sulfur and Selenium Stabilization

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Glossary

Carbanion A carbanion is an anion in which the tetravalent carbon atom has an unshared pair of electrons and bears a negative charge usually with three substituents for a total of eight valence electrons. If the anion has resonance structures, it should have at least one major contributing structure with an unshared pair of electrons on a tetravalent carbon atom.

Carbenoid A carbenoid is an electron neutral reactive intermediate that displays the reactivity characteristics of carbene. It is usually an alkylmetal reagent with a nucleofuge at the α-carbon atom.

Dynamic kinetic resolution A resolution process in which the substrate can epimerize under the reaction conditions and the faster reacting stereoisomer is continually removed from the system. Epimerization must be a fast process relative to the rate of substrate stereoisomer transformation and transformation of substrate stereoisomers should proceed at different rate.

Dynamic thermodynamic resolution A resolution process in which the enantiomeric substrates form diastereomeric complexes in different populations with an external chiral environment and the further reaction of the complexes provides the enantiomeric products. The diastereomeric populations of the complexes are usually controlled by their different thermodynamic stabilities.

Hoffmann test A method established by Hoffmann to determine the configurational stability of chiral organometallic reagents based on kinetic resolution. It is performed by the reactions of a racemic organometallic

reagent with either a racemic or chiral electrophile, usually an aldehyde.
Negative fluorine effect A term coined to describe the negative (unfavorable) influence of fluorine substitution on the thermal stability and reactivity of the carbanions. The word 'negative' implies both the negative (unfavorable) influence and negatively charged carbanion.

1.12.1 Introduction

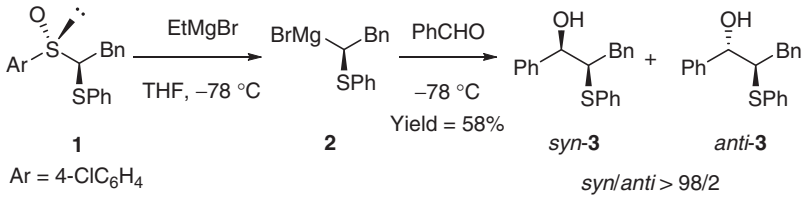
Since the first publication of this handbook in 1991, significant progress has been made on the synthetic application of organosulfur reagents. This is due to the ease with which sulfur can be introduced into and removed from organic molecules, the valence variety that sulfur occurs, and the diversity of selective reactions that can be performed on organosulfur compounds. These allow the synthesis of various sulfur-free structures assisted by a sulfur-containing auxiliary moiety. In view of the wide application of nucleophilic chemistry in the construction of new C–C bonds, sulfur-stabilized carbanions have played a vital role in such developments. Several books containing sections on chemistry of sulfur-stabilized carbanions have been published in the past 20 years.[1–3] The chemistry of sulfur-stabilized carbanions are also involved in several elegant review papers related to the reactivity of sulfur-containing compounds.[4–5] In contrast, little progress has been made on the chemistry of selenium-stabilized carbanions since 1990s. Most of the methods applied in the synthesis of organoselenium compounds have been developed some 20 years ago. In the first edition of this book,[6] A. Krief had conducted an exhaustive review on organoselenium chemistry, so only some reactions and examples that have been developed during the past 20 years are listed as a supplementary and no detailed discussion is made on this topic. As an updated review, this chapter mainly covers new aspects on the synthesis of sulfur and selenium-stabilized carbanions and their nucleophilic addition to C=O and C=N double bonds, especially aldehydes, ketones, and imines.

1.12.2 Sulfenyl-Stabilized Carbanions

1.12.2.1 Configuration of Sulfenyl-Stabilized Carbanions

α-Thio carbanions are configurationally more labile than α-oxy carbanions.[3] Hoffmann and coworkers made a systematic research on the mechanism of racemization of α-lithiated sulfides using dynamic nuclear magnetic resonance (NMR) and molecular calculations.[7,8] By performing two reactions of the racemic α-sulfenyl carbanions with either a racemic or a chiral aldehyde (so-called Hoffmann test), they found that α-lithio derivative of butyl phenyl sulfide is configurationally stable in tetrahydrofuran (THF) at $-120\ ^{\circ}C$ on the time scale of its addition to aldehydes.[9–11]

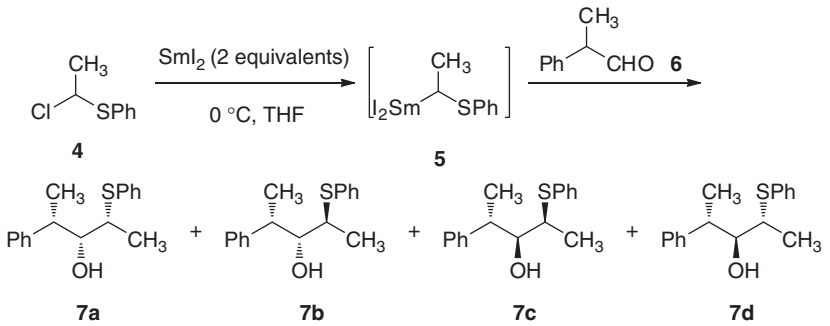
Nell showed that α-(phenylthio)alkyl Grignard reagent **2** can be generated in enantiomerically pure form by a sulfoxide-magnesium exchange reaction from **1**, and that this reagent is configurationally stable at $-78\ ^{\circ}C$.[12] The trapping of **2** by benzaldehyde affords beta-hydroxy sulfide **3** with very high diasteroselectivity (Scheme 1).[12]



Scheme 1

Matsubara and coworkers disclosed that α-(phenylthio)alkylsamarium reagents are configurationally much more stable.[13] A reaction of organosamarium reagent **5** with racemic aldehyde **6** at 0 °C in THF afforded racemic product **7a** predominantly, whereas that with (*S*)-**6** showed lower diastereoselectivity (Scheme 2 and Table 1). Use of excess organosamarium reagent **5** did not improve the diasteroselectivity significantly. These results suggest that the configuration of the organosamarium reagent **5** is stable and the kinetic resolution for selecting one diastereomer did not operate under the reaction condition. The lack of kinetic resolution may be caused by an aggregation of the organosamarium species.[13]

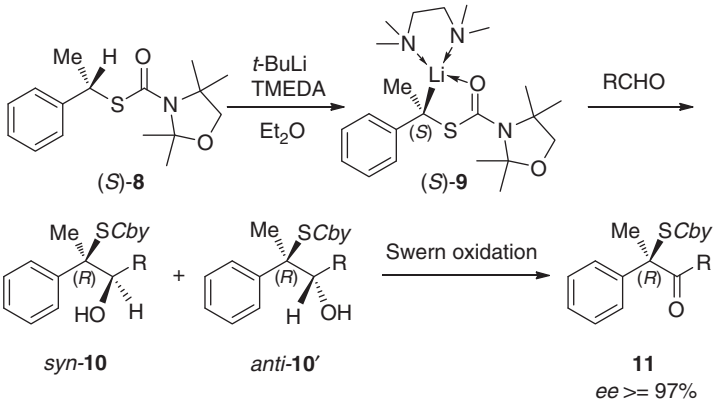
Although a simple α-(phenylthio)alkyllithium is configurationally unstable,[3] the configurational stability of α-thioalkyllithium can be improved by the attachment of a neighboring chelating group.[14] The lithiated thiocarbamate (*S*)-**9** is configurationally stable at $-70\ ^{\circ}C$ and racemizes very slowly even at elevated temperatures. The smooth addition of (*S*)-**9** to aldehydes gives rise to mixtures of the epimeric *syn*/*anti* alcohols **10** (*Cby* = 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyl) with high stereospecificity (*ee* ≥ 97% after oxidation) and complete inversion of the configuration of the benzylic carbon stereogenic center, albeit without significant diastereoselectivity concerning the addition step toward the carbonyl group (Scheme 3).[14]



Scheme 2

Table 1 Rection of α-(phenylthio)alkylsamarium reagent **5** with chiral aldehyde **6** (Scheme 2)

4 (mmol)	*6 (mmol)*	*Yield (%)*	*Ratio (**7a**/**7b**/**7c**/**7d**)*
Racemic-**4** (1.0)	Racemic-**6** (1.0)	65	83/10/6/1
Racemic-**4** (2.0)	Racemic-**6** (1.0)	>99	83/11/5/1
Racemic-**4** (1.0)	(S)-**6** (1.0)	54	59/31/11/<1
Racemic-**4** (2.0)	(S)-**6** (1.0)	87	63/23/12/2



Scheme 3

1.12.2.2 Synthesis of Sulfenyl-Stabilized Carbanions

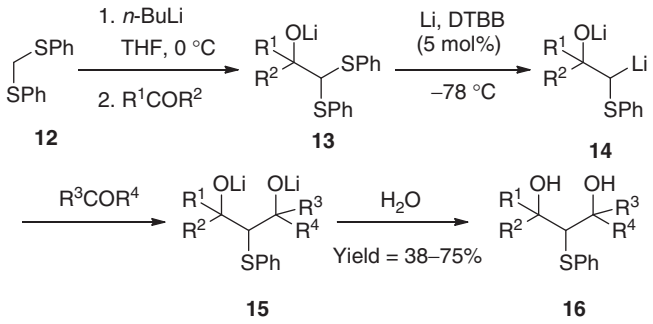
Besides the routine deprotonation reaction,[15] other reported methods for the generation of α-thio carbanion or its equivalent are mainly based on the reductive metallation, heteroatom–metal exchange reaction, desilylation by a Lewis base, and addition of organolithiums to vinyl sulfides.

1.12.2.2.1 Reductive lithiation

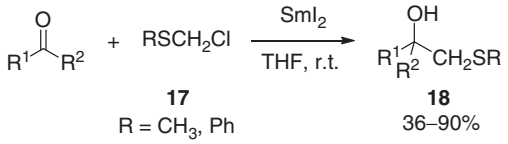
Lithium alcoholate **13**, obtained by addition of dithioacetal **12** to carbonyls, can be lithiated *in situ* with an excess of lithium and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) at −78 °C to give a β-oxido organolithium intermediate **14**.[16] The reaction of this dianion with a second carbonyl compound at −78 °C gives the corresponding dihydroxy thioethers **16** (Scheme 4).[17,18] β-Oxido organolithium intermediate can also be produced by reductive lithiation of α-(phenylthio)epoxides using lithium 4,4′-di-*tert*-butylbiphenylide (LDBB).[19]

1.12.2.2.2 Reductive metallation with reagents other than lithium metal

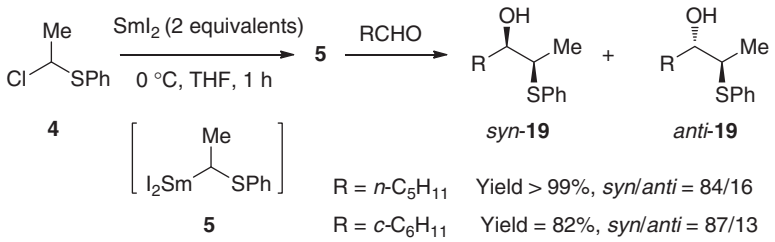
SmI_2-promoted reactions between carbonyls and chloromethyl sulfides **17** has to proceed in a Barbier reaction manner due to the instability of the alkylsamarium reagent (Scheme 5).[20] The reaction with aldehydes gives β-hydroxy thioethers **18** in lower yields than the reaction with ketones, probably due to the facile reductive coupling of aldehydes. Unlike the α-thiomethylsamarium reagents derived from **17**, the α-(phenylthio)ethylsamarium reagent **5** is relatively stable. The pregenerated organosamarium reagent **5** can react with aldehydes in Grignard reaction manner yielding the corresponding β-hydroxy thioethers **19** in good yields with *syn* selectivity (Scheme 6).[13] For more details on this topic within the reference work (*see* Chapter 1.09).



Scheme 4

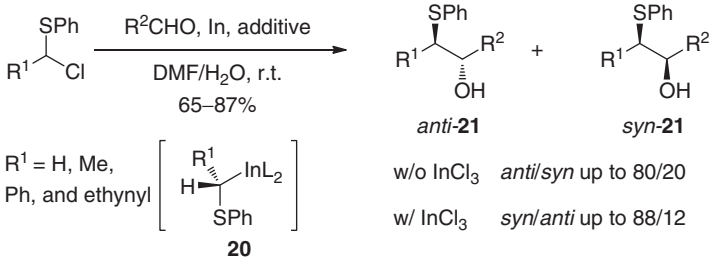


Scheme 5



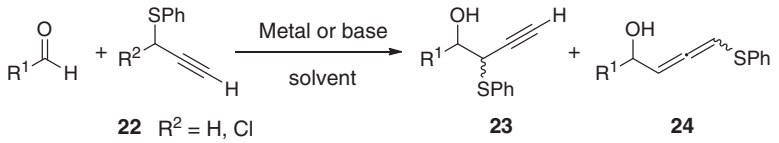
Scheme 6

Indium-promoted reactions between α-chlorosulfides and aldehydes can proceed in the presence of water giving β-hydroxy thioethers **21** in good yields (Scheme 7).[21,22] The absence of $InCl_3$ results in the predominant formation of the *anti* diastereomer, whereas the presence of $InCl_3$ results in the predominant formation of the *syn* diastereomer. The reaction is postulated to proceed via two possible pathways, a nonchelated route and a chelated one.[21,22] Moreover, indium plays an important role in controlling the regioselectivity. When propargylic nucleophiles with terminal alkynes are used, the indium reagent gives the propargyl alcohol **23** exclusively. In contrast, a lithium, magnesium, or a copper reagent shows low regioselectivity to produce propargyl alcohol **23** and allenyl alcohol **24** (Scheme 8 and Table 2).[22]



Scheme 7

A γ-thioallylzirconocene species can be generated by hydrozirconation of allenyl sulfide. Allenyl phenylsulfide **25** undergoes clean hydrozirconation by reaction with $Cp_2Zr(H)Cl$, and the resulting γ-(phenylthio)allylzirconium **26** smoothly reacts with aldehydes at −78 °C giving the *anti*-adducts **27** in high yield with high regioselectivity.[23] The addition of **26** to α,β-unsaturated aldehydes proceeds in a 1,2-addition mode and none of the 1,4-adduct is observed. With ketones, the thioallylation occurs

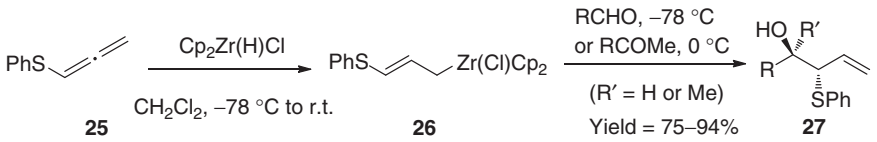


Scheme 8

Table 2 Coupling reactions using various propargyl metal reagents (**Scheme 8**)

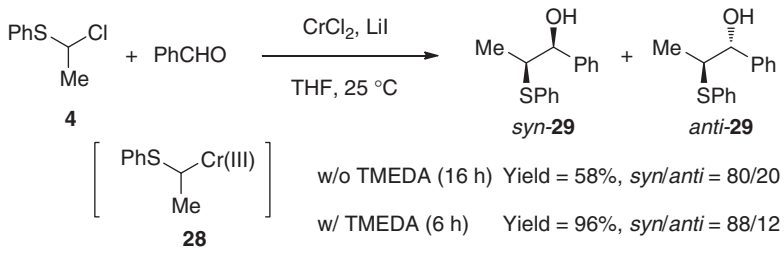
R^2	*Metal*	*Solvent*	*Regioisomer ratio (**23**/**24**)*
Cl	Mg^0	THF	NR
Cl	Rieke Mg^0	THF or DMF	~1.3/1.0
Cl	Rieke Mg^0/CuCl	THF	~1.0/1.7
H	*n*-BuLi	THF	~1.3/1.0
H	EtMgBr	THF	~1.3/1.0
Cl	In^0	H_2O/ DMF	100/0

at 0 °C; when the steric demand of the two substituents of ketones is sufficiently different, good to high diasteroselectivity is observed (**Scheme 9**).[23] For more details on this topic within the reference work (*see* Chapter 1.05).



Scheme 9

α-Thioalkylchromium reagents can be generated by reduction of α-chloroalkylsulfides with chromium(II) chloride[24] and add to aldehydes selectively in a chemo- and stereoselective manner (**Scheme 10**). α-(Phenylthio)ethylchromium reagent **28** reacts with benzaldehyde giving *syn*-**29** as the major product. Pretreatment of $CrCl_2$ with TMEDA could accelerate the reaction rate and improve both the yield and the diastereoselectivity.[24] For more details on this topic within the reference work (*see* Chapter 1.06).

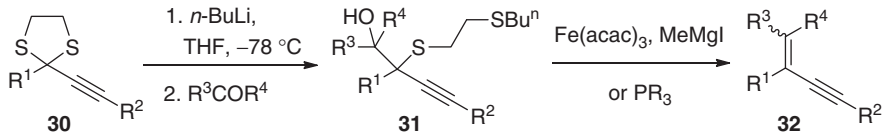


Scheme 10

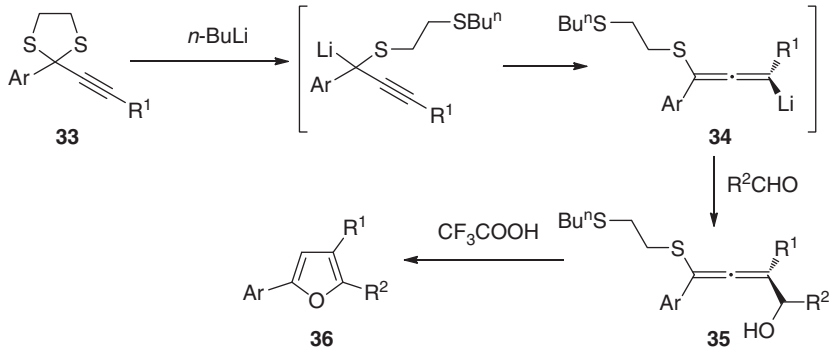
1.12.2.2.3 Heteroatom–metal exchange reaction

The heteroatom–metal exchange between sulfides substituted by another heteroatom (such as S,[25–29] Se,[30] Sn,[30] and halogen[31]) and organometallic reagents, which is usually much more efficient than deprotonation, can afford structurally diverse sulfenyl-stabilized carbanions.

In the case of cyclic dithioacetals, ring-opening reactions take place selectively with an organolithium or organocopper reagent to give the corresponding sulfur-stabilized carbanions.[27] When an alkyl-substituted propargylic dithioacetal **30** is employed, homopropargylic alcohols **31** are obtained exclusively in good yields.[28] Alcohols **31** can be transformed into olefins **32** by elimination of SR and OH moieties (**Scheme 11**).[28,29] However, lithiation of aryl-substituted propargylic dithioacetals **33** with *n*-BuLi leads to an allenyl lithium **34**, which can be trapped by aldehydes affording carbinols **35**. Allenyl carbinols **35** undergo cyclization on treatment with trifluoroacetic acid to give corresponding trisubstituted furans **36** (**Scheme 12**).[28]



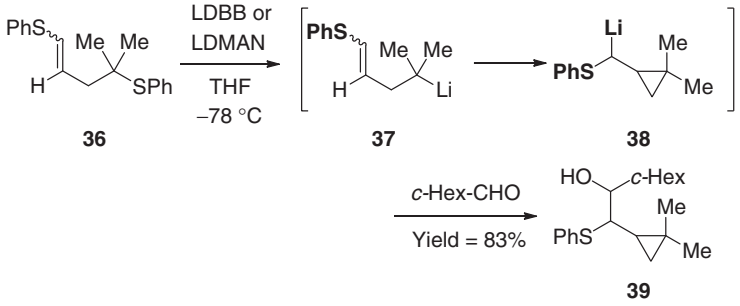
Scheme 11



Scheme 12

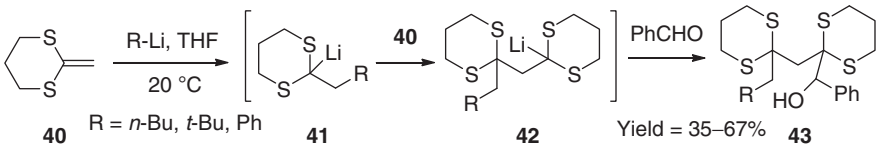
1.12.2.2.4 Addition of organolithiums to vinyl sulfides

Organolithiums can add to vinyl sulfides in both intramolecular and intermolecular modes.[32–34] In the case of intramolecular addition, a cycloalkyl-substituted lithium reagent is formed. The tertiary alkylithium **37**, generated from reductive lithiation with lithium LDBB or lithium 1-(dimethylamino)naphthalenide (LDMAN), undergoes anionic cyclization to form a cyclopropyl-substituted lithium reagent **38** (Scheme 13).[33] Due to the stabilization effect of the phenylthio group, the lithium reagent **38** is stable at $-78\ ^{\circ}C$ and no further rearrangement takes place.[35,36]



Scheme 13

Intermolecular addition of a lithium reagent to 2-methylene-1,3-dithiane (MDTA, **40**) produces a sulfur-stabilized dithianyl anion **41**.[37] The second addition of **41** to MDTA produces the bis-dithianyl anion **42**. The bis-dithianyl anion **42** is less reactive toward MDTA, which allows for its selective accumulation in the reaction mixture. The bis-dithianyl anion **42** can be trapped by an aldehyde, such as benzaldehyde, giving the alcohols **43** in moderate yields (Scheme 14).[34]

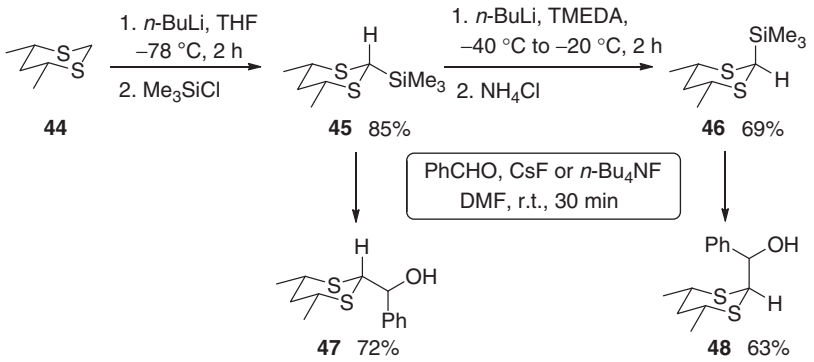


Scheme 14

1.12.2.2.5 Desilylation

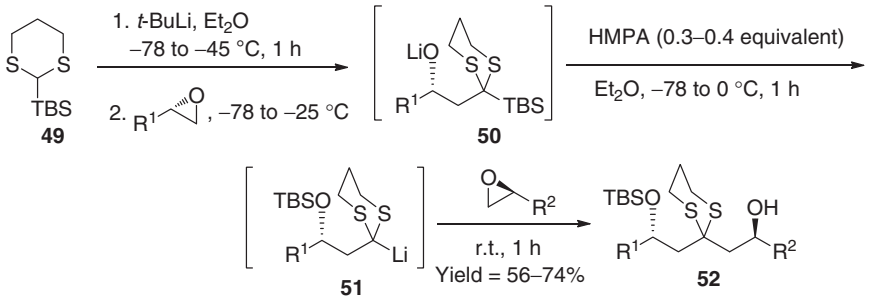
Although deprotonation is a facile method to generate α-thio carbanions, the use of a considerably strong base may hammer its application in the synthesis of complicated molecules due to the functional group incompatibility. The activation of α-thioalkylsilanes with a Lewis base under mild conditions provides an alternative for the generation of α-thio carbanions by deprotonation, which has been used in the addition to carbonyls and imines.[38–41]

Due to the low configurational stability of the axial-lithium salts, axial functionalization could not be realized by lithiation of 1,3-dithianes.[42–44] However, the treatment of *trans*-4,6-dimethyl-2-trimethylsilyl-1,3-dithiolanes **46** with benzaldehyde in the presence of a fluoride affords *trans*-adduct **48** with retention of configuration.[45] Reaction of *cis*-silane **45** also gives adduct **47** with complete retention of the configuration at C-2 (**Scheme 15**).[45] These results suggest that the reactions of benzaldehyde with the above two silane reagents proceed through hypervalent silicon species rather than free carbanions.[46]



Scheme 15

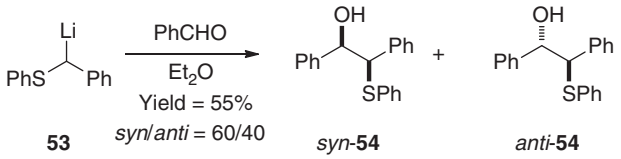
Unlike the intermolecular desilylation, the intramolecular silyl migration from carbon to oxygen can lead to a free dithiane anion.[47–50] For example, oxyanion intermediate **50** resulted from alkylation of lithiated 2-trimethylsilyl-1,3-dithiane **49** with an epoxide, undergoes a solvent-controlled 1,4-Brook rearrangement when being treated with hexamethylphosphoramide (HMPA), giving dithiane anion **51**. The newly formed anion **51** can react with a second electrophile (**Scheme 16**).[48] To avoid formation of complex reaction mixtures, completion of the first alkylation must be achieved before triggering the Brook rearrangement.[48] For more details on this topic within the reference work (*see* Chapter 1.02).



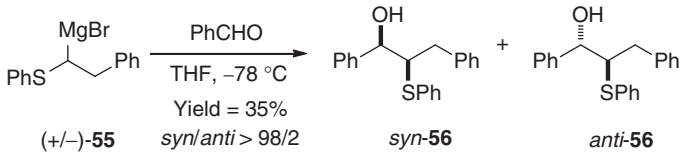
Scheme 16

1.12.2.3 Addition of Sulfenyl-Stabilized Carbanions to C=O Bonds

The counterion not only influences the configurational stability of an α-sulfenyl carbanion but also influences the diastereoselectivity in the addition with carbonyls. α-Sulfenyl lithium reagent **53** reacts with benzaldehyde affording adducts **54** with low diastereoselectivity (equation 1),[51] whereas the reaction of the α-sulfenyl Grignard reagent **55** shows excellent diastereoselectivity (equation 2).[52] It is postulated that Grignard reagents add to carbonyls in a concerted polar process with a late transition state, which favors significant stereodifferentiation. In the case of organolithium reagents, the reaction occurs by single electron transfer (SET) with an early transition state, which disfavors stereodifferentiation.[52,53]

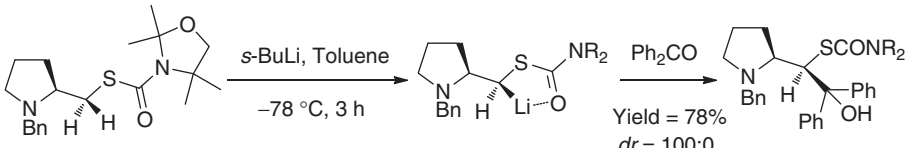


53 *syn*-**54** *anti*-**54** (1)



(+/–)-**55** *syn*-**56** *anti*-**56** (2)

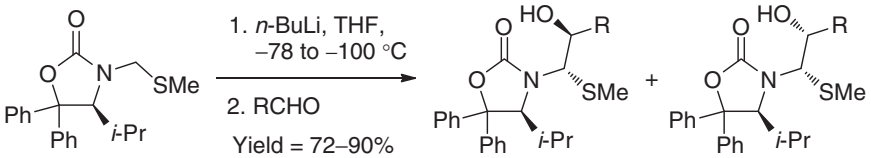
Deprotonation from the prochiral methylene group in chiral thiocarbamate (*S*)-**57** by 1,2-asymmetric induction affords the lithiated α-thiocarbanions (*S*,*S*)-**58** with high diastereoselectivity.[54] (*S*,*S*)-**58** is persistent under the reaction conditions, due to its high thermodynamic stability in comparison with (*S*,*R*)-**58**. (*S*,*S*)-**58** undergoes electrophilic substitution reactions with various electrophiles, such as ketones, with retention of configuration to furnish the products (*S*,*R*)-**59** in good to excellent yields and high diastereoselectivity (Scheme 17).[54]



(*S*)-**57** (*S*,*S*)-**58** (*S*,*R*)-**59**

Scheme 17

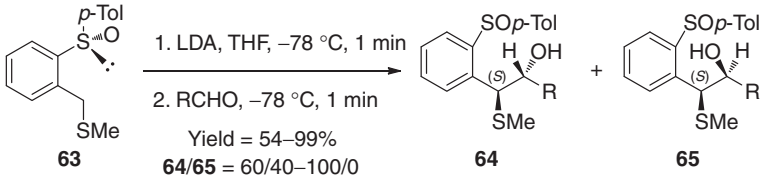
The deprotonation of *N*,*S*-acetal **60** affords a lithiated *N*,*S*-acetal, which undergoes diastereoselective addition reactions to aldehydes, giving adducts **61** and **62** in high yields.[55] Only two of the four possible diastereoisomers are formed. The major isomer **61** and minor isomer **62** have the same configuration at C(1′)-SMe and are epimeric at C(2′)-OH, which indicates that the lithiated *N*,*S*-acetal generated by 1,3-asymmetric induction is of high diastereoselectivity (Scheme 18).[55]



60 **61** **62**

Scheme 18

1,4-Asymmetric induction by chiral *ortho*-sulfinyl group at a phenyl ring can lead to complete control of the configuration at the benzylic position. The reaction of (*S*)-2-(*p*-tolylsulfinyl)benzyl sulfide **63** with a symmetrical ketone yields only one diastereomer in higher than 98% diastereomeric excess. Reactions of **63** with aldehydes afford easily separable mixtures of β-hydroxy sulfides **64** and **65**, which are epimers at the hydroxylic carbon (Scheme 19).[56,57]

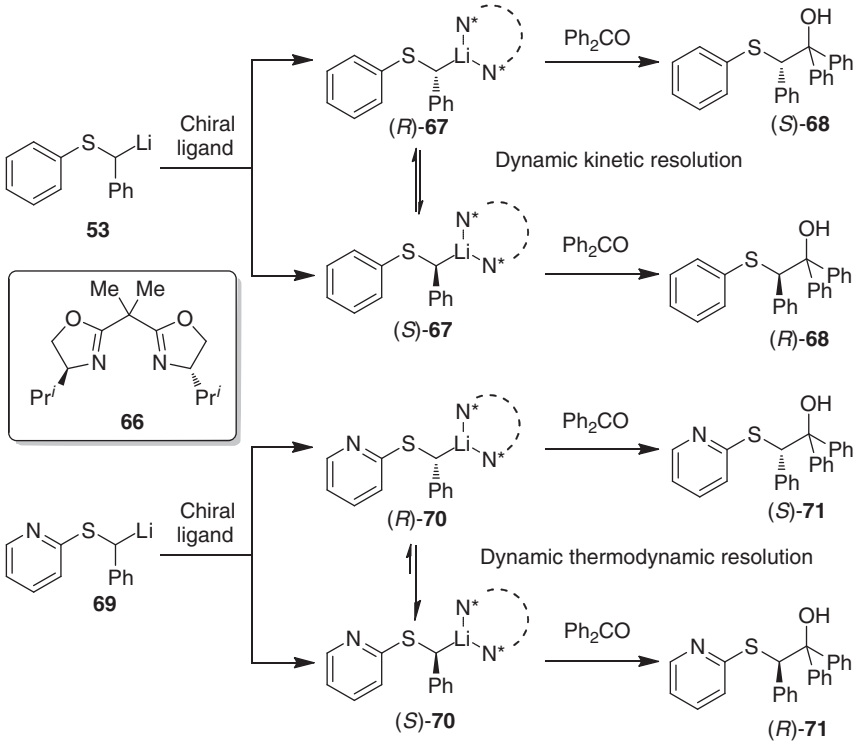


63 **64** **65**

Scheme 19

Enantioselective reaction of α-lithiated sulfide with carbonyls can be realized using a chiral ligand (Scheme 20).[30] Toru and coworkers reported that the reaction of α-lithiated benzyl phenyl sulfide **53** with ketones such as benzophenone in the presence of (*R*,*R*)-bis(oxazoline)s **66** at lower temperature (–98 °C) shows very high enantioselectivity (99% *ee*), giving the adduct (*S*)-**68** as the

major enantiomer.[30] It is confirmed that the reaction proceeds through a dynamic kinetic resolution pathway, in which diastereomeric complexes (*R*)-**67** and (*S*)-**67** undergo epimerization much faster than their reaction with an electrophile, and the diastereomeric complex (*R*)-**67** preferentially reacts with ketones to give the adduct (*S*)-**68**. On the contrary, the enantioselective reaction of α-lithiated benzyl 2-pyridyl sulfide **69** gives the adduct (*R*)-**71** as the major enantiomer.[30] In this case, the reaction proceeds through a dynamic thermodynamic resolution pathway, in which the diastereomeric complex (*S*)-**70** is thermodynamically more stable than (*R*)-**70** and the interconversion between these two diastereomeric complexes proceeds slower than their addition to benzophenone.[30]

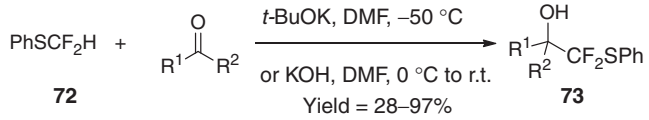


Scheme 20

1.12.2.4 Addition of α-Halo Sulfides to C=X Bonds

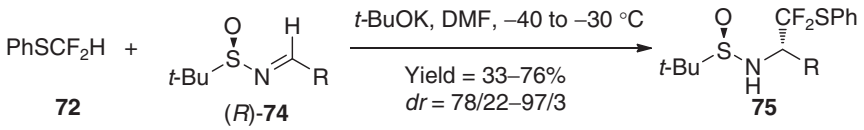
The stabilization effect of the sulfenyl group, which is derived from the interaction with negative hyperconjugation between the nonbonding orbital and σ^* orbital for the S–C bond, as well as the polarizability of sulfur atom, not only can improve the α-proton acidity of sulfides but also can stabilize negative charges of the carbanion.[3] A difluoromethyl anion (CF_2H^-) is thermally unstable due to the repulsion between the lone pair electrons occupying the *p*-orbital of the anionic carbon and the lone pair electrons on the fluorine atoms. Replacing the hydrogen atom with a sulfenyl group facilitates both the generation of a difluoromethyl anion equivalent and its further reaction with electrophiles.[58]

Difluoromethyl phenyl sulfide **72** reacted with ketones and nonenolizable aldehydes in the presence of a base producing the α-(phenylthio)difluoromethyl alchohols **73** in good to excellent yields (Scheme 21).[59] In the case of (*R*)-*N*-*tert*-butylsulfinyl imines **74** without active α-hydrogens, the reaction afforded α-(phenylthio)difluoromethyl amines **75** in moderate to good yields with high diastereoselectivity (Scheme 22).[59]

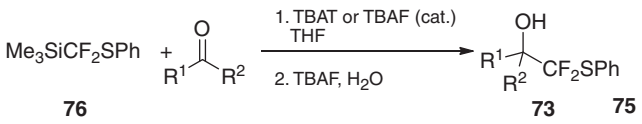


Scheme 21

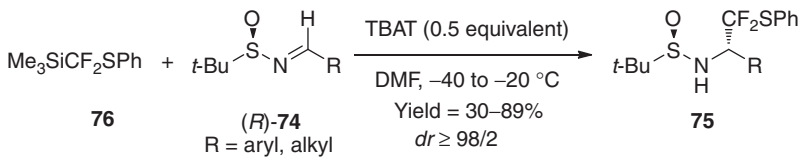
(Phenylthio)difluoromethyl silane **76**, as a difluoromethyl anion equivalent, can be utilized under very mild conditions. Nucleophilic (phenylthio)difluoromethylation of carbonyls with **76** initiated by catalytic amount of fluorides gave alcohols **73** in good to excellent yields. Both nonenolizable and enolizable aldehydes and ketones are compatible under these reaction conditions (Scheme 23).[60–62] Addition to (*R*)-*N*-*tert*-butylsulfinyl imines **74** promoted by tetrabutylammonium triphenyldifluorosilicate (TBAT) afforded the corresponding amines **75** in good yields and with high diastereoselectivity (Scheme 24).[63]



Scheme 22

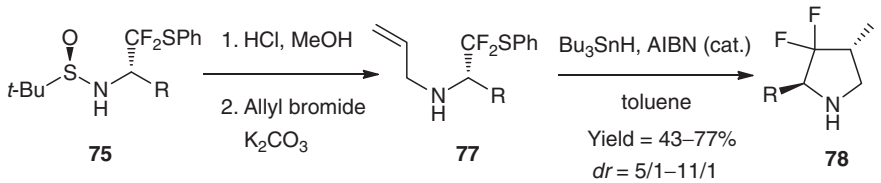


Scheme 23

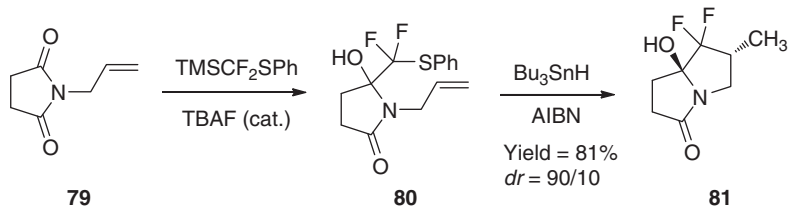


Scheme 24

The obtained $PhSCF_2$-containing alcohols and amines, not only can be converted to α-difluoromethyl alcohols and amines after a radical desulfanation with Bu_3SnH[62,63] but also can undergo intramolecular radical cyclization reaction with the olefin moiety (Schemes 25 and 26).[53–65]



Scheme 25



Scheme 26

1.12.3 Sulfinyl-Stabilized Carbanions

Sulfinyl-stablized carbanions are useful synthetic intermediates that have a number of applications in asymmetric synthesis. Although several recent reviews containing the chemistry of sulfinyl-stabilized carbanions are available,[3,66,67] they mainly deal with the diastereoselective reactions of nonhalogenated carbanions. This part will focus on the addition of α- or remote sulfinyl-stablized halogenated carbanions to C=O or C=N bond and the further transformations of the adducts.

1.12.3.1 Configuration of Sulfinyl-Stabilized Carbanions

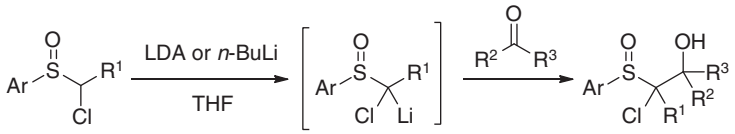
Due to the moderate acidity of the sulfoxides,[68] sulfinyl-stabilized carbanions are usually generated by deprotonation of sulfoxides with alkali metal bases. The attachment of the stereogenic sulfinyl moiety to the anionic carbon center makes the sulfinyl-stabilized carbanions diastereomeric, so their reaction with electrophiles usually shows diastereoselectivity.[3] In the past 50 years, numerous research on α-sulfoxide anions has established that the geometry of an α-sulfinyl carbanion can be either pyramidal or planar.[3] However, little is known about the α-halo sulfoxide anions. In 1984, Seebach and coworkers made an NMR study on the structure of fluoro(phenylsulfinyl)methyllithium **82** in THF solution.[69] They found that the carbon atom is deshielded on lithiation, the C–H coupling is hardly affected, whereas the C–F coupling strongly increases. Moreover, no C–^{6}Li coupling can be detected. By comparing with the NMR data of the other hetero-substituted carbanions, structure **83** involving an O–Li interaction was proposed. This structure can be used to explain the lack of the C–^{6}Li coupling (Figure 1).[69]

82 **83**

Figure 1 Structure of fluoro(phenylsulfinyl)methyllithium.

1.12.3.2 Addition of α-Halo Sulfoxides to C=O Bonds

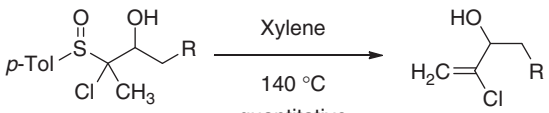
The nucleophilic addition of α-chloro sulfoxide anions **85** to aldehydes or ketones affords β-chloro-β-sulfinyl alcohols **86** (Scheme 27).[70–72] The alcohols can undergo elimination or rearrangement to afford a series of synthetically useful molecules.[70–72]



84 **85** **86**

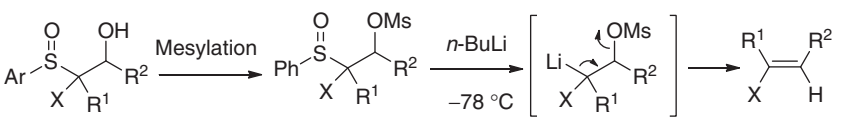
Scheme 27

Heating the diastereomeric mixture of **87** in refluxing xylene results in the elimination of sulfinic acid, giving vinyl chlorides **88** in quantitative yield. In this transformation, only β-hydrogen at the less-substituted carbon is eliminated (Scheme 28).[70] In the presence of *n*-BuLi, α-halo-β-mesyloxy sulfoxides **90** undergo a ligand-exchange reaction to afford intermediate **91**, which can be further transformed to haloalkenes **92** by elimination of mesylate (Scheme 29).[71]



87 **88**

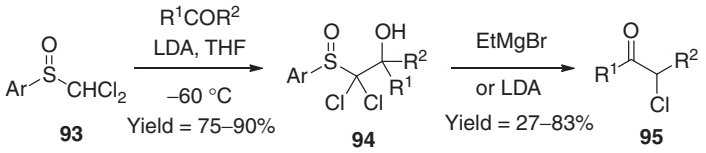
Scheme 28



89 (X = F, Cl) **90** **91** **92** 70–99%

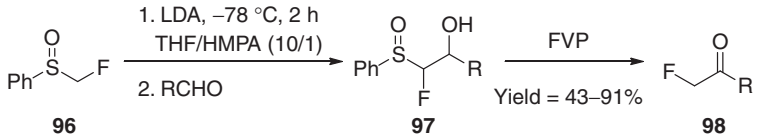
Scheme 29

Similarly, dichloromethyl sulfoxide **93** adds to carbonyls, affording the dichlorinated alcohols **94** in good to excellent yields.[72] The desulfination rearrangement to α-chloroketones **95** can be promoted either by EtMgBr or by lithium diisopropanylamide (LDA) (Scheme 30).[72]

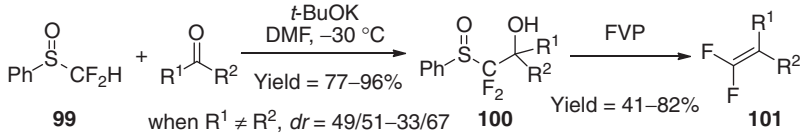


Scheme 30

The nucleophilic addition of α-fluoro sulfoxide anions to carbonyls affords the corresponding sulfinyl-substituted alcohols, which can be further transformed to fluorinated ketones and fluoroalkenes.[71,73,74] Flash vacuum pyrolysis of monofluorinated alcohols **97** at 180 °C gives monofluoromethyl ketones **98** in good yields (Scheme 31),[73] whereas the pyrolysis of difluorinated alcohols **100** leads to the formation of *gem*-difluoroalkenes **101** in moderate to good yields (Scheme 32).[61,71]

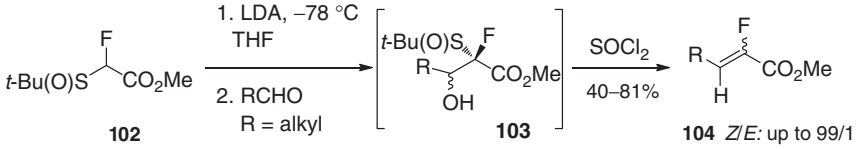


Scheme 31



Scheme 32

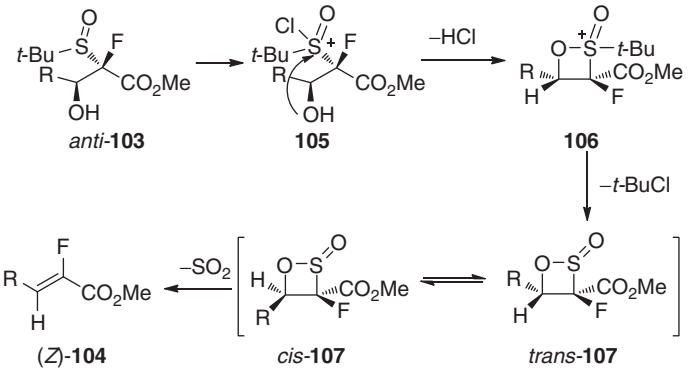
Lithiated 2-(*tert*-butylsulfinyl)-2-fluoroacetate reacts with aliphatic aldehydes to afford β-hydroxy sulfoxides **103**, however, due to the retro-reaction, no adducts are formed when the aromatic aldehydes are used. Alcohols **103** undergo a formal *tert*-butylsulfinic acid elimination in the presence of $SOCl_2$ giving α-fluoroalkenoates **104** in fair yields with good (*Z*)-selectivity (Scheme 33).[75] The (*Z*)-selectivity of alkenes **104** is independent on the relative configuration of the *tert*-butylsulfinyl alcohol **103**. Both 2,3-*syn* and 2,3-*anti* diastereomers of **103** give the (*Z*)-fluoroolefins preferentially. The particular (*Z*)-selectivity observed from the 2,3-*anti* diastereomer would probably be a thermodynamic equilibration between the sultines *cis*-**107** and *trans*-**107** (Scheme 34).[75]



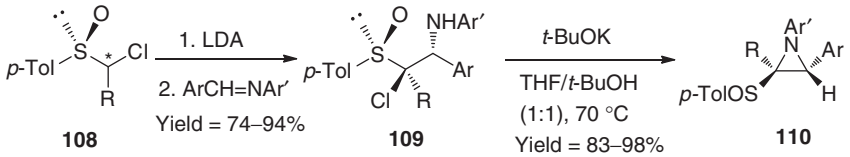
Scheme 33

1.12.3.3 Addition of α-Halo Sulfoxides to C=N Bonds

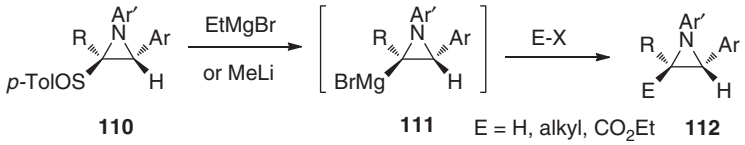
Lithiated α-chloro sulfoxide **108** reacts with *N*-(benzylidene)aniline derivatives to afford the chlorinated amines **109** as the sole isomer in high yields (Scheme 35).[76] This excellent diastereoselectivity indicates that 1,2- and 1,3-chiral induction take place simultaneously during the addition reaction.[76] The chlorinated amines **109** can be transformed into tetra-substituted aziridines **110** by treatment with *t*-BuOK.[76–79] Aziridine **110** undergoes desulfinylation by the action of EtMgBr or MeLi to generate aziridine anion **111**. The anion **111** can be trapped by many electrophiles, such as H_2O, alkyl halides and chloroformate, affording structure-diverse aziridines **112** (Scheme 36).[77–79]



Scheme 34



Scheme 35

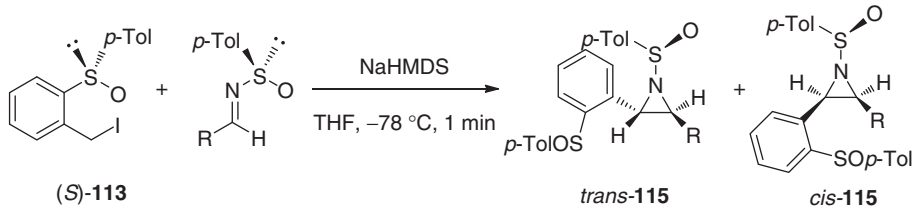


Scheme 36

1.12.3.4 Addition of Remote Sulfinyl-Stabilized Carbanions to C=X Bonds

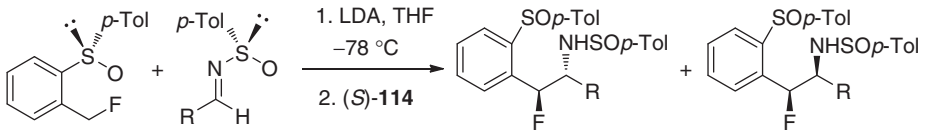
A remote sulfinyl group, especially when the sulfinyl group and the anionic carbon are connected by a conjugated system, can significantly stabilize the negative charge on the anionic carbon. Moreover, the stereochemical results in nucleophilic reactions can also be controlled by the remote sulfinyl group.[80–83]

α-Iodobenzyl anion, generated *in situ* by deprotonation of (*S*)-2-(*p*-tolylsulfinyl)benzyl iodide **113**, reacts with (*R*)-imines **114** giving *trans*-aziridines **115** in high yields with almost complete control of both facial and *anti*/*syn* stereoselectivity (Scheme 37).[84] However, the pregenerated α-iodobenzyl anion fails to react with imines due to its ready homocoupling reaction. Although (*S*)-2-(*p*-tolylsulfinyl)benzyl bromide can also react with imines, the diastereoselectivity is lower than that of the iodide **113**.[84]



Scheme 37

Differing from the anions of (*S*)-2-(*p*-tolylsulfinyl)benzyl bromide and iodide, the anion of (*S*)-2-(*p*-tolylsulfinyl)benzyl fluoride **116** is stable enough to be pregenerated. Deprotonation of benzyl fluoride **116** followed by the addition of (*S*)-imines **114**, affords *anti*-2-fluoro-2-phenethylamines **117** in good yields with excellent control of diastereoselectivity (Scheme 38).[85]



(*S*)-**116** (*S*)-**114** *anti*-**117** *syn*-**117**

Scheme 38

1.12.4 Sulfonyl-Stabilized Carbanions

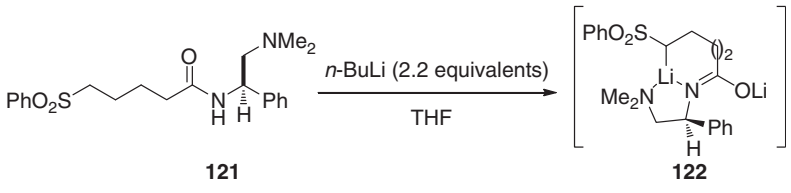
Due to their versatile application in organic synthesis, sulfones are often regarded as chemical chameleons. As many recent reviews on the chemistry of sulfone or sulfur-containing compounds have covered sulfonyl-stabilized carbanions,[1–3] we do not intend to make a full list of their addition to C=X bonds in this part. Instead, focus will be on the addition reactions of sulfonyl-stabilized halogenated carbanions.

1.12.4.1 Configuration of α-Sulfonyl-Stabilized Carbanions

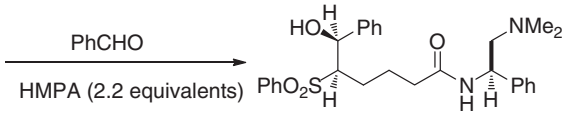
A number of studies disclose that the configuration and configurational stability of α-sulfonyl carbanions depends on the substituents on the anionic carbon and the sulfur.[3] As for the configuration, the α-aryl-α-alkyl-substituted sulfonyl carbanion has a planar C_α-atom,[86,87] whereas that of α,α-dialkyl-substituted carbanion is strongly pyramidalized.[88,89] As for the stability, the lithium salts of (trifluoromethyl)sulfonyl-substituted carbanions carrying two alkyl groups or an alkyl and an aryl group at the C_α-atom are configurationally more stable than the corresponding phenylsulfonyl-substituted carbanions.[86,90,91] For the sulfonyl-stabilized α-halo carbanions, X-ray crystallographic studies have shown that α-fluorobis(phenylsulfonyl)methyl anion $(PhSO_2)_2CF^-$ (**118**) has a pyramidal structure,[92] whereas the bis(phenylsulfonyl)methyl anion $(PhSO_2)_2CH^-$ (**119**)[93] and α-bromobis(perfluorobutylsulfonyl)methyl anion $(C_4F_9SO_2)_2CBr^-$ (**120**) adapt a planar structure.[94] The critical pyramidalization angle (Φ) around the carbanion center of anion **118** is found to be closer to that of a standard tetrahedral structure (Φ = 49.9° vs. Φ = 60°), which indicates that **118** is strongly sp^3 rather than sp^2 hybridized. However, the bond length of C_α–F in **118** is 1.404 Å, which is considerably longer than the typical C_{sp^3}–F bond length in fluorohydrocarbons and is very close to the 'upper limit' of a tertiary C–F bond (1.408 Å).[95] In contrast, the C–Br bond of **120** is much shorter than the regular C–Br bond (1.884 Å vs. 1.95–1.98 Å). NMR and computational studies further confirm that the highly electronegative fluorine substituent plays an important role on pyramidalization of the C_α atom.[92]

1.12.4.2 Addition of Sulfonyl-Stabilized Carbanions to C=O Bonds

In chiral auxiliary-assisted stereoselective reactions, the chiral moiety is usually proximal to the reactive center. However, sometimes a distal chiral auxiliary can also induce good diastereoselectivity.[96] Deprotonation of the enantiomerically pure sulfone **121** with *n*-BuLi and the treatment of the dilithium amide-enolate **122** with benzaldehyde in the presence of HMPA gives **123** as the major diastereomer, which consists of 81.8% of all four possible diastereomers (**Scheme 39**). This example shows that the chiral information can be transmitted with remarkable selectivity through a large distance to give predominantly one diastereomer.[96] However, an intermolecular asymmetry induction could not be ruled out, in which the dilithium amide enolate serves as a chiral ligand.



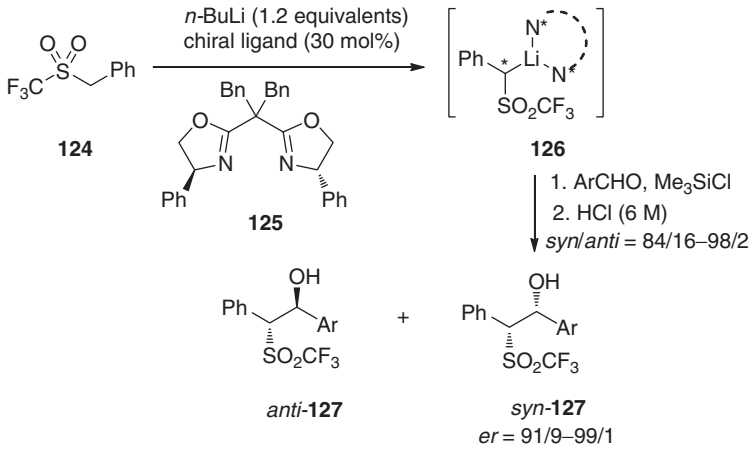
121 **122**



123

Scheme 39

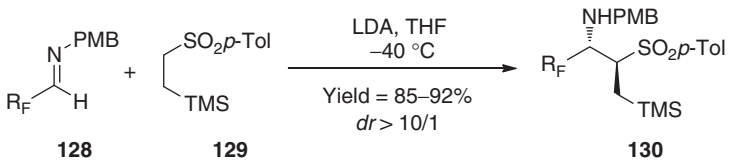
Taking advantage of the configurational stability of trifluoromethyl sulfone anions, the catalytic enantioselective addition to aldehydes can be achieved using a chiral ligand. Treatment of the trifluoromethyl sulfone **124** with *n*-BuLi in the presence of catalytic amount of the bis(oxazoline) **125**, followed by the successive addition of an aromatic aldehyde and Me_3SiCl, afforded a mixture of the alcohols *syn*- and *anti*-**127** with high enantio- and diastereoselectivity in good yields (Scheme 40). The addition of Me_3SiCl serves to trap the lithium alcoholates, thereby suppressing the retro-aldol-type reaction.[97,98] The enantioselective reaction was confirmed to proceed through a dynamic thermodynamic resolution pathway.[98]



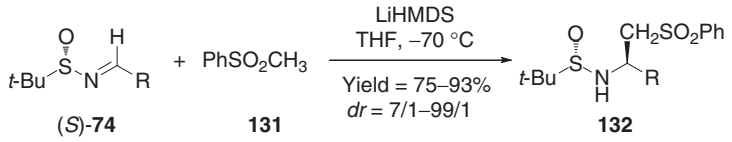
Scheme 40

1.12.4.3 Addition of Sulfonyl-Stabilized Carbanions to C=N Bonds

Nucleophilic addition of sulfonyl anions to C=N bonds affords structurally diverse *β*-amino sulfones (Schemes 41 and 42), which can be further transformed into chiral amines or nitrogen-containing heterocycles.[99–105] In the case of *N*-*tert*-butylsulfinylimines (Scheme 42), the good diastereoselectivity can be rationalized either with a six-membered chelated boat-like transition state mode or with a nonchelation-controlled transition-state mode.[103]



Scheme 41



Scheme 42

1.12.4.4 Addition of α-Halo Sulfones to C=O Bonds

α-Halo alkylmetal reagents, also known as carbenoids, display the reactivity of both carbanions **134** and carbocations **135**, as is shown in their resonance structures (Figure 2).[106] The introduction of a negative charge-stabilizing substituent will increase its carbanionic character and improve its nucleophilic reactivity. Due to its strong electron-withdrawing ability, a sulfonyl group can serve as an excellent activation group in nucleophilic haloalkylations.[58]

α-Chloro sulfones add to carbonyls to afford Darzen-type products in the presence of a base. In 1998, Arai et al. realized the enantioselective reaction using chiral quaternary ammonium salt **137** as phase-transfer catalyst (Scheme 43). The resulting *trans*-*α*,*β*-epoxysulfones **138** are obtained in good yields with enantioselectivities in the range of 64–81% *ee*.[107,108] In 2007, Jew and coworkers developed a improved catalytic system for this reaction, giving rise to **138** in up to 95% yield, 97% *ee*.[109]

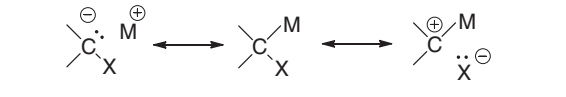
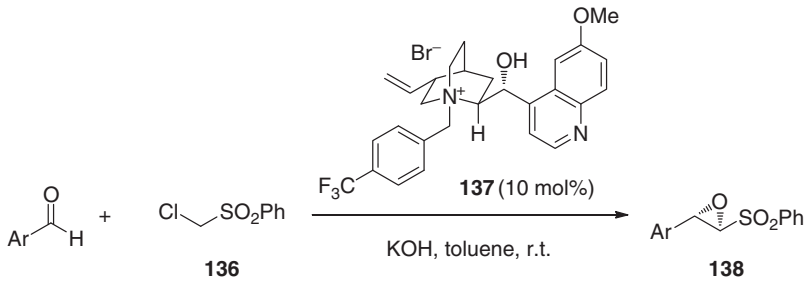
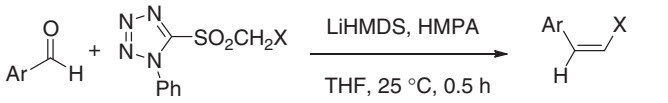


Figure 2 Resonance structures of α-halo alkylmetal reagents.



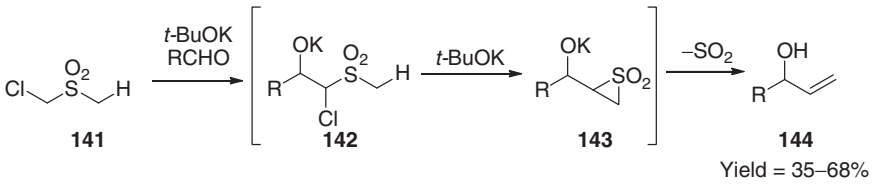
Scheme 43

The reaction between α-halomethyl heteroaryl sulfones **139** and a variety of aldehydes takes place in a Julia–Kocienski olefination model, affording haloalkenes **140** in good to excellent yields with high (*Z*)-stereoselectivities (Scheme 44).[110]



Scheme 44

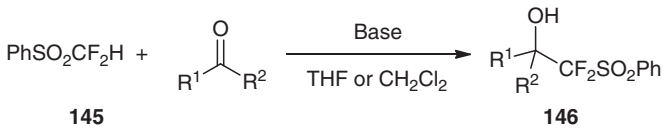
Addition of the carbanion of chloromethyl methyl sulfone **141** to aldehydes and ketones proceeds faster than its degradation via the Ramberg–Bäcklund reaction.[111] In the presence of excess base, the intermediates **142** undergo Ramberg–Bäcklund reaction giving allylic alcohols **144** (Scheme 45),[111] whereas the reaction of ketones gives the oxiranes.[112] For more details on this topic within the reference work (*see* Chapter 3.18).



Scheme 45

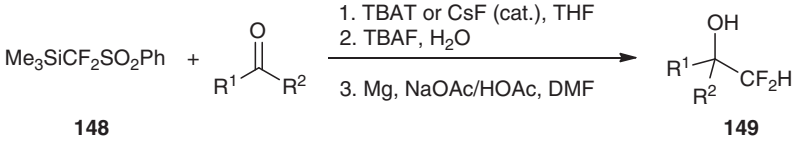
The presence of fluorine atoms on a carbanion center will dramatically influence the nucleophilic alkylation reactions. It is found that fluorine substitution on the carbanionic carbon poses a negative effect in many nucleophilic fluoroalkylation reactions. The introduction of sulfonyl groups can effectively tune the negative fluorine effect (NFE).[58] The sulfonyl group not only can reduce the electron repulsion between the electron pairs on the carbanionic carbon and those on the fluorine atoms through electron delocalization, but also can act as a good auxiliary group that can be readily removed by reductive desulfonylation. So α-fluoro sulfones are very powerful fluoroalkylation reagents.[58]

In 1989, Stahly reported the reaction between difluoromethyl sulfone **145** and aldehydes with NaOH as the base under phase-transfer conditions, giving (phenylsulfonyl)difluoromethylated alcohols **146** in good yields.[113] In 2005, Prakash et al. modified the procedure using lithium hexamethyldisilazide (LiHMDS) as a base.[114] The *in situ* generated (phenylsulfonyl)difluoromethyllithium ($PhSO_2CF_2Li$, **147**) adds effectively to ketones and nonenolizable aldehydes, affording alcohols **146** in good to excellent yields (Scheme 46).[114]



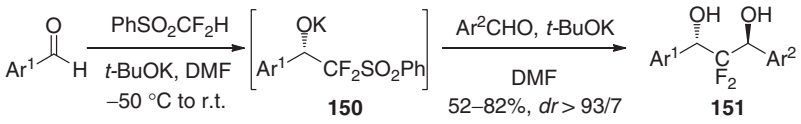
Scheme 46

To overcome the enolization problem in the reaction with aliphatic aldehydes, a much milder (phenylsulfonyl)difluoromethylation reagent $Me_3SiCF_2SO_2Ph$ (**148**) was prepared from $PhSO_2CF_2Br$ by Br–Li exchange.[115] By using **148** as the reagent via a fluoride-induced fluoroalkylation protocol, an improved nucleophilic difluoromethylation of carbonyl compounds is achieved (Scheme 47).[115] Compared with $PhSO_2CF_2H$ reagent method,[114] this method avoids the use of excess amount of base and carbonyl compounds and is rather effective with enolizable aldehydes.[115] Meanwhile, a mild and environment-benign desulfonylation method using magnesium metal as reductive reagent in HOAc–NaOAc buffered solution is also developed.[115]



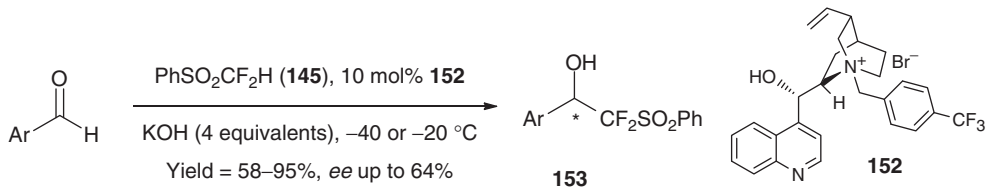
Scheme 47

When *t*-BuOK is used as a base, the $PhSO_2CF_2H$ (**145**) reagent can react with 2 equivalents of aromatic aldehydes to afford difluorinated *anti*-1,3-diols **151** in high yields and diastereoselectivity (Scheme 48).[116]



Scheme 48

By using $PhSO_2CF_2H$ (**145**) as a difluoromethylation reagent, a catalyzed-enantioselective difluoromethylation of aromatic aldehydes is realized (Scheme 49).[117] With KOH as a base and cinchonium salt **152** as a phase-transfer catalyst, the reaction of $PhSO_2CF_2H$ (**145**) and aromatic aldehydes proceeds smoothly to give (phenylsulfonyl)difluoromethyl-substituted alcohols (**153**) in good yields with moderate enantioselectivity.[117]

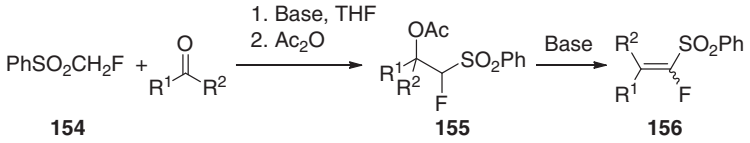


Scheme 49

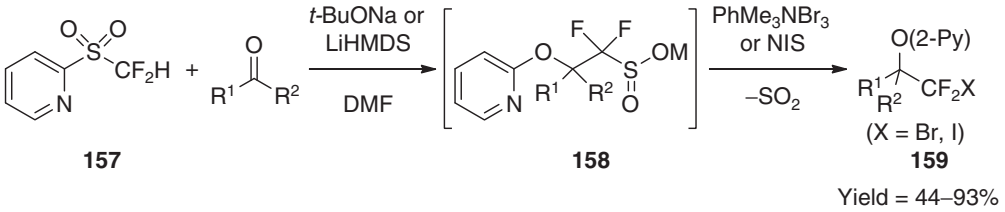
Although the reaction of $PhSO_2CH_2F$ (**154**) and carbonyls has been used to prepare monofluoromethyl carbinols,[118] it is more often used to prepare fluoroalkenyl sulfones **156** by *β*-acetic acid elimination from acetates **155** (Scheme 50).[119,120]

The reaction of *α*-fluorinated heteroaryl or electron-deficient aryl sulfones with a variety of carbonyls takes place in a Julia–Kocienski olefination model, affording fluorokenes in good to excellent yields. However, in the cases of monofluoroalkenes, the *Z*/*E* stereoselectivities are poor.[121–124] By controlling the reaction conditions, the reaction pathway can be switched from olefination[122] to alkylation, therefore a formal iodo- and bromodifluoromethylation of carbonyls is realized (Scheme 51). The key strategy of the transformation is the halogenation of *in situ* generated sulfinate intermediates **158**.[125]

The nucleophilic addition reaction between $(PhSO_2)_2CHF$ (**160**) and an aldehyde, a reaction that was previously believed to be unattainable,[126] has been recently accomplished by Hu and coworkers.[127] Among the lithium, sodium, and potassium hexamethyldisilazides (KHMDSs), LiHMDS serves as the best base for this addition reaction, which indicates that the strong Li–O

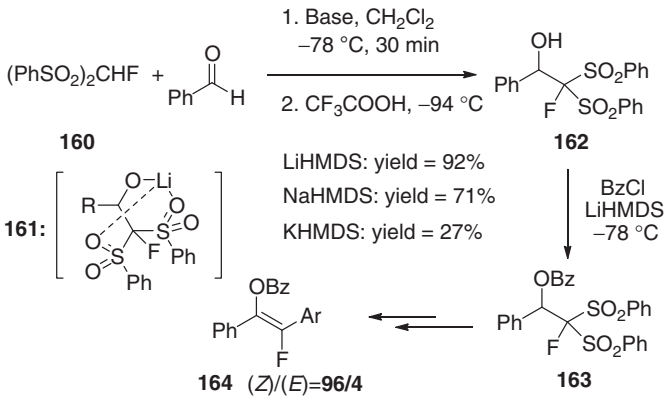


Scheme 50



Scheme 51

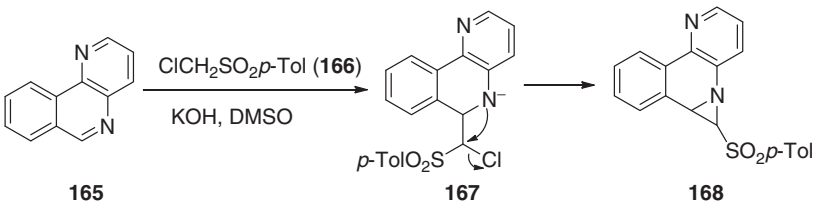
coordination in the carbinolate intermediate **161** plays a very important role in the success of the reaction (Scheme 52). Furthermore, under the same reaction conditions, the similar nucleophilic addition reactions between $(PhSO_2)_2CHX$ (X=Cl or H) and PhCHO are unsuccessful. That means the fluorine substitution is also very important for the nucleophilic fluoromethylation reaction, which is further supported by DFT calculations.[127] Benzoate **163** derived from carbinol **162** can be transformed into fluorinated stilbene derivative **164** with high (*Z*)-stereoselectivity.



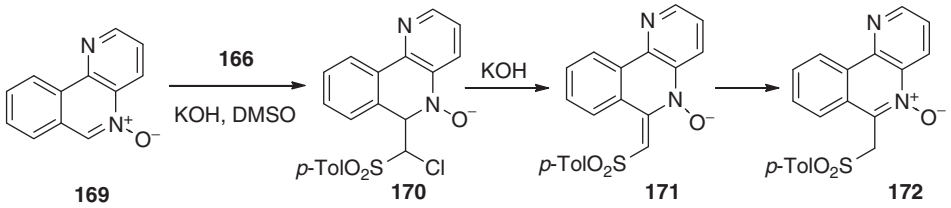
Scheme 52

1.12.4.5 Addition of α-Halo Sulfones to C=N Bonds

The carbanion of chloromethyl *p*-tolyl sulfone **166** reacts with benzonaphthyridine **165** in an annelation pathway, giving aziridine **168** (Scheme 53); while its reaction with *N*-oxide **169** gives (*p*-tolylsulfonyl)methyl-substituted *N*-oxide **172** via base-induced β-elimination and subsequent aromatization (Scheme 54).[128,129]



Scheme 53



Scheme 54

Diastereoselective nucleophilic addition of fluorinated sulfone anions to *N*-*tert*-butylsulfinyl imines constitutes the most effective protocol for the synthesis of chiral difluoromethyl and monofluoromethyl amines.[130] Nucleophilic mono- and difluoromethylation of aldimines with the *in situ* generated $PhSO_2CHF^-$ or $PhSO_2CF_2^-$ anion can readily take place to afford the adducts in good yields (No. 1, 2, 4, 5, 7, and 8 in Table 3),[131,133,134,136] whereas the nucleophilic fluoroalkylation of ketimines is relatively difficult due to the low electrophilicity of ketimines (compared to aldimines) and low nucleophilicity of fluorinated carbanions (compared to nonfluorinated carbanions).[131] However, a pregeneration of $PhSO_2CHF^-$ anion facilitates the monofluoromethylation reaction, and monofluoromethyl amines containing quaternary carbon centers could be prepared with high diastereoselectivity starting from ketimines (No. 3 in Table 3).[131]

Unlike aldimines, the reaction between the $PhSO_2CF_2^-$ anion and simple *N*-*tert*-butylsulfinyl ketimines highly depends on the metal cations. Among lithium, sodium, and KHMDS, KHMDS gives the best results. It is believed that the kinetically preferred generation of the $PhSO_2CF_2^-$ anion by KHMDS and nucleophilic addition of the $PhSO_2CF_2^-$ anion to ketimines over the undesired aza-enolization of ketimines are the key factors for the success of difluoromethylation of simple ketimines (No. 6 in Table 3).[135]

Except for the diastereoselective nucleophilic addition reactions, the enantioselective reactions are also available. Shibata and coworkers reported an enantioselective fluorobis(phenylsulfonyl)methylation of *in situ* generated aldimines (from α-amino sulfones **185**) under the combination of Mannich-type conditions.[137] By using $CsOH \cdot H_2O$ as a base and quinidinium salt **186** as the phase-transfer catalyst, the reaction could proceed smoothly at $-80\ ^\circ C$ to give α-fluorobis(phenylsulfonyl)methylated amines **187** with excellent enantioselectivity (Scheme 55). The amines **187** can be converted to α-monofluoromethyl amines **188** by reductive desulfonylation.[137] Other fluorinated sulfones including $PhSO_2CHFNO_2$ (**189**) and $PhSO_2CHFCOCH_3$ (**190**) can also add to imines enantioselectively to afford *β*-amino sulfones.[138]

1.12.4.6 Miscellaneous

The sulfonyl group in sulfonates and sulfonamides can also stabilize the carbanions. In 2007, Li and Liu reported a nucleophilic introduction of a difluoromethylene sulfonamide group ($-CF_2SO_2NR_2$) into aromatic aldehydes. Sulfamoyldifluoromethyl anion **192**, *in situ* generated from diamide **191**, reacts with aromatic aldehydes to afford *β*-hydroxy sulfonamide **193** in good yields (Scheme 56).[139]

Using 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose as the chiral auxiliary, the aldol-type reaction of the anion of sulfonates **194** and aromatic aldehydes affords predominantly *syn*-**195** in diastereo- and enantiomeric excesses (Scheme 57).[140]

Using ketouridine **196** as a chiral substrate, the addition of *N*-benzyl-α,*N*-dilithio methanesulfonamide **197** to **196** with $CeCl_3$ as a Lewis acid, affords uridine-sulfonamide **198** as a single diastereomer (Scheme 58).[141]

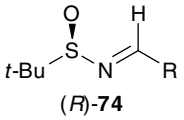
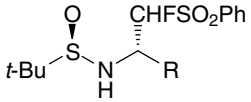
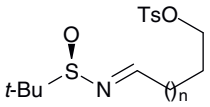
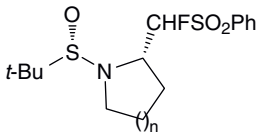
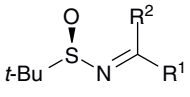
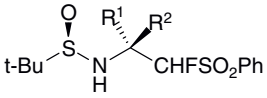
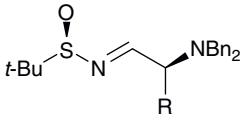
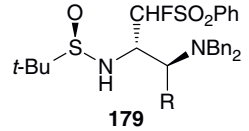
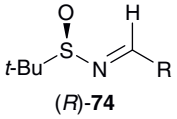
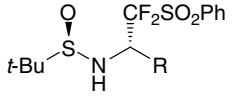
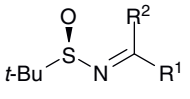
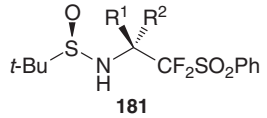
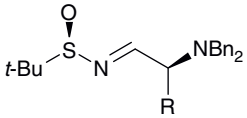
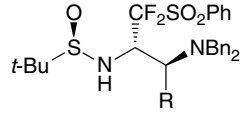
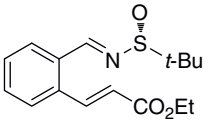
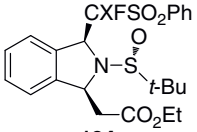
1.12.5 Sulfonimidoyl-Stabilized Carbanions

1.12.5.1 Configuration of Sulfonimidoyl-Stabilized Carbanions

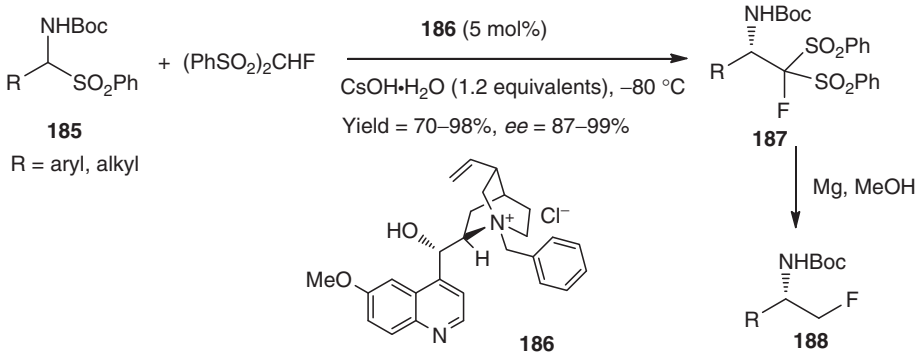
The structure of monolithiated sulfoximines have been established by X-ray ananlysis in the solid state and NMR studies in solution. However, very little is known regarding the structures and the reactions with dilithiated sulfoximines.[142–144] In 1997, Müller et al. reported the preparation and X-ray characterization of a sulfoximine-stabilized chiral dilithiocarbanion.[145] Treatment of racemic *S*-ethyl-*N*-methyl-*S*-phenylsulfoximine **199** with 2 equivalents of *n*-BuLi in *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA) in the presence of Li_2O at $-78\ ^\circ C$ to $25\ ^\circ C$ produces species **200**, a mixed aggregate containing mono- and dilithiated *S*-ethyl-*N*-methyl-*S*-phenylsulfoximine units in a 2/2 ratio coordinated by three TMEDA ligands (Figure 3).

In the dianionic subunit **201**, both the *ortho*-position of the phenyl ring and the α-carbon are deprotonated. However, no $C_{(\alpha)}$–Li bond is observed and the $C_{(\alpha)}$–S bond length is found to be much shorter than that in the nondeprotonated sulfoximine (1.62 Å vs. 1.73 Å). This is in consistence with a substantial S–C multiple bond character. Morever, the 122.0° bond angle of S–$C_{(\alpha)}$–$C_{(\beta)}$ illustrates that the anionic $C_{(\alpha)}$ atom has a nearly planar configuration. In contrast to monolithiated sulfoximines, the lone pair at $C_{(\alpha)}$ adopts a conformation in which it is oriented between the imino N-atom and the phenyl group instead of being gauche to both heteroatoms (Figure 4).[145]

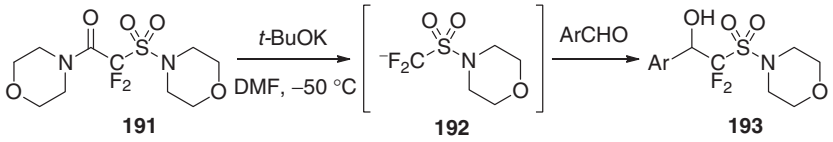
Table 3 Nucleophlic fluoroalkylation of imines with fluorinated sulfones

No.	*Imines*	*sulfones*	*Products*	*Conditions*
1	 (*R*)-**74** R = aryl, alkyl	$PhSO_2CH_2F$ (**154**)	 **173** ^{19}F NMR yield >99%	LiHMDS, THF, −78 °C, 10–20 min[131]
2	 (*R*)-**174** *n* = 1, 2	**154**	 **175**	LiHMDS, THF, −78 °C, 10–20 min[131]
3	 (*R*)-**176**	**154**	 **177** Yield = 47–93%, *dr* ≤ 99/1	*n*-BuLi or KHMDS, THF, −78 °C, 30 min[132]
4	 (*Rs*,*S*)-**178**	**154**	 **179** Yield = 87–99%, *dr* > 99/1	NaHMDS, THF, −78 °C[133]
5	 (*R*)-**74** R = aryl, alkyl	$PhSO_2CF_2H$ (**145**)	 **180** Yield = 85–95%, *dr* > 99/1	LiHMDS, THF, −78 °C, 10–20 min[134]
6	 (*R*)-**176**	**145**	 **181** Yield = 32–96%, *dr* > 90/10	KHMDS or NaHMDS, THF, −78 °C, 2–4 h[135]
7	 (*Rs*,*S*)-**178**	**145**	 **182** Yield = 87–99%, *dr* > 99/1	NaHMDS, THF, −78 °C[133]
8	 (*R*)-**183**	**145** or **154**	 **184** X = F, yield = 63% X = H, yield = 93%	1. LiHMDS, THF, −78 °C 2. −78 °C to −20 °C[136]

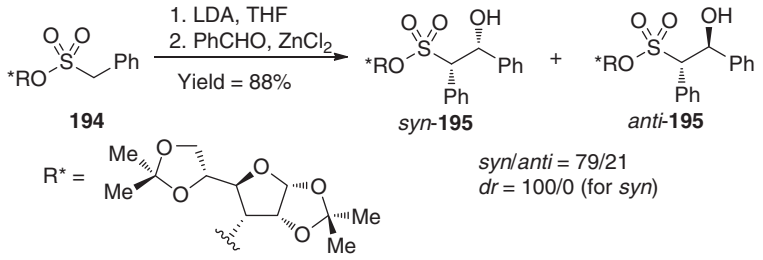
In the monoanionic subunit **202**, a $C_{(\alpha)}$–Li contact is observed (2.25 Å). In this case, the $C_{(\alpha)}$ atom has a distinct pyramidal configuration as supported by the angles Li–$C_{(\alpha)}$–$C_{(\beta)}$ (109.4°), Li–$C_{(\alpha)}$–$H_{(\alpha\text{-}C)}$ (112.9°), $C_{(\beta)}$–$C_{(\alpha)}$–$H_{(\alpha\text{-}C)}$ (105.1°), and S–$C_{(\alpha)}$–$H_{(\alpha\text{-}C)}$ (111.0°). A Newman projection along the S–$C_{(\alpha)}$ bond of **202** shows that the C(α)–Li bond is arranged in a gauche conformation between the N- and O-atoms of the sulfoximine moiety. A significant shortening of the S–C(α) bond (1.66 Å) is also found in the monoanion **202**, but not as pronounced as for the dianionic species **201** (Figure 5).[145]



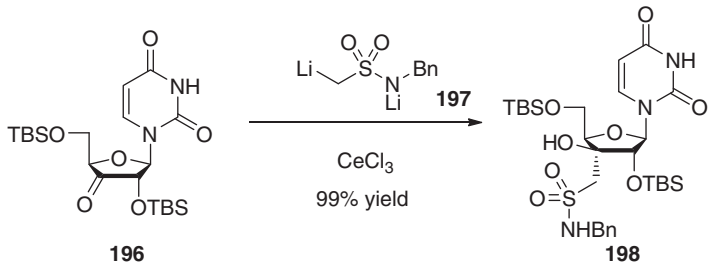
Scheme 55



Scheme 56



Scheme 57

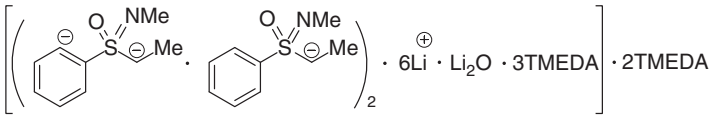


Scheme 58

1.12.5.2 Addition of Sulfonimidoyl-Stabilized Carbanions to C=X Bonds

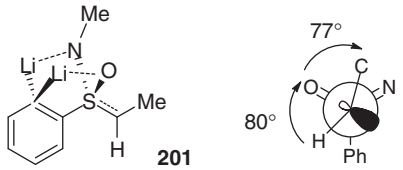
Many applications of sulfoximines rely on the excellent chiral induction ability and the good leaving group ability of sulfonimidoyl groups. A handful of examples on the diastereoselective 1,2-addition of sulfoximine anions to C=X (X=O, N) bonds affording alcohols or amines have been reviewed in a recent book chapter.[3] Here, we will illustrate some typical reactions on sulfoximines anions, especially the fluorinated sulfoximines anions.

Highly sterically demanding substituents at the sulfoximine nitrogen are beneficial for the high diastereoselectivity in the addition to carbonyls or imines.[146,147] *N-tert*-butyldiphenylsilyl-*S*-methyl-*S*-phenylsulfoximine (**204**) shows higher diastereoselectivity than *N*-methylsulfoximine (**203**) in the reaction with imines. Lithiated *N*-methylsulfoximine (**203**) undergoes 1,2-addition to imines giving a 50/50 mixture of the two possible diastereomeric adducts (**205**) and (**206**), whereas lithiated *N-tert*-butyldiphenylsilylsulfoximine (**204**) gives a 88/12 mixture of the two diastereomeric products (**205**) and (**206**) (Scheme 59).[146]



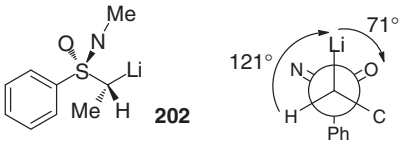
200

Figure 3 Structural formula of the aggregated mono- and dilithiated species.



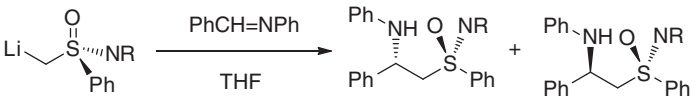
201

Figure 4 Structure of the dilithiated species **201**.



202

Figure 5 Structure of the monolithiated species **202**.

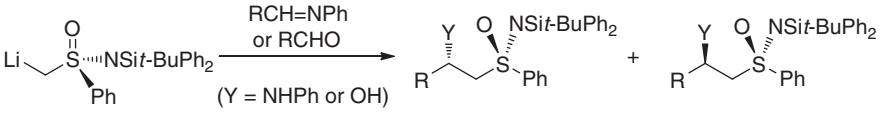


203 R = Me
204 R = Si*t*-BuPh$_2$

205 **206**

Scheme 59

Reaction between lithiated *N-tert*-butyldiphenylsilylsulfoximine (*Rs*)-**204** and a series of imines shows that the product diastereoselection progressively decreases as the steric demand of the substituent R increases (Scheme 60 and Table 4). When R is relatively small (R=*i*-Bu), high product diastereoselection (95/5) is observed; whereas when R is sterically demanding (R=*t*-Bu), the reaction proceeds with modest diastereoselectivity (79/21). Among the two possible chelated cyclic transition states for this reaction, the preference for the diastereomeric adduct **207** over **208** suggests that the chair transition state **209** is favored (Figure 6), which is in accordance with the decreasing diastereoselection as the steric demand of R increases.[147]



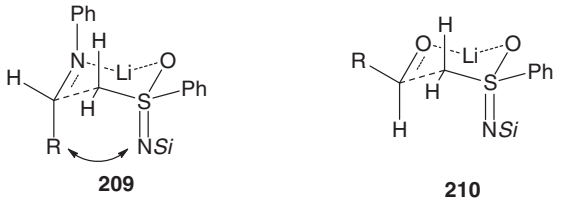
(R_S)-**204** (S, R_S)-**207** (R, R_S)-**208**

Scheme 60

Table 4 Addition of (*Rs*)-*N-tert*-butyldiphenylsilylsulfoximine **204** to imines and aldehydes (Scheme 60)

R	*Imine (Y=NHPh)*		*Aldehyde (Y=OH)*	
	207/208	*Yield (%)*	***207/208***	*Yield (%)*
Et	94/6	68	8/92	82
i-Bu	95/5	76	4/96	79
i-Pr	90/10	70	7/93	74
Ph	88/12	90	9/91	89
t-Bu	79/21	24	6/94	86

When aldehydes are used as electrophiles, the product diastereoselection was generally high and independent of the steric demand of the aldehyde substituent R (Scheme 59 and Table 4). Accoding to the diastereoselective outcome, a chair-like transition state **210** is proposed for this reaction (Figure 6).[147]

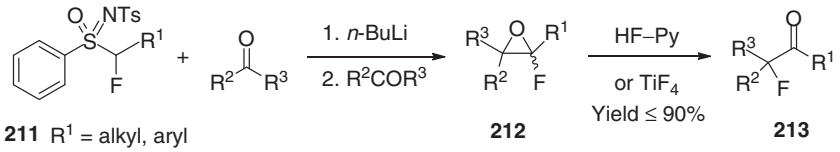


209 **210**

Figure 6 Proposed transition state for the addition of **204** to imines and aldehydes.

1.12.5.3 Addition of α-Halo Sulfoximines to C=X Bonds

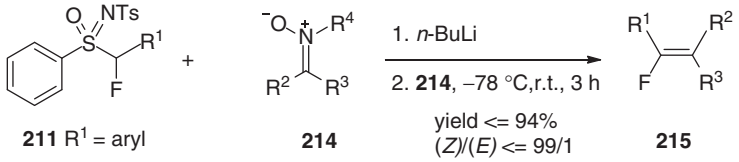
Taking advantage of the good leaving group ability of sulfonimidoyl, sulfoximines are often used in the synthesis of epoxides and aziridines.[148] In 2010, Zhang and Hu reported an *O*-cyclization reaction between α-fluorosulfoximines **211** and ketones to synthesize monofluorinated epoxides **212**, in which the electron-withdrawing sulfonimidoyl group not only stabilizes the α-fluorinated carbanions but also serves as a good leaving group.[149] The obtained fluoroepoxides **212** are found to undergo an interesting ring-opening process (involving both a C–F bond cleavage and another C–F bond formation) in the presence of titanium tetrafluoride or pyridinium poly(hydrogenfluoride) to afford α-fluorinated ketones **213** (Scheme 61).



211 R^1 = alkyl, aryl **212** **213**

Scheme 61

When nitrones are used as electrophiles, the reaction between lithiated α-monofluorinated sulfoximines **211** and nitrones **214**, affords monofluoroalkenes **215** in high yields with excellent (*Z*)/(*E*) stereoselectivity.[150] This novel fluoroolefination reaction proceeds via an addition–elimination pathway (Scheme 62). When fluorinated sulfone compound $TMSCF_2SO_2Ph$ (**148**), in place of a sulfoximine, is used to react with a nitrone, a fluoroalkylated hydroxylamine product is obtained, and no alkene product is formed, which demonstrates a remarkable reactivity difference between fluorinated sulfoximines and sulfones.[150]



211 R^1 = aryl **214** **215**

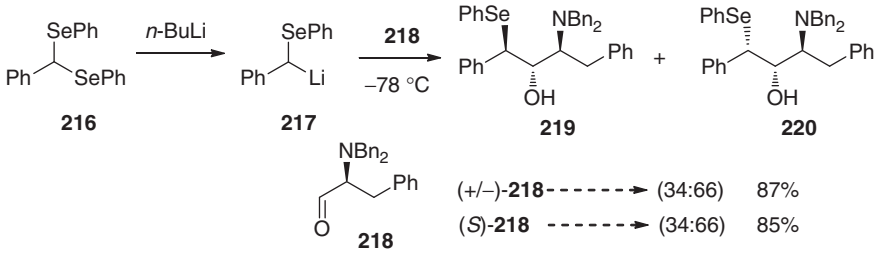
Scheme 62

1.12.6 Selenium-Stabilized Carbanions

An exhaustive review on the chemistry of selenium-stabilized carbanions before 1990 has been published in the first edition of this book.[6] A review concerning the generation and the reactivity of selenium-stabilized carbanions from 1990 to 2000 is also available.[151] In recent years, some progress has been made on the asymmetric reactions with selenium-stabilized carbanions. Here, the authors briefly summarize the diastereoselective and enantioselective addition of selenium-stabilized carbanions to C=X bonds. Besides, some reactions involving α-halo selenides also include in this part. For more details on this topic within the reference work (*see* Chapter 3.02).

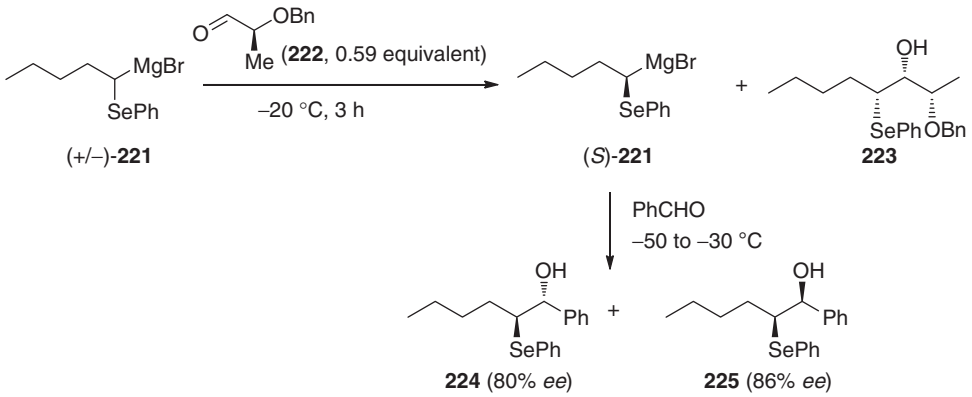
1.12.6.1 Configuration of Selenium-Stabilized Carbanions

The configurational stability of a selenyl-stabilized carbanion on the reaction time scale is tested by Hoffmann et al. (Scheme 63).[11] The selenium-substituted benzyllithium compound **217** is generated by the action of *n*-BuLi on the selenoacetal **216** via selenium–lithium exchange.[152] Addition of **217** to the racemic aldehyde **218** at −78 °C furnishes only two adducts **219** and **220** in a stereoisomer ratio of 34/66. When the enantiomerically pure aldehyde **218** is used, the adducts are obtained in the same diastereomeric ratio. The identity of the two diastereomeric ratios indicates that the enantiomerization of **217** at −78 °C is faster than the addition of **217** to the aldehyde **218** – that is, the lithiated selanyl carbanion **217** is configurationally labile in THF at −78 °C.[11]



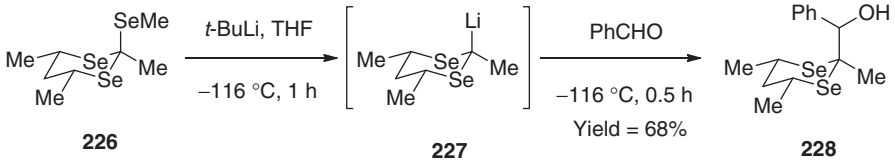
Scheme 63

Similar to the sulfenyl-stabilized carbanions, the configurational stability of selenyl-stabilized carbanions is also affected by the associated metal cations. It is found that α-selenyl Grignard reagents are configurationally more stable than the lithium reagents.[152] Based on this, a dynamic resolution of racemic α-selenyl Grignard reagent **221** with enantiopure aldehydes **222** affords the enantioenriched Grignard reagents (*S*)-**221**. Addition of benzaldehyde gives a mixture of **224** and **225** with enantiomeric enrichment (Scheme 64).[153]



Scheme 64

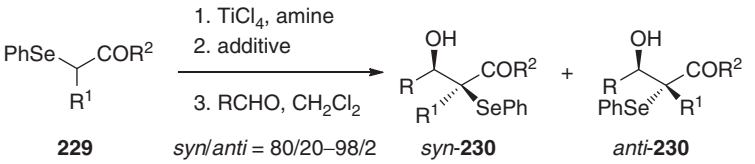
In cyclic systems, 2-lithio-1,3-diselenanes bearing the lithium in axial position are configurationally stable at −130 °C and slowly epimerize at −78 °C. Deuteration occurs exclusively from the axial side if carried out at −130 °C.[154] The axial organolithium compounds **227**, derived from **226** and *t*-BuLi, reacts efficiently with benzaldehyde to provide the corresponding *β*-hydroxy-selenoacetals **228** with almost complete stereocontrol (Scheme 65).[154]



Scheme 65

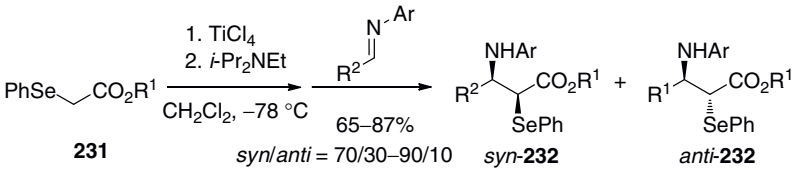
1.12.6.2 Addition of Selenium-Stabilized Carbanions to C=X Bonds

The addition of α-selenyl carbonyl compounds to C=X bonds promoted by Lewis acids takes place with good to excellent diastereoselectivity. The reaction of the titanium enolates of α-seleno esters or ketones with aldehydes and imines gives the products with high stereoselectivity favoring the *syn* isomers (Schemes 66 and 67).[155,156] The direct addition of selenyl-stabilized alkyllithium reagents to carbonyls leads to β-hydroxy selenides, which can be transformed to allylic alcohols **236** by selenoxide fragmentation. However, in the addition step, the diaostereoselectivity is relatively low and substrate-dependent (Scheme 68).[157,158]



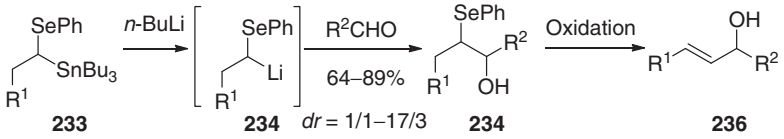
229 *syn*/*anti* = 80/20–98/2 *syn*-**230** *anti*-**230**

Scheme 66



231 *syn*/*anti* = 70/30–90/10 *syn*-**232** *anti*-**232**

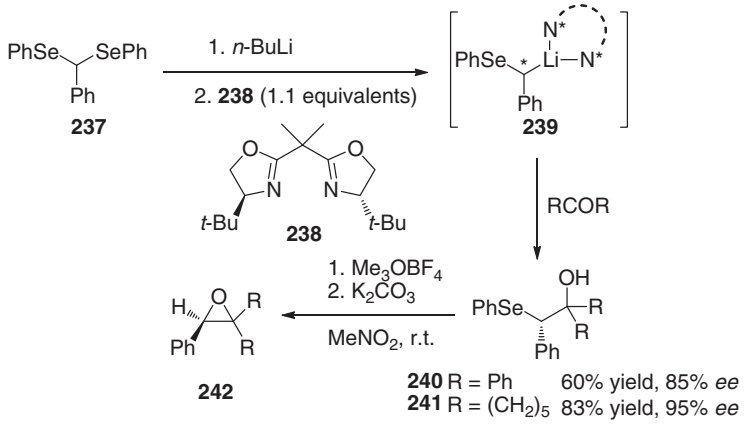
Scheme 67



233 **234** *dr* = 1/1–17/3 **234** **236**

Scheme 68

When a chiral ligand is used, the lithiated selenide complexes react with carbonyls to give enantioenriched adducts. Toru and coworkers reported an enantioselective reaction of the lithio-derivative of diselenide **237** with symmetric ketones in the presence of bis(oxazoline) **238**.[159,160] The reaction with benzophenone at −78 °C in cumene affords alcohol **240** in 60% yield with 85% *ee*, whereas cyclohexanone affords the alcohol **241** with much higher enantioselectivity (95% *ee*).[160] The chiral β-hydroxy selenide **240** can be converted to chiral epoxides **242** using the Meerwein reagent under basic conditions (Scheme 69).[160]

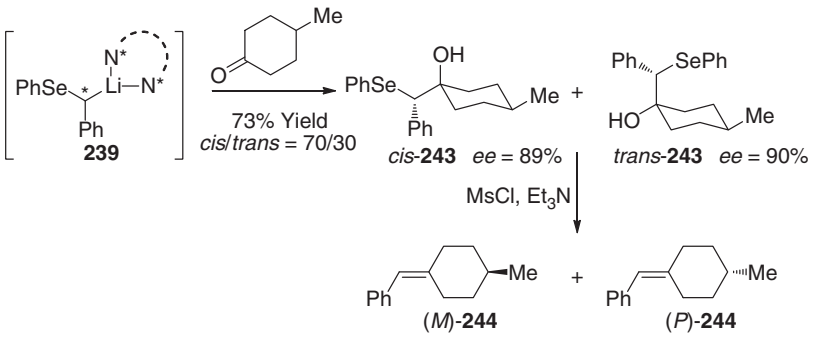


237 **239** **238** **242**

240 R = Ph 60% yield, 85% *ee*
241 R = $(CH_2)_5$ 83% yield, 95% *ee*

Scheme 69

The reaction of lithiated benzyl phenyl selenide **239** with 4-methyl cyclohexanone affords the adducts **243** and **244** with only moderate diastereoselectivity but excellent enantioselectivity (Scheme 70).[160] After the separation of the diastereomers, the

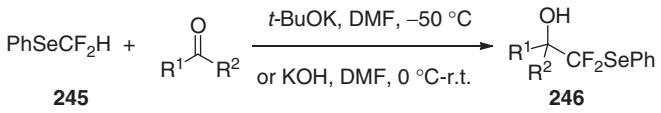


Scheme 70

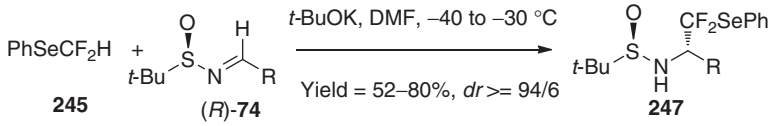
stereospecific elimination of the selenyl and hydroxyl groups on treatment with methanesulfonyl chloride and triethylamine gives the axially chiral olefins **244**.[160]

1.12.6.3 Addition of α-Halo Selenides to C=X Bonds

In the presence of a base, difluoromethyl phenyl selenide **245** reacts with ketones and nonenolizable aldehydes affording the α-(phenyseleno)difluoromethyl alchohols **246** in good to excellent yields (Scheme 71).[60] In the case of *N*-*tert*-butylsulfinyl aldimines, the reaction gives α-(phenyseleno)difluoromethyl amines **247** in moderate to good yields with high diastereoselectivities (Scheme 72).[60]

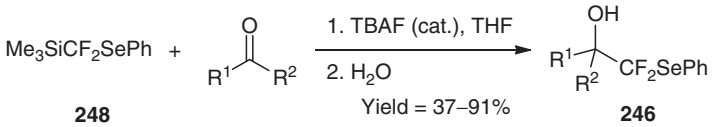


Scheme 71

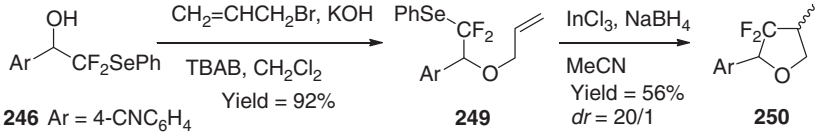


Scheme 72

Under the initiation of catalytic amount of fluorides, (phenylseleno)difluoromethyl silane **248** reacts with carbonyls giving alcohols **246** in good to excellent yields (Scheme 73).[161] Alcohols **246** can be further transformed into difluoromethyl alcohols by a radical deselenylation reaction.[161] The intramolecular radical cyclization of the corresponding allyl ether, such as **249**, affords difluorinated cyclic ether **250** in high diastereoselectivities (Scheme 74).[162]



Scheme 73



Scheme 74

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1.13 Benzoin and Aza-benzoin

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Glossary

Acyl anion equivalent Any organic molecule that can combine with an electrophile resulting in its formal nucleophilic acylation.

Breslow intermediate Key reactive species resulting from the combination of an *N*-heterocyclic carbene and an aldehyde, in which the carbon of the carbonyl has gained nucleophilic character.

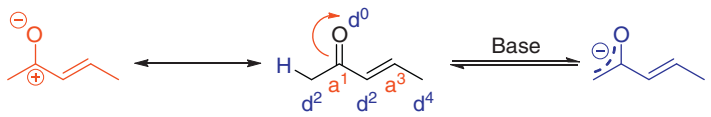
***N*-Heterocyclic carbenes (NHCs)** Carbene (neutral divalent carbon atom) included in heterocyclic structures, which confers unusual stability and nucleophilic properties to it compared with other carbenes.

Umpolung Chemical modification of a functional group of an organic molecule in order to inverse its innate reactivity.

1.13.1 Introduction

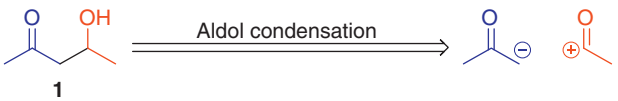
1.13.1.1 Normal and Inverse Polarity Reactions

The description of polar reactions in organic chemistry relies on the combination of nucleophiles with electrophiles to create new bonds. One of the most important class of transformations, but arguably also one of the most challenging, is the formation of C–C bonds. This comes from the fact that the carbon atom possesses an intermediate electronegativity (2.55 in the Pauling scale), which generally renders positively or negatively charged carbons, respectively, carbocations or carbanions, difficult to attain. The presence of a heteroatom can alter the reactivity of the carbon atom to which it is attached, but also of remote positions through mesomery. The description of these electronic effects can be rationalized using the notions of donor and acceptor positions. In the case of the carbonyl functionality, the strong electronegativity of the oxygen atom induces an inductive effect but also creates the possibility to delocalize the π-bond (equation 1). As a consequence, the carbon of the carbonyl exhibits strong electrophilicity and can be described as an acceptor (a) position. Besides this, deprotonation in the α-position generates an enolate, the negative charge of which is stabilized by delocalization on the oxygen. This illustrates the donor (d) properties of the α-position of carbonyls.



(1)

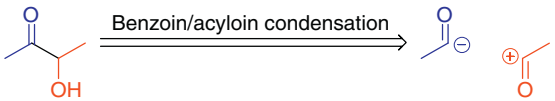
The usefulness of these two properties is illustrated in many reactions including the aldol condensation (*see* Chapters 2.07, 2.08, 2.09, and 2.10), which consists of the addition of an enolate to another carbonyl derivative (equation 2). It allows the preparation of β-hydroxyaldehydes and β-hydroxyketones **1**, organic compounds containing polar functionalities in a 1,3 pattern. They can be viewed as normal polarity molecules since the alternative attributions of donor and acceptor position starting from each one of the oxygen atoms match each other.



1

(2)

The situation is reversed for 1,2 substitution patterns such as the α-hydroxyketones **2**, also named benzoins and acyloins, respectively, when the ketone bears an aromatic or an aliphatic substituent (equation 3). Their synthesis will require the use of an acyl anion synthon, whose polarity is in contradiction with the innate reactivity of this position. Such a transformation belongs to the general synthetic strategy known as "umpolung," the German word for "inversion of polarity," which was first introduced by Wittig[1] and then popularized by the exceptional contribution of Seebach. (First used by Seebach at a lecture, given in the University of Hamburg, 7 July 1972.)[2]

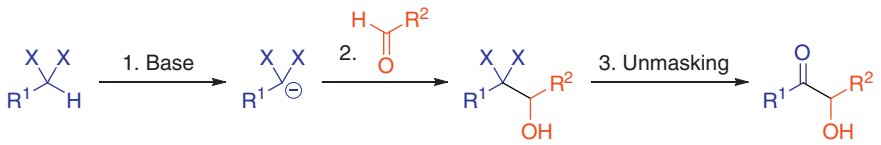


2 (3)

1.13.1.2 The Benzoin and Aza-Benzoin Reactions: Diversified Strategies

Because of the very low acidity of the aldehydic proton and the ensuing lack of stability of the acyl anions, their preparation by direct deprotonation is definitely not a viable strategy for the elaboration of complex molecules.[3] To circumvent this problem and achieve the synthesis of benzoins[4] (in this chapter, except when explicitly notified, this generic term will be used to encompass all α-hydroxyketones, no matter what the substituents on the ketone are), chemists had to design synthetic equivalents for the acyl anion. Most of these strategies are based on the same principle (**Scheme 1**):

1. An organic function is elaborated, which bears one or several substituents that are able to stabilize a negative charge;
2. The acyl anion equivalent is allowed to react with an aldehyde (or ketone); and
3. The carbonyl is unmasked to reveal the α-hydroxyketone.



Scheme 1

The selected examples commented in this chapter, covering the literature up to September 2012 will be sorted by the type of acyl anion equivalent, and advantages and drawbacks of each strategy, in terms of chemoselectivity, stereoselectivity, and practical usefulness, will also be discussed.

1. Stoichiometric acyl anion equivalents (see Section 1.13.2), including *O*-protected cyanohydrins and dithianes.
2. Cyanide-mediated and catalyzed transformations (see Section 1.13.3).
3. *N*-Heterocyclic carbene (NHC)-catalyzed benzoin condensations (see Section 1.13.4).
4. Miscellaneous other catalytic methods (see Section 1.13.5).

The stoichiometric acyl anion equivalents had been extensively discussed in the previous edition of this book series in 1991.[5] As most of the research carried out since then has tackled the development of catalytic variants of the benzoin condensation, the central focus of this chapter will be put on these ones. It should be noted that most of the catalytic systems are highly reminiscent of the corresponding stoichiometric methods that inspired them.

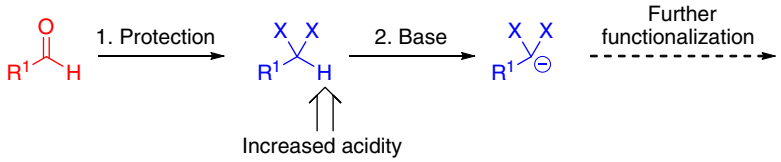
As a complement, the vinylogous extension of this umpolung reactivity will also be briefly presented (see Section 1.13.6). Finally, the carbonyl derivative that undergoes the attack of the acyl anion equivalent can be replaced by an imine or an iminium. These transformations, generically called aza-benzoin condensations, give an access to highly valuable α-aminoketones and key examples of these transformations will be included for umpolung strategies that extend to these nitrogen-containing substrates. However, conjugate addition of acyl anion equivalents (*see* Chapter 4.23) or their reactions with other types of electrophiles will not be discussed in this chapter.

A comprehensive survey of all published literature on this topic would be outside the scope of such a chapter. For this reason, the authors decided to discuss only the seminal reports and key developments, with an emphasis put on the most recent methods, and especially the catalytic ones. References to more specialized reviews on each strategy discussed here will also be provided.

1.13.2 Benzoin and Aza-Benzoin Condensations with Stoichiometric Acyl Anion Equivalents

Since aldehydes are very potent electrophiles, many protecting groups have been designed to mask this reactivity and allow the functionalization of other parts of the molecule.[6] In some cases, this protection of the carbonyl has another consequence: it

renders the aldehydic proton more acidic and enables its deprotonation in reasonably mild conditions (Scheme 2). Different types of protected aldehydes and their use in the benzoin condensation will be presented in this section.

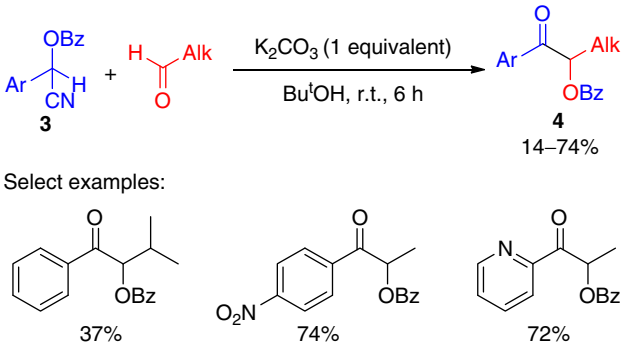


Scheme 2

1.13.2.1 *O*-Protected Cyanohydrins

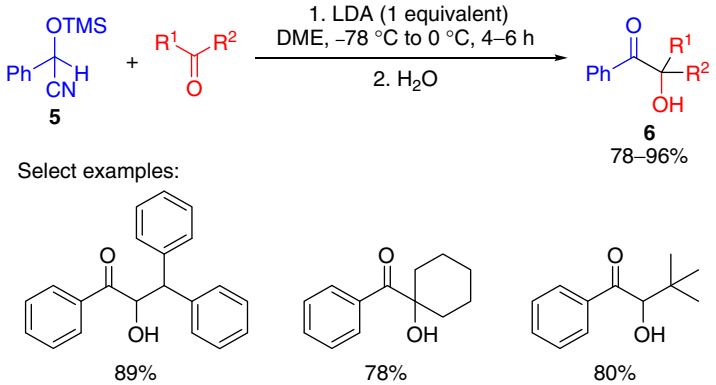
1.13.2.1.1 Early developments, variations of the protecting group

Reminiscent of the cyanide-catalyzed dimerization of benzaldehyde described by Wöhler and Liebig in 1832 (see Section 1.13.3),[7] the chemistry of *O*-protected cyanohydrins started its development in the 1970s.[8] Following seminal work by Stork and Maldonado on their alkylation and use in conjugate additions[9] the group of Hamana showed that readily available *O*-benzoyl mandelonitriles **3** were suitable substrates for the preparation of benzoins (Scheme 3).[10] With a base as weak as K_2CO_3 in Bu^{t}OH, they reacted with different aliphatic aldehydes to give the *O*-benzoyl benzoin products **4** after C–C bond formation, benzoyl group migration, and cyanide elimination. Extension of this reaction to more diversified substrates including aromatic aldehydes as coupling partners has then been achieved. Phase transfer reaction conditions appeared to be especially suitable for this transformation.[11]



Scheme 3

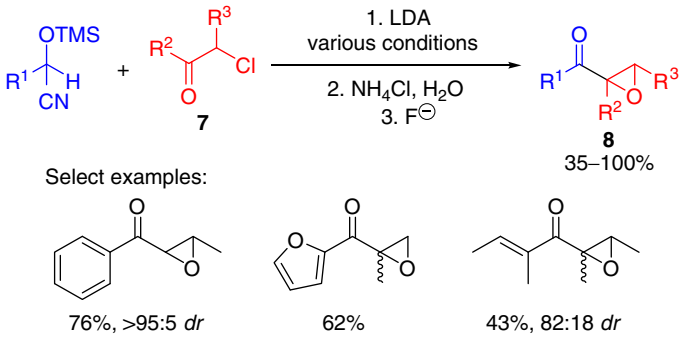
A few years later, the group of Hünig identified *O*-silylated cyanohydrins **5** as exceptional precursors for acyl anion equivalents.[12] The acidification of the proton caused by the silyl group is smaller as the one provided by the benzoyl group, therefore a strong base such as lithium diisopropylamide (LDA) had to be used. The corollary is that a more nucleophilic acyl anion equivalent is obtained, which is able to add to a large variety of aldehydes, including hindered ones, but also ketones (Scheme 4).[13] This addition is probably reversible but the irreversible silyl group transfer and cyanide elimination allow a



Scheme 4

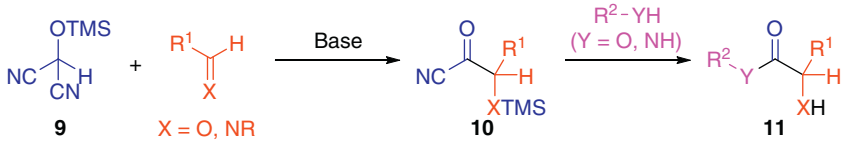
quantitative transformation and, after a simple aqueous treatment to remove the silyl group, the benzoins **6** were obtained in high yields.

Following their initial work, Hünig and coworkers extended their methodology to a plethora of other substrates. For example, when enones were used as electrophilic partners, the ratio between 1,2-addition (benzoin condensation) and 1,4-addition (Stetter-like reaction) could be controlled by the fine tuning of the reaction conditions.[14] In Et_2O, where the acyl anion equivalent and the lithium countercation stayed as a tight ion pair, the 1,4-addition product was exclusively obtained, whereas conducting the reaction in tetrahydrofurans (THF) in the presence of HMPT completely switched the selectivity toward the formation of the benzoin. The substituents on the aromatic ring of the *O*-silylcyanohydrin also have a strong influence on the 1,2/1,4-addition ratios.[15] Further studies of the addition to enones concluded that the 1,2-addition product results from the kinetically preferred attack.[16] However the reversibility of this reaction can allow the equilibration to the thermodynamically more stable 1,4-adduct. *O*-Silylcyanohydrins generated from enals are also suitable reagents for this transformation.[17] Notably exclusive α-selectivity was observed. Very interestingly, γ-selectivity is attainable when an ethoxyethyl protecting group is present on the oxygen and the reaction allowed coming back to 0 °C. Further studies on the regioselectivities were conducted with α,β-unsaturated systems either in the electrophilic or the nucleophilic reaction partners.[18] Finally, when α-chlorocarbonyl derivatives **7** were chosen as electrophiles, the treatment of the primary product with a fluoride source resulted in the 3-*exo*-tet cyclization to the α,β-epoxyketone **8** (Scheme 5).[19]



Scheme 5

In 1990, Nemoto and coworkers disclosed a special class of *O*-silylated acyl anion equivalents **9** that they called masked acyl cyanides (MAC) (Scheme 6).[20] In these reagents, the carbon atom with inversed polarity bore a second cyanide group, having several consequences on its behavior. At first, the acidity of the α proton was increased allowing its deprotonation with a milder base. After addition to an aldehyde or an imine, an acyl cyanide **10** was generated, on silyl group transfer. Its trapping with an alcohol or an amine afforded α-hydroxy or α-amino esters or amides **11**. This reactivity will not be discussed here since it does not lead to the preparation of benzoins. Nevertheless, further details can found in the numerous publications of the group of Nemoto on this topic.[21] The same group also studied the chemistry of *O*-ethoxyethyl MAC reagents under metal catalysis[22] and their *O*-acetyl counterparts.[23]

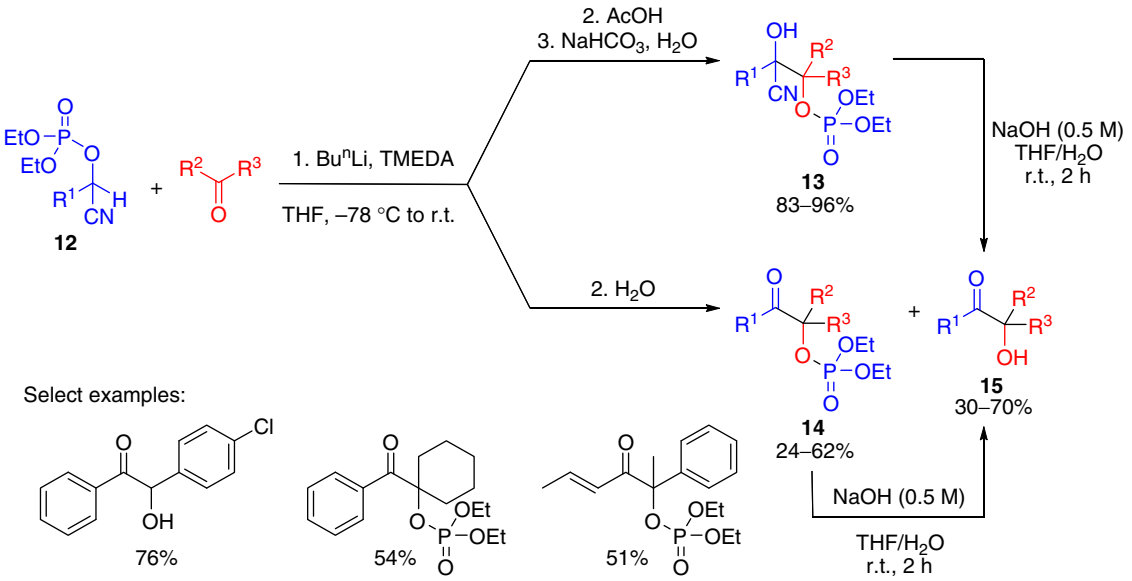


Scheme 6

Acyl anion equivalents could also be generated by deprotonation of α-cyanophosphates **12** with a strong base (Scheme 7).[24] After addition to a carbonyl derivative, different products could be obtained depending on the conditions used to quench the reaction. With AcOH, the integrity of benzoin cyanohydrin phosphate **13** was preserved, whereas the addition of water afforded a mixture of diethylphosphonobenzoin **14** and benzoin **15**. A basic aqueous treatment could convert any of the intermediates into the benzoin.

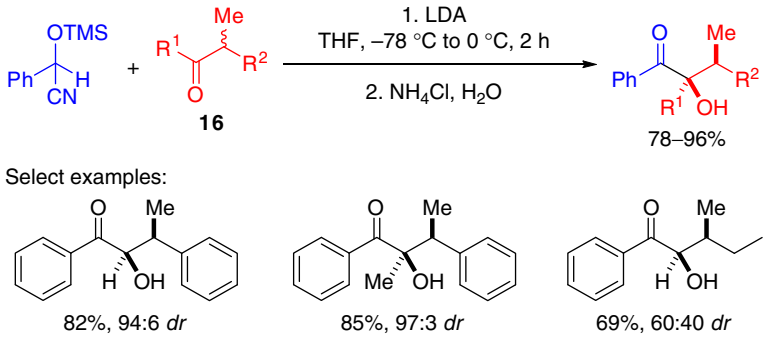
1.13.2.1.2 Studies on the diastereoselectivity of the reaction

The addition of the anions of *O*-protected cyanohydrins to carbonyl compounds often results in the formation of a stereogenic center. Several diastereoselective methods have been elaborated in order to control its formation. Hünig and coworkers studied the influence of the stereogenic center α to the carbonyl functionality of derivatives **16** (Scheme 8).[25] They realized that excellent induction could be obtained with an α-phenyl group whereas alkyl chains resulted in poor diastereoselectivities. This *syn*/*anti*



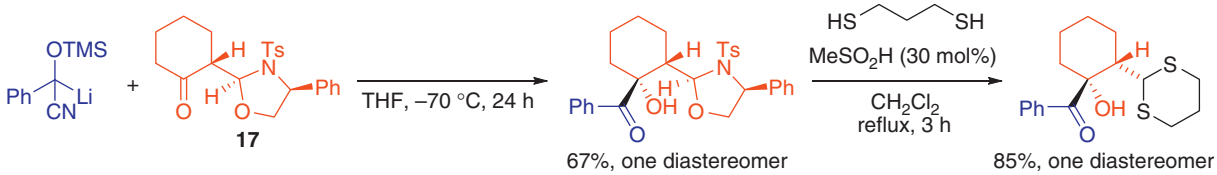
Scheme 7

selectivity could be rationalized following the Felkin–Ahn model. It should be noted that the replacement of the trimethylsilyl unit by another protecting group had only a limited influence on this process.



Scheme 8

At the same time, Hoppe and coworkers showed that this method could be applied to the synthesis of enantiopure benzoins by using a chiral auxiliary (Scheme 9).[26] The chiral ketone **17**, that bore a phenylglycinol-derived oxazolidine underwent a completely diastereoselective addition of an *O*-silylated cyanohydrin. Cleavage of the chiral auxiliary occurred smoothly without loss of the chiral integrity of the product.

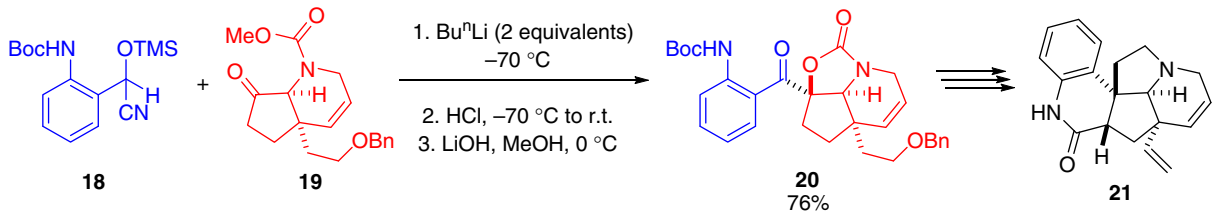


Scheme 9

Other examples of diastereoselective additions of *O*-protected cyanohydrins to carbonyls were reported using cyanosugars deriving from glucose,[27] *P*-chiral cyanohydrin phosphates,[28] or substrates substituted with a chiral sulfoxide.[29] Diastereoselective variants of the use of Nemoto's MAC reagent **9** can also be found in the literature.[30]

1.13.2.1.3 Synthetic applications

The preparation of benzoins from *O*-protected cyanohydrins has been used in numerous syntheses of complex molecules. In 1991, the group of Overman developed a general strategy to access several members of the alkaloid families *melodinus* and *aspidosperma*, including (±)-deoxoapodine, (±)-meloscine **21**, (±)-epimeloscine, and (±)-1-acetylaspidoalbidine (Scheme 10).[31] The dianion of *O*-trimethylsilyl cyanohydrin **18** reacted with ketone **19** and the product **20** was formed after cyclization of the newly formed alcohol on the carbamate. Quenching conditions had to be finely optimized to prevent a side reaction consisting of an α-ketol rearrangement.



Scheme 10

Other complex products synthesized by this strategy include the ABC ring system of aquayamycin,[32] sesquiterpenes (±)-AM6898A and (±)-AM6898D,[33] (±)-rocaglamide,[34] naphthylcombretastatins,[35] rocaglaol analog,[36] and (±)-rossinone B.[37] In 2010, Vedejs also used a related cyclization on a lactam as a key step en route to aziridomitosanes.[38]

1.13.2.2 Other α-Heterosubstituted Nitriles

In addition to cyanohydrins, other α-heterosubstituted nitriles can also serve as precursors for acyl anion equivalents, provided that their subsequent hydrolysis can regenerate the carbon–oxygen double bond. Among these possibilities, α-(dialkylamino)-nitriles are the most commonly used even if scarce examples of other derivatives can also be found in the literature.[9]

1.13.2.2.1 α-(Dialkylamino)nitriles

Just like *O*-protected cyanohydrins, α-(dialkylamino)nitriles **22** can be deprotonated and become acyl anion equivalents; these compounds were first studied by Hauser in alkylation reactions (Figure 1).[39] Their synthetic utility was then extended by combining them with various electrophiles, especially by the groups of Stork and Reutrakul, who used them in different nucleophilic acylation reactions.[40] Two recent reviews discussed their reactivity in a very detailed way.[41] One interesting feature of this family of anion equivalents is that they can be easily converted to ketones but also different other functionalities. The usefulness of this stepwise benzoin condensation via α-(dialkylamino)nitriles was for example demonstrated in the synthesis of analogs of capsaicin.[42] One of the alkyl chains on the nitrogen atom could also be replaced by an electron-withdrawing group, so that an amide or a carbamate is now part of the precursors **23** and **24**. Similar reactivity was then observed, accompanied by an acyl group migration or a cyclization on the carbamate after initial addition to the carbonyl compound.[41a,43]

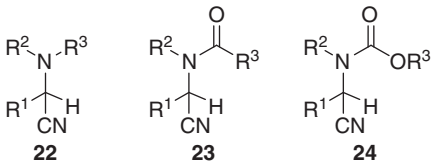


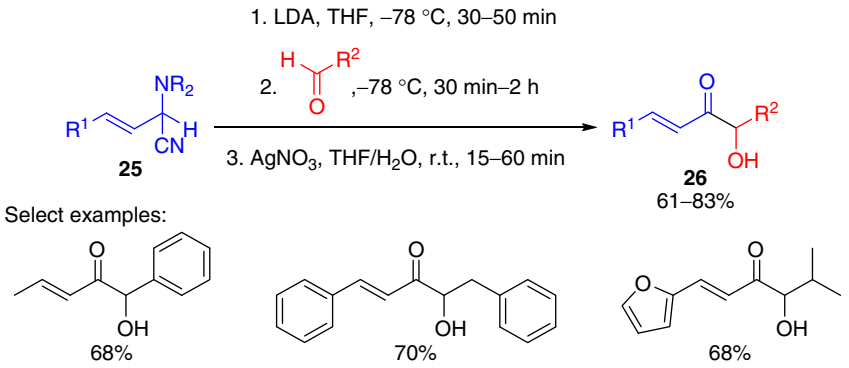
Figure 1 α-Aminonitriles as precursors of acyl anion equivalents.

When α-(dialkylamino)nitriles derived from enones **25** were used, a regioselective reaction in the α-position was observed (Scheme 11).[44] After metallation, addition to the aldehyde and hydrolytic deprotection with silver nitrate, the α-hydroxyenones **26** were obtained with good overall yields.

In addition to this, the principal advantage of α-(dialkylamino)nitriles over *O*-protected cyanohydrins is that a variety of chiral secondary amines are readily available, which allowed, after coupling and deprotection, to obtain enantiomerically enriched benzoins. For example, *O*-methylprolinol or axially chiral amines based on a binaphthyl unit were used as chiral auxiliaries, affording the target compounds with moderate optical purities.[45]

1.13.2.2.2 Use of other heteroatoms

α-Thionitriles[46] and α-selenonitriles[47] are also known to act as acyl anion equivalents. However, the complete sequence of their reaction with a carbonyl derivative and subsequent unmasking of the ketone to generate the benzoin has not been reported.



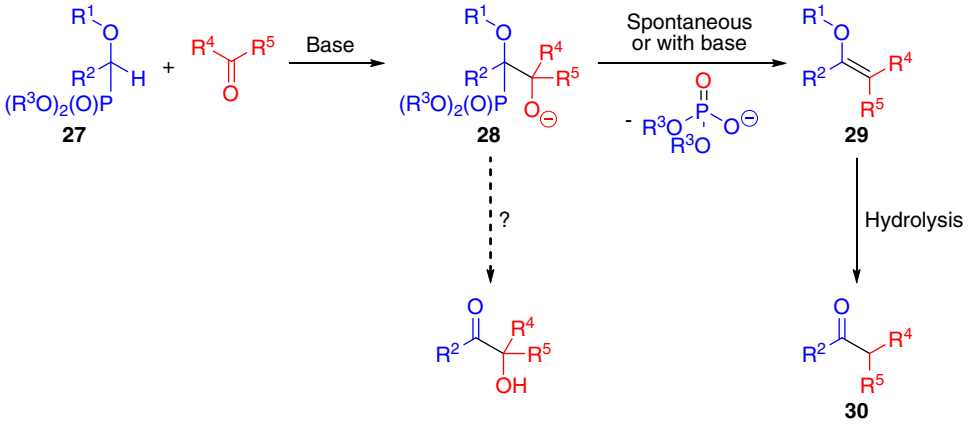
Scheme 11

The first family of compounds has already been condensed with aldehyde but the intermediate products were only oxidatively processed. In the same time, the second type or precursors have only been engaged in alkylations and conjugate additions.

1.13.2.3 Heterosubstituted Phosphonates

1.13.2.3.1 Innate reactivity: Horner–Wadsworth–Emmons and Wittig-Horner olefinations

Phosphorus-based functional groups have long been known to stabilize negative charges on the atoms to which they are linked. This property has been widely used, especially in the textbook Wittig olefination and its variants.[48] When the carbon atom α to the phosphorous also bears a (protected) oxygen substituent, a reactivity similar to the one of *O*-protected cyanohydrins could be expected. However, one can soon realize that, after addition of an α-heterosubstituted phosphonate **27** to a carbonyl derivative, the intermediate **28** that is formed can naturally evolve toward the olefination product (Scheme 12). This strategy has been used on numerous occasions, especially with R^1 being an alkyl chain, to prepare enol ethers **29** and, after hydrolysis, homologated carbonyl compounds **30**.[49] This synthetically useful competitive pathway[50] has long precluded the development of a synthesis of benzoins from heterosubstituted phosphonates.

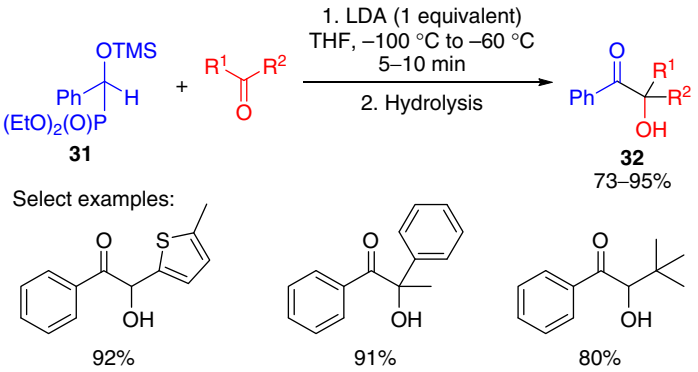


Scheme 12

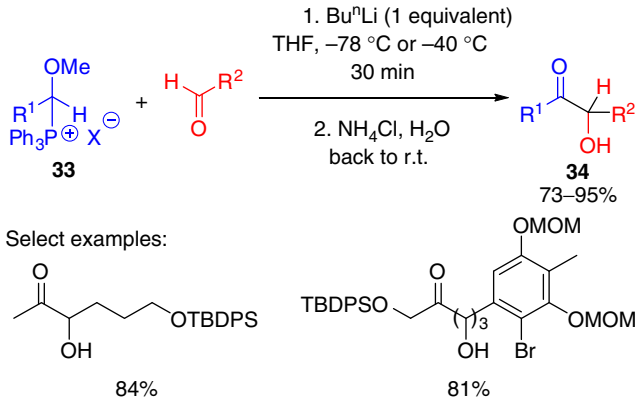
1.13.2.3.2 Reactivity alteration: The benzoin condensation of heterosubstituted phosphonates

In 1980, Koenigkramer and Zimmer engaged the anion of α-trimethylsilyloxy phosphonate **31** in a reaction with different aldehydes and ketones and obtained, after hydrolysis, the benzoins **32** (Scheme 13).[51] This shift in the reaction outcome could be ascribed to a 1,4 *O*→*O* silyl group transfer occurring faster than the olefination. This benzoin preparation was used for, *inter alia*, the synthesis of analogs of oxybutynin.[52]

More recently, an interesting extension of this reactivity was provided by the group of Saikawa and Nakata, using (1-methoxyalkyl)phosphonium salts **33** (Scheme 14).[53] An acidic hydrolysis of the primary adduct at low temperature prevented the Wittig olefination, thereby affording the benzoins **34** in good yields. Depending on the substrates, allowing the reaction mixture to come back to room temperature before quench partially or completely reversed the selectivity back to the Wittig product (not the enol ether but the ketone was obtained because of the acidic workup). An advantage of this method is that it allows the umpolung of aliphatic aldehydes, for which fewer methods exist than for the aromatic ones.



Scheme 13



Scheme 14

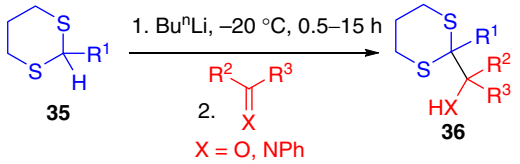
1.13.2.3.3 Related acyl anion equivalents

1-(Alkylthio)alkylphosphonates are related acyl anion equivalents that were first used by Corey to prepare α-hydroxyketones after deprotonation, condensation with a carbonyl derivative and Hg(II)-promoted deprotection.[54]

1.13.2.4 Dithianes and Related Compounds

1.13.2.4.1 Seminal studies

The dehydrative condensation of aldehydes with 1,3-propanedithiol affords 1,3-dithianes **35** that are very useful protecting groups because of their good stability in many different reaction conditions.[6,55] Although masking the electrophilicity of the carbonyl, this synthetic operation also increases the acidity of the aldehydic proton, that has now a pKa value of approximately 39.[56] Its deprotonation still requires a strong base but can nevertheless be achieved in conditions that are tolerated by various functional groups. Moreover, the moderate stabilization of the anion awards it a high nucleophilicity. For these reasons, 1,3-dithianes have become the most widely used stoichiometric anion equivalents. Their reactivity is detailed in another chapter of this book (*see* Chapter 1.12) therefore only key references in the preparation of benzoins will be discussed here. In seminal reports, Corey and Seebach demonstrated that 2-lithio-1,3-dithianes can react with a large variety of electrophiles, including aldehyde, ketones, and imines (Scheme 15).[57] Despite its wide applicability, this strategy finds its limitations in the fact that it is a three-step process and also in the problems often encountered during the deprotection of the dithiane **36**. Many variations of both starting materials are possible and several reviews extensively present the possibilities of this transformation.[58]



Scheme 15

1.13.2.4.2 Synthetic applications

Countless applications of the dithiane strategy for the preparation of complex natural and/or bioactive compounds can be found in the literature. Selected remarkable examples include the synthesis of (–)-lycoserone,[59] (+)-hydroxyjatrophone A and B,[60] phomoidrides,[61] spirastrellolides,[62] amphidinolide T1,[63] cephalostatin 1,[64] and aldingenin B.[65]

1.13.2.4.3 Other sulfur-substituted acyl anion equivalents

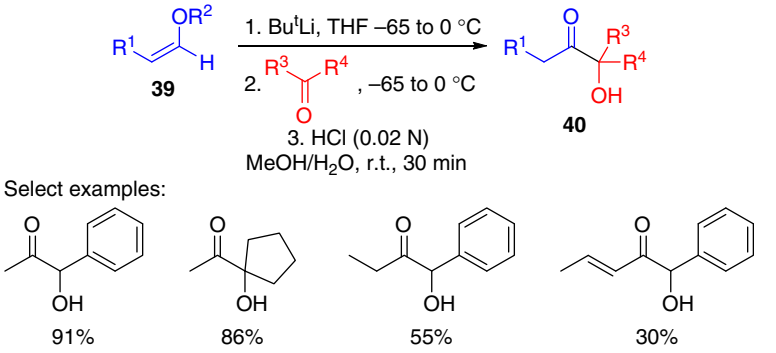
In addition to dithianes, other related acyl anion equivalents were also used. If bis(alkylthio) acetals did not perform really well, their aromatic-substituted counterparts, bis(arylthio) acetals **37** (Figure 2), drew the attention of several research groups, who studied their behavior in metallations and subsequent additions to carbonyl compounds.[66] Oxidized thioacetals such as **38** were also shown to have interesting potential as stoichiometric acyl anion equivalents.[67]

Figure 2 Other sulfur-substituted precursors of acyl anion equivalents.

1.13.2.5 Heteroatom-Substituted Alkenes

1.13.2.5.1 Vinyl ethers

In the 1970s, the groups of Schöllkopf and Baldwin made the first reports on the metallation of vinyl ethers **39** and their use in the formation of C–C bonds.[68] Strong base was needed to generate the nucleophilic species that could then react with different electrophiles including aldehydes and ketones (Scheme 16). A mild acidic aqueous treatment could then easily afford the target α-hydroxyketones **40** in high yields. This method has found wide application in the formal addition of acetyl anions starting from unsubstituted alkyl vinyl ethers but precursors of higher complexity, such as crotyl anion equivalents, can also be used. In terms of scope, the limitation is that this strategy can only address the umpolung of enolizable aliphatic carbonyl derivatives. An overview of its potential can be found in specialized reviews related to this topic.[69] Synthetic applications include studies on the preparation of (±)-granaticin,[70] oligomycin B,[71] and rubromycins.[72]



Scheme 16

1.13.2.5.2 Vinyl sulfides and selenides

Deprotonation of vinyl thioethers **41**[73] and selenoethers **42**,[74] and the subsequent addition of the metallated species to carbonyl compounds represent an alternative to the aforementioned vinyl ethers for the preparation of benzoins (Figure 3). Their behavior is similar to the one of their oxygenated analogs but the intermediate products are more stable, requiring harsher hydrolysis conditions.

Figure 3 Vinyl sulfides and selenides as precursors of acyl anion equivalents.

1.13.2.6 Miscellaneous Acyl Anion Equivalents and Related Compounds

1.13.2.6.1 Miscellaneous acyl anion equivalents

A certain number of other acyl anion equivalents were designed and proved efficient in solving synthetic problem for which the classic strategies were finding limitations. Among these less widely used precursors, the following can be cited (Figure 4):

- *tert*-Butyl hydrazones **43** introduced by Baldwin.[75]
- *N*,*N*-Dialkylhydrazones **44**, the reactivity of which was thoroughly studied notably by the group of Lassaletta.[76] These neutral derivatives that can be seen as azaenamines could lead to the preparation of enantioenriched benzoins when chiral hydrazines were used as precursors.[77]
- Benzotriazole-containing synthons **45**, which were developed by the group of Katritzky.[78]

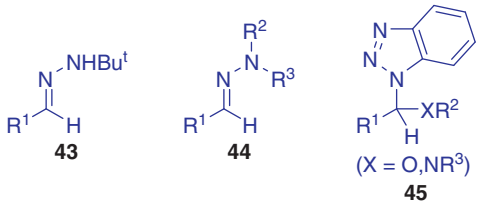
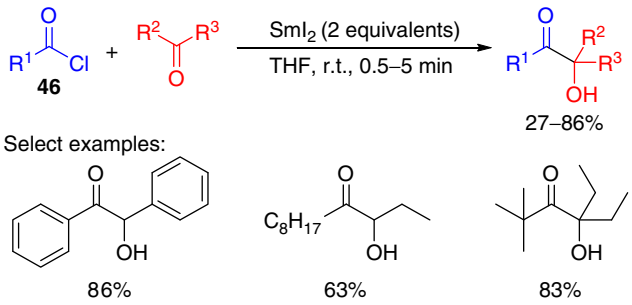


Figure 4 Miscellaneous nitrogen-substituted acyl anion equivalents.

1.13.2.6.2 Benzoin condensation through acyl radicals

When treated with SmI_2, aromatic, and aliphatic acyl chlorides **46** generate acyl radicals. Their *in situ* trapping with carbonyl derivatives led to the synthesis of benzoins (Scheme 17).[79] The products of this reductive benzoin condensation, including some containing a tetrasubstituted carbon, were obtained very rapidly in moderate to good yields. A related reaction using acyl cyanides as reactants and $TiCl_3$ as the one-electron reductant in AcOH was also reported.[80] α-Hydroxyketones can also be prepared by the reductive coupling of esters via monoelectronic transfers: these reactions are discussed in another chapter of the present book series (*see* Chapter 3.12).



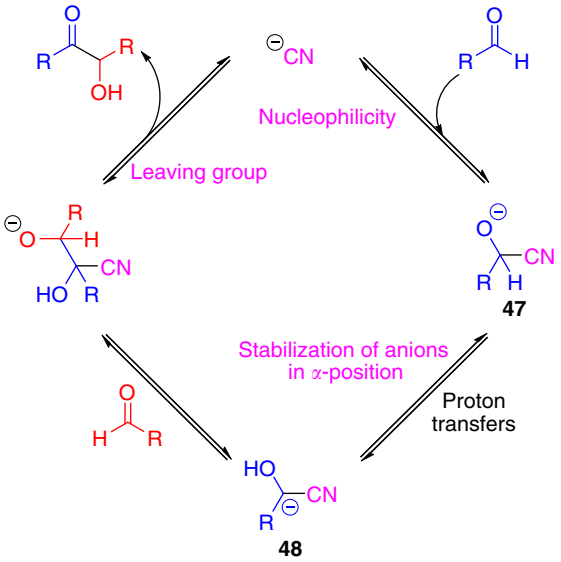
Scheme 17

1.13.3 Cyanide Ion-Catalyzed Benzoin Condensations

1.13.3.1 Homobenzoin: Discovery and Mechanism

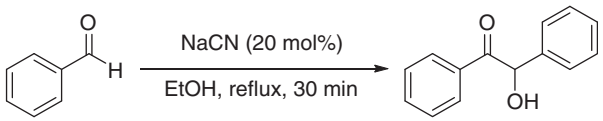
Apparently the first observation of dimerization of an aldehyde in the presence of cyanide ions was done by Stange in 1824 by mixing the soluble form of the pigment Prussian blue ($K[Fe^{III}Fe^{II}(CN)_6]$) and almond oil extract (benzaldehyde).[81] Nevertheless, the real discovery of this reaction is often credited to Wöhler and Liebig in 1832,[7] and, a few years later, to Zinin, who realized that a substoichiometric amount of cyanide ions could successfully lead to the almost complete conversion into the benzoin product.[82] The next historical event came with the understanding of how this reaction proceeds. In 1903, Lapworth proposed a mechanism for the cyanide-catalyzed benzoin condensation, which has gained general acceptance (Scheme 18).[83] The nucleophilic cyanide ion adds to the electrophilic aldehyde to form the conjugate base of cyanohydrin **47** (*see* Chapter 1.18). Proton transfers can result in the migration of the anion on the carbon, where it is stabilized by mesomery. Combination with a second molecule of aldehyde affords the last intermediate, which is a deprotonated form of the cyanohydrin of benzoin. Expulsion of the cyanide ion liberates the product and the catalyst. This mechanism relies on three fundamental properties of the cyanide ion: (1)

its nucleophilicity; (2) its ability to stabilize a negative charge in α-position; and (3) its good leaving group properties. Initial kinetic studies indicated that the reaction was second order in aldehyde and first order in cyanide ions.[84] This would speak in favor of the fast formation of the key intermediate **48**, the rate-limiting step being its addition to the second molecule of aldehyde. However, these results were subject to discussion[85] and studies in the second part of the twentieth century concluded that, even though the C–C bond formation step has the highest free energy of activation, all the steps are partially rate determining.[86] Recent computational studies, considering the reaction in protic or aprotic solvents, also went in the same direction.[87] In both cases, these calculations show that the conversion of **47** to **48** does not occur via an intramolecular 1,2-proton shift, which is symmetry forbidden. In the former case, the protic solvent can catalyze this tautomerization whereas it is probably assisted by another molecule of benzaldehyde in aprotic solvents such as dimethyl sulfoxide. An important feature of this cyanide-catalyzed benzoin condensation is that it is an equilibrium and it generally leads to the formation of the thermodynamic products.[88]



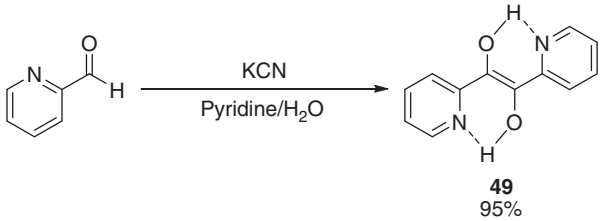
Scheme 18

From a practical point of view, the benzoin reaction has traditionally been carried out in boiling ethanol, solvent that is the best one to ensure the solubility of both the cyanide salt and the organic aldehyde (equation 4).[89] The pure product was obtained in high yields after purification by a single recrystallization, highlighting the practicality of this method.



(4)

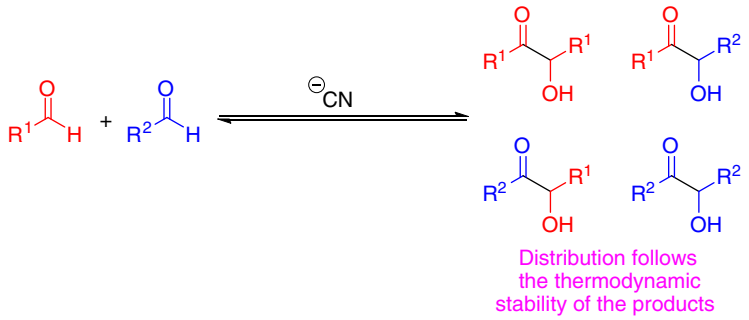
A variety of aromatic aldehydes were amenable to this transformation[90] but it could be plagued by side reactions when the electronic properties of the aromatic ring are too extreme. For example, *o*-nitrobenzaldehyde was at first thought to undergo benzoin condensation[91] but further structural analysis of the products concluded that it was not the case because of competitive redox processes.[92] On the other side of the reactivity scale, the electron-rich salicylaldehyde also failed to provide the benzoin product.[93] Heteroaromatic aldehydes such as furfural,[94] thiazole-2-carboxaldehyde,[95] or pyridine-2-carboxaldehyde,[96] are also suitable substrates for the cyanide-catalyzed benzoin condensation. In the last case, the product was obtained as the enediol form **49** that is stabilized by intramolecular hydrogen bonding (equation 5). Aliphatic aldehydes are less commonly used, but especially interesting substrates such acetaldehyde[97] and pivaldehyde[98] can undergo the benzoin condensation.



(5)

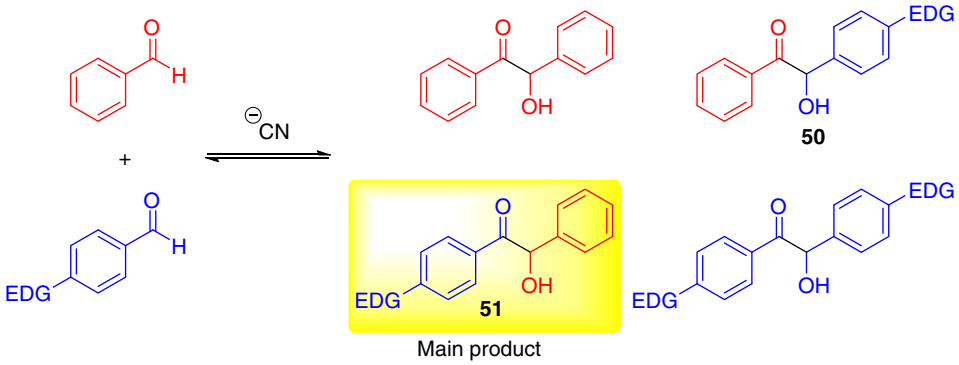
1.13.3.2 Cross-Benzoin Reactions Between Two Aldehydes

The main drawback of the cyanide-catalyzed benzoin reaction, when compared with the stoichiometric generation of an acyl anion equivalent and its addition to a carbonyl, is that the roles of the two reaction partners are not distinguished: both the acyl donor and the electrophile are aldehydes. For this reason, developing a selective cross-benzoin condensation has been a difficult challenge and many research groups have tackled this problem. When a mixture of two different aldehydes is treated by a catalytic amount of cyanide ions, one can expect to obtain a mixture of four different compounds: two products of dimerization and two products of cross-benzoin (equation 6). Because of the reversibility of the reaction, the product distribution should reflect their respective thermodynamic stabilities.



(6)

When two aromatic aldehydes with close electronic properties were used, the expected mixture was observed. However, when one of the reaction partners was notably more electron-rich than the other, reasonable selectivity could be achieved (equation 7). Seminal work by Staudinger suggested that product **50**, in which the ketone group is on the side of the less electron-rich aromatic, was preferentially formed.[99] However, follow-up thorough studies by Buck and Idle established that the structures were misassigned.[100] In a series of publications, they systematically studied the outcome of cross-benzoin condensation, discriminating between the two isomers by converting them to oximes and effecting Beckmann rearrangements.[101] In doing so, they established that the more stable isomer formed in these cross-benzoin condensations is **51** where the electron-donating group is on the side of the ketone. A general discussion on this controversy and analytical proofs for the structures of the product have recently been published.[90b]

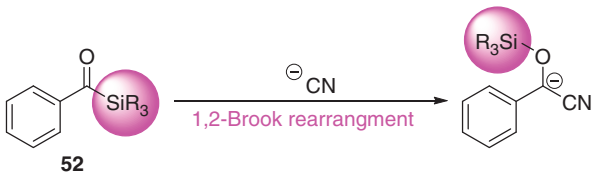


(7)

1.13.3.3 Cross-Benzoin Reactions: Use of Alternative Acyl Anion Precursors

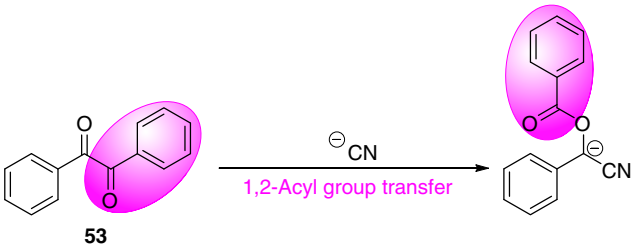
Although studies on the selectivity of the benzoin condensation between two differently substituted aldehydes allowed the preparation of several cross-benzoin products and helped in the understanding of the process, they did not solve all the issues. More precisely, it was still not possible to achieve the synthesis of the thermodynamically least stable isomer or to cross-couple aldehydes with similar electronic properties. A valuable alternative could be to replace one of the coupling partners by another chemical species that would be superior to the aldehyde for the generation of the acyl anion but not reactive in the C–C bond formation step. By analogy with the chemistry of stoichiometric acyl anion equivalents, three suitable substrates were designed:

1. Acyl silanes **52**, for which a 1,2-Brook rearrangement is involved (equation 8);[102]



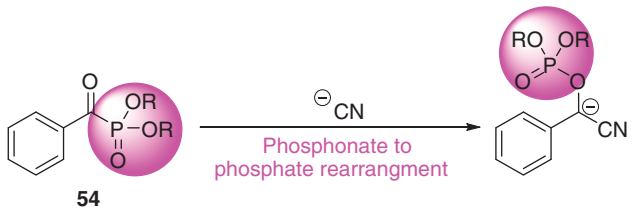
(8)

2. Benzils **53**, which leads to the acyl anion equivalent via transfer of an acyl group with C–C bond cleavage (equation 9);[103]



(9)

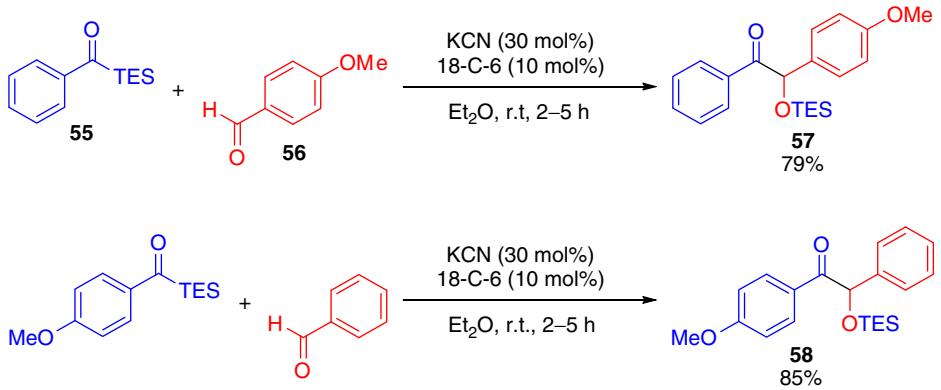
3. Acyl phosphonates **54**, which afford the nucleophilic species via a phosphonate–phosphate rearrangement (equation 10).[104]



(10)

1.13.3.3.1 Acyl silanes

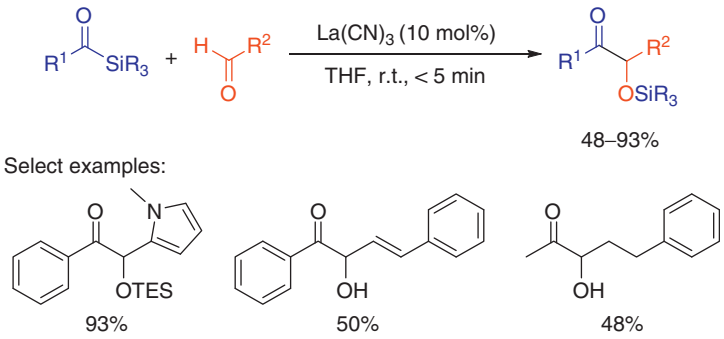
Although Portella reported preliminary studies on the cyanide-catalyzed cyclization of bis-acyl silane,[105] it is only in 2004, with the work of Johnson et al. that the synthetic potential of the generation of acyl anion equivalents from acyl silanes was realized.[103] When a mixture of acyl triethylsilane **55** and aldehyde **56** were exposed to a catalytic amount of KCN and crown ether at room temperature in Et_2O, the *O*-silyl benzoin **57** was formed as the only product in high yield (**Scheme 19**). Interestingly, when the aromatic groups of the two reactants were interchanged, the isomeric product **58** was obtained with the same efficiency. This transformation also applied to a variety of other substrates, including with aliphatic substituents on both reaction partners.



Scheme 19

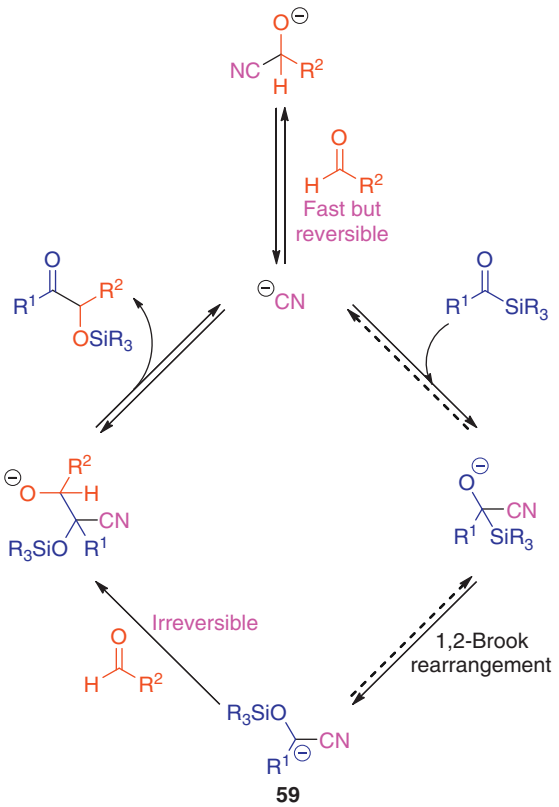
A screening of catalysts for this transformation was then conducted.[106] Many cyanide salts of rare earths were able to promote this reaction, $La(CN)_3$ being the most efficient one, since only 10 mol% of this salt could lead to complete conversion within less than 5 min (**Scheme 20**). With these optimized catalytic conditions in hands, the scope of the reaction was extended, especially to heteroaromatic aldehydes and to the synthesis of bis-alkyl cross-benzoin products. Different trialkylsilyl group were also used and free benzoins were obtained directly from acyl trimethylsilanes.

A detailed mechanistic study allowed to fully understand how this impressive selectivity could be achieved (**Scheme 21**).[107] The reaction follows a pathway with strong similarities to the mechanism described by Lapworth for the cyanide-catalyzed dimerization of aldehydes, except that the proton transfers are replaced by silyl-group migrations. Attack of the cyanide ion on the more electrophilic aldehyde occurs but is not productive and is easily reversible. On the contrary, addition of the catalyst to the acyl silane can be followed by a kinetically favored intramolecular 1,2-Brook rearrangement, affording the key intermediate **59**.



Scheme 20

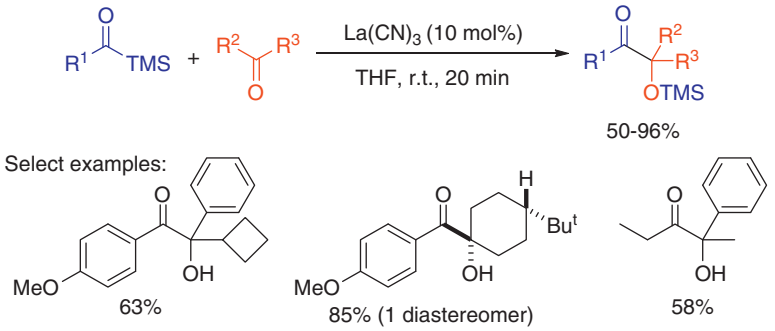
No evidence of the reversibility of these two steps could be found. The reaction then proceeds via an irreversible addition to the more electrophilic aldehyde. Reversible 1,4-silyl group migration and cyanohydrin collapse complete the catalytic cycle.



Scheme 21

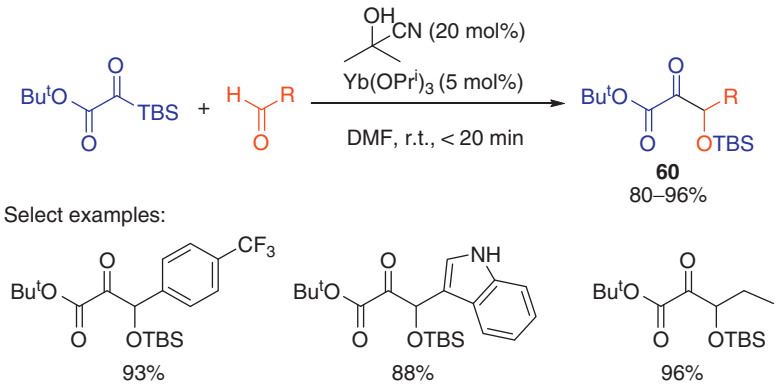
After this breakthrough in the cross-benzoin condensation between acyl silanes and aldehydes, the group of Johnson showed that this reactivity could be extended to ketones (Scheme 22).[108] Reaction conditions were very similar to the ones used for aldehydes, except that reaction times had to be somewhat increased. Dialkyl and alkyl aryl ketones were suitable substrates and diaryl ketones could also be used, provided that the acyl silane was added dropwise to prevent its dimerization. The diastereoselectivity of the addition to substituted cyclohexanones and protected α-hydroxyketones was studied. Finally, α,β-unsaturated ketones furnished a mixture of 1,2- and 1,4-adducts depending on the respective steric hindrance of both positions.

The glyoxylate unit is present in numerous biologically active compounds. The high electrophilicity of the carbonyl group in glyoxylate derivatives render the direct cross-benzoin of this compound with another aldehyde not conceivable. The implementation of the acyl silane strategy allowed the preparation of the cross-benzoin products of *tert*-butyl glyoxylate **60** with aromatic and aliphatic aldehydes (Scheme 23).[109] The reaction conditions had to be carefully tuned to prevent the isomerization of the product to the corresponding α-hydroxy-β-oxoester. The best catalytic conditions consisted in a combination of catalytic



Scheme 22

amounts of acetone cyanohydrin and $Yb(OPr^i)_3$, which once again resulted in a very fast and high-yielding reaction at room temperature.

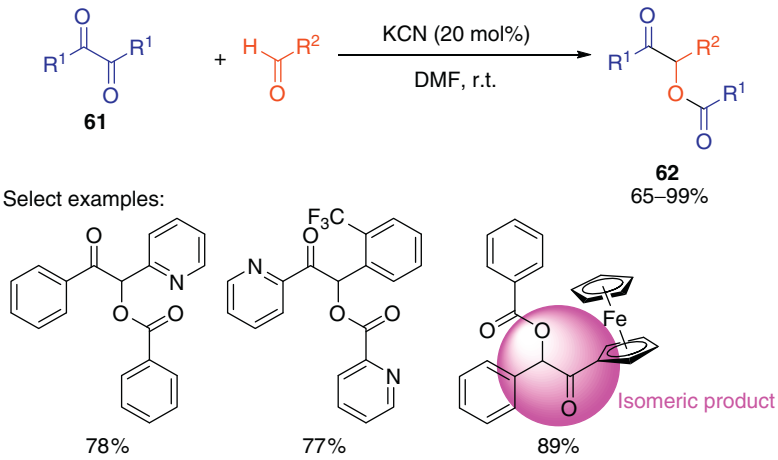


Scheme 23

It should also be added that acyl silanes could similarly be converted into acyl anion equivalents in the presence of other nucleophilic anions such as fluoride, hydroxide, or methoxide ions. Their combination with aldehydes and ketones afforded α-hydroxyketones in modest yields.[110]

1.13.3.3.2 Benzils

It has been known for long that cyanide ions in an alcoholic reaction medium decompose benzils **61** by cleavage of the C–C bond between the two ketone groups.[111] In 2004, the group of Demir managed to turn this phenomenon into a productive transformation, namely the synthesis of *O*-benzoyl cross-benzoins **62** (Scheme 24).[104] In a process related to the one with acyl silanes,

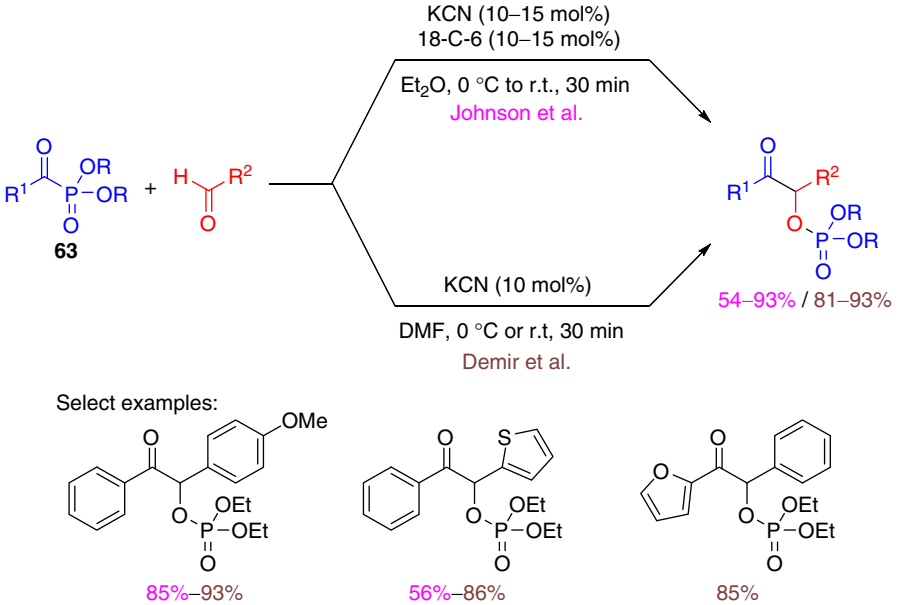


Scheme 24

readily available benzils offered the possibility of a catalytic preparation of an acyl anion equivalent that could selectively react with an aldehyde. Products were formed in good yields and saponification allowed to obtain the free benzoins, generally without isomerization. With some electron-rich aldehydes, such as ferrocenecarboxaldehyde, the isomeric product was obtained. It is not clear whether the expected benzoin had formed and then isomerized or whether the electron richness of the aldehyde could provoke a change in the reaction mechanism. Unlike the cross-benzoin condensation with acyl silanes, this variant with benzils does not seem to extend to aliphatic substrates.

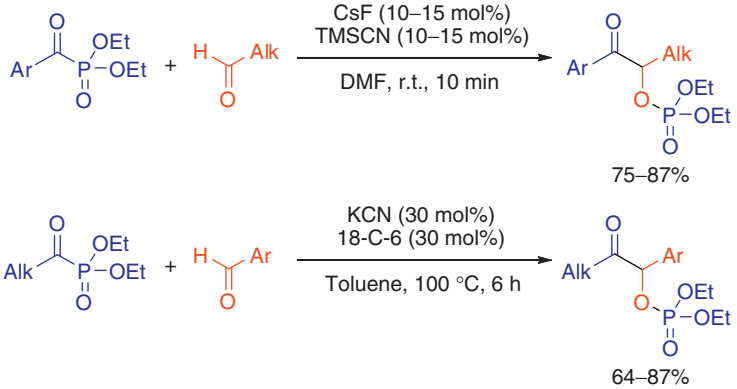
1.13.3.3.3 Acyl phosphonates

The last class of acyl anion precursors used in the cyanide-catalyzed benzoin condensation are acyl phosphonates **63** (Scheme 25).[105] Two reports on this reactivity were published in 2005 by the groups of Johnson and Demir. Acyl phosphonates are especially interesting substrates since they are very easily prepared from acyl chlorides and phosphites via the Michaelis–Arbuzov reaction. In the presence of cyanide ions, a phosphonate to phosphate rearrangement gives rise to acyl anion equivalents that react efficiently with various aldehydes.



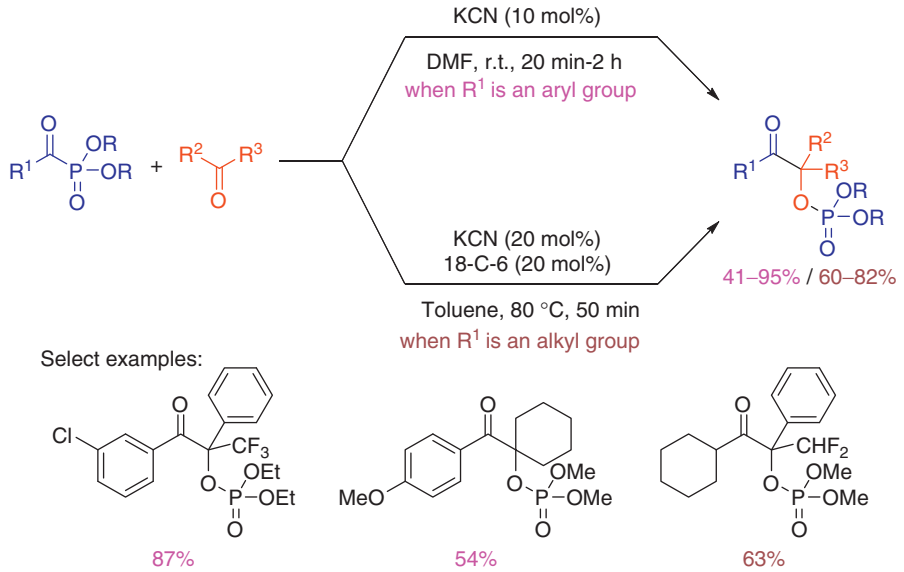
Scheme 25

If Johnson only used aromatic acyl phosphonates and aromatic aldehydes, Demir managed to incorporate aliphatic substituents in both reaction partners with modified reactions conditions (Scheme 26).[105b] When an aliphatic aldehyde was used, the catalytic species was prepared by premixing catalytic amounts of CsF and trimethylsilyl cyanide (TMSCN) in dimethylformamide (DMF). Aliphatic acyl phosphonates were even more problematic, presumably because of the high instability of the acyl anion equivalent. Nevertheless, the cyclohexyl- and *tert*-butyl-substituted ones could be reacted with benzaldehyde in refluxing toluene in the presence of KCN and a crown ether.



Scheme 26

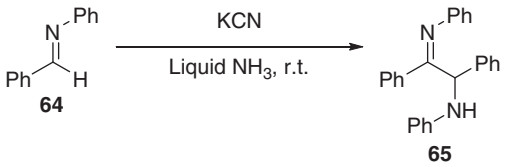
Unlike acyl silanes, acyl phosphonates can also react with ketones in conditions that were close to the ones for the reactions with aldehydes (Scheme 27).[112] It should be pointed out that most examples required the use of aromatic ketones that bear an electron-withdrawing fluorinated group. Nonetheless, 1,1,1-trifluorobutanone and even cyclohexanone were also amenable to this cross-benzoin coupling, provided that a cocatalyst is used: $Cu(OTf)_2$ in the first case and 3,5-bis(trifluoromethyl)thiourea in the second one.



Scheme 27

1.13.3.4 Cyanide Ion-Catalyzed Aldimine Couplings

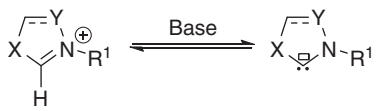
Cyanide ion-catalyzed aldimine coupling is the aza-equivalent of the benzoin condensation and was mentioned on a few occasions in the literature. Because of its analogy with benzoin condensation, this transformation will be briefly presented in this section. In 1928, Strain realized that aldimines **64** can dimerize in a similar fashion as aldehydes in the presence of cyanide ions giving the α-aminoimines **65** (equation 11).[113] The mechanism of their formation is believed to be similar to the one of the benzoin condensation and nitrogen-containing analogs of the intermediates of the Lapworth mechanism could be isolated.[114] Only a few other publications mentioned the study of this transformation, either in an intramolecular or intermolecular fashion.[115] Moreover, it seems that the products often exist predominantly as their enediamine tautomer and are very easily oxidized to the diimines.[116]



(11)

1.13.4 NHC-Catalyzed Benzoin Condensations

Although several reports on the use of organic molecules to catalyze transformations can be found very early in the literature and all along the twentieth century, it is only at the beginning of the third millennium that chemists start to realize the potentialities of what is now called organocatalysis. Since then, this field has developed exponentially with the discovery of new classes of organocatalysts and modes of action.[117] NHCs **67** are organic molecules consisting of a neutral divalent carbon atom flanked with two heteroatoms (generally nitrogen or sulfur), all of which are included within a cyclic structure, which is often aromatic (equation 12).[118]



X = S, NR^2; Y = CH, CH_2, N

(12)

These chemical species, which are conveniently obtained by deprotonation of the corresponding azolium salts **66**, exhibit impressive stability compared with other carbenes, which can be understood both in terms of electronic and steric effects (Figure 5). The lone pairs present on the nitrogen(s) and sulfur atoms give electron density to the empty p-orbital of the carbene center, thereby attenuating its π-electron deficiency. Besides this, inductive effects from the electronegative heteroatoms tame the electron richness of the lone pair located in the sp^2 orbital of the central carbon. Lastly, the steric bulk on the two aforementioned heteroatoms plays an important role in preventing the potentially destructive dimerization of the carbene. Because of their unique properties in terms of nucleophilicity, Lewis basicity,[119] and Brønsted basicity[120] which originate from their strong σ-donation and weak π-accepting abilities,[121] NHCs have become very popular reagents, ligands for metals,[122] and organocatalysts.[123,124]

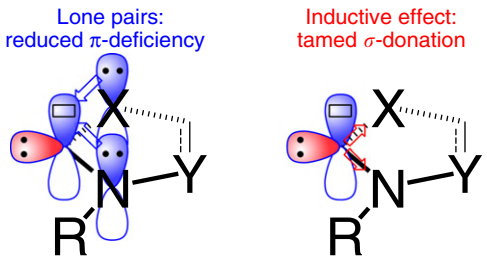


Figure 5 Electronic effects in NHCs.

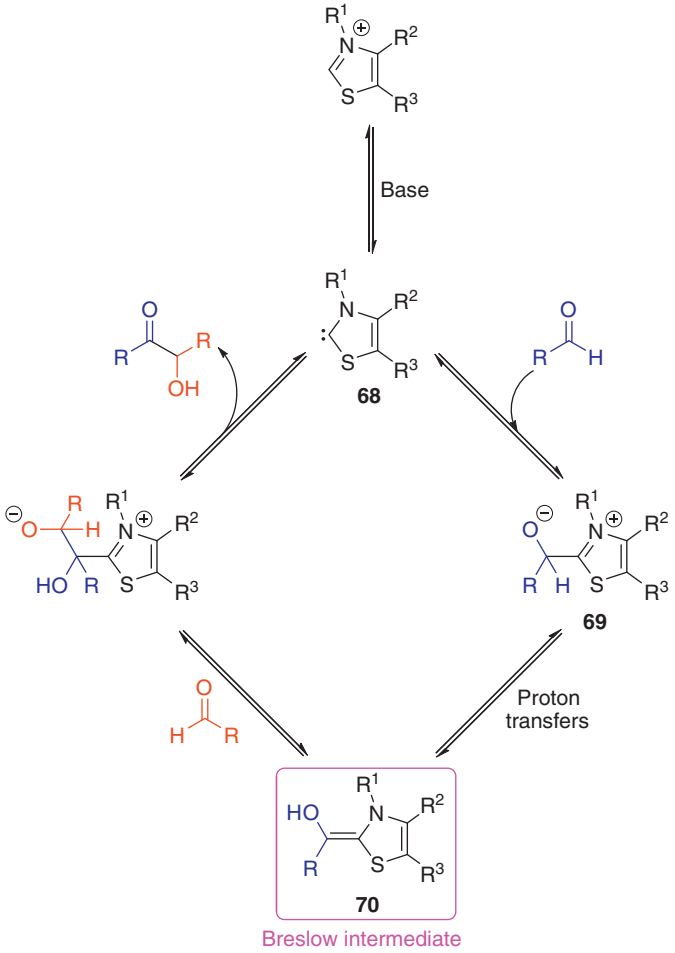
1.13.4.1 Homobenzoin: Discovery, Mechanism, and Reversibility

1.13.4.1.1 Discovery and mechanism

In 1943, Ukai and coworkers discovered that a combination of a thiazolium salt and a base generated a reactive species that was able to transform an aldehyde into the corresponding benzoin product.[125] A few years later, Breslow proposed a mechanism for this transformation (Scheme 28),[126] which is related to the one of the cyanide-catalyzed benzoin condensation.[84] Indeed the NHC **68** generated from the thiazolium salt has similarities with the cyanide ion in terms of nucleophilicity, increase of the acidity of protons in α-position and leaving group abilities. However, NHCs possess intrinsic superiority as they are not toxic and their reactivity can be modulated by tuning their electronic and steric properties. Moreover, the design of chiral NHCs opens the way to catalytic enantioselective benzoin condensations. The NHC can add to the aldehyde and a formal 1,2-proton transfer from the alcoholate **69** affords the key hydroxyenamine **70**, which is known as the Breslow intermediate. If the first step seems straightforward, the proton transfer still remains poorly understood, as it is the case for the cyanide-catalyzed reaction. In protic reaction conditions, fast exchanges promoted by the solvent can be envisaged. In aprotic solvents, several hypotheses have been proposed such as the intermediacy of an epoxide,[127] the assistance by a heteroatom of the substrate,[128] or by the base used to generate the NHC.[129] In the Breslow intermediate, the carbon atom of the aldehyde has now gained nucleophilic properties and can combine with a second aldehyde. Proton transfer and release of the catalyst complete the catalytic cycle and afford the benzoin product. All the steps of the catalytic cycle are generally reversible, making it possible to trap the Breslow intermediate with another electrophile.[130] Examples in cross-benzoin and aza-benzoin condensations will be discussed throughout Section 1.13.4. However, this reversibility, combined with the low stability of the catalytic species complicated the study of the kinetics of this reaction.[131] It appears that under standard reaction conditions, the NHC does not dimerize and that the reaction is close to be first order in aldehyde. In addition to this, the three steps considered in this study (addition of the NHC to the aldehyde, proton transfers and C–C bond formation) have relatively similar activation free energies and are all partially rate determining.

In addition to thiazolium salts **71**, other families of azoliums, including imidazoliums **72**,[132] imidazoliniums **73**, benzimidazoliums **74**,[133] and triazoliums **75**,[134] are also potent precatalysts for the benzoin condensation (Figure 6). Besides this, azolium-based room-temperature ionic liquids are suitable reaction media for the benzoin condensation, where they serve both as catalysts and solvents.[135]

Even though numerous studies toward the characterization of the Breslow intermediate were conducted, including the preparation of closely related species, it has long remained elusive.[136] It is only in 2012 that the group of Berkessel managed to characterize it (equation 13).[137] They speculated that the use of a partially saturated NHC-precursor would reduce the reactivity of the Breslow intermediate and increase its stability. By simply combining imidazolinylidene **76** with one equivalent of an aromatic or α,β-unsaturated aldehyde, they observed by NMR the quantitative formation of the Breslow intermediate **77**, which was stable for several hours under inert atmosphere but decomposed instantaneously when exposed to air. Its formation still occurred when an excess of aldehyde was used and, by choosing appropriate reaction partners, a slow conversion into the benzoin product was observed. This low reactivity is probably the corollary of the stability needed to visualize the intermediate and is not surprising since very hindered NHCs such as **76** are known to be poor catalysts for the benzoin condensation. The authors also reported the preparation of *O*-methyl Breslow intermediates and the unambiguous attribution of their structure by X-ray analysis.



Scheme 28

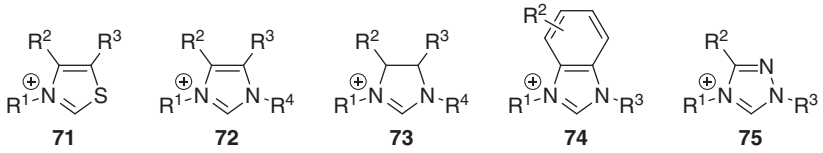
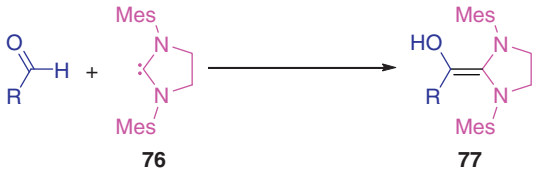


Figure 6 Precursors of NHCs able to catalyze the benzoin condensation.



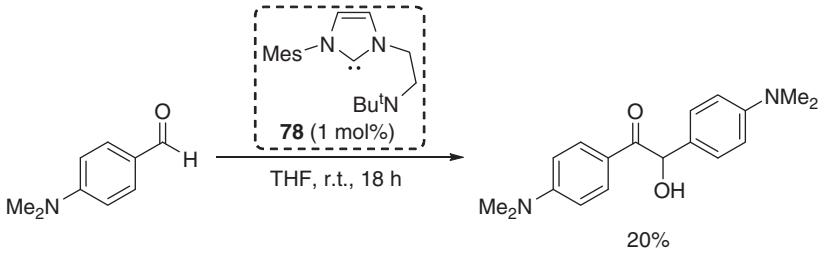
(13)

1.13.4.1.2 Scope and limitations

Although the reaction generally works well with nonenolizable aldehydes, and especially aromatic and heteroaromatic ones, several classes of aldehydes are more problematic substrates. Five examples will be detailed below:

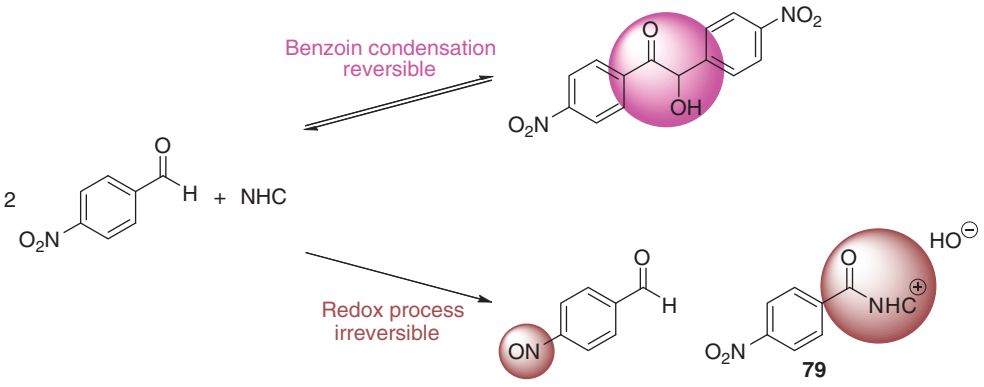
1. Electron-rich aromatics tend to give sluggish reactions and full conversion is difficult or even impossible to attain. For example, there is only one report of the preparation of the benzoin product from 4-(dimethylamino)benzaldehyde with 20% yield,

which required the use of a more active amino-functionalized NHC **78** as the catalyst (equation 14).[138] Likewise, the benzoin product of pyrrole-2-carboxaldehyde remains unknown.

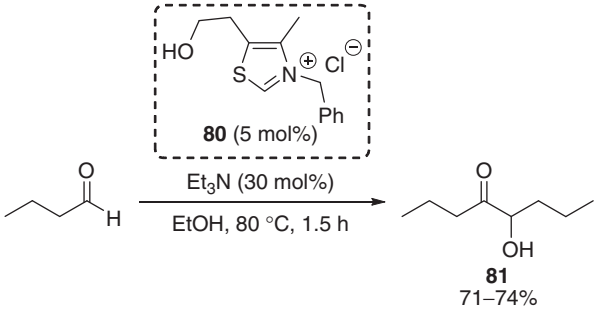


(14)

2. On the opposite side of reactivity scales, nitro-substituted benzaldehydes are also tricky substrates,[139] because of their high oxidation potential that induces the oxidation of one of the intermediates (the tetrahedral adduct resulting from the addition of the NHC to the aldehyde or the Breslow intermediate) into an acyl azolium **79** (**Scheme 29**).[140] Even though benzoin can be formed, the reversible nature of this reaction, combined with the irreversibility of the oxidation has long precluded the development of an efficient NHC-catalyzed benzoin condensation of nitrobenzaldehydes.[141] The acyl azolium **79** can be produced on purpose using diverse stoichiometric or catalytic oxidants and their trapping by various nucleophiles has been used in a productive way on numerous occasions.[142]
3. Steric effects also have a dramatic influence on the benzoin condensation. For example, *o*-tolualdehyde generally yielded rather low yields of the benzoin product (<40%).[140] Once again, the recently described amino-functionalized NHC **78** could improve the yield of this transformation to 65%.[138] As for *o*,*o*′-disubstituted benzaldehydes, only two discrete examples of electron-poor substrates with small halogens (fluorine of chlorine atoms) have already been shown to undergo an NHC-catalyzed benzoin condensation.[140a,143]
4. Generally, aliphatic aldehydes are less prone to undergo benzoin condensation than their aliphatic counterparts; however, efficient reaction conditions were designed that allowed to prepare them in high yields, especially thanks to the work of Stetter.[134,144] For example, butyroin **81** was prepared on a 50-g scale with more than 70% yield in the presence of 5 mol % of thiazolium salt **80** (equation 15).

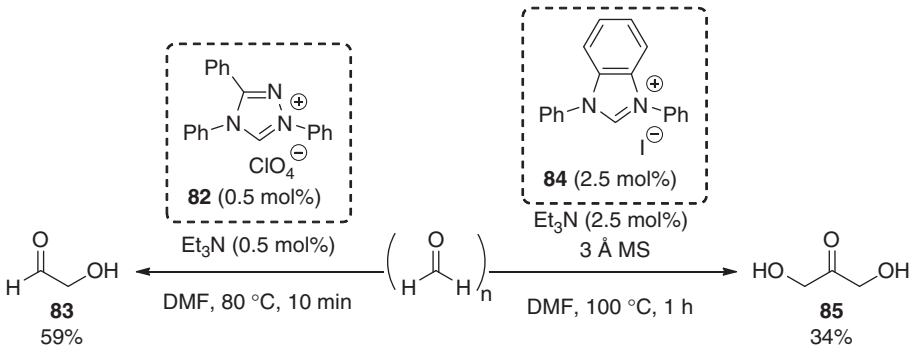


Scheme 29



(15)

5. To finish, formaldehyde is also a troublesome substrate since the corresponding benzoin product **83** still bears an aldehyde functionality that could potentially lead to overreactions.[145] The process is also complicated by competitive aldol reactions of the products with the highly reactive formaldehyde that affords more complex carbohydrates. Teles and coworkers showed that the proper choice of catalyst and reaction conditions could convert polymeric paraformaldehyde $(CH_2O)_n$ either in glycolaldehyde **83** (with triazolium salt **82**) or in dihydroxyacetone **85** (when benzimidazolium salt **84** is used) (Scheme 30). This example further demonstrates the superiority of NHCs over cyanide ion since simple catalyst tuning can result in spectacular product selectivities.[146]

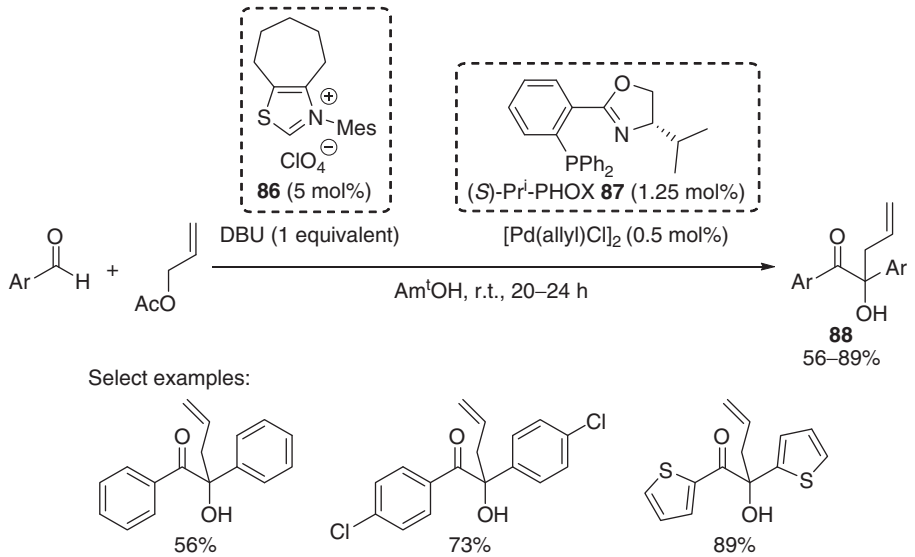


Scheme 30

Compared with intermolecular benzoin condensations, their intramolecular counterparts are scarcely encountered in the literature. A remarkable example is the cyclization of glutaraldehydes to 2-hydroxycyclopentanones when they are treated with a thiazolium salt and a base as reported by Cookson and Lane in 1976.[147] When the starting material was not symmetrically substituted, then a mixture of two regioisomeric products was obtained.

1.13.4.1.3 Domino reactions

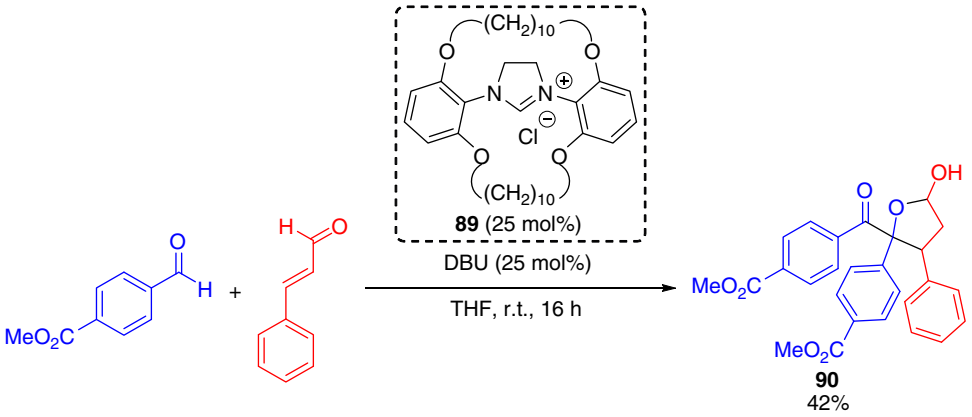
A few domino processes initiated by a homobenzoin condensation can be found in the literature.[148] In 2008, the group of Glorius showed that the NHC derived from thiazolium salt **86** and a palladium complex could be used at the same time without mutual deactivation, enabling the synthesis of *C*-allylated benzoins **88** directly from (hetero)aromatic aldehydes and allyl acetate (Scheme 31).[149] Negligible enantioinduction from the chiral ligand **87** was observed.



Scheme 31

When studying reactions between methyl 4-formylbenzoate and cinnamaldehyde in the presence of bimacrocyclic imidazolinium salt **89**, Lüning et al. discovered an unexpected pseudo-three component coupling that consisted in the homobenzoin condensation of the first substrate followed by a Michael addition to the second one and a hemiacetalization, producing lactol **90**

in modest yield (equation 16).[150] Another report on this transformation catalyzed by a sulfoalkyl-substituted NHC was subsequently published.[151] From these two publications, it appears that this reactivity is specifically observed for 4-formylbenzoates, probably because of the easier enolization of the intermediate benzoin product that bears the two electron-withdrawing ester groups on the 4- and 4′-positions.

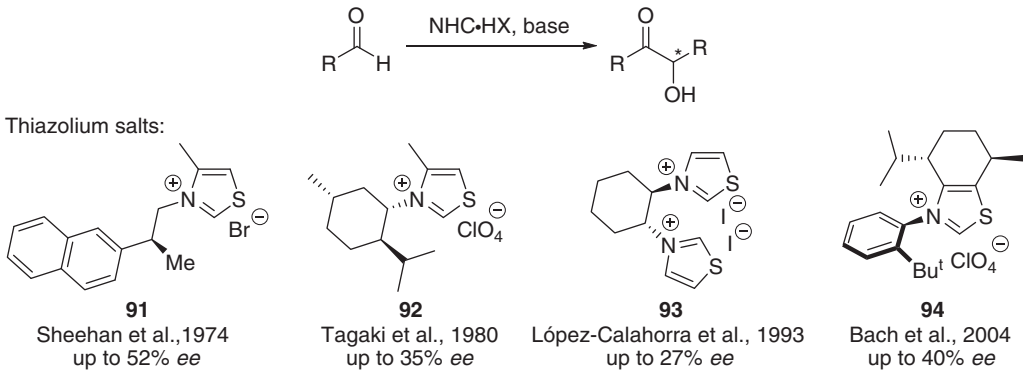


(16)

Phthalaldehydes, because of their two *ortho* formyl groups close to each other are likely to give domino reactions. Once again, a dichotomy in their reactivity was observed depending of the type of NHC, with which they were reacted.[152] In the presence of an imidazolium salt, a benzoin-aldol-hemiacetal formation sequence led to the formation of spiro-dihydroxyindenones whilst the corresponding triazolium salt furnished the tetracyclic trihydroxyindeno[2,1-*a*]inden-5-one motif.

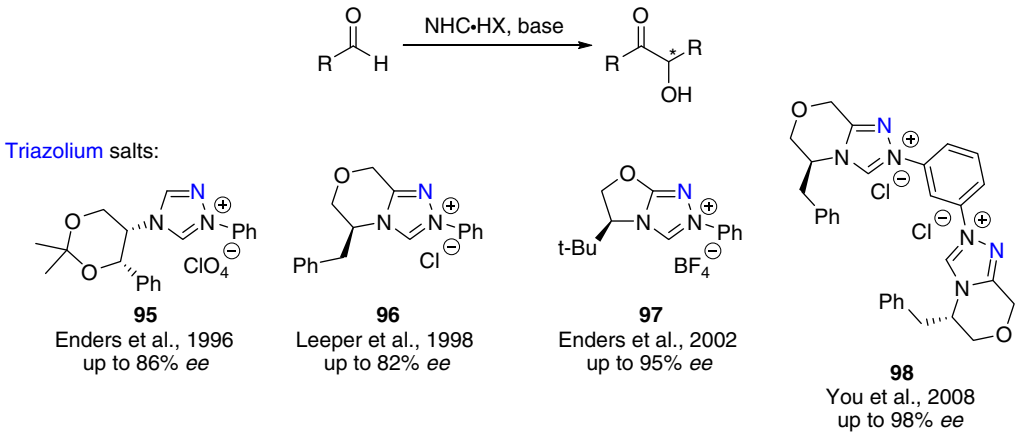
1.13.4.2 NHC-Catalyzed Enantioselective Benzoin Condensations

Besides the control of reaction rates and product selectivity, the variability of the structures of NHCs awards them an invaluable advantage over stoichiometric anion equivalents and cyanide ions: the design of chiral NHCs enables the catalytic control of the geometry of the stereogenic center formed during the benzoin condensation. The first efforts in this direction were reported by Sheehan in the late-1960s and early-1970s (Scheme 32).[153] Since thiazolium salts were mostly used at this time, they designed the *N*-(2-naphthylpropyl)-substituted precatalyst **91** and obtained enantioselectivities up to 52% but with very low yields. During several decades, this level of enantioselectivity in enantioselective NHC-catalyzed benzoin condensations was not surpassed, despite contributions by several groups including the ones of Tagaki with the menthol-derived thiazolium salt **92**[154] and López-Calahorra with chiral bis-thiazolium salts such as **93**.[155] Precatalyst **94** prepared by Bach, which combined both central and axial chirality, did not outperform the other thiazolium salts.[156]



Scheme 32

The popularization of triazolium salts as NHC precursors in the 1990s[135] brought about a major breakthrough (Scheme 33). Synthetically useful enantioselective excesses up to 86% were first obtained by Enders with precatalyst **95**.[157] Shortly after, the group of Leeper designed a modular approach to precatalysts such as **96**, in which the chiral element is annulated to the azolium salt, hoping that increased rigidity would favor the transfer of the chiral information.[158] Interesting results were obtained and this report served as the starting point for the development of numerous chiral triazolium salts that have found plenty of applications in NHC-catalyzed transformations.[159] Further optimization of the catalyst structure led Enders et al. to prepare chiral triazolium salt **97** in 2002, which allowed for the first time to reach enantioselectivities greater than 90%.[160] A few years after, related bis-triazolium salt **98** prepared by You brought the enantiomeric excess (*ee*) up to 98%.[161]



Scheme 33

This striking superiority of triazolium salts compared with their thiazolium counterparts raises questions about its origin. Calculations by the groups of Houk and Yates pointed out two phenomena that could account for these differences.[162] Compared with imidazolium or triazolium salts, the thiazoliums lack a substituent on the sulfur atom, rendering the approach of the electrophile less selective since it can attack on the less hindered side, eluding the controlling effect of the chiral element. (Figure 7).

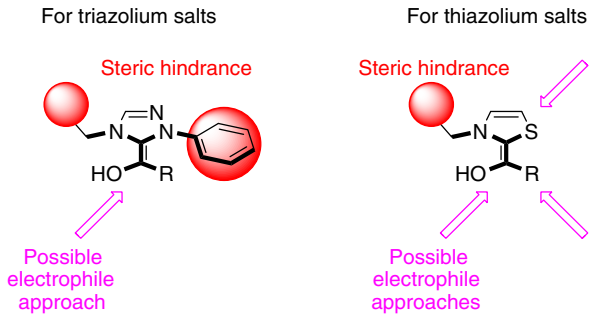


Figure 7 Enantioinduction by triazolium and thiazolium salts: steric effects.

In addition to this, the Breslow intermediate can exist as two diastereomers (Figure 8). In order to achieve high enantioselectivities, it is required for the catalyst to control the selective formation of one of this form over the other one. With imidazolium salt, rather similar electron densities do not allow to achieve this differentiation. On the contrary, the additional nitrogen atom of triazolium salts adds more electron density on one side, resulting in the orientation of the oxygen atom of the Breslow on the other side.

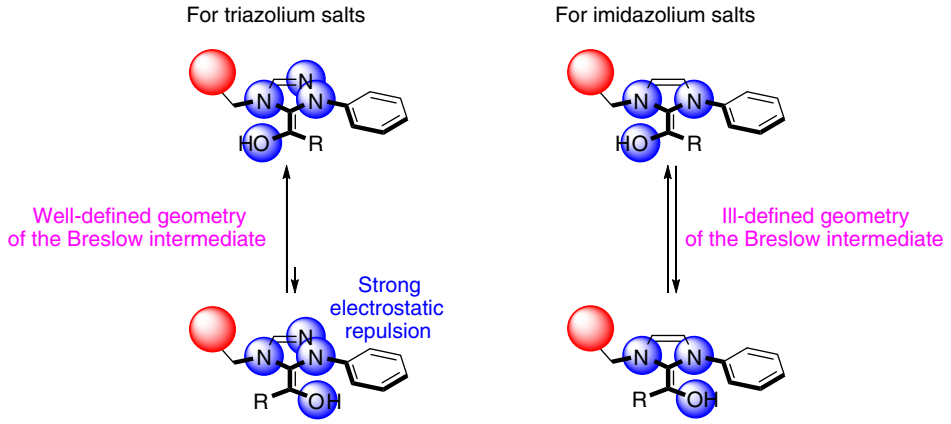
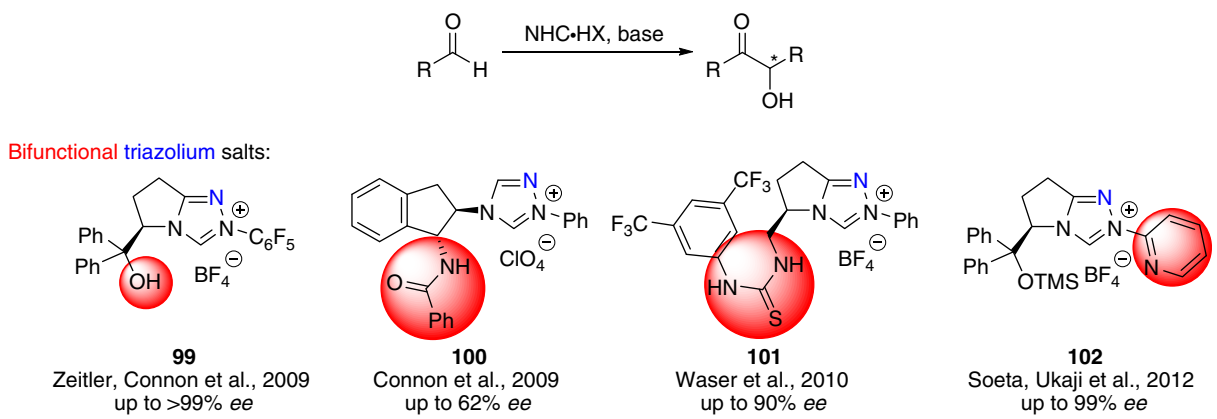


Figure 8 Enantioinduction by triazolium and imidazolium salts: electronic effects.

The most recent research on the improvement of enantioselective homobenzoin condensations have focused on the design of bifunctional organocatalysts that bear a pendant functional group able to interact with the substrates. This was thought to increase the level of organization of the transition state, thereby offering a better control of the enantioselective C–C bond formation (Scheme 34). Selected examples include triazolium salts containing the following functionalities:

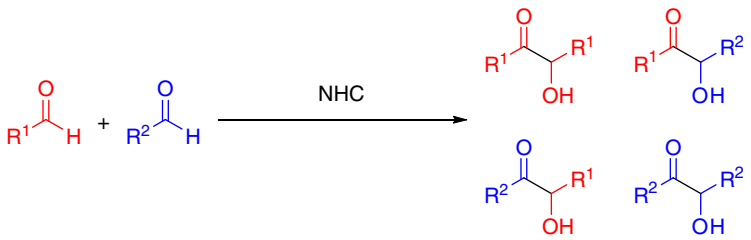
- A free alcohol: first described by Ye,[163] this alcohol-containing *N*-pentafluorophenyl-triazolium salt **99** allowed Connon and Zeitler to reach almost perfect enantioselectivities.[164]
- A hydrogen bond donor such as an amide (Connon, **100**)[165] or a thiourea (Waser, **101**):[166] these triazolium salts bearing hydrogen bond donors gave rather disappointing results. It can be suspected that the weakly Lewis basic oxygen atom of the aldehyde offers only limited possibilities for strong hydrogen-bonding interactions with the amide or the urea. However these interesting catalysts will probably provide more successful results in other transformations in the near future.
- A 2-pyridyl substituent at N1, instead of the commonly used carbocycles, was incorporated by Soeta and Ukaji in the structure of triazolium salt **102**, which provided very high enantioselectivities.[167] Hydrogen bonding of the nitrogen of the pyridine ring is thought to rigidify the structure of the Breslow intermediate and also potentially to interact with the electrophilic aldehyde in the transition state. Improving the control of the geometry of the Breslow intermediate by tuning the properties of the aromatic ring at N1 on the triazolium is a still overlooked strategy in enantioselective NHC-organocatalysis. However, the authors' finding, along with results on the influence of *ortho* methoxy groups in other transformations clearly demonstrate the possibilities for further interesting developments using this approach.[168] Recent in-depth studies by the groups of O'Donoghue and Smith have provided a better understanding of the influence of the aromatic substituent at N1 on the reactivity in benzoin and Stetter reactions.[169] However, more investigations on its impact on the enantioselectivity of these processes are still needed.



Scheme 34

1.13.4.3 Cross-Benzoin Condensations

The NHC-catalyzed dimerization of aldehydes possesses synthetic limitations since the structure of the product includes twice the same structural unit. One way to increase its potential would be to carry out a cross-benzoin reaction between two different aldehydes. However, selectivity problems arise since both aldehydes can be transformed into the Breslow intermediate and serve as electrophilic reaction partners, thereby leading to the production of four different isomers (equation 17). Two strategies exist in order to gain selectivity in these transformations: either conducting it in an intramolecular fashion or using two reaction partners with very different electronic and/or steric properties.

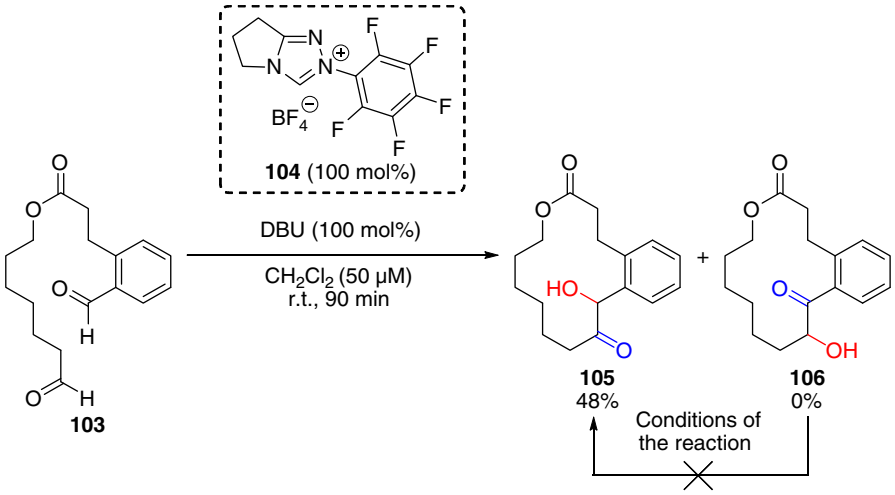


(17)

1.13.4.3.1 Intramolecular cross-benzoin condensations

As it is the case for homobenzoin condensations, the intramolecular variants of cross-benzoin reaction of two tethered aldehydes are hardly found in the literature. Indeed, to be synthetically interesting it requires the selective activation of one of the aldehydes

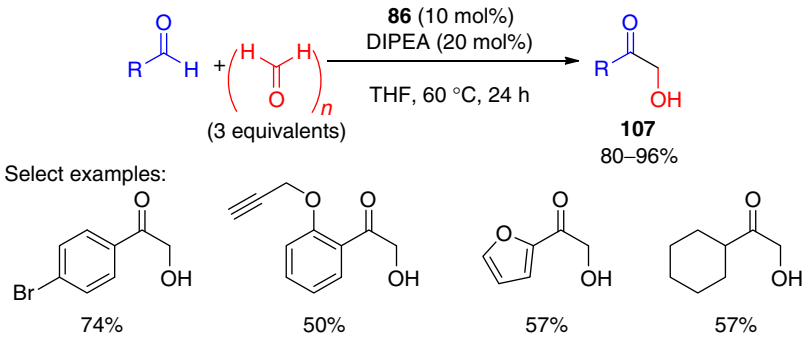
by the NHC and its subsequent cyclization. Potential pitfalls are the dimerization of the starting material but also the equilibration toward the thermodynamic mixture, because of the reversibility of the reaction. A very elegant report is the study of the macrocyclization by benzoin condensation to produce *trans*-resorcyclide precursors, which was published by Miller in 2007.[170] For example, when placed in the presence of 1 equivalent of pentafluorophenyl-triazolium salt **104** in high-dilution conditions, dialdehyde **103** was converted to the acyloin **105** in 48% yield (Scheme 35). A careful study conducted in order to understand why the yields were only moderate showed that the product was not very stable under the reaction conditions and that low temperature and short reaction times had to be preferred to prevent its degradation via dimerization or aldol reactions. Remarkably the product results from the activation of the aliphatic aldehyde by the catalyst preferentially to the aromatic one. Resubmitting the regioisomer of the product **106**, prepared by another method, to the reaction conditions resulted in extensive degradation but no isomerization, indicating that the observed selectivity was probably kinetically driven and not the result of a thermodynamic equilibration.



Scheme 35

1.13.4.3.2 Cross-benzoin condensations with formaldehyde

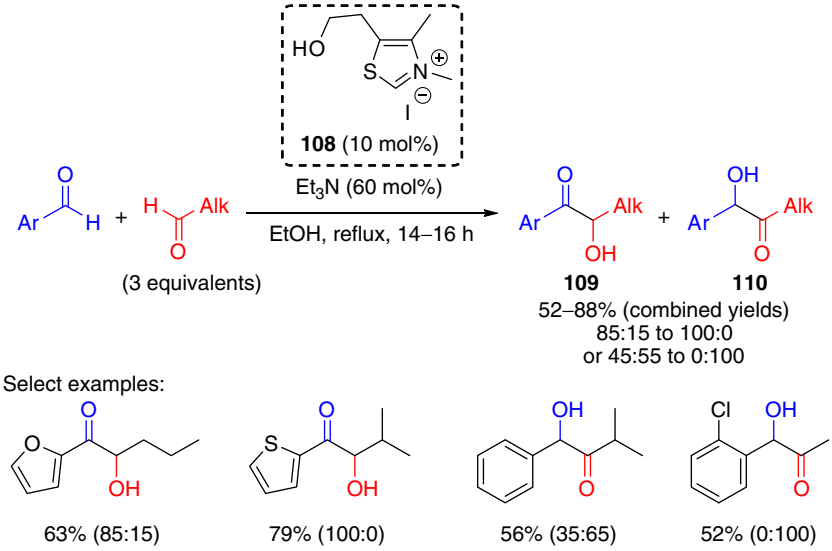
Since its electronic and steric properties are very different than other aldehydes, formaldehyde appears as an ideal candidate to perform selective cross-benzoin condensation. Indeed the Breslow intermediate deriving from formaldehyde being less substituted will be less stable: for this reason, selective activation of the other coupling partner can be foreseen. Moreover, because of its low steric hindrance, formaldehyde exhibits high electrophilicity and it is expected to react faster than the other aldehyde in the C–C bond formation step. Preliminary studies by Inoue in 1985 proved the feasibility of such a transformation, albeit with very low yields (only up to 17%).[171] In 2011, the group of Glorius optimized this transformation to define reaction conditions that rendered it synthetically useful (Scheme 36). Using only 3 equivalents of the polymeric paraformaldehyde in the presence of thiazolium salt **86**, both aromatic and aliphatic aldehydes were converted to hydroxymethyl ketones **107** with moderate to good yields.



Scheme 36

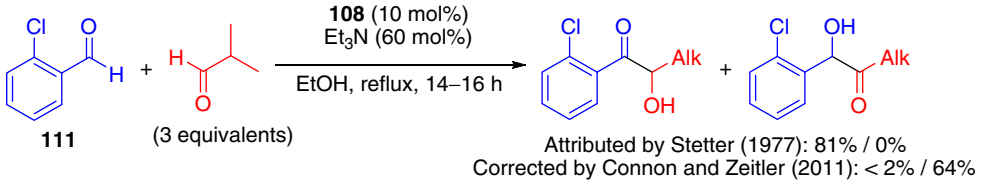
1.13.4.3.3 Toward a generalization of cross-benzoin condensations

Seminal studies on NHC-catalyzed cross-benzoin condensations were conducted by the group of Stetter, who studied the reaction of differently substituted aromatic aldehydes with a threefold excess of aliphatic aldehydes in the presence of thiazolium salt **108** (Scheme 37).[172] Depending on the substitution patterns of both starting materials, a mixture of regioisomeric cross-benzoins **109** and **110** were obtained with low to excellent regioselectivities. The observed ratios of products can stem from selective product formation but also from the impossibility for some of them to undergo retro-benzoin. The same authors also reported one example of cross-benzoin condensation between two aliphatic aldehydes, reactions which was further investigated by the groups of Rétey and Golding, who established rules for the choice of ratio between starting material to maximize the formation of cross-benzoin products.[173]



Scheme 37

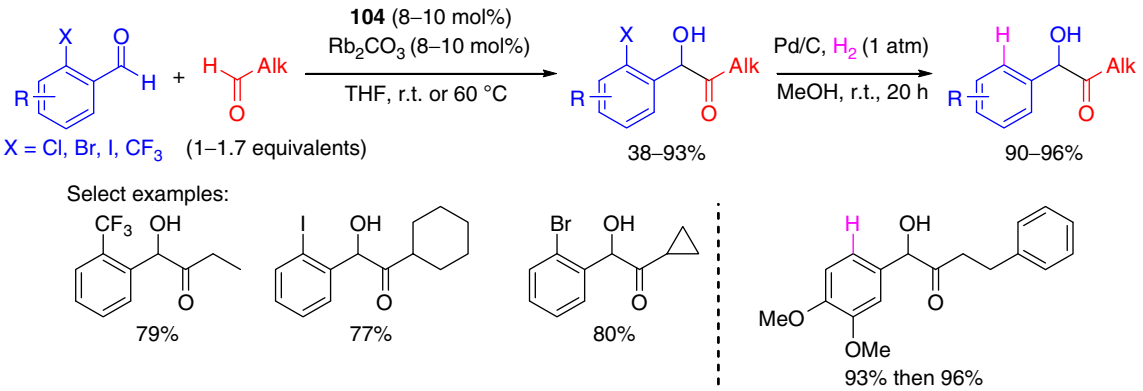
In 2011, Connon and Zeitler published a thorough study about the selectivity of couplings between aromatic and aliphatic aldehydes.[174] They demonstrated that triazolium salts, and especially pentafluorophenyl-substituted ones, were especially efficient catalysts to that purpose and also that the process was surprisingly rather solvent-independent. When reevaluating the results of Stetter with *ortho*-chlorobenzaldehyde **111**, they found that the product structures had been misassigned as the isomer which is formed selectively is the one with the ketone on the side of the aliphatic chain (Scheme 38). It appears that the *ortho*-halogen substituent precludes the formation of the Breslow intermediate for steric reasons but that its inductive electron-withdrawing effect increases the electrophilicity of the aldehyde favoring its attack in the C–C bond formation step.



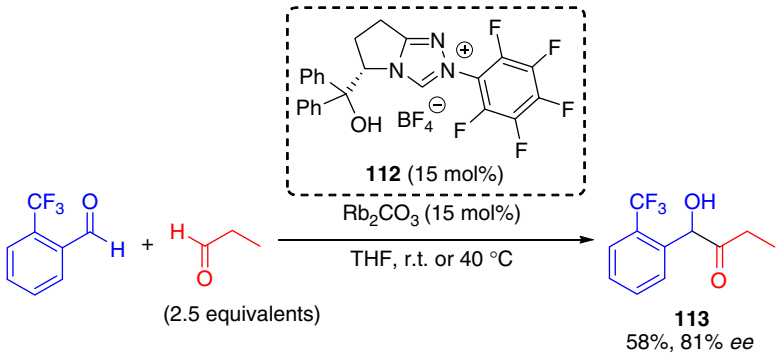
Scheme 38

This observation enabled the design of a very selective coupling where an *ortho* electron-withdrawing group on the starting material controlled the selective cross-benzoin reaction (Scheme 39). When the *ortho* substituent was a bromine atom, it could play the role of a temporary chemoselectivity-controlling group since its removal by hydrogenolysis afforded the unsubstituted benzoins. Other aromatic aldehydes, such as benzaldehyde, also gave reasonable selectivities.

In the same publication, the authors disclosed the results of preliminary investigations toward an enantioselective cross-benzoin condensation (equation 18). Product **113**, the absolute configuration of which was not determined, was obtained with an encouraging *ee* of 81% using chiral triazolium salt **112**.

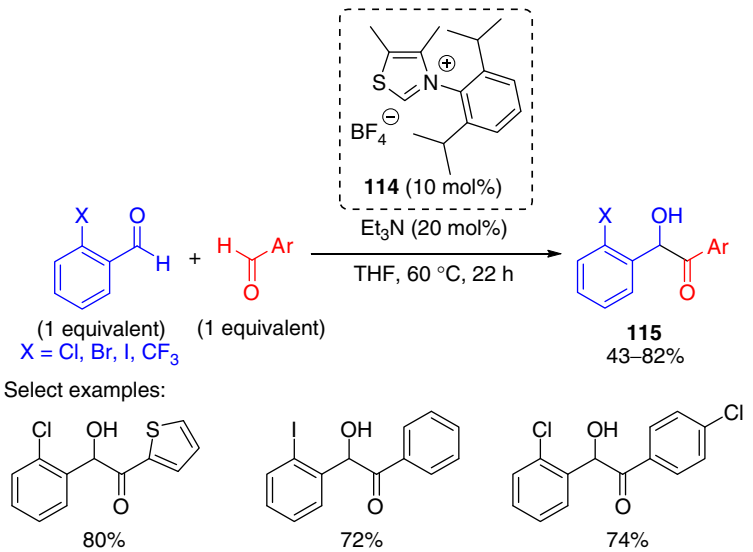


Scheme 39



(18)

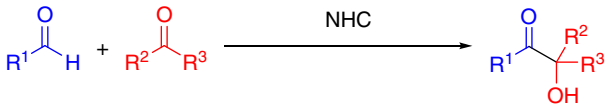
At the same time, the group of Glorius decided to tackle the problem of the selective cross-benzoin condensation between two differently substituted aromatic aldehydes, also using the lower propensity of hindered aromatic aldehydes to build up the Breslow intermediate (Scheme 40).[175] Mixing equal amounts of an *ortho*-substituted benzaldehyde and another (hetero)aromatic aldehyde in the presence of a catalytic amount of thiazolium salt **114**, benzoins **115** were obtained selectively with moderate to good yields. *ortho*-Anisaldehyde and -tolualdehyde were also evaluated in this transformation but they gave very unselective results, showing that the electron-withdrawing nature of the *ortho* substituent is an important key parameter for the success of the reaction. Interestingly, despite the high temperature, no retro-benzoin seemed to occur in these reaction conditions, so that the observed selectivity must reflect the kinetic discrimination between the substrates in the different steps of the mechanism.



Scheme 40

1.13.4.4 Benzoin Condensations with Ketones

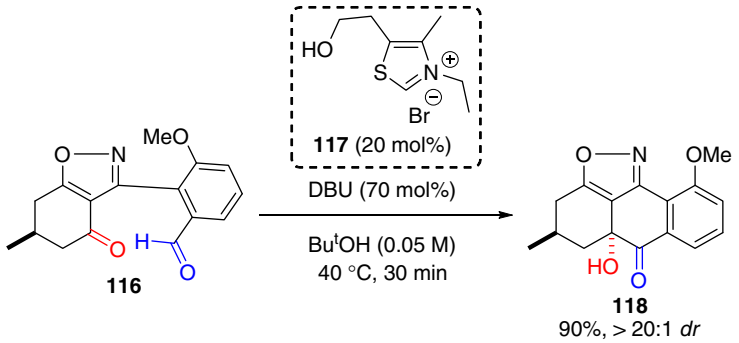
Since the homobenzoin condensation is a reversible reaction, one can envisage incorporating another electrophile in the reaction mixture to drive the reaction toward the formation of a cross-product. Ketones are the first family of electrophiles that comes to mind since they would afford benzoin products that bear a tetrasubstituted carbon α to the carbonyl (equation 19). This time, selectivity is no longer the main problem, since ketones cannot build up the Breslow intermediate, but rather reactivity. Possibilities encompass the study of tethered bis-electrophiles in intramolecular reactions or the use of highly electrophilic ketones. Enantioselective variants of these two strategies have also been published.



(19)

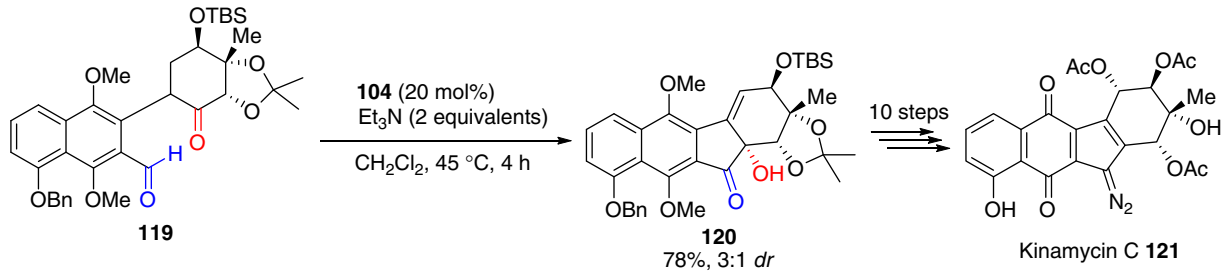
1.13.4.4.1 Intramolecular cross-benzoin condensations

Illustrating the power of natural product to inspire chemists, the first study on benzoin condensation with ketones was part of a research program aiming at a mild synthesis of functionalized preanthraquinones that could serve as potential precursors for the synthesis of tetracyclines or angucyclines (equation 20).[176] For example, oxoaldehyde **116** was very efficiently transformed into the tetracycle **118** in the presence of thiazolium salt **117**. A preexistent stereogenic center controlled the diastereoselective formation of the new one. The products could then be transformed into anthraquinones by a two-step sequence.



(20)

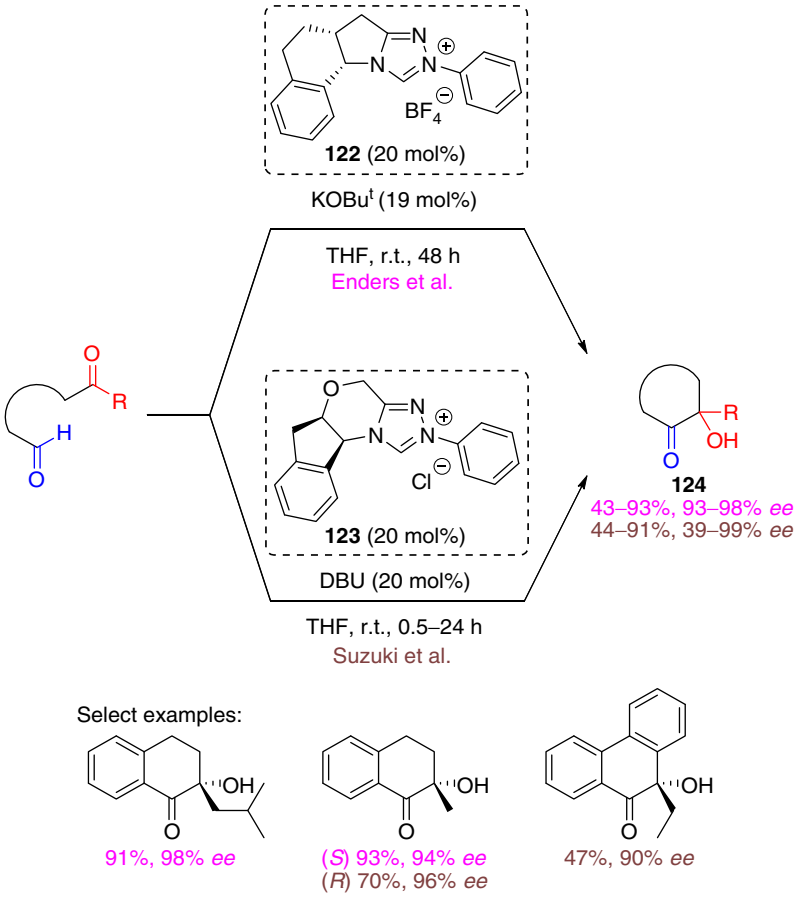
Shortly after, this new reactivity was extended to several simple oxoaldehyde substrates by Enders and coworkers.[177] Reasonably good results were obtained when at least one of the carbonyl groups was linked to an aromatic ring, but yields stayed low for linear aliphatic oxoaldehydes. Further studies on the scope and limitations of this reaction by the group of Suzuki demonstrated that it could be largely applied to different systems leading to the formation of five- or six-membered rings, but was unsuccessful for seven-membered ones.[178] Recently, naphthalenones were also prepared using an intramolecular cross-benzoin condensation with a ketone.[179] Nicolaou confirmed the potential of this transformation for the total synthesis of natural products by using it as a key step to kinamycins C **121** (Scheme 41), F and J and of the monomeric unit of the lomaiviticin aglycone.[180] For the first of these syntheses, oxoaldehyde **119** was cyclized in the presence of pentafluorophenyl-triazolium salt **104** to afford product **120** with good yield and moderate diastereoselectivity. Ten more steps were necessary to complete the total synthesis.



Scheme 41

1.13.4.4.2 Intramolecular enantioselective cross-benzoin condensations

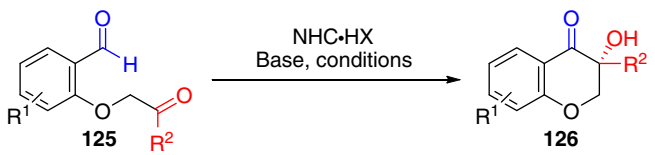
The groups of Enders and Suzuki were also involved in the development of the enantioselective variant of the intramolecular aldehyde-ketone benzoin condensation (Scheme 42).[181] Cyclization using precatalysts **122** or **123** afforded different types of cyclic benzoins **124** generally with good yields and excellent *ee*s.

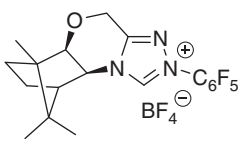


Scheme 42

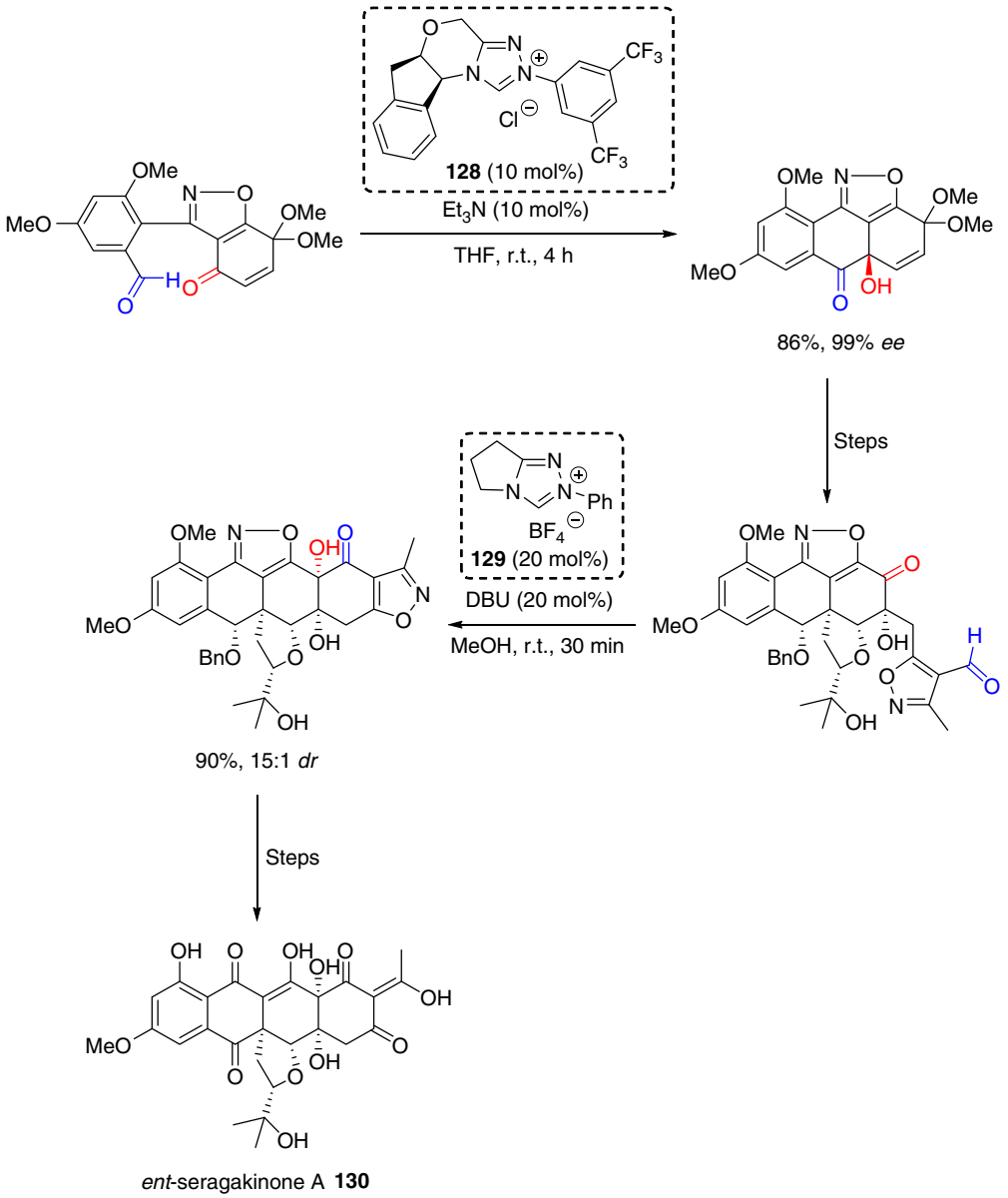
This method is not limited to the synthesis of carbocycles. Oxygen-tethered oxoaldehydes **125** could also be enantioselectively cyclized to chromanones **126** (Table 1).[181b,182] Three different catalytic systems were used in this transformation using either the precatalysts previously developed by Enders and Suzuki or D-camphor derived triazolium salt **127**.

Table 1 Synthesis of chromanones by enantioselective benzoin condensation on ketones



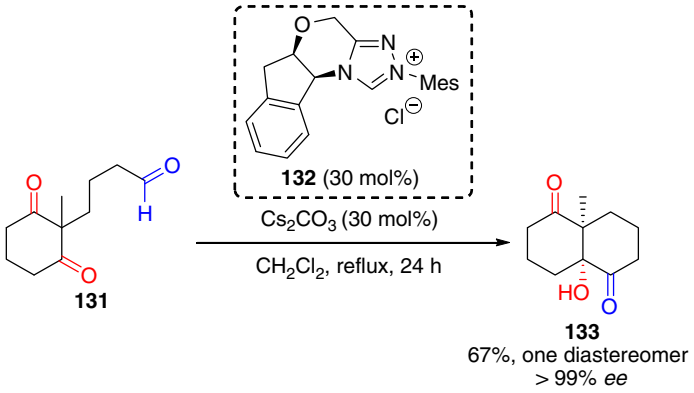
Entry	*NHC · HX*	*Base, conditions*	*Yield (%), ee (%)*	*References*
1	123 (10 mol%)	Et_3N (10 mol%) THF, r.t., 26 h	56, 88	181b
2	122 (10 mol%)	KHMDS (9 mol%) THF, 0 °C, 5 °C r.t. or 45 °C, 18–72 h	24–93, 76–95	182a
3	 **127** (6 mol%)	DBU (5 mol%) THF, r.t., 18–72 h	92–99, 76–93	182b

Again, the usefulness of this reaction was proved by its application to the total synthesis of a natural product, namely *ent*-seragakinone A **130** (Scheme 43).[183] The group of Suzuki used two different intramolecular condensations catalyzed by triazolium salts **128** and **129** in their synthetic plan, the first one being enantioselective and the second one diastereoselective, with impressive selectivities in both cases.



Scheme 43

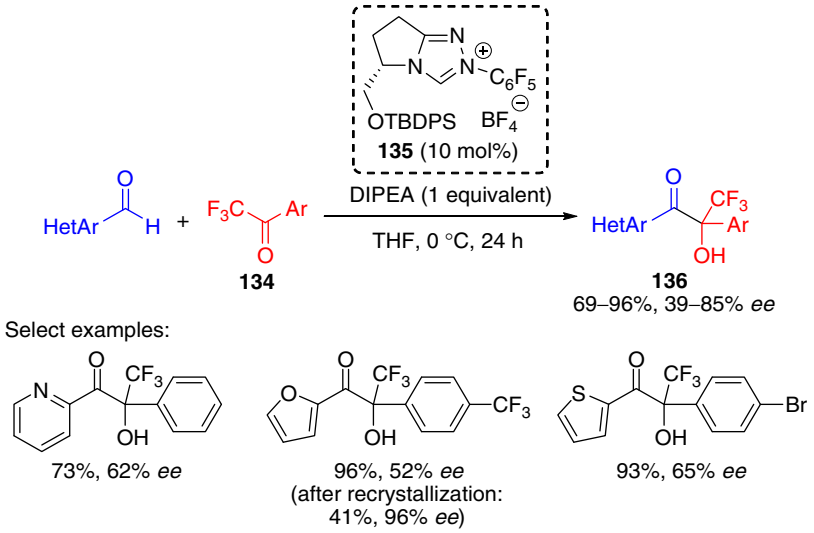
The enantioselective intramolecular benzoin condensation can also be applied to desymmetrizations (equation 21).[184] With prochiral substrates such as **131** that bear two ketone groups surrounding a quaternary center, the cyclization in the presence of precatalyst **132** led to bicyclic product **133** with the creation of two adjacent tetrasubstituted stereocenters. Extremely high enantioselectivity and complete diastereoselectivity were observed. Ring-size and substitution patterns could be varied, albeit with the necessity to reoptimize the reaction conditions almost for each substrate.



(21)

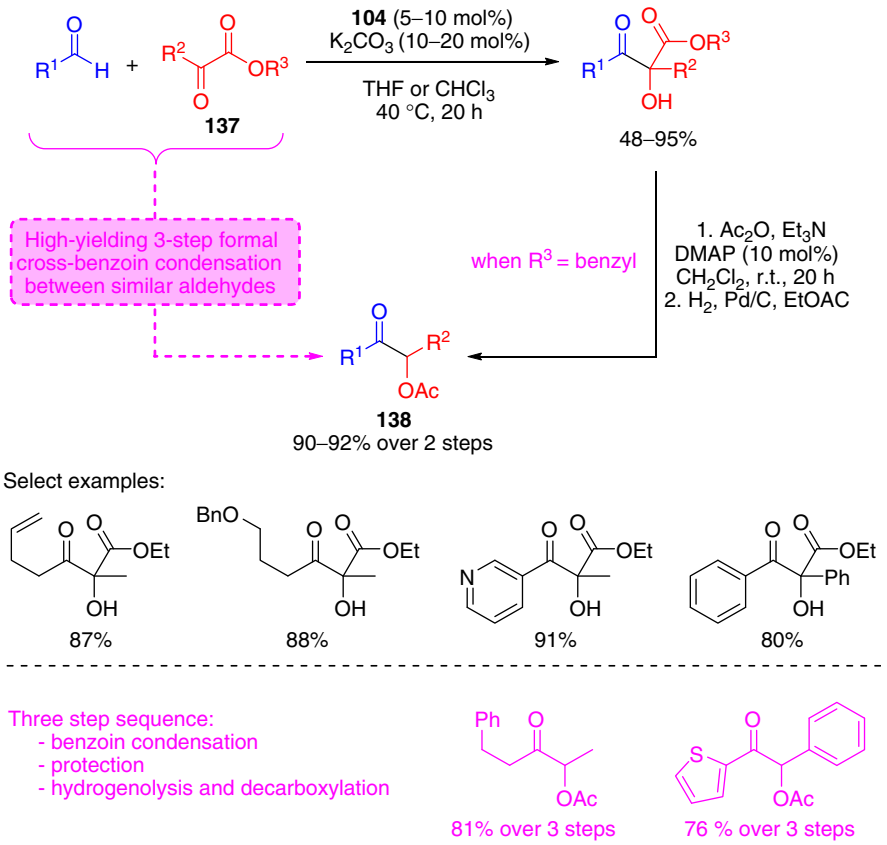
1.13.4.4.3 Intermolecular cross-benzoin condensations with activated ketones

Because of their low electrophilicity compared with aldehydes, ketones usually do not react with aldehydes in intermolecular cross-benzoin condensations. However, the attachment of an electron-withdrawing group to the carbonyl can increase its electrophilicity. In 2009, Enders showed that trifluoromethyl ketones **134** were sufficiently electrophilic to undergo cross-benzoin condensation with aromatic aldehydes.[131a] Homobenzoin of the latter starting material was occurring in the reaction conditions but its reversibility allowed the crossed product to be obtained. Immediately after, the same group disclosed an enantioselective variant of this transformation (Scheme 44).[185] Despite a thorough optimization of the precatalyst **135**, only heteroaromatic aldehydes were suitable substrates and the trifluoromethyl carbinols **136** were generally obtained with moderate enantioselectivities, which could however be increased by recrystallization.



Scheme 44

In principle, α-oxoesters **137** could also be envisaged as suitable substrates. However, their utilization has long been plagued by a competitive redox process involving a hydride transfer from the tetrahedral intermediate formed by the addition of the NHC to the aldehyde.[186] Recently, an intensive catalyst screening showed that electron-poor triazolium salt **104** had a unique ability to suppress this nonproductive side reaction, thereby allowing the benzoin condensation (Scheme 45).[187] Very interestingly, when benzyl α-oxoester was used, the protection of the alcohol and the hydrogenolysis of the benzyl group followed by spontaneous decarboxylation allowed protected benzoins **138** to be obtained. The total three-step sequence stands for a formal cross-benzoin between two different aldehydes used in identical amounts without any electronic or steric bias, a transformation that still cannot be achieved directly. A preliminary example of an enantioselective coupling was also reported in the same publication, with an *ee* of 76%. A related formation of acyl anion equivalents from dialkyl diketones in the presence of thiamine in polyethylene glycol followed by its dimerization or addition to α-oxoesters was also recently reported.[188] Finally, benzoin condensation on 4-oxoenones was also invoked in the mechanism of their reaction with enals to produce enantioenriched functionalized cyclopentenes via a benzoin-oxy-Cope pathway.[189]



Scheme 45

1.13.4.4.4 Domino reactions

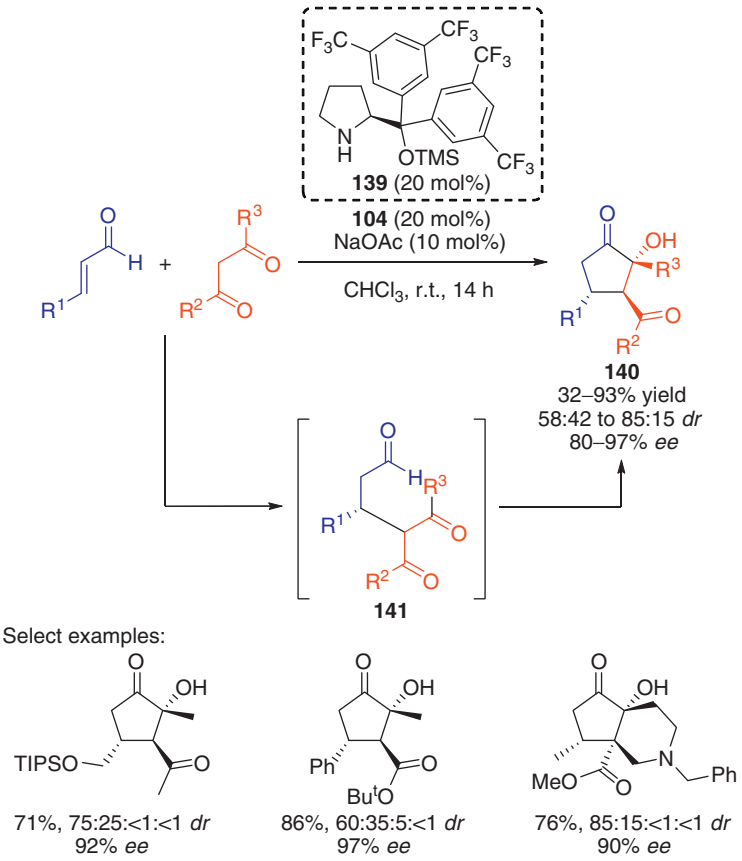
Domino processes that allow the creation of several bonds in the same reactions conditions are especially interesting transformations since they allow the fast elaboration of molecular complexity. Several of them that include an intramolecular benzoin condensation with a ketone were described in the recent years. Generally, these reactions rely on a first step which is catalyzed by a secondary amine and leads to the formation of an intermediate that bear both an aldehyde and a ketone and is therefore amenable to cyclization via a NHC-catalyzed benzoin condensation. In 2009, Rovis and coworkers reported a Michael addition-benzoin cascade under cooperative catalysis conditions, with the use of Hayashi–Jorgensen catalyst **139** and triazolium salt **104** (Scheme 46).[190] The first catalyst activated the enal to control the enantioselective Michael addition of 1,3-diketones or -oxoesters whereas the second one enabled the diastereoselective benzoin condensation to furnish functionalized cyclopentanones **140** bearing three stereogenic centers with high enantioselectivities. A rather poor diastereoselectivity was observed during the Michael addition, which is typical from reactions in these conditions. Conversely, good control of the tetrasubstituted center was achieved during the final cyclization. When the authors tried to carry out the two steps sequentially, with isolation of the intermediate aldehyde **141**, an erosion of the *ee* of the final product was observed. This phenomenon, which can be ascribed to a racemization of **141** in the reaction conditions, highlights one of the biggest advantages of domino sequences since they can allow the trapping of a sensitive intermediate before its degradation. Subsequently, very similar transformations using 1,3-ketosulfones and 1-acetylindolin-3-ones were published.[191]

Moreover, it is also possible to rely on the enamine mode of activation of secondary amine catalysts. With the combination of diphenylprolinol trimethylsilyl ether **142** and chiral triazolium salt **143**, differently functionalized cyclopentanones **144** were synthesized with impressive enantio- and diastereoselectivities (Scheme 47).[192] Interestingly, when the enantiomer of the NHC-precursor *ent*-**143** was used, reduced yields and diastereoselectivities (from 87% yield and 19:1 *dr* to 59% yield and 4:1 *dr* on the studied example) were observed, attesting for a match/mismatch scenario during the cyclization by benzoin condensation. In 2012, the group of Melchiorre described a one-pot sequence consisting of a Diels–Alder reaction via trienamine activation followed by a benzoin condensation.[193]

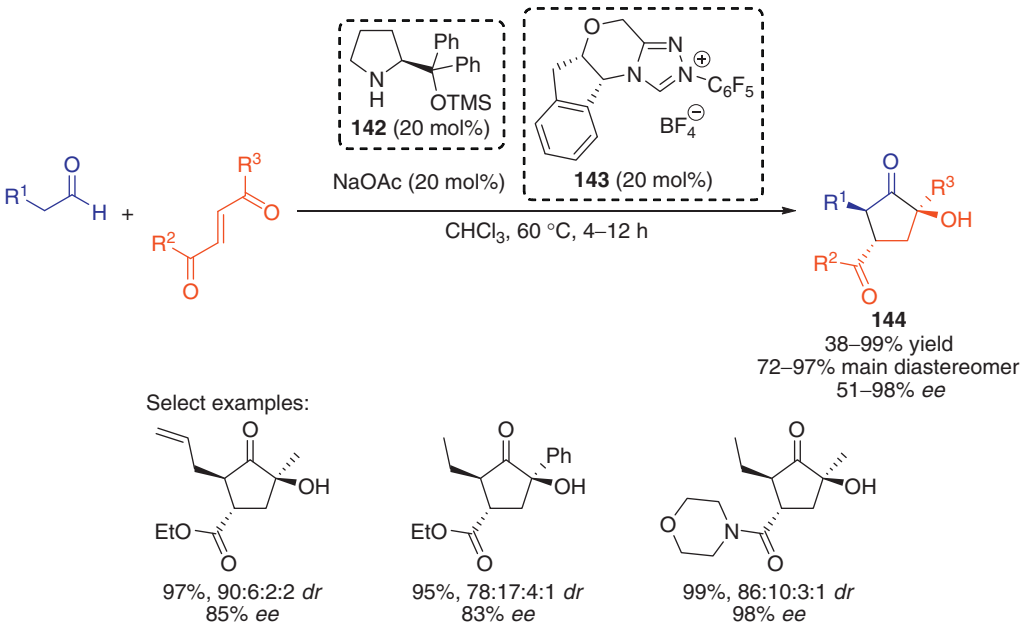
1.13.4.5 Aza-Benzoin Condensations

1.13.4.5.1 Racemic aza-benzoin condensations

The replacement of the second carbonyl coupling partner in cross-benzoin condensations by an imine allowed the preparation of valuable α-aminoketones. The first report was made in 1988 by the group of López-Calahorra who showed that a thiazolium salt



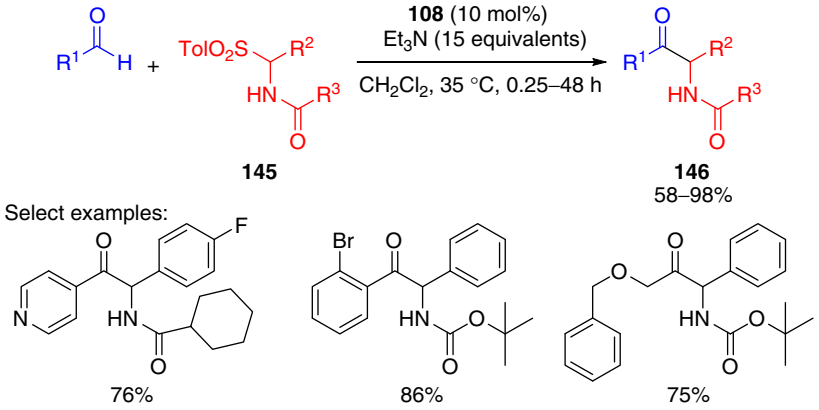
Scheme 46



Scheme 47

or a bis(thiazolin-2-ylidene) could catalyze the addition of aromatic and aliphatic aldehydes to iminiums, formed *in situ* from paraformaldehyde and cyclic secondary amines.[194] Even though the reaction is limited to formaldehyde derivatives, this was an important achievement since cyanide ions are not suitable catalysts for this transformation because of their irreversible binding with iminium ions. More generally dealing with the possible deactivation of the catalyst by the nitrogen-containing electrophile is

a permanent challenge in aza-benzoin condensations. Quite surprisingly, no follow-up studies were published during more than 10 years before Murry and Frantz disclosed the first general NHC-catalyzed aza-benzoin condensation using derivative **145** as precursor for the *in situ* generation of activated imines (Scheme 48).[195] Both aromatic and aliphatic aldehydes could participate in the reaction but only aromatic imines were tolerated. It should be noted that product **146** was obtained under kinetic control as the homobenzoin was never observed in these reaction conditions. The usefulness of these compounds could be demonstrated by utilizing them in an expedient synthesis of polysubstituted imidazoles.[196]



Scheme 48

After this breakthrough, a handful of other reports on aza-benzoin condensations appeared in the literature, with variations of the imine (Figure 9). For example, *N*-diarylphosphinoylimines **147**[197] were reacted with acyl silanes. *N*-arylimines **148**,[198] trifluoromethyl *N*-arylimines **149**,[199] and *N*-aryliminoacetates **150**[198] were all suitable substrates, contrary to *N*-tosylimines **151**, for which a trapping of the catalyst can be assumed because of their very high electrophilicity. In all these cases, the reaction occurs under thermodynamic control with fast reversible formation of the homobenzoin product followed by a slower but irreversible hydroacylation of the imine.

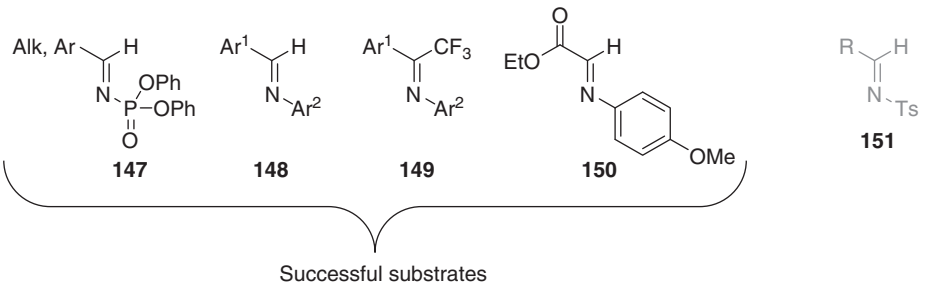
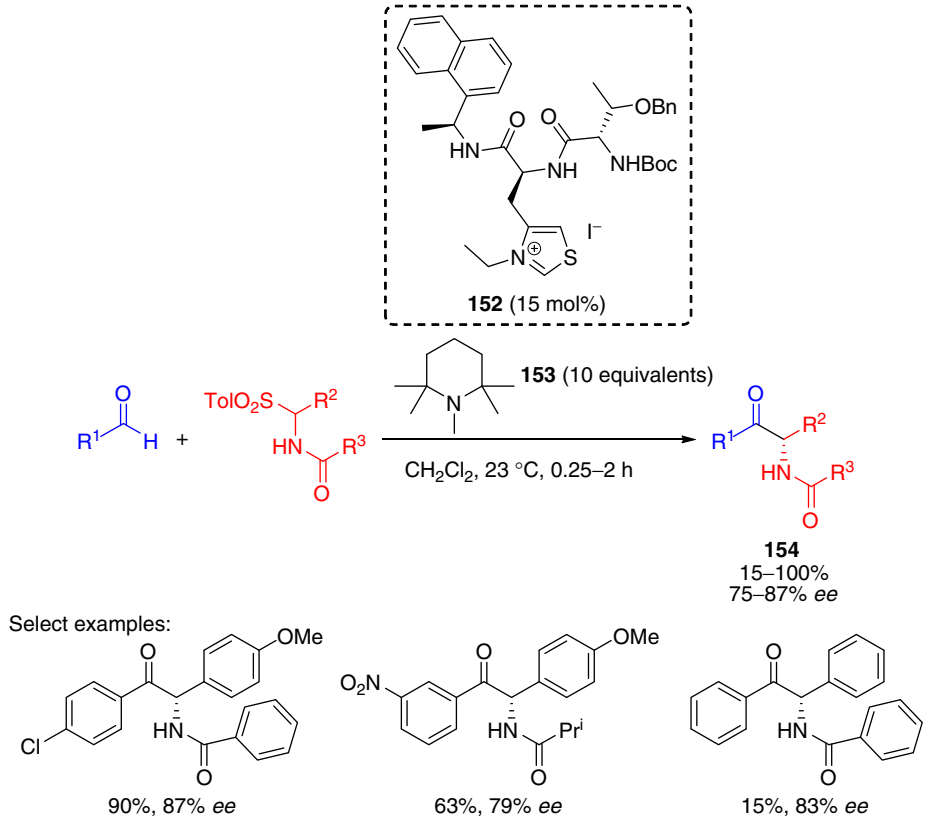


Figure 9 Imine coupling partners for the NHC-catalyzed aza-benzoin condensation.

1.13.4.5.2 Enantioselective aza-benzoin condensations

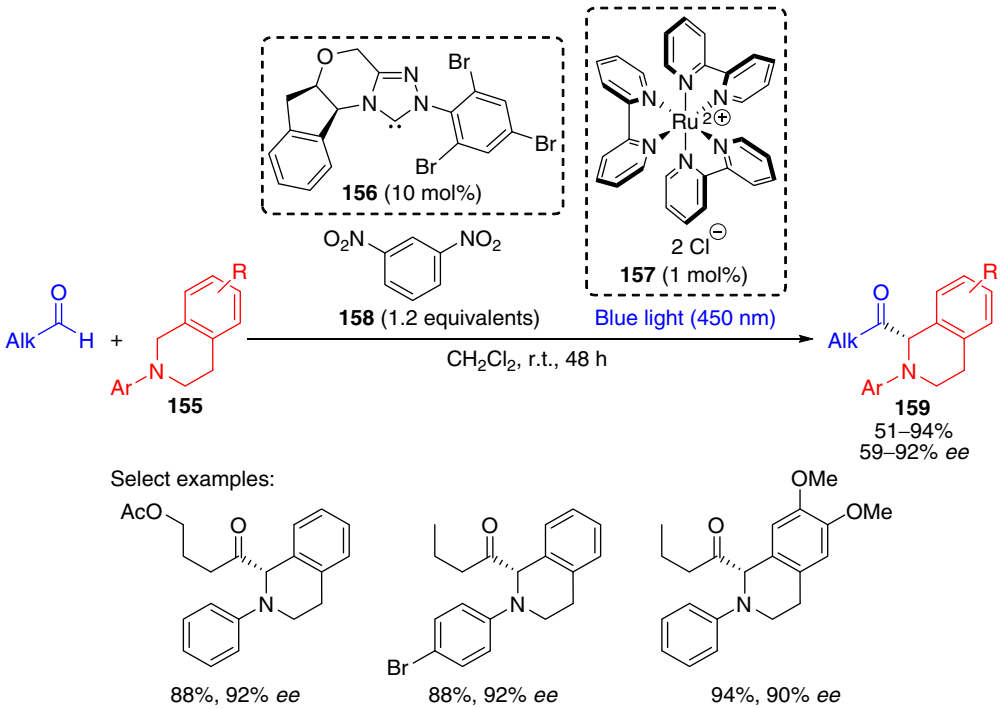
As for its reactions with aldehydes or ketones, the condensation of the Breslow intermediate with imines can produce new stereogenic centers. The first report of an enantioselective aza-benzoin condensation was made in 2005 by Miller and coworkers (Scheme 49).[200] Using reaction conditions close to the ones of Murry and Frantz and introducing the dipeptide-derived thiazolium salt **152** as a new chiral catalyst, α-aminoketones **154** were rapidly formed with good *ee*'s . The authors observed that the products were subject to racemization under the reaction conditions. Despite the use of the hindered base **153**, a compromise had to be found between yield and enantioselectivity, especially for less reactive substrates that required longer reaction times. It should also be noted that this reaction, among all the transformations that use thiazolium catalysis, is the only one that delivers the target compounds with high enantioselectivities.

During several years, the work of Miller remained the only enantioselective methodology for the preparation of aza-benzoins by NHC-organocatalysis. In 2012, DiRocco and Rovis published two very innovative solutions to this problem.[201] In their first publication, *N*-aryltetrahydroisoquinolines **155** were oxidized to the corresponding iminium ions via photoredox catalysis and intercepted by the Breslow intermediate generated from linear aliphatic aldehydes thanks to the chiral NHC **156** (Scheme 50).[201a] $Ru(bpy)_3Cl_2$ **157** was used as the photocatalyst and *m*-dinitrobenzene **158** as an oxidative quencher. 2-Acyl



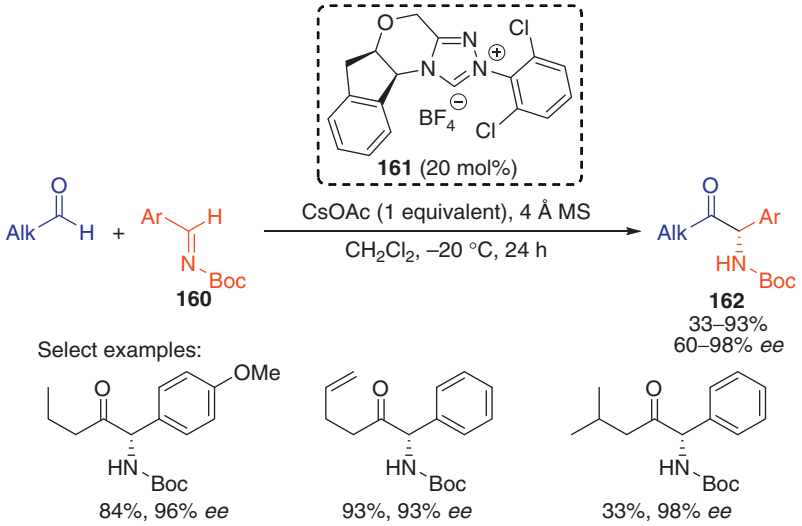
Scheme 49

N-aryltetrahydroisoquinolines **159** were obtained in good yields with *ee*'s generally higher than 90%. Notably, the NHC can add to the highly electrophilic iminium ion to afford an aza-Breslow intermediate,[137b] the formation of which is reversible in the reaction conditions.



Scheme 50

In the second report, aliphatic aldehydes were reacted with simple aromatic *N*-Boc imines **160** to efficiently afford the enantioenriched α-aminoketones **162** (Scheme 51).[201b] A fine tuning of the catalyst properties was achieved by using a 2,6-dichlorophenyl substituent at N1 of triazolium salt **161**. At the same time, the weak base CsOAc was found to be the best one, presumably because its conjugate acid formed during the generation of the NHC helped to prevent the deactivation of the catalyst by addition to the imine.



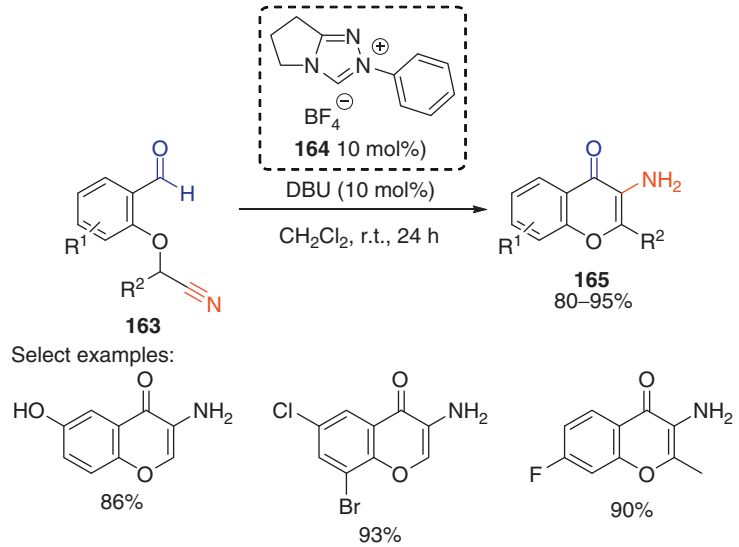
Scheme 51

1.13.4.5.3 Domino reactions

As it is the case for the benzoin condensation, the use of polyfunctionalized substrates can allow domino sequences that are initiated by an aza-benzoin condensation, such as aza-benzoin-Michael of aza-benzoin-aldol sequences.[202]

1.13.4.5.4 Hydroacylations of nitriles

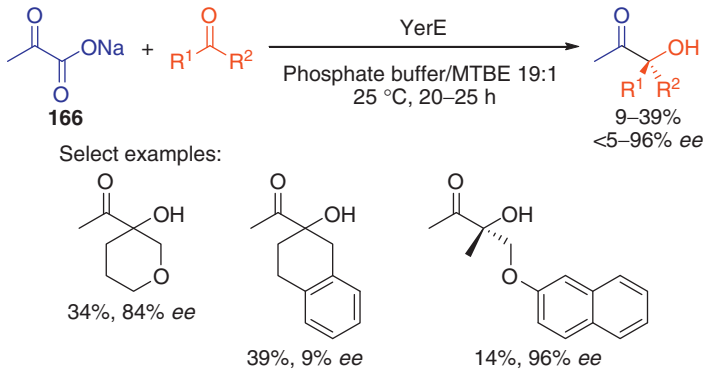
In addition to amines, another class of nitrogen-containing electrophiles was shown to undergo the attack of the Breslow intermediate. Aldehydes **163** that bear a tethered nitrile functionality were cyclized in the presence of triazolium salt **164** to afford, after tautomerization, 3-aminochromones **165** in high yields (Scheme 52).[203]



Scheme 52

1.13.4.6 Enzymatic Benzoin Condensations

Since they inspired the use of thiazolium salts to achieve benzoin condensation, thiamine diphosphate-dependant enzymes can of course act directly as catalysts for this transformation.[204] Impressive work, especially by the group of Müller, showed that they were often more efficient than artificial catalysts at solving the key challenges of the benzoin condensation, that is to say: (1) the control of the enantioselectivity; (2) the discrimination between different aldehydes in cross-benzoin condensations;[205] and (3) the benzoin condensation with ketones, especially not activated ones.[206] As it is generally the case for enzymatic reactions, they often provide high selectivities, but can sometimes be limited in terms of substrate scope. For example, the enzyme YerE, produced by amplification of its coding gene in the chromosomal DNA of *Yersinia pseudotuberculosis*, was able to cross-couple sodium pyruvate **166** with a variety of functionalized nonactivated ketones (Scheme 53). Although yields were generally modest, high enantioselectivities were obtained for some substrates and these results are very impressive since no chemically-designed catalyst is able to achieve a similar transformation.



Scheme 53

1.13.5 Other Catalytic Benzoin Condensations

In addition to the use of cyanide ions and the conjugate bases of azolium salts, other reaction conditions allow the catalytic generation of acyl anion equivalents and their coupling with a carbonyl group. These less-developed methods, some of them having great potential for further development and broader applicability, will be discussed in this section.

1.13.5.1 Organocatalysis with Metallophosphites

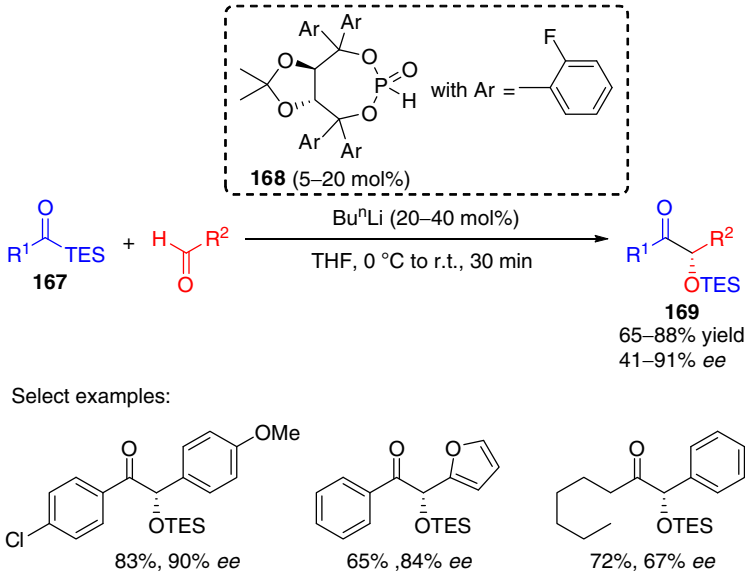
1.13.5.1.1 Cross-benzoin condensations

In the same way that the use of a substoichiometric amount of cyanide anion parallels the chemistry of *O*-protected cyanohydrins, one can envisage to catalytically generate the anion of α-hydroxyphosphonates (see Section 1.13.2.3). In 2004, the group of Johnson showed that the cross-benzoin reaction between acyl silane **167** and an aldehyde could be achieved in the presence of a catalytic amount of the chiral α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol-derived phosphite **168** and a strong base (Scheme 54).[207] Silyl-protected benzoins **169** were obtained with good yields and moderate to good enantioselectivities. Later on, terpenol-derived metallophosphites were also shown to be active catalysts in this transformation even though modest enantioselectivities were obtained.[208] Little is known about the influence of the catalyst structure but both the ring-size of the cyclic phosphite and the presence of fluorine atoms seems to strongly impact the reactivity, chemoselectivity, and enantioselectivity of this cross silyl benzoin condensation.[209]

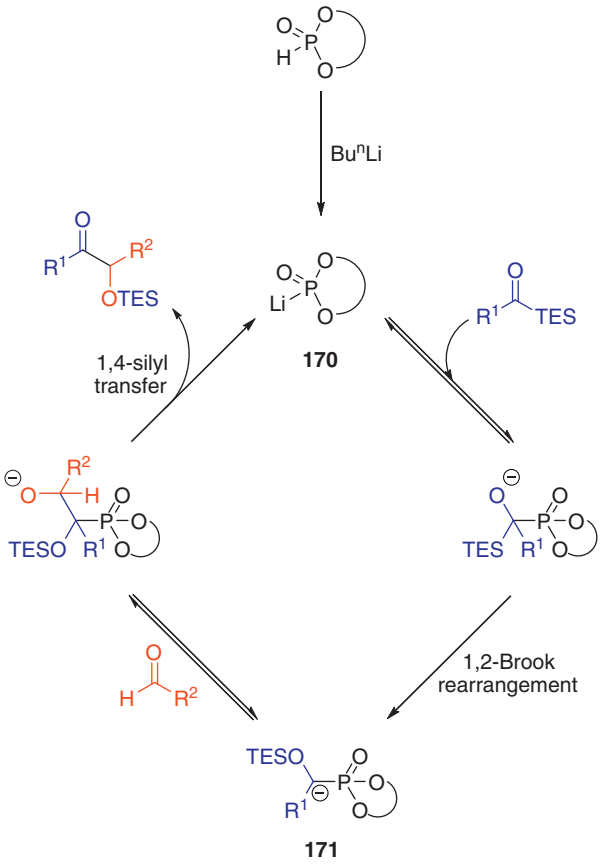
This transformation is likely to occur via a mechanism that is similar to the one proposed by Breslow for the corresponding NHC-catalyzed transformation, except that the proton transfer steps are replaced by migrations of the silyl group (Scheme 55). The deprotonation of the phosphite catalyst by Bu^nLi generates the metallophosphite **170**, which is the true catalytic species. Even though a metal is contained in its structure, it is still viewed as an organocatalyst since the lithium cation is only a counterion and does not play an active role in the reaction. Although it is less nucleophilic than an NHC,[210] the metallophosphite can add to the acyl silane. A subsequent 1,2-Brook rearrangement affords the acyl anion equivalent **171**. The preference for the inversion of polarity of the acyl silane over the one of the aldehyde stems from the energetically favorable $C \rightarrow O$ silyl transfer, which occurs with lower activation barrier than the proton transfers required for the umpolung of the aldehyde. After C–C bond formation, the cross-benzoin product is obtained via a 1,4 $O \rightarrow O$ silyl transfer with release of the catalyst.

1.13.5.1.2 Aza-benzoin condensations

Developing the aza-benzoin variant of the umpolung of acyl silanes by metallophosphite brought about an additional challenge. Indeed, after addition of the acyl anion equivalent to an imine, an endothermic 1,4 $O \rightarrow N$ silyl transfer was required to complete

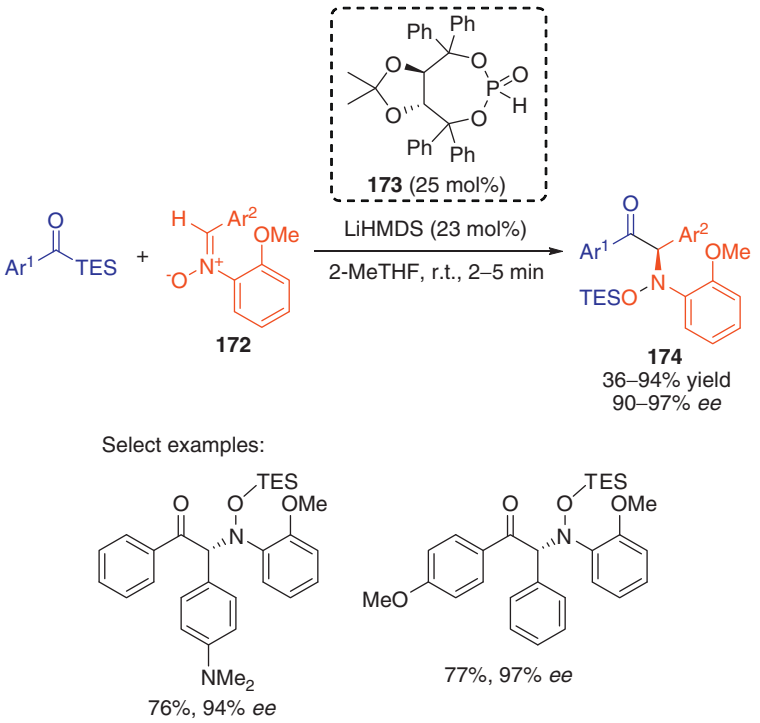


Scheme 54



Scheme 55

the catalytic cycle.[211] To solve this problem, Johnson et al. introduced nitrones as electrophiles in this transformation, replacing the turnover limiting step with a more favorable 1,5 $O \rightarrow O$ silyl transfer. After optimization, *N*-(*o*-methoxyphenyl)-substituted nitrones **172** proved to be the substrates of choice and phosphite **173** the best precatalyst to prepare α-(*N*-silyloxy)aminoketones **174** with excellent enantioselectivities (Scheme 56).

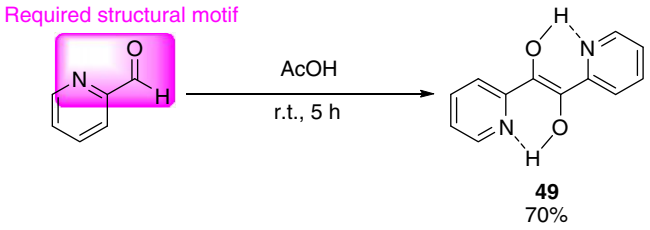


Scheme 56

1.13.5.2 Benzoin Condensations by Activation with Hydrogen-Bond Donors, Brønsted, and Lewis Acids

1.13.5.2.1 Acid-catalyzed pyridoin condensations

In 1953, Hensel et al. reported that pyridoin **49** was formed when equal amounts of pyridine-2-carboxaldehyde and glacial acetic acid were mixed (equation 22).[212] Among all other substrates that were tested, only quinoline-2-carboxaldehyde exhibited the same behavior, highlighting the necessity of the presence of a basic nitrogen *ortho* to the aldehyde.[213] The proposed mechanism requires both its basicity for protonation (so as to increase the electrophilicity of the aldehyde) and its nucleophilicity. Moreover, pyridoin was also formed in low yield along with its oxidation product, pyridil, when chilled pyridine-2-carboxaldehyde was saturated with BF_3.[214]



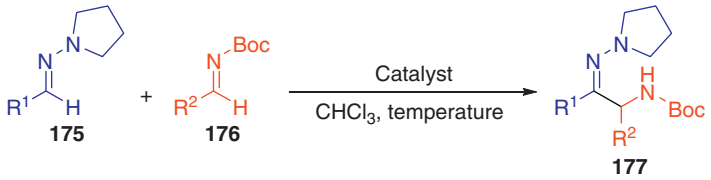
(22)

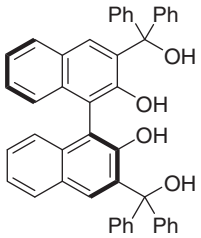
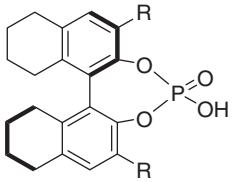
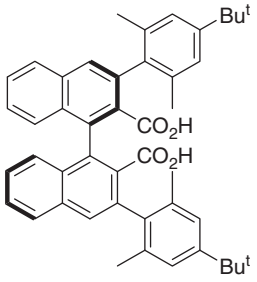
1.13.5.2.2 Organocatalytic enantioselective reactions of hydrazones

The aza-enamine reactivity of hydrazones has been widely used in reactions with different coupling partners, including diastereoselective transformations (see Section 1.13.2.6). In the past years, it was realized that an organocatalyst that suitably activates the electrophile would allow the development of enantioselective variants. Hundreds of publications document the use of chiral Brønsted acids to activate imines toward the attack of carbon nucleophiles and control the geometry of the newly formed C–C bond.[215] There are three different reports of the catalytic enantioselective addition of azaenamines **175** to *N*-Boc imines **176** (Table 2).[216] The group of Dixon used biphenol **178** as the catalyst, the one of Rueping phosphoric acid **179** and the one of Maruoka carboxylic diacid **180**. An increase of the *ee* was observed from the first catalytic system to the last one, which also allowed the use of aromatic-substituted azaenamines whereas the other ones were limited to formaldehyde-derived azaenamines. After the addition reaction, the carbonyl group can conveniently be restored by ozonolysis of **177** followed by reductive hydrolysis.

Extension of this reactivity to carbonyl compounds was not straightforward since they usually are worse candidates than imines for the activation by Brønsted acids. In 2012, the groups of Fernández and Lassaletta reported that formaldehyde *tert*-butyl

Table 2 Brønsted acid-catalyzed enantioselective imino-azaenamine reactions



Entry	*R^1, R^2*	*Catalyst*	*Temperature (°C)*	*Yield (%), ee (%)*	*References*
1	H, Ar	 **178** (20 mol%)	r.t.	44–87, 16–65	216a
2	H, Ar	 R = 9-phenanthryl **179** (10 mol%)	0 °C	48–82, 74–90	216b
3	Ar^1, Ar^2	 **180** (5 mol%)	−30 °C	35–77, 84–95	216c

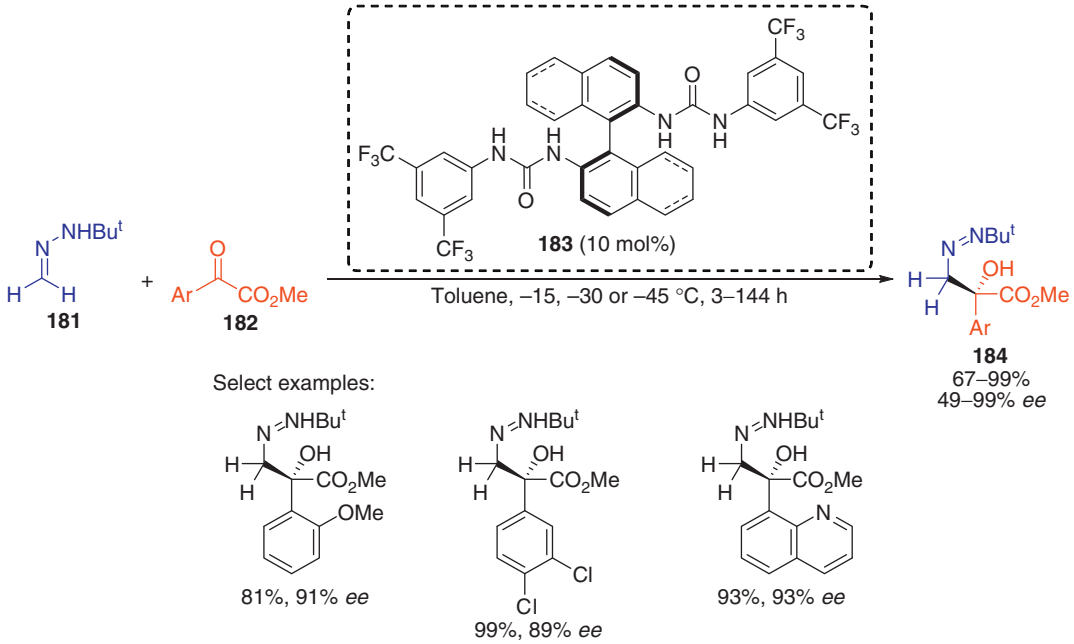
hydrazone **181** can react with aromatic α-oxoesters **182** in the presence of bis-urea catalysts **183** (Scheme 57).[217] The proposed mode of activation invokes the formation of a ternary complex, in which one of the two ureas activates the α-oxoester whereas the second one guides the approach of the hydrazone through hydrogen bonding with the N–H. The products **184** were obtained with very good yields and *ee*s up to 99%.

1.13.5.2.3 Catalytic enantioselective benzoin condensations of N-silyl oxyketenes

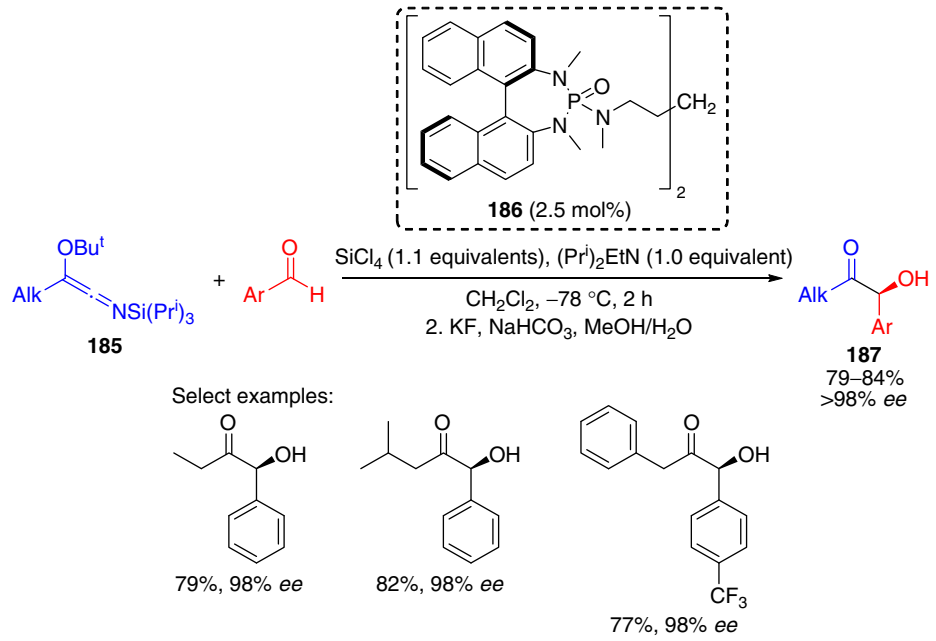
The deprotonation of *O*-protected cyanohydrins and the trapping of the anion with a silylating agent afforded *N*-silyl oxyketene imines **185** (Scheme 58). Like in the Mukaiyama aldol reaction, Denmark realized that it was possible to promote the enantioselective addition of **185** to aromatic aldehydes by treating them with a Lewis acid and a catalytic amount of an activating chiral Lewis base **186** [218] After a fluoride anion-promoted desilylation and cleavage of the *tert*-butyl group, the enantioenriched cross-benzoin products **187** were obtained in high yields and impressive enantioselectivities.

1.13.5.3 Benzoin Condensations by Photolysis

A few reports can be found in the literature of benzoin condensations in photolytic conditions, by irradiation at high concentrations (>1 mol l^{-1}).[219] NMR studies supported a mechanism initiated by an intermolecular hydrogen abstraction followed by radical collapse to create the C–C bond.[220] When the aldehyde molecule was included in the cavity of a chiral β-cyclodextrin, a modest enantioinduction (15%) was observed.[221]



Scheme 57



Scheme 58

1.13.6 Vinylogous Reactivity: The Homoaldol Reaction

1.13.6.1 Stoichiometric Homoenolates

Unlike aldol products **189** that can be prepared by normal polarity reactions, the synthesis of both benzoins **188** and homoaldol motifs **190** requires an inversion of polarity (Figure 10). The most intuitive strategy is to condense a homoenolate with a carbonyl derivative. Several methods allow one to prepare homoenolates, the reactivity of which is discussed in detail in another chapter of the present book series (*see* Chapter 2.15).

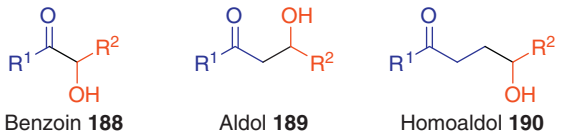
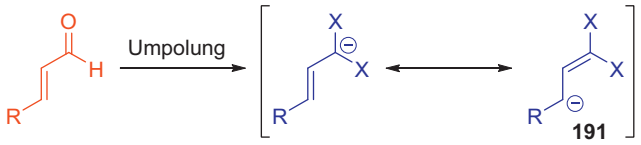
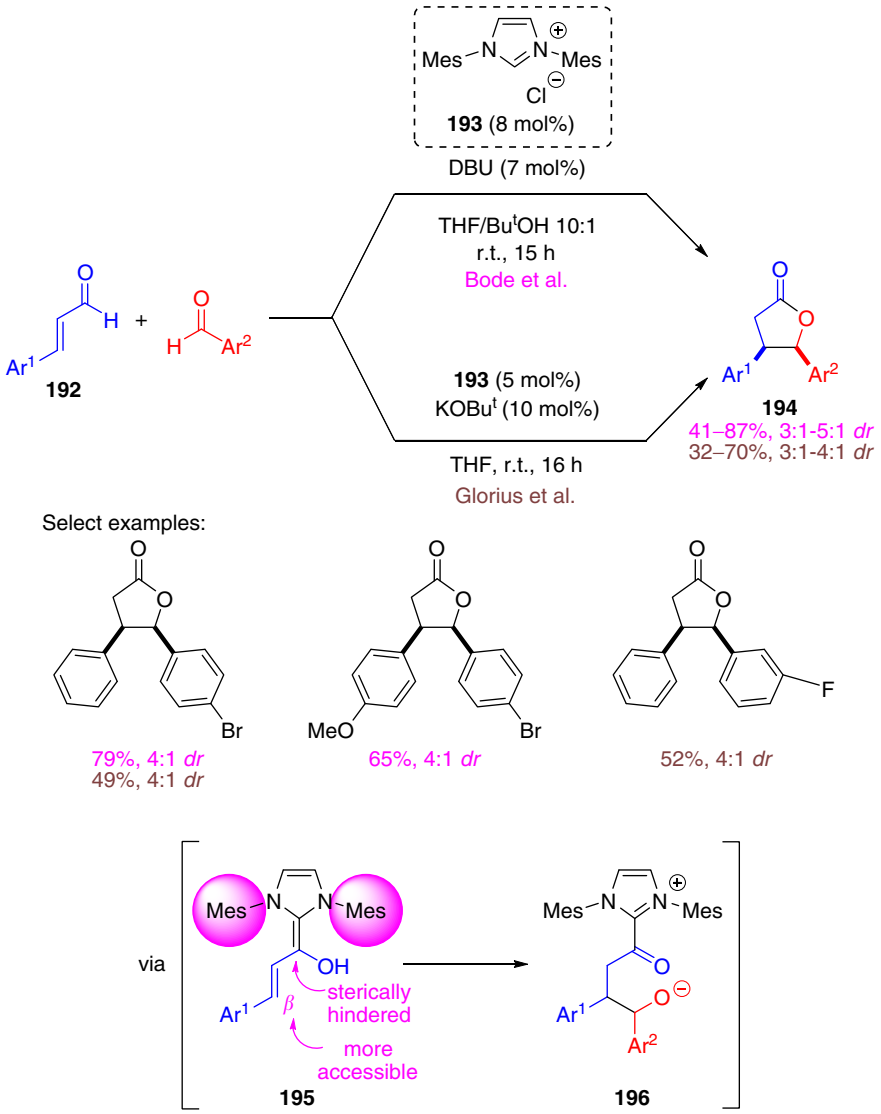


Figure 10 Benzoin, aldol, and homoaldol structural motifs.

When the methods for the inversion of polarity described in the present chapter (see Section 1.13.2) are applied to α,β-unsaturated aldehydes, the newly acquired nucleophilic properties can potentially transfer by mesomery from the carbonyl position to the β position, affording species **191**, which are a special class of homoenolates (equation 23). This phenomenon raises questions about the regioselectivity of the attack on the electrophilic carbonyl coupling partner and strategies were design to control it. Several reviews that summarize the efforts in the design of stoichiometric conjugate umpolung reagents can be found in the literature.[222]



(23)



Scheme 59

1.13.6.2 NHC-Catalyzed Generation of Homoenolates

In 2004, the groups of Bode and Glorius independently reported the first NHC-catalyzed transformation that was proceeding through a homoenolate intermediate. It consisted in the chemoselective annulation of an enal **192** with an aromatic aldehyde to afford the γ-butyrolactone **194** with moderate diastereoselectivities, favoring the *syn* isomer (**Scheme 59**).[223] Reaction conditions were very similar and the key to the success was the use of the sterically hindered imidazolium salt **193** that could avoid classical umpolung to occur and guide the reactivity of the extended Breslow intermediate **195** toward the β-position. Its addition to the aldehyde resulted in the formation of an acyl azolium **196** that was trapped intramolecularly by the alcoholate to form the product and release the catalyst.

This breakthrough opened a new field of research in NHC-organocatalysis and many transformations, including enantioselective ones have been published since then. These results will not be further discussed here but more details on this topic can be found in recent reviews published by the group of Nair.[224]

1.13.7 Acknowledgments

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1.14 Oxygen-Stabilized Carbanions

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Glossary

Anion translocation A process in wich an anion, formed under kinetic control, undergoes an intramolecular proton transfer.

Carbenoid A chemical species, often a reactive intermediate, that is not a free carbene but shares reaction characteristics with a carbene.

Contact ion pair (CIP) An ion pair, the constituent ions of which are in direct contact.

Kinetic isotopic effect The effect exerted on the reaction rate by an isotopic substitution at a site of bond breaking (or bond making) in the rate determining step of a reaction mechanism.

SET mechanism A reaction mechanism characterized by the transfer of a single electron between the species occurring on the reaction coordinate of one of the reaction steps.

Solvent separated ion pair (SSIP) An ion pair, the constituent ions of which are separated by an intervening solvent or other neutral molecule.

1.14.1 Introduction

Among carbanions, organolithiums are reactive intermediates of paramount utility in synthetic organic chemistry. α-Heterosubstituted organolithium compounds, namely those bearing an adjacent heteroatom, are available by deprotonation, halogen–lithium exchange, transmetallation (mainly tin–lithium exchange), carbon–heteroatom bond cleavage, reductive lithiation, and carbolithiation.[1] Particularly interesting and especially useful are those in which the heterosubstituent is compatible with the carbon–lithium bond and eventually permits synthetic elaboration to other useful compounds.

Generation of an α-heterosubstituted organolithium is particularly easy when the heterosubstituent is an electron-withdrawing group (EWG) such as RSO_2, RSO, or $PO(OR)_2$ due to their known acidifying effect, but can also take place adjacent to other heteroatoms such as oxygen or nitrogen-based functional groups, which apparently even decrease the acidity of the adjacent protons, provided these groups, which, even if apparently decrease the acidity of the adjacent protons, are able to coordinate strongly to the organolithium thus stabilizing it. They can be acyclic and cyclic sp^3- and sp^2-hybridized or something in between sp^3 and sp^2 as in the case of α-lithiated oxiranes. In a sense, deprotonation of α to oxygen is unfavorable: the antibonding interaction of the oxygen lone-pairs with the C–Li bond overcomes the electron-withdrawing effect of the oxygen atom. The repulsion is lessened if the lone-pairs are lowered in energy by delocalization, especially into a carbonyl group as in the case of hindered esters and carbamates. The mechanism of this sort of α-lithiation has been investigated and a model has been proposed which involves a preliminary complex between the lithiating agent and the substrate. This is believed to represent the first step in the lithiation sequence, which is followed by the deprotonation step. The configurational stability of these organolithiums jointly with the stereochemistry of their reactions is a synthetically useful aspect which has deserved a deep investigation. When dealing with α-oxygen organolithiums it must be taken into account that they have properties of lithium

carbenoids, as proved by the numerous studies that have been carried out over the years on them with special reference to their methods of generation, structural features, reactivity, spectroscopic and computational studies, and applications in synthesis.[2]

α-Oxygenated organolithium compounds (O-alkyl, O-alkoxyalkyl, O-carbamoyl, O-carbonyl organolithiums, Figure 1) as well as α-lithiated oxiranes have been extensively studied as reported in reviews, books, book chapters, and papers. Figure 1 contains a compilation of α-oxygenated organolithiums where groups linked to the oxygen can be alkyl, alkoxyalkyl, carbonyl, carbamoyl, or sp^2-hybridized carbon atom. Classification of α-oxygen organolithiums in 'stabilized' and 'nonstabilized' state depending on the presence or absence of an electron-withdrawing group in the α-position has been considered useful for the reader.

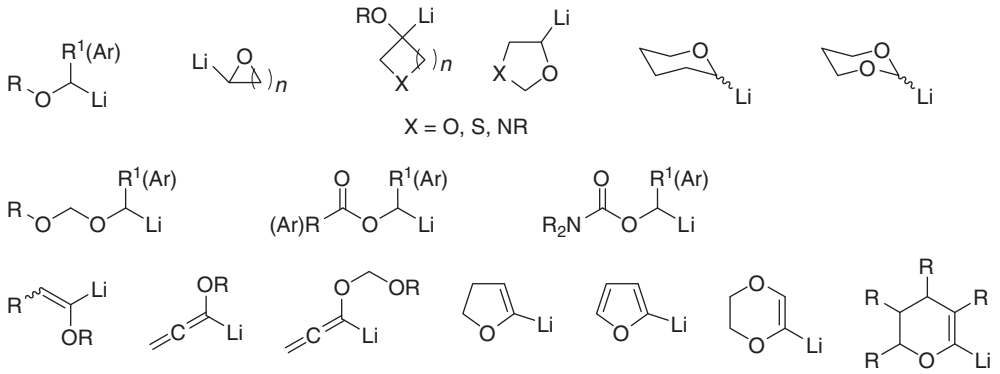
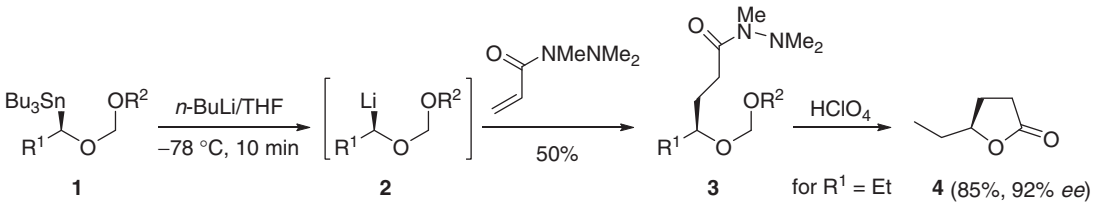


Figure 1 Compilation of α-oxygenated organolithiums.

1.14.2 sp^3-Hybridized α-Oxygenorganolithiums

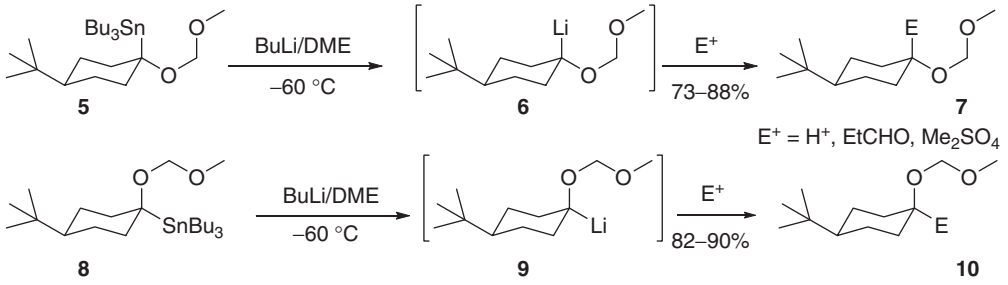
1.14.2.1 α-Alkoxy Organolithiums

Alkoxy groups are very good heterosubstituents for α-heterosubstituted organolithiums. Indeed, α-alkoxyorganolithiums can be stereospecifically prepared by Sn–Li exchange from α-alkoxystannanes and are configurationally stable, and trapping with electrophiles occurs usually with retention of configuration. The role of the alkoxy group is to stabilize the incoming organolithium by intramolecular chelation. A peculiar example is represented by Sn–Li transmetallation of enantiomerically pure organostannane **1** with *n*-BuLi at −78 °C in THF that produces stereospecifically the organolithium **2**, which undergoes conjugate addition to **3** to give the lactone **4** in 92% *ee* (Scheme 1).[3]



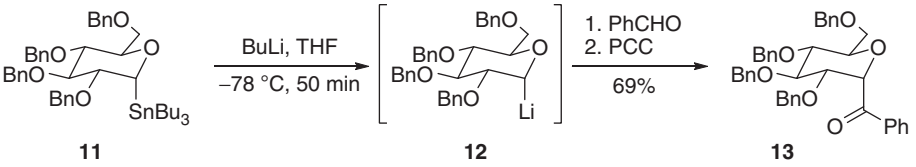
Scheme 1

Treatment of stannanes **5** and **8** with butyllithium furnished by Sn–Li exchange, axial **6** and equatorial **9** organolithiums α to *O*-alkoxyalkyl groups that are configurationally stable over a period of minutes at −60 °C and can be trapped stereospecifically with retention of configuration to give functionalized cyclohexanes **7** and **10** (Scheme 2).[4]



Scheme 2

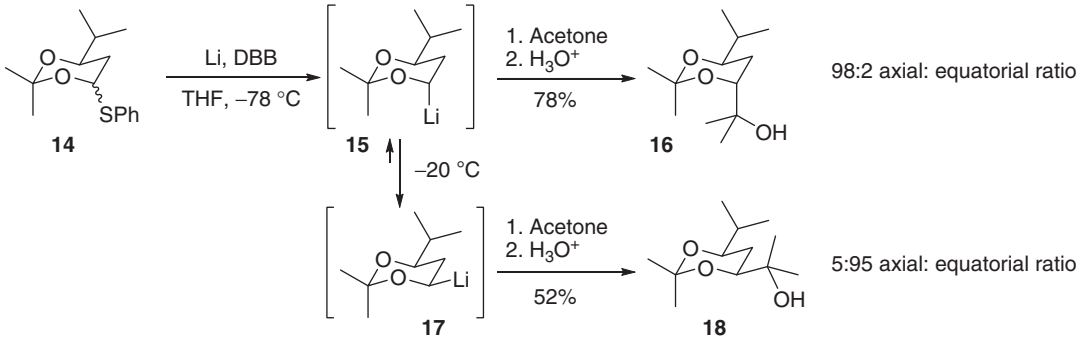
Cyclic α-alkoxy organolithiums are also configurationally stable at −78 °C. The axial stannane **11**, for example, gives the axial organolithium **12** which retains its stereochemistry for 50 min at −78 °C and can be quenched stereospecifically with benzaldehyde leading to the benzoyl derivative **13** on oxidation with pyridinium chlorochromate (PCC) (Scheme 3).[5]



Scheme 3

Cyclic α-alkoxy organolithiums can also be obtained by reductive lithiation from arylsulfides, a method of generating organolithiums α to oxygen mainly developed by Cohen and Rychnovsky.[6]

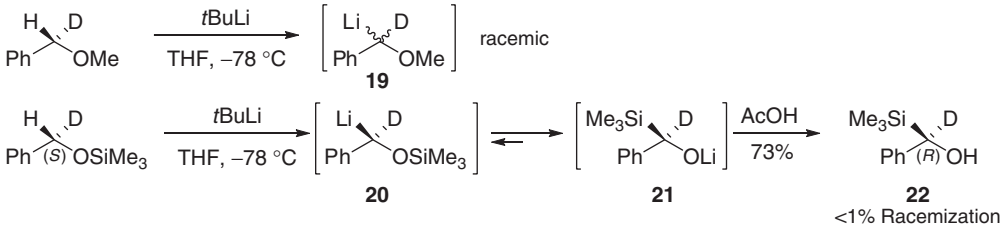
Reductive lithiation (lithium and di-tert-butylbiphenyl, DBB) of both the diastereomers of arylsulfide **14** at −78 °C gives the axial organolithium **15**, which can be quenched with acetone to give the axial alcohol **16** with a very high axial selectivity (98:2 axial:equatorial ratio) (Scheme 4). The same axial organolithium tends to epimerize to the thermodynamically more stable equatorial isomer **17** on warming. Quenching with acetone results in the formation of the equatorial alcohol **18** (5:95 ax:eq).



Scheme 4

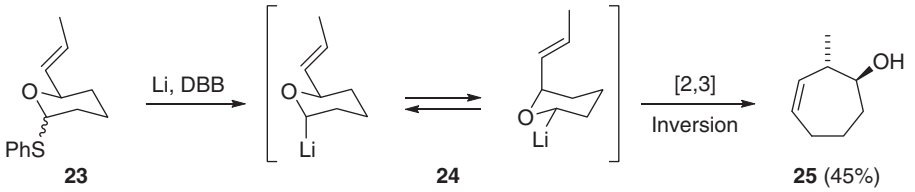
Several examples have been reported in which the stereochemical outcome has been strictly controlled by tuning the experimental conditions in order to afford products with the desired stereochemistry.

In the process of generation of an α-oxygenated organolithium, it must be stressed that all that favors lithiation by stabilizing the resulting lithiated species (structural features of the starting material and experimental conditions), tends to cause racemization of the organolithium once formed. Accordingly, α-alkoxy benzyllithiums and allylithiums are usually configurationally unstable and tend to racemize because of their highly planarized structures with highly delocalized charge.[7] The rate of racemization may depend on the nature of the alkoxy group. Indeed, while α-methoxy benzyllithium **19** racemizes in seconds, the trimethylsilyloxy benzyllithium **20** does it much more slowly (Scheme 5). At −50 °C, it undergoes a Brook rearrangement to **21** which on acidic trap leads to the trimethylsilyl benzyl alcohol **22** with 99% inversion of stereochemistry.[8]



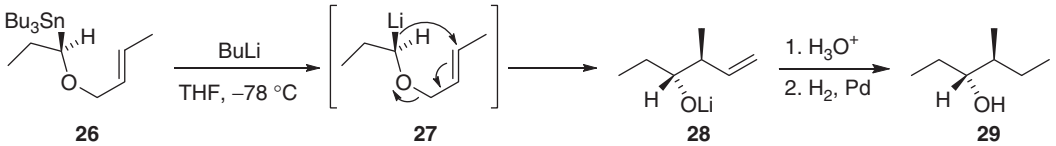
Scheme 5

Suitably β-functionalized α–O–alkyl organolithiums may undergo a variety of reactions including cyclizations and rearrangements. Cohen used the known axial preference of the formation of organolithiums by reduction of 2-vinylthiopyran **23** to produce the organolithium **24** diastereoselectively, the vinylic and lithio substituents lying *trans* each other (Scheme 6). After 12 h at −78 °C, a mixture of [1,2]- and [2,3]-Wittig products were produced, both stereoselectively; the [2,3]-product **25** results from inversion at one reacting center and retention at the other. Since the migration must be suprafacial across the allylic system, the conclusion must be that the reaction proceeds with inversion at the organolithium center.[9]



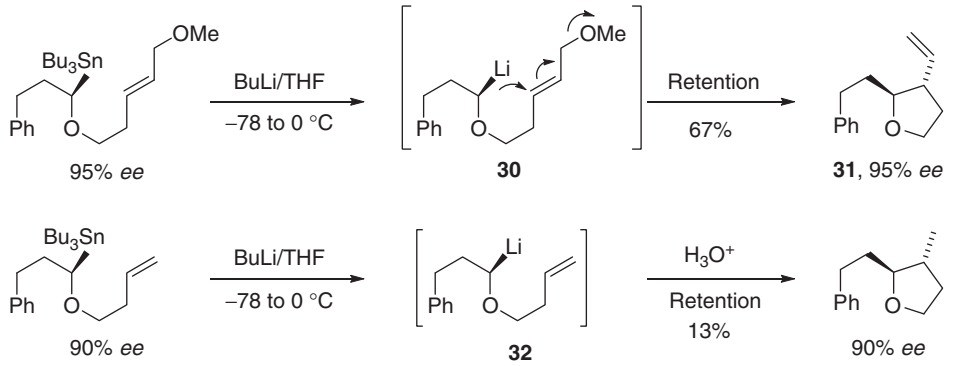
Scheme 6

Transmetallation of **26** (62% *ee*) gives **27** which rearranges to **28** (62% *ee*) (Scheme 7). The stereochemistry of product **28**, which was proved by conversion to the naturally occurring ant pheromone **29** of known absolute configuration, demonstrates that the rearrangement proceeds with inversion of stereochemistry, assuming that the Sn–Li exchange step proceeds with retention of configuration.[10,11]



Scheme 7

Both the alkoxy organolithiums **30** and **32** cyclize with retention of configuration, but lithiated species **30** does it much faster than **32** likely because it enjoys the methoxy group effect which promotes the lithium methoxide elimination to **31** but has no effect on the stereospecificity of the cyclization reaction (Scheme 8).[12]

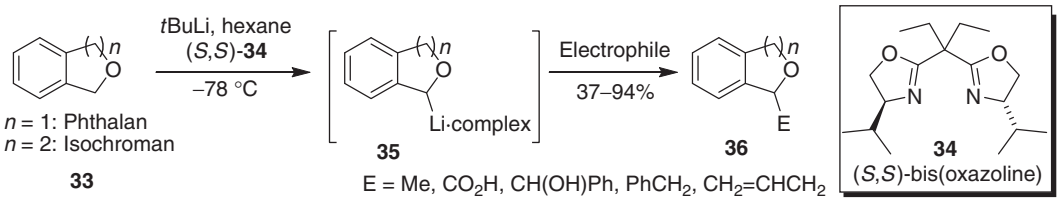


Scheme 8

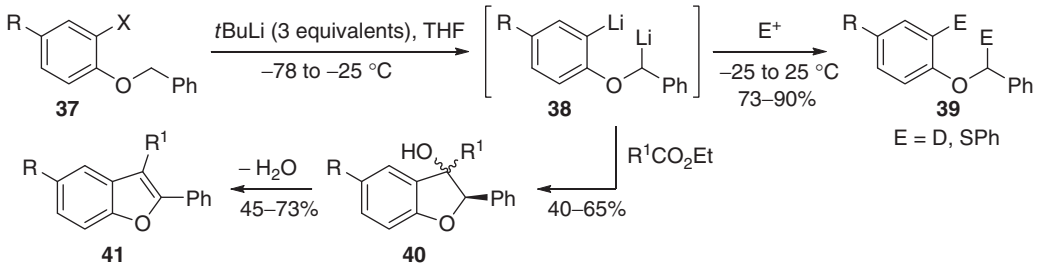
Studies carried out by Nakai and coworkers have demonstrated that the use of the chiral bis(oxazoline) **34**, or (–)-sparteine, as an external chiral ligand, provides remarkably high enantioselectivity in the lithiation/S_E2 reactions of benzyl methyl ethers, [1,2]-Wittig rearrangement of dibenzyl ethers, and the [2,3]-Wittig rearrangement of allylic, benzyl, and propargyl ethers. Treatment of isochroman and phthalan **33** with a *t*-BuLi/chiral bis(oxazoline) **34** complex resulted in the generation of organolithium **35**; the subsequent reaction with carbon-electrophiles is shown to afford the α-substituted derivatives **36** in moderate to high enantioselectivities (up to 97% *ee* and 83% *ee*, respectively) (Scheme 9). Reactions with other electrophiles proceeded with much lower *ee* values. The asymmetric induction is proved to occur at the postlithiation step. Complex *t*-BuLi(*S*,*S*)-**34** was first formed by mixing *t*-BuLi with chiral bis(oxazoline) and then the electrophile was added. Significantly, the reactions with CO_2 and benzaldehyde afforded the corresponding adducts in remarkably high % *ee* (up to 97% *ee* and 83% *ee*, respectively), whereas the alkylation reactions provided moderate *ee* values.[13]

Dianions **38**, generated by the double lithiation of benzyl 2-halophenyl ethers **37** with 3 equivalents of *t*-BuLi in THF (− 78 to − 25 °C) can be trapped with electrophiles to give **39** (Scheme 10). Their reactions with carboxylic esters afford the corresponding 2-aryl-3-hydroxy-2,3-dihydrobenzo[b]-furans **40** as a mixture of diastereomers. Subsequent acid-catalyzed dehydration gives moderate to good overall yield of a variety of 2-aryl-3-substituted benzo[b]-furans **41**.[14]

Lithiation of allyl, benzyl, and propargyl 2,3-epoxy ethers by treatment with the Schlosser's base (butyllithium/potassium *tert*-butoxide) or other superbasic mixtures such as lithium diisopropylamide/potassium *tert*-butoxide (LIDAKOR) proceeds in a highly regio- and stereoselective manner. The formation of 2-vinyl-, 2-phenyl-, or 2-alkynyl-3-(α-hydroxyalkyl) oxetanes is favored over the alternative five-, six- and seven-membered ring cyclizations.

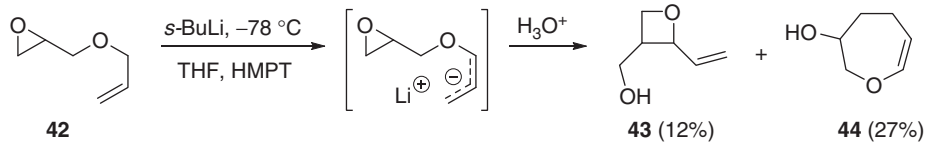


Scheme 9



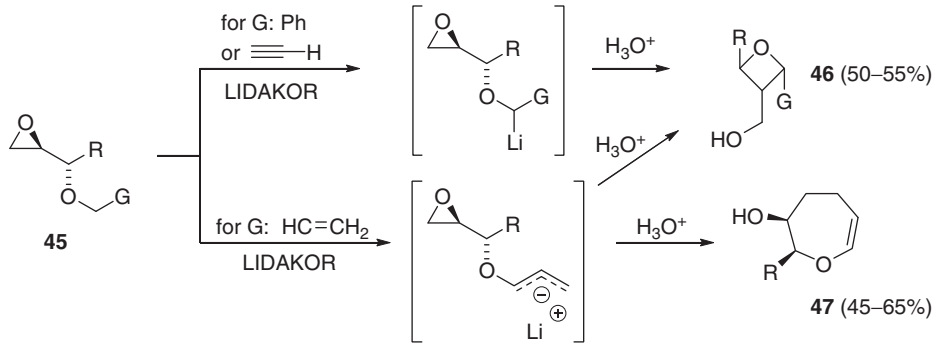
Scheme 10

Allyl glycidyl ether **42** is converted into a mixture of *trans*-3-(hydroxymethyl)-2-vinyloxetane **43** and hydroxytetrahydrooxepine **44** on treatment with *sec*-butyllithium in THF/HMPT at −78 °C (Scheme 11).[15a,b]



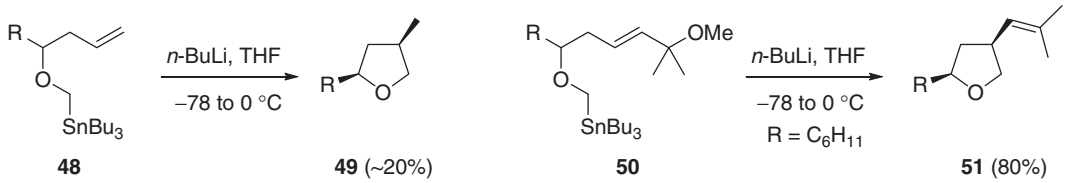
Scheme 11

Compounds such as **45** have been smoothly converted into 2-phenyl- and 2-alkynyl-substituted oxetanes **46** in good yields by treatment with the superbase LIDAKOR (a mixture of *i*-Pr_2NLi and *t*-BuOK) (Scheme 12). The relative stereochemistry of substituents in positions 3 and 4 of the oxetane ring is due to the configuration of the starting epoxy ether, whereas the *cis* or *trans* relationship between the substituents in positions 2 and 3 arises during the cyclization step. The selectivity is the one expected according to previous findings,[15c] the *trans* isomers being always preferred. Compounds **46** are particularly interesting in view of an application to the synthesis of the oxetane containing nucleoside oxetanocin, which has received a great deal of attention in recent years, due to its potent activity as an antiviral, antibiotic, and antitumor agent. Cyclization of **45** (G=CH=CH_2) using the Schlosser's base resulted in the formation of tetrahydrooxepine derivatives **47**, which tend to isomerize. It is reasonable to assume that the formation of the oxepine derivatives has to be ascribed to the higher preference of the allyl potassium species, compared with the lithium analogs, to react at their terminal position.[15]



Scheme 12

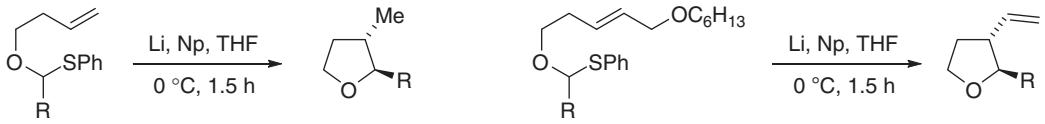
The Sn–Li exchange is a key step in the cyclization of stannanes **48** and **50** into *cis*-configured disubstituted tetrahydrofurans **49** and **51**, respectively (Scheme 13). The presence of the methoxy group (acting as leaving group) makes stannane **50** much more reactive than **48**.[16]



48 **49** (~20%) **50** **51** (80%)

Scheme 13

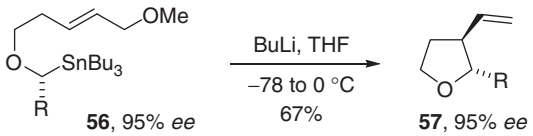
α-Alkoxy organolithiums can also be made from aryl sulfides using Cohen's lithium naphthalene reduction method. This allows the formation of tetrahydrofurans **53** and **55** from monothioacetals **52** and **54**, the yields being best when the trap is an allylic ether (Scheme 14). However, compared to stannanes **48** and **50**, the lithiation-trapping sequence of **52** and **54** proceeds with inversion of configuration.[17]



52 **53** (52%) **54** **55** (75%)

Scheme 14

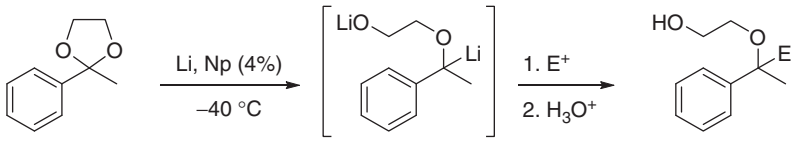
Cyclization of a stereodefined organolithium derived from enantiomerically enriched α-alkoxy stannane **56** gives a tetrahydrofuran **57** with no loss of enantiomeric excess and with overall retention (Scheme 15).[12]



56, 95% *ee* **57**, 95% *ee*

Scheme 15

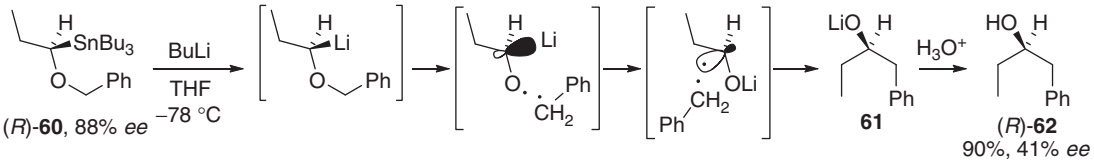
The reductive lithiation of dioxolanes **58** to give **59** requires the formation of an allylic or benzylic organolithium and represents a valuable umpolung method for the functionalization of carbonyl compounds (Scheme 16).[18]



58 **59**

Scheme 16

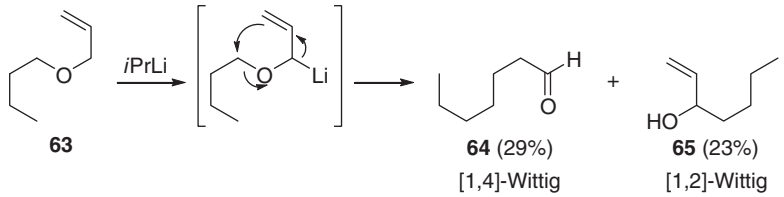
Allylic and propargylic ethers can be easily transformed into the α-alkoxyorganolithiums that can be trapped with electrophiles or undergo Wittig rearrangements. The topic has been extensively investigated over the years and very well described by Clayden[1a] with reference to all the relevant aspects including the mechanistic features, regiochemistry, stereochemistry, synthetic utility, and application to the preparation of important target molecules. Systems that can give rise to Wittig rearrangements are allyl alkyl, propargyl alkyl, benzyl alkyl, diallyl, benzyl allyl, benzyl propargyl, allyl propargyl, dipropargyl ethers. Mechanistic studies have demonstrated that the [1,2]-Wittig rearrangement reaction of alkoxy organolithiums is consistent with the formation of a radical pair that rearranges by lithium migration to oxygen to form a product radical pair that then recombines to give the alcohol. For example, stannane (*R*)-**60** (88% *ee*) rearranges, on transmetallation with *n*-BuLi, to the lithium alkoxide **61** and then to the alcohol **62** (41% *ee*), a reaction demonstrating 74% of inverted stereospecificity (Scheme 17).[11]



(*R*)-**60**, 88% *ee* **61** (*R*)-**62** 90%, 41% *ee*

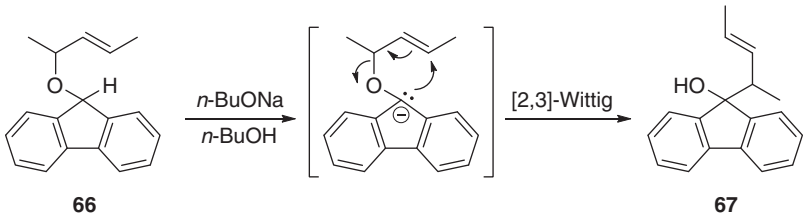
Scheme 17

The [1,4]-rearrangement, for which the mechanism has not been ascertained, may compete with [1,2]-Wittig rearrangement, as in the case of the following allyl ether **63** which, on treatment with *i*-PrLi and trapping, leads to the Wittig products **64** and **65** (Scheme 18).[19]



Scheme 18

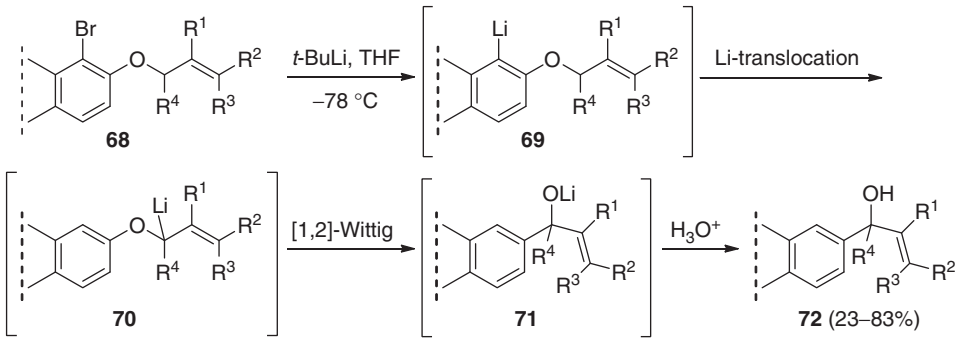
The mechanism of [2,3]-Wittig rearrangement is quite different from that described above for the [1,2]-Wittig reaction: it is a suprafacial six-electron pericyclic process, as shown in the rearrangement of **66** which ends up with the formation of compound **67** (Scheme 19).[20]



Scheme 19

Several examples of the Wittig rearrangements of α-alkoxyorganolithiums have been reported over the years. Attention will be focused here on the most recent and significant examples.

Allyl and benzyl 2-lithioaryl ethers **69**, generated by bromine–lithium exchange of **68** in THF, undergo an anion translocation to allyllithiums **70** and, subsequently, [1,2]-Wittig rearrangement to lithium alkoxide **71** allowing the isolation, after acidic quench of the corresponding benzylic alcohols **72** (Scheme 20).[21]



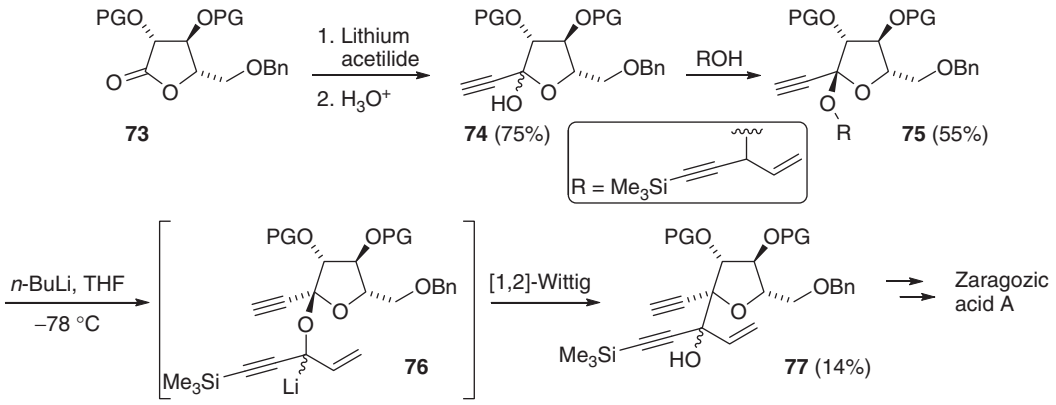
Scheme 20

An acetal [1,2]-Wittig rearrangement is a key step in a stereoselective total synthesis of zaragozic acid A, which is a potent inhibitor of squalene synthase. In this synthesis hemiketal **74**, prepared from lactone **73** and lithium acetilide, is transformed into O-glycoside **75** on reaction with $CH_2{=}CHCH(OH)CC\text{-}SiMe_3$ (Scheme 21). The glycoside **75** is then reacted with *n*-BuLi/THF at −78 °C to give the lithiated ether **76**, which undergoes the [1,2]-Wittig rearrangement to the alcohol **77**.[22]

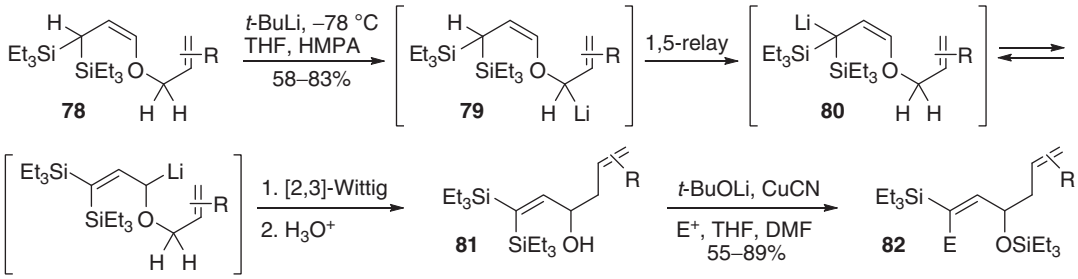
The [1,5]-anion relay/[2,3]-Wittig rearrangement of 3,3-bis(silyl) enol allyl ethers **78** has been employed for the synthesis of versatile vinyl bissilanes which can be transformed into trisubstituted vinylsilanes (Scheme 22). The ether **78** is first lithiated to **79**; 1,5-lithium transmetalation takes place to give the lithiated derivative **80**. The [2,3]-Wittig rearrangement follows to give **81**, which converts into the substituted vinylsilane **82** through a [1,4]-Brook rearrangement/alkylation protocol.[23]

The chirality transfer in the [2,3]-Wittig rearrangement can be remarkably influenced by the base. Treatment of allylic ether (*S*)-**83** with LDA at − 100 °C in THF followed by warming to r.t. and quenching with NH_4Cl results in the formation of the rearranged

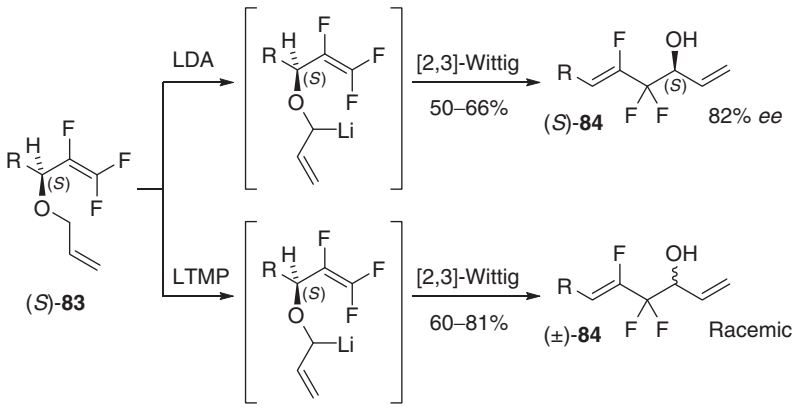
product (*S*)-**84** with 82% *ee* and 58% yield (Scheme 23). In contrast, the use of lithium tetramethylpiperidide (LTMP) as the base causes a drastic reduction in the optical purity of the rearranged product. The rearrangement reaction inhibited by 2,2,6,6-tetramethyl-1-piperidine-1-oxy free radical (TEMPO) suggested a radical pathway mechanism.[24]



Scheme 21

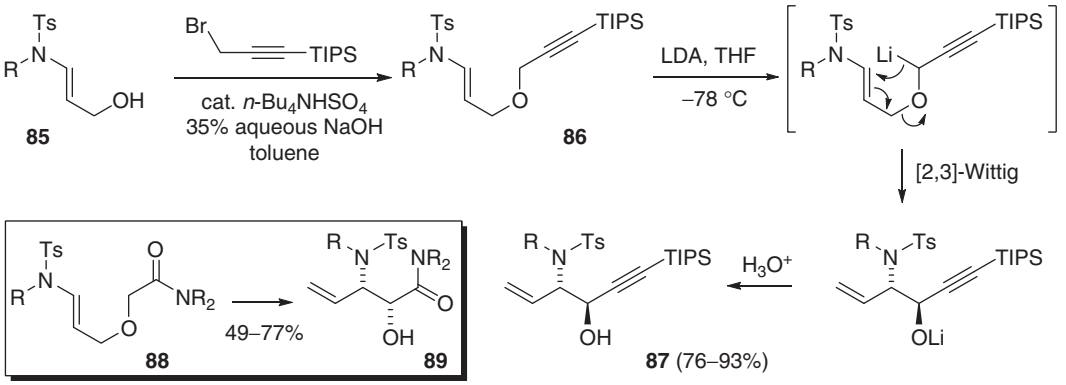


Scheme 22



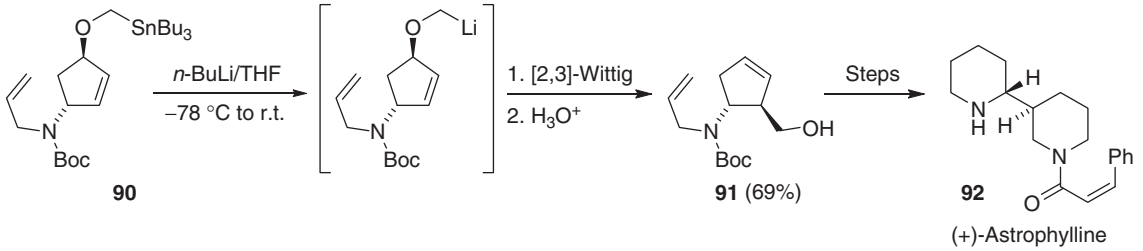
Scheme 23

[2,3]-Wittig rearrangements of (*E*)-3-aza-allylic propargylic alcohol derivatives can provide access to functionalized 1,2-aminoalcohols with high *anti* diastereoselectivity. A one-step propargylation protocol of alcohols **85** was developed under phase transfer conditions with the propargylic bromide, bearing a TIPS (*tert*-butyldiphenylsilyl chloride) group (Scheme 24). The propargylic ethers **86** were obtained in high yields (86–91%). Despite the presence of other potential acidic hydrogens in substrates, metalation at the propargylic position was successfully achieved by treatment with lithium diisopropylamide (LDA) (THF, −78 °C), then the subsequent [2,3]-Wittig rearrangement proceeded cleanly to afford the corresponding 1,2-aminoalcohols **87** in good yields (74–93%) and with high 1,2-*anti* diastereoselectivity (*anti*/*syn* 11:1 to >24:1). Interestingly, 1,2-aminoalcohols **89** of *syn* configuration could be obtained starting from the amide derivative **88**.[25]



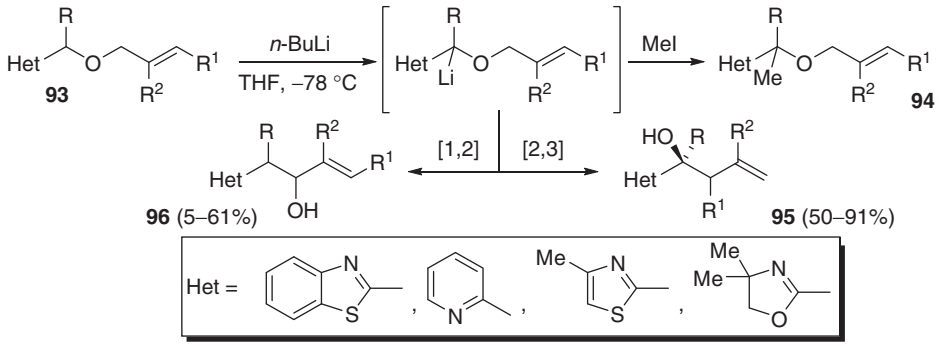
Scheme 24

The first asymmetric total synthesis of (+)-astrophylline **92** was accomplished in Blechert's laboratory. The Still variant of the [2,3]-Wittig rearrangement was used to generate the 1,2-*trans* relationship between the substituents of the key cyclopentene intermediate. The tributylstannylmethyl ether substrate **90** was transmetalated with *n*-BuLi, which initiated the desired [2,3]-sigmatropic shift to afford the expected homoallylic alcohol **91** as a single enantiomer (Scheme 25).[26]



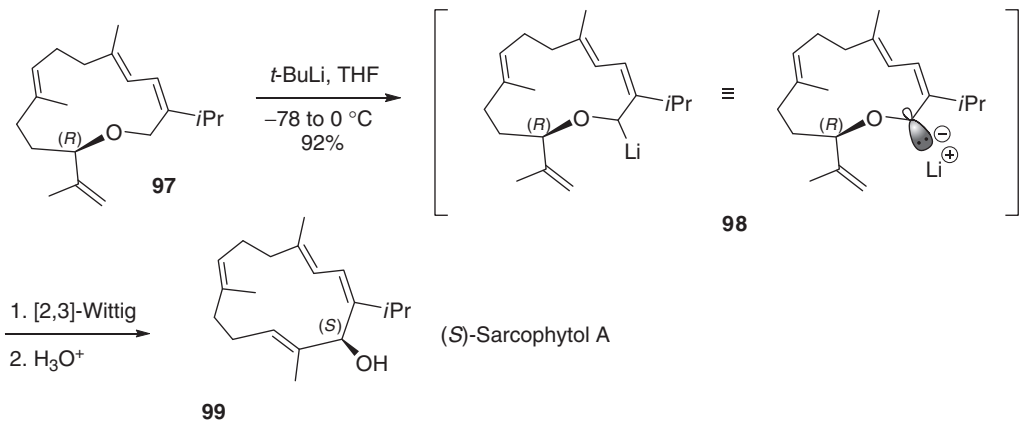
Scheme 25

Lithiation of allyl heteroarylalkyl ethers **93** with *n*-BuLi in THF at $-78\,^{\circ}C$ results in the generation of the corresponding lithiated ethers which can be captured with electrophiles to furnish alkylated compounds **94** (Scheme 26). In the absence of an external electrophile the α-lithiated intermediates undergo a [2,3]- and/or [1,2]-Wittig rearrangement to furnish the homoallylic **95** and allylic alcohols **96** depending on the nature of the heterocyclic system and with good diastereoselectivity. The [2,3]-Wittig rearrangement carried out in the presence of (–)-sparteine produced fairly good enantiomeric enrichments.[27]



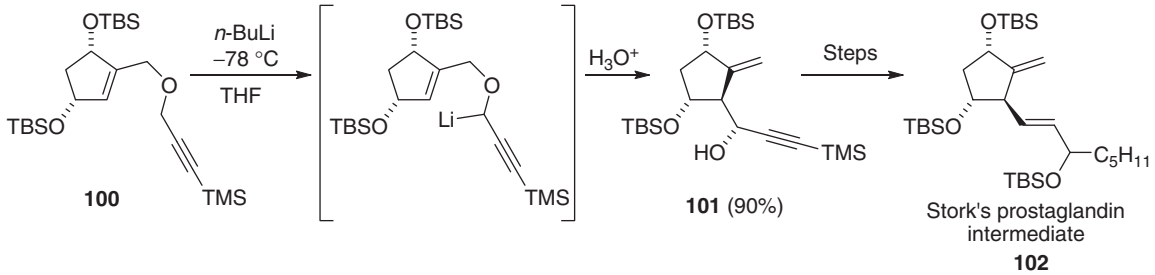
Scheme 26

The final and key step in the total synthesis of both enantiomers of sarcophytols **99** by Fukuyama et al. was a stereospecific [2,3]-Wittig rearrangement. The deprotonation of the macrocyclic bis-allylic ether precursor **97** occurred with complete regioselectivity at the less-substituted position to generate the lithium species **98** (Scheme 27). The rearrangement proceeded in excellent yield and exhibited an unexpectedly high level of stereospecificity even though the substrate was highly flexible. The reaction could occur either via a *syn*- or *anti*-carbanionic intermediate, but the (*S*)-stereochemistry of the product **99** indicated that the *anti*-carbanion was operational.[28]



Scheme 27

A novel approach to the asymmetric synthesis of Stork's prostaglandin intermediate **102** was developed by Nakai et al. This was the first example of asymmetric [2,3]-Wittig rearrangement, in which three contiguous chiral centers were created in a cyclic system. On deprotonation, the rearrangement of the allyl propargyl ether **100** took place in excellent yield and gave rise to a single stereoisomer **101**, which is an intermediate on the route to **102** (Scheme 28). Interestingly, when the Trimethylsilyl (TMS) group was replaced with an amyl group (C_5H_{11}), the stereoselectivity diminished to only 3:1.[29]



Scheme 28

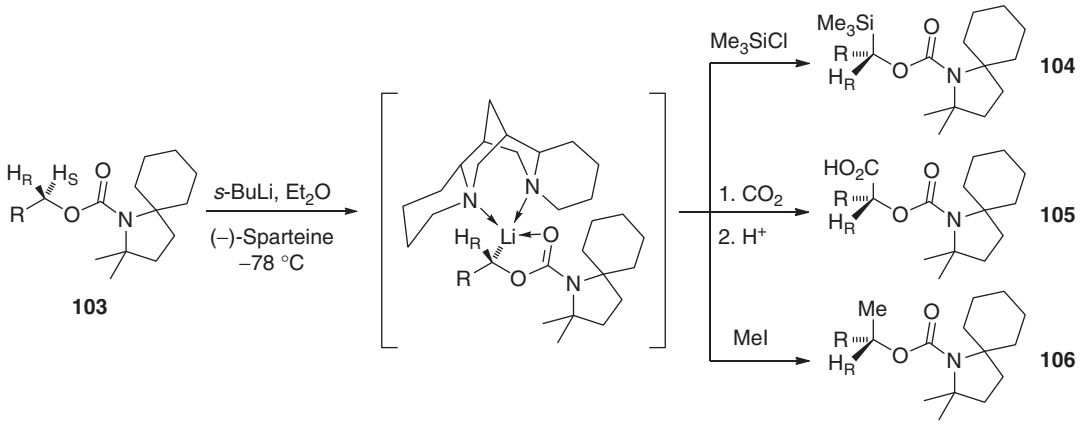
1.14.2.2 α-*O*-Carbamoyl Organolithiums

The carbamoyl group has proved to be by far the best activating and protecting group in the generation of organolithiums α to oxygen. Indeed, the carbamoyl group can be easily introduced, facilitates deprotonation α to oxygen by its electronic and coordinating effects, stabilizes the resulting lithiated intermediate by intramolecular chelation, and finally can be easily removed, being a very good leaving group in nucleophilic substitution reactions. Additionally, it may participate to make the α-lithiated carbamate configurationally stable and, therefore, contributes to determine the stereochemistry of the trapping reactions with electrophiles.

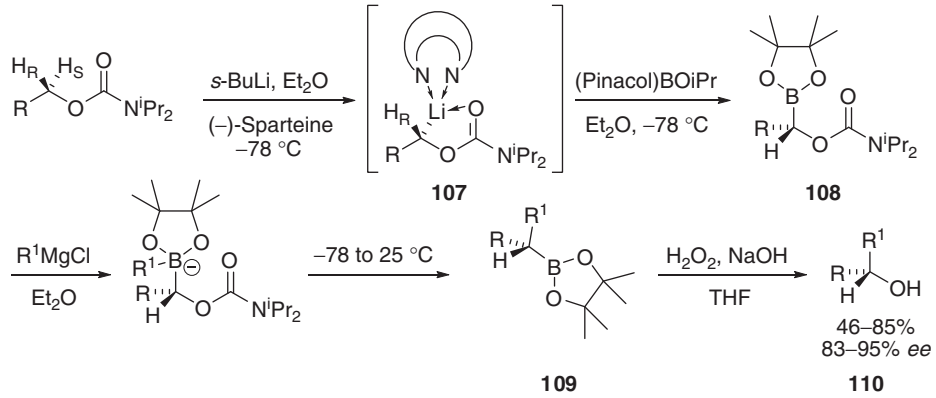
It was in 1990 that Hoppe et al. showed that enantioenriched α-lithium oxyalkylamides can be formed by deprotonating achiral alkyl carbamates **103** with sBuLi in the presence of (–)-sparteine. The α-lithiated species could be easily silylated, methylated, and carboxylated to give stereospecifically compounds **104**, **105**, and **106** (Scheme 29).[30]

Hoppe and coworkers also described the trapping of the lithiated carbamates **107** with borates. Treating the formed α-carbamoyl alkyl boronate **108** with a Grignard reagent to effect the 1,2-metallate rearrangement resulting in the expulsion of the carbamate moiety, followed by oxidation of the boronic ester **109**, gave the corresponding alcohol **110** in high enantiomeric excess (Scheme 30).[31]

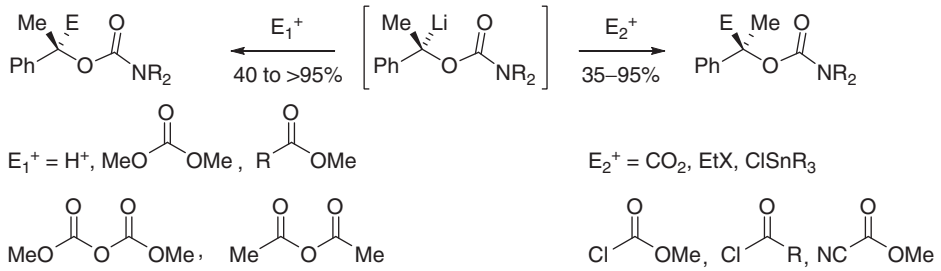
In general, an adjacent π-system gives to the C-Li bond more p-character, increasing the planarity of the organolithium and opening up to a greater extent, both electronically and sterically, possibilities for attack on the rear lobe of the C–Li σ bond. Hoppe carried out a thorough study of the stereochemical course of the reaction of a range of acylating agents and other electrophiles with the configurationally stable tertiary benzylic organolithiums. The stereochemistry of the organolithium is deduced from the presumed retention during deprotonation, and the stereochemistry of the products was proved by comparison with known compounds. In general, retention of configuration is seen when the electrophile has a leaving group capable of coordination to the lithium counterion (MeO, AcO); conversely, inversion is seen with halide or cyanide leaving group or after addition to CO_2 or CS_2 (Scheme 31).[32]



Scheme 29



Scheme 30

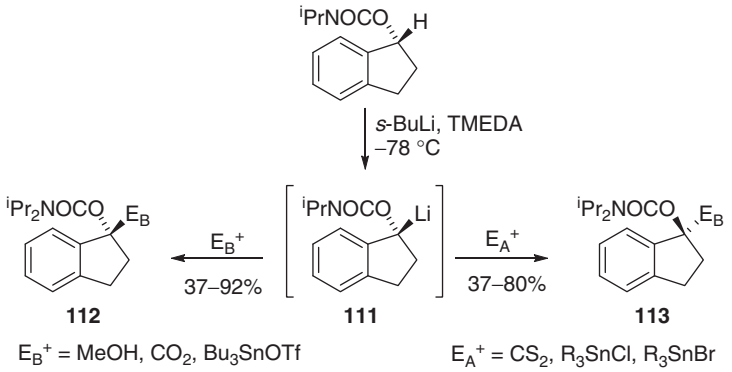


Scheme 31

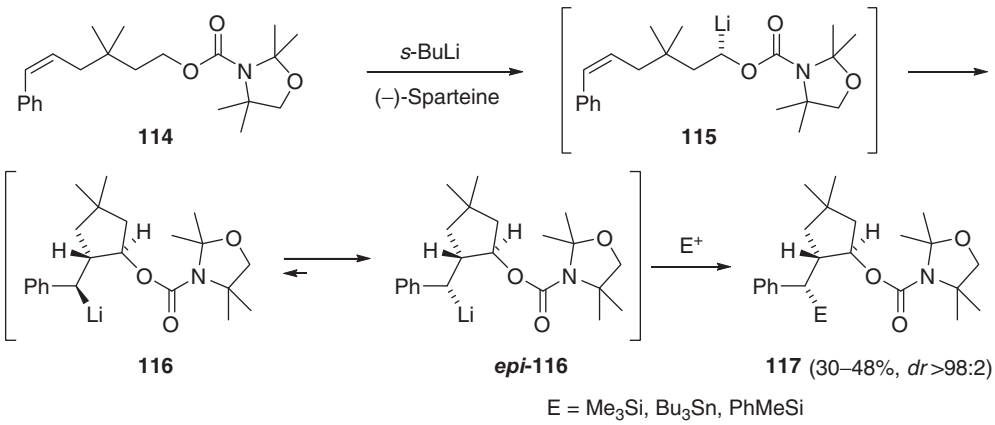
Altering the structure of the benzyllithium by introducing a ring creates indenylcarbamate **111**. Its reactions follow a pattern similar to benzyllithium but with a shift toward retentive substitution **112** or inversion **113** depending on the electrophile (Scheme 32).[33]

Asymmetric deprotonation in the presence of (–)-sparteine could, in principle, give the configurationally defined organolithiums required for comparable stereoselective cyclizations. In the pyrrolidine series, sparteine induces only low levels (<30%) of enantiomeric excess in the cyclization of α-amino organolithiums, but it is rather more effective with α-carbamoyloxy substituents. Deprotonation of **114** using *s*-BuLi-(–)-sparteine gives an organolithium **115** essentially as a single enantiomer, which cyclizes to **116** (Scheme 33). Quenching with an electrophile provides, with an inversion of configuration, the oxazolidinyl cyclopentane **117** with three stereogenic centers.[34]

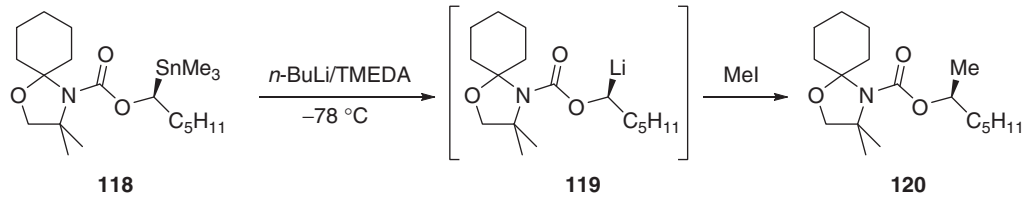
A great configurational stability has been reported for α-*O*-carbamoyl organolithiums of the kind of **119** formed by treating the enantiomerically pure stannane **118** with *n*-BuLi and TMEDA at − 78 °C (Scheme 34). The carbamoyl group plays a crucial role in



Scheme 32



Scheme 33



Scheme 34

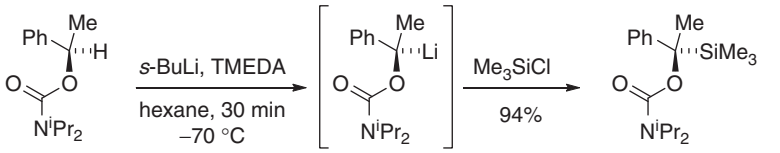
providing stability to the lithiated intermediate because of its EWG property and chelating ability. Methylation to give **120** occurred with the retention of configuration (96% *ee*).[35]

α-*O*-carbamoyl organolithiums have been found to be configurationally stable even when they are benzylic. Indeed, tertiary α-*O*-carbamoyl allyl- and benzyllithiums are configurationally stable for relatively long periods of time. Enantiomerically enriched carbamate **121** (97% *ee*) is lithiated (*s*-BuLi in TMEDA/hexane in 30 min) at $-70\ ^{\circ}C$ and a Me_3SiCl quench gives almost no loss of the enantiomeric purity in the silylated product **122** (Scheme 35).[32,36]

Secondary allylic as well as benzylic α-alkoxyorganolithiums **124**, generated from stannanes **123**, are configurationally unstable on a macroscopic timescale (Scheme 36).[37]

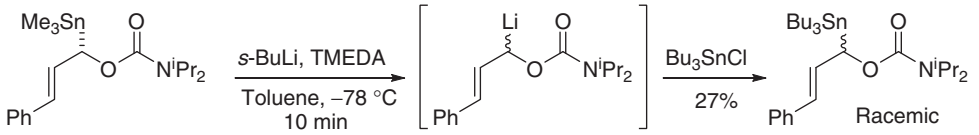
Deprotonation of *O*-alkyl carbamates may be achieved in an enantioselective manner by using *s*-BuLi-(–)-sparteine and the most effective of these reactions employ the oxazolidine system. Enantioselective lithiation of **125** followed by carboxylation and methylation with diazomethane generates the protected hydroxy acid **126** in >95% *ee* (Scheme 37).[38]

This method has been applied to the synthesis of the pheromone (*S*)-sulcatol **130** starting from carbamate **127** through an enantioselective lithiation-methylation sequence to obtain compound **128** (Scheme 38).[38] The oxazolidine protecting group features a safety-catch, which is released by treatment with an acid: the intramolecular assistance to hydrolysis of the carbamate **129** rapidly generates the free alcohol product.



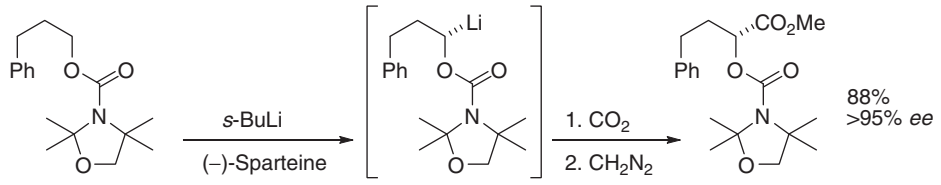
121 **122** (96% *ee*)

Scheme 35



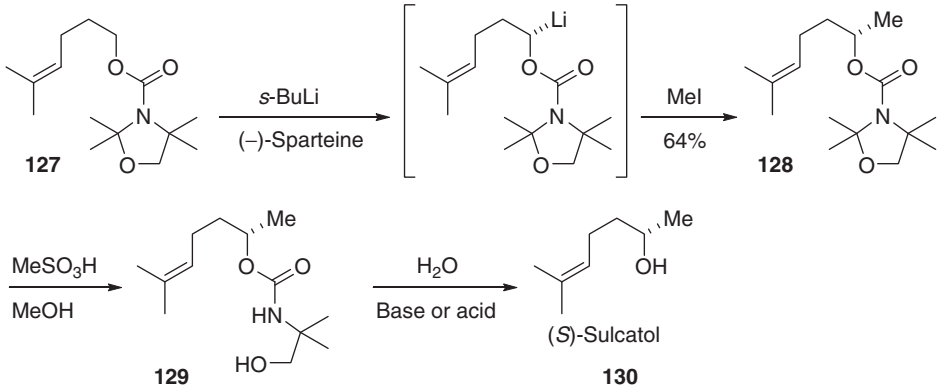
123 **124**

Scheme 36



125 **126**

Scheme 37



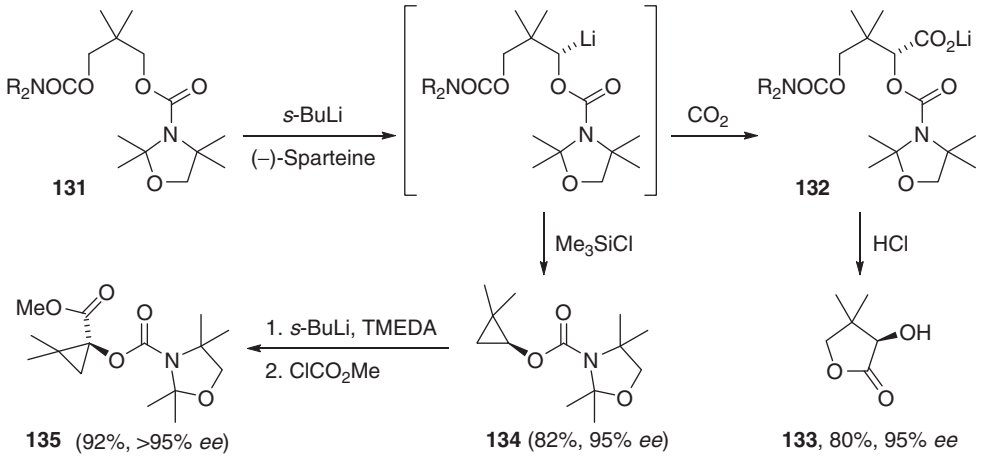
127 **128** **129** **130**

Scheme 38

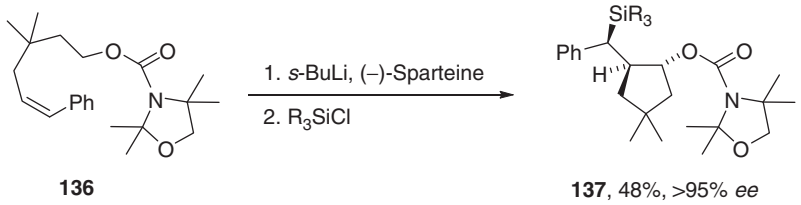
(*R*)-Pantolactone **133** has been prepared in high yield and *ee* from the bis-carbamate **131** after lithiation, carboxylation to **132**, and lactonization to **133**.[39] Me_3SiCl promoted the cyclopropanation reaction of the lithiated bis-carbamate to furnish the cyclopropane derivative **134**, which underwent the stereospecific carboxylation of the ring to give **135** on treatment with *s*-BuLi and then with methyl chloroformate (Scheme 39).

Lithiation with *s*-BuLi/(–)-sparteine of carbamate **136** containing an unsaturated functionality may undergo enantioselective cyclization to give cyclopentane **137** (Scheme 40).[34]

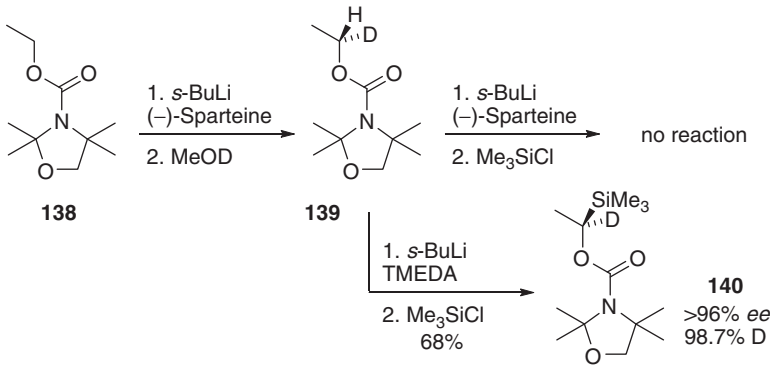
Although the lithiation-deuteration sequence of the alkyl carbamate **138** using *s*-BuLi and (–)-sparteine takes place rapidly to generate **139**, the second deprotonation using the same lithiation conditions does not occur, due to a powerful kinetic isotopic effect (a value >70 at $-78\ ^{\circ}C$) (Scheme 41). The second deprotonation takes place when *s*-BuLi-TMEDA is used as the lithiating agent: the kinetic isotopic effect now ensures that the product **140** retains its deuterium almost entirely. It also ensures that the deprotonation is stereospecific and because of the configurational stability of the intermediate, a single enantiomer of the product **140** is formed.[39]



Scheme 39



Scheme 40

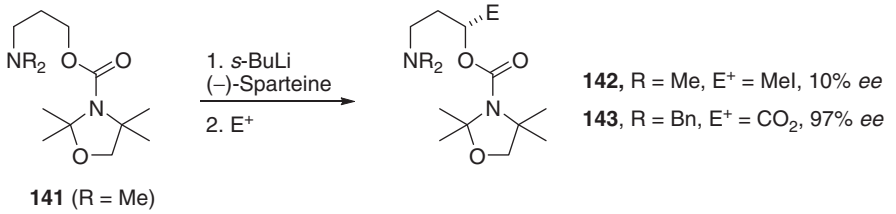


Scheme 41

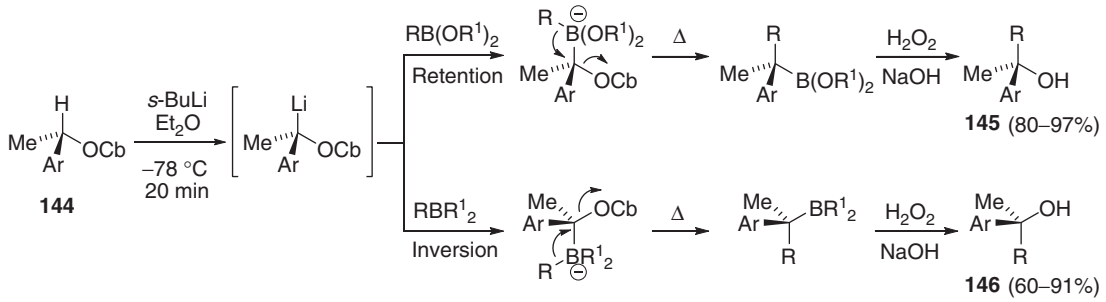
Alkyl carbamates of the kind discussed cannot be deprotonated in the absence of sparteine or TMEDA. The reaction is truly an instance of ligand accelerated catalysis (neither can they be deprotonated by using *n*-BuLi or *t*-BuLi/(–)-sparteine). Furthermore, if the *s*-BuLi/(–)-sparteine complex is first treated with a non-deprotonatable *O*-isopropyl carbamate, it becomes inactive toward deprotonation of further carbamates: presumably a *s*-BuLi/sparteine/carbamate complex is formed irreversibly and it can be deduced that such a complexation is the first step in the deprotonation of other alkyl carbamates.

In the event that the alkyl carbamate contains further lithium-coordinating heteroatoms, enantioselective deprotonation becomes impossible because sparteine is displaced from the lithium in this reactive complex. Because of this, the *N*,*N*-dimethylamine **141** (R=Me) is lithiated with only 10% *ee* to **142**, whereas its dibenzyl analog is lithiated in 97% *ee* to furnish **143**.[39] Most oxygen-containing functional groups do not have this effect (Scheme 42).[40]

Using the methodology based on the sequence lithiation-borylation of carbamates, Aggarwal and his group have developed an enantiodivergent conversion of chiral secondary alcohols into tertiary alcohols.[41] Commercially available (*S*)-1-phenylethanol was converted into the corresponding *N*,*N*-diisopropyl carbamate, which was subjected to deprotonation with *s*-BuLi in Et_2O. Subsequent addition of the borane or boronic ester followed by oxidation gave the tertiary alcohol in good yield and very high enantiomeric ratio (Scheme 43).



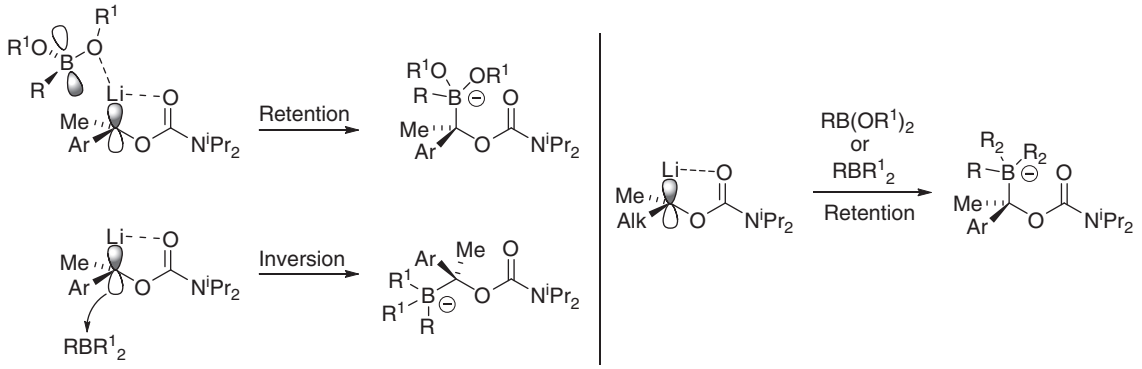
Scheme 42



Scheme 43

A broad range of boronic esters and boranes were explored, in all cases observing high levels of selectivity. The most intriguing outcome was that in all cases the reactions occurred with almost complete inversion of stereochemistry when boranes were used, whereas almost complete retention of stereochemistry was observed with boronic esters. For a broad set of reactions to occur with such complete and yet opposite selectivity for the two sets of related reagents is unique. The consequence is that from a single enantiomer of a carbamate **144** derived from a secondary alcohol, either enantiomer of a tertiary alcohol **145** or **146** can now be prepared in high yield with very high enantioselectivity (Scheme 43).

The origin of this difference in selectivity between the two reagents can be rationalized as follows: in the case of boronic esters, the oxygen of the ester complexes with the lithium of the metallated carbamate and so is delivered on the same face as the metal. In the absence of such complexation, as in the case of boranes, reaction occurs on the face opposite to the metal where there is significant electron density owing to the partially flattened nature of the carbanion (Scheme 44).

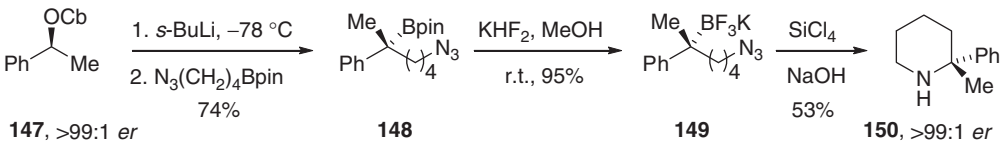


Scheme 44

However, it should be noted that reactions of lithiated alkylcarbamates derived from nonbenzylic primary alcohols occur with complete retention of stereochemistry with both boranes and boronic esters, presumably because in this case the non-mesomerically stabilized carbanion is essentially sp^3 hybridized and has very little electron density opposite to the metal.

Optically active tertiary boronic esters, promptly available by stereoselective lithiation-borylation of carbamates, have become useful versatile intermediates in the asymmetric synthesis of a variety of substances including alcohols, amines, and saturated and unsaturated hydrocarbons. Although common approaches to tertiary amines such as nucleophilic addition to ketimines are often highly substrate-dependent even though occurring with high levels of stereocontrol, the amination of tertiary boronic esters proved to be a very useful asymmetric procedure. Indeed, the tertiary boronic ester **148**, prepared *via* lithiation-borylation of the

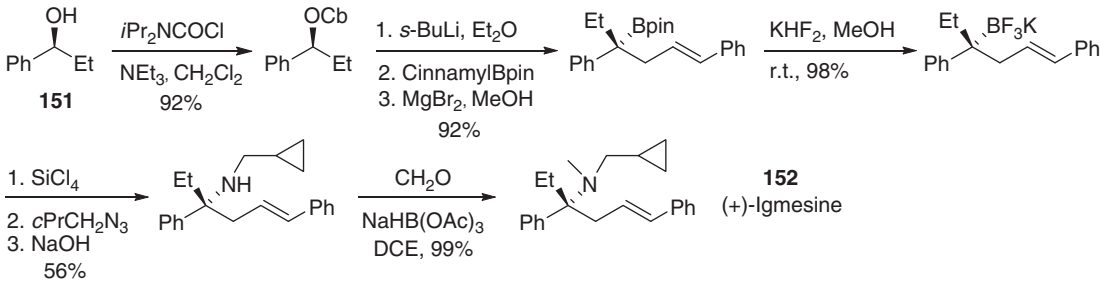
appropriate carbamate **147**, is transformed into the tertiary potassium trifluoroborate salt **149**. Subsequent treatment with $SiCl_4$ in 1,2-dichloroethane furnished the piperidine **150** in very high *er* (Scheme 45).[42]



147, >99:1 *er* **148** **149** **150**, >99:1 *er*

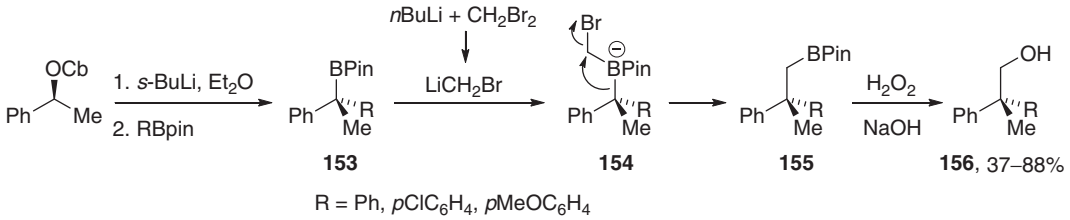
Scheme 45

The synthetic utility of this amination methodology has been applied to the stereocontrolled preparation of the pharmaceutical (+)-Igmesine **152**, a compound that shows significant activity across a spectrum of challenging diseases including depression, cancer, and diarrohea, and that can be prepared starting from a commercially available secondary alcohol **151** (Scheme 46).[42]



Scheme 46

The broad utility of chiral tertiary boronic esters in asymmetric syntheses is nowadays amply demonstrated. Indeed, tertiary boronic esters can be homologated to generate quaternary stereocenters. Following Matteson's homologation protocol for primary and secondary boronic esters,[43] bromomethyllithium, generated from dibromomethane and *n*-BuLi, was added to the tertiary boronic esters **153** to give borate complexes **154** that spontaneously evolve into the borane **155** (Scheme 47).[42] Oxidative workup resulted in the formation of alcohols **156** bearing a quaternary center in excellent enantiomeric ratio. Both electron-rich and electron-deficient aromatic substituents worked well, as did boronic esters bearing an allylic substituent.

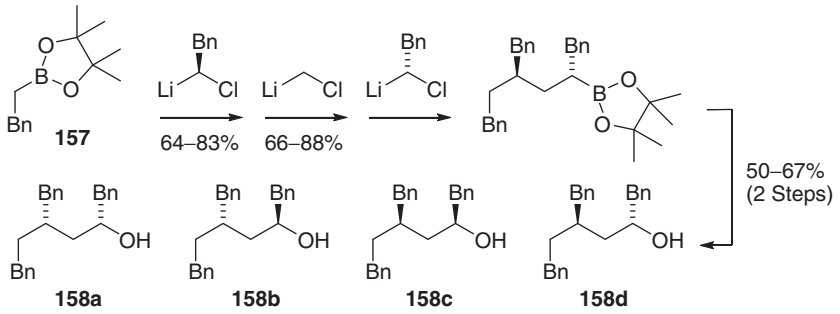


Scheme 47

Compounds with a quaternary center bearing a variety of substituents including alkyl, aryl, vinyl, allyl, and hydroxyalkyl groups have been prepared.[44]

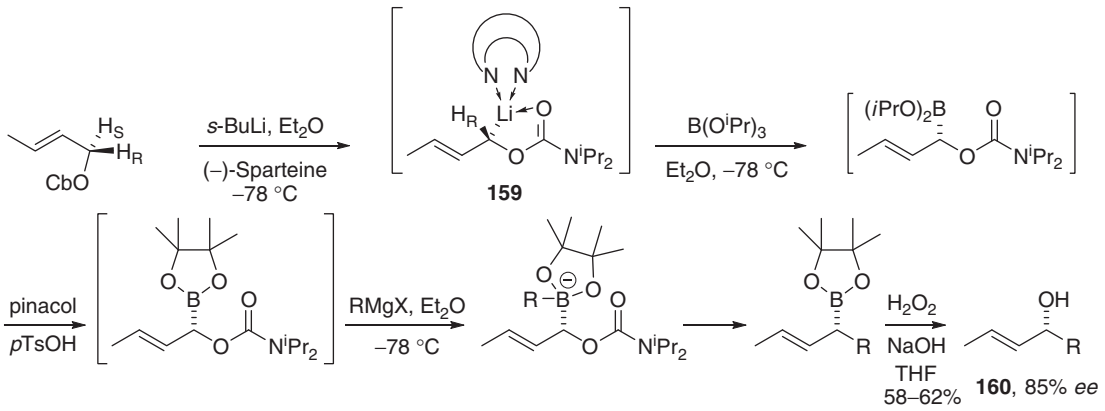
The homologation of chiral boronic esters introduced by Matteson[43] and coworkers represents a landmark contribution in the field of asymmetric synthesis. However, despite achieving exceptionally high enantioselectivities with simple, readily accessible reagents, the methodology has not been widely adopted, likely because of its substrate control nature. Indeed, the stereogenic center created during the homologation is dictated by the substrate diol of the boronic ester. If the opposite stereoisomer is required, a three-step sequence is needed to invert (by exchange) the diol stereochemistry. To obviate this, the reagent control strategy has been introduced by several authors. Blakemore et al. described the application of Hoffmann's α-chloro Grignard reagents to effect iterative homologation of boronic esters. Reaction of pinacol boronates with putative enantioenriched α-chloroalkyllithium species, generated *in situ* from homochiral α-chloroalkylsulfoxides by sulfoxide ligand exchange with *t*-BuLi in PhMe at $-78\ ^{\circ}C$, gave chain-extended boronic ester products with generally excellent stereochemical fidelity. Iteration of this stereospecific reagent-controlled homologation (SRCH) process, starting from the commercially available boronate **157**, enabled

the programmed synthesis of all four stereoisomers of a stereodiad-containing model system (4-benzyl-1,6-diphenylhexan-2-ol) **158a–d** with *er* ≥ 97:3 in all cases (Scheme 48).[45]



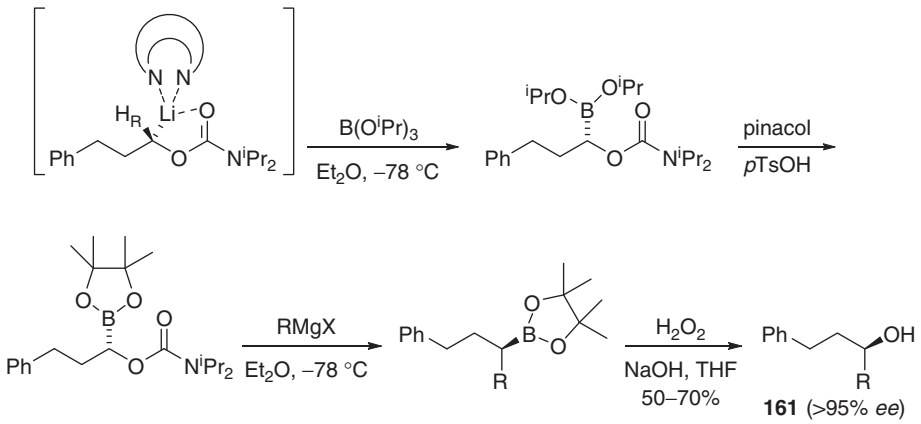
Scheme 48

Hoppe-type lithiated carbamates **159** represent a class of chiral carbenoids; applied to borates and boronates they give access to optically active allylic alcohols **160** (Scheme 49).[31]



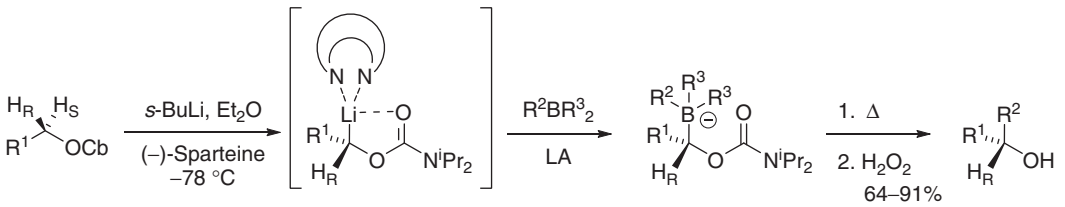
Scheme 49

Following the same procedure it was possible to prepare secondary alcohols **161** from primary alcohols (Scheme 50).



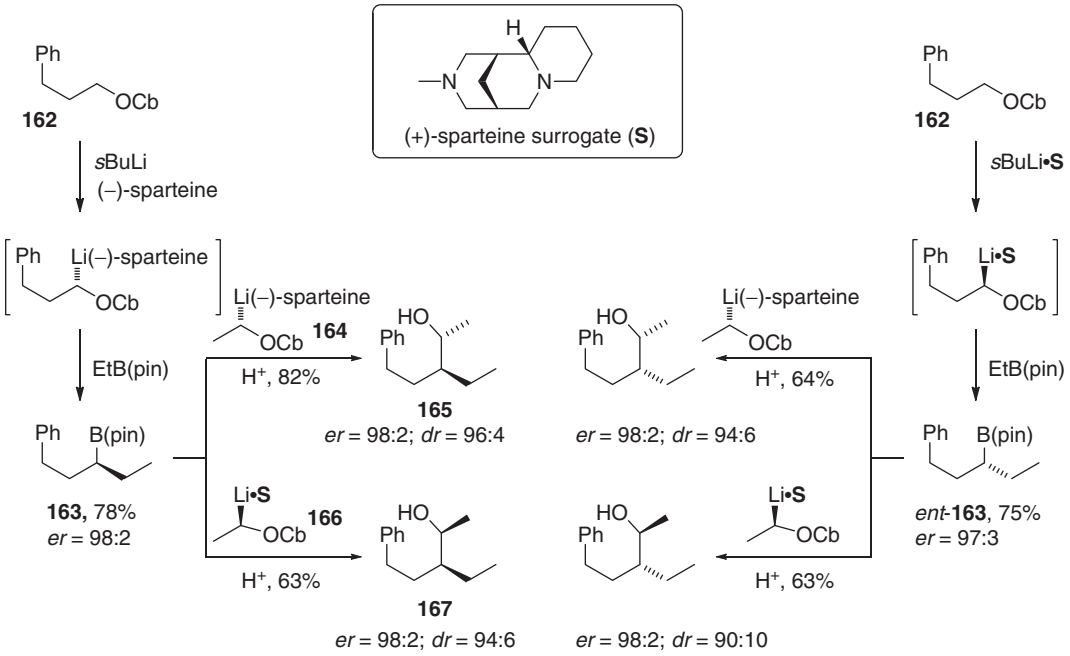
Scheme 50

The direct reaction of lithiated carbamates with boranes or boronates for the iterative process of homologation has been reported for the first time by Aggarwal and coworkers. Both the reactions using boronates or boranes proceed with retention of configuration (Scheme 51).[46]



Scheme 51

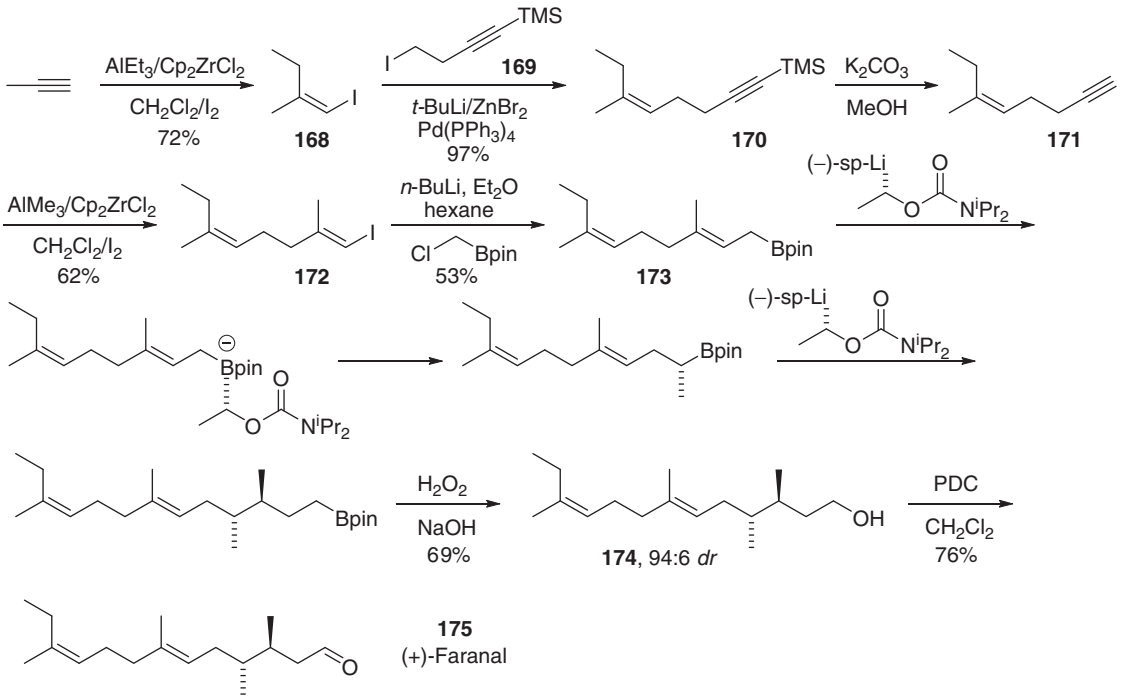
In the iterative homologation process, lithiation of **162** (in the presence of (–)-sparteine) with subsequent trapping with EtB(pinacol) gave the desired boronic ester intermediate **163** in 78% yield and 98:2 *er* (Scheme 52). Reaction of boronic ester **163** with lithiated carbamate **164** gave, after oxidative workup, alcohol **165** as a 96:4 mixture of diastereomers with *er* >98:2 (major diastereomer **165**; Scheme 52). The other diastereomer **167** is potentially accessible by using the opposite enantiomer of the lithiated carbamate **166**. In practice, this goal was easily achieved using O'Brien's enantiomeric (+)-sparteine surrogate derived from (–)-cytisine. Indeed, O'Brien and coworkers have shown that diamine (+)-sparteine surrogate (**S**) can be effectively used in Hoppe-type lithiation of carbamates to deliver the opposite enantiomer obtained with (–)-sparteine with high enantiomeric ratio. Thus, using the opposite enantiomeric carbamate **166** in the same process gave the alternative diastereomer **167** with similarly high diastereo- (94:6 *dr*) and enantioselectivities (*er* > 98:2; Scheme 52). The enantiomeric pair to **165** and **167** was readily obtained with similarly high *dr* and *er* by using the same protocol but starting from ent-**163**, which was itself derived from the first homologation using O'Brien's enantiomeric (+)-sparteine surrogate (Scheme 52). These levels of enantio- and diastereoselectivity clearly show that the reaction is dominated by reagent control with no 'matching' issues affecting the outcome of the second homologation, even though adjacent stereocenters are created.[46]



Scheme 52

Based on lithiation-borylation sequence of carbamates, Aggarwal and coworkers have developed a methodology for the stereocontrolled synthesis of carbon chains bearing contiguous methyl groups and applied it to a short synthesis of (+)-faranal **175** (Scheme 53).[47] This multiple-homologation process is akin to a molecular assembly line in which successive groups are added to a growing chain with control of a relative and absolute stereochemistry. Remarkably, these successive additions can be carried out in one pot with improved efficiency (yield and manpower!) and without detriment to selectivity.

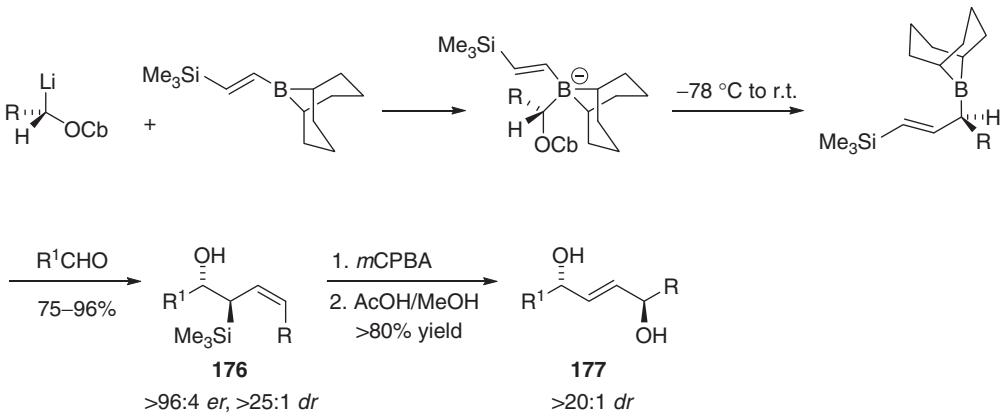
The route began with a zirconium-catalyzed ethyl alumination of propyne followed by quenching with I_2, to furnish the *E* vinyl iodide **168** (Scheme 53). Subsequent Negishi cross-coupling with the alkyl iodide **169** gave the unsaturated alkyne **170**. Desilylation to **171** followed by a second zirconium-catalyzed carboalumination and trapping with I_2 gave the vinyl iodide **172**, which was lithiated and coupled with the chloromethyl boronic ester to furnish **173** with complete *E* selectivity. Application of the one-pot, triple-homologation sequence then furnished alcohol **174** in 69% yield, >98:2 *er*, 94:6 *dr*, >98:2 *E*/*Z*. Finally, the alcohol **174** was converted into (+)-faranal **175** by pyridinium dichromate (PDC) oxidation. The asymmetric, fully



Scheme 53

stereocontrolled synthesis of (+)-faranal was completed in just six steps from propyne, a substantial improvement over previously reported synthesis.

Lithiated carbamates have been successfully used for the synthesis of allyl silanes **176** and ene-diols **177** (Scheme 54).[48]

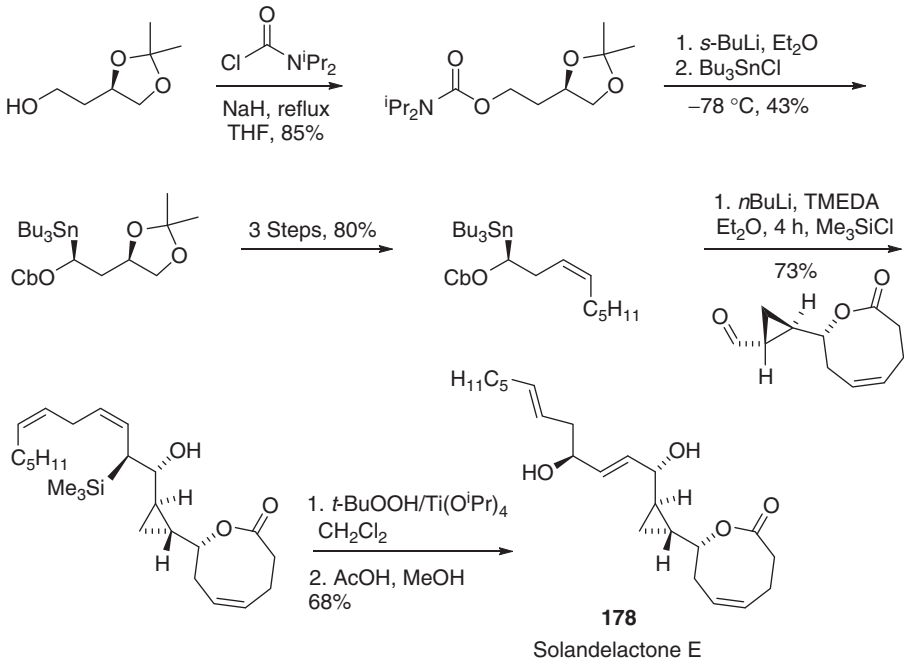


Scheme 54

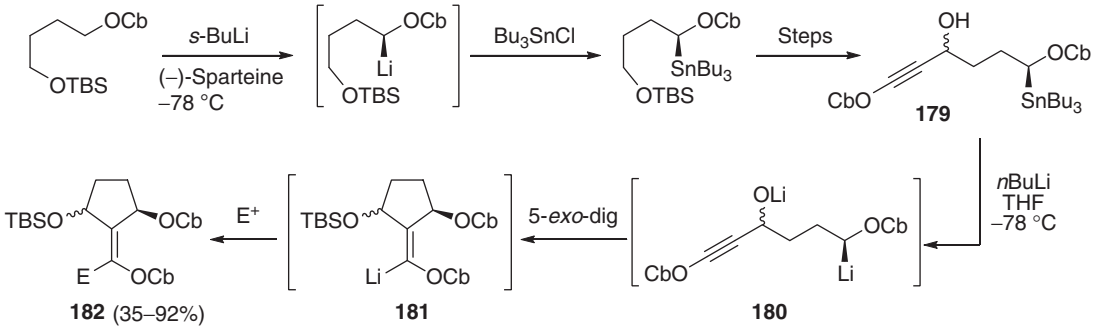
The total synthesis of solandelactone E **178** starting from the chiral lithiated carbamate to form a scalemic α-allyl-9-BBN reagent has been also reported. The synthesis started from the 1,2-acetonide of 1,2,4-butanetriol (Scheme 55).[48]

The configurational stability of α-oxygen lithiated carbamates has been exploited in the highly *trans*-selective cyclocarbolithiation of a lithiated alkynyl carbamate **180** utilizing lithiodestannylation of **179** to highly enantioenriched protected 2-alkylidene cyclopentane-1,3-diols **182**, bearing a masked carbonyl group (Scheme 56). The ring closure of the α-lithiated 4-substituted 5-hexynyl carbamate **180**, through the vinillithium **181**, proceeds with complete regioselectivity (5-*exo*-*dig* exclusively), avoiding the prior use of the toxic reagent HMPA.[49]

α-Metallo-carbamate chemistry introduced in 1980 by Hoppe and coworkers have become very useful chiral carbanionic synthons which have permitted the development of new strategies in asymmetric synthesis.

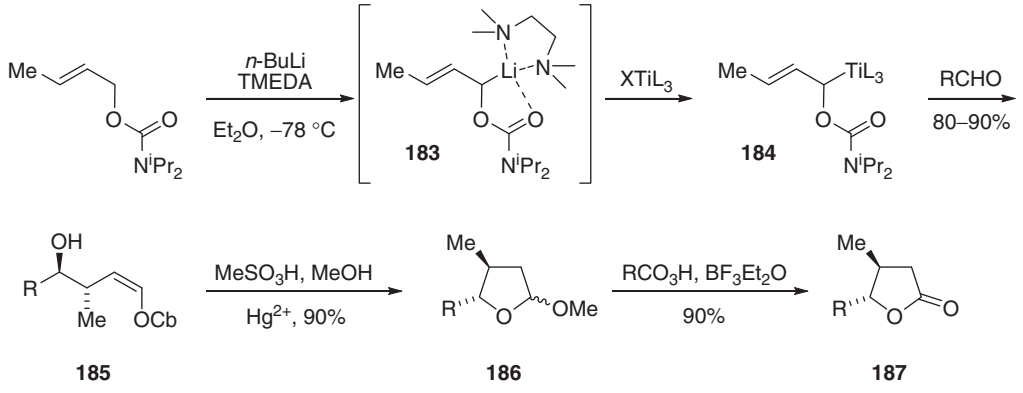


Scheme 55



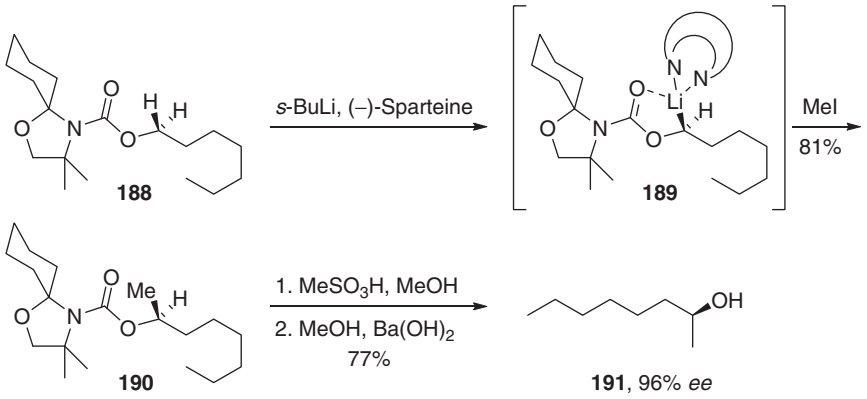
Scheme 56

α-Metallated 2-alkenyl *N,N*-diisopropylcarbamates are recognized to be valuable homoenolate equivalents. In particular, after exchange of the lithium ion with titanium [TiL_3 = Ti(O*i*-Pr)$_3$, or Ti(NEt)$_3$] to give **184** from **183**, the carbonyl addition proceeds with high regio- and diastereoselectivity leading to **185** (Scheme 57).[5] Mercuric acetate catalyzed methanolysis affords γ-lactol ethers **186**, which are oxidized to yield racemic 3,4-trans-butanolides **187**.[5] The sequence is outlined in Scheme 57 for a typical 'homoaldol reaction,' starting with the (*E*)-butenyl carbamate.[50]



Scheme 57

Subjected to lithiation with *s*-BuLi/(–)-sparteine, the carbamate **188** derived from a cyclohexane-spiro-l,3-oxazolidine generates the *s*-BuLi/(–)-sparteine complex which undergoes an efficient enantiotopos-differentiation to form the configurationally stable lithium (*S*)-α-oxyalkanide **189** (Scheme 58).[31] Methylation to **190**, as well as carboxylation, or stannylation, proceeds with >95% *ee*. It seems that these are general reactions, because the high enantioselectivity holds for all alkyl carbamates (heptyl, ethyl, butyl, isobutyl ester) (Scheme 58). The final cleavage of carbamate moiety furnished the secondary alcohol **191** with good optical purity.



Scheme 58

1.14.2.3 α-Lithiated Cyclic Ethers

1.14.2.3.1 α-Lithiated aryloxiranes

Among the oxygen-stabilized carbanions, α-lithiated oxiranes represent a special class of organolithiums for exhibiting both nucleophilic and electrophilic behavior. Such ambiphilic character has to be ascribed to the strongly polarized C – Li bond on the strained three-membered ring thus giving the α-lithiated oxiranes the bias to undergo ring-opening reactions through 'carbene-like' (or 'carbenoids') species.[51] The structure of a metalated epoxide is intermediate in nature between the structures (**A**) and (**B**) (Figure 2).

Figure 2 Carbanionic (**A**) and carbenoid (**B**) structures of an α-lithiated epoxide.

The existence of this intermediacy is supported by computational studies which have shown that the α – C – O bond of oxirane elongates by ~12% on α-lithiation.[52] Furthermore, experimentally, the α-lithiooxycarbene (**D**) derived from diazirine (**C**) returned cyclopentene oxide among its decomposition products; indeed, computational studies suggest that the intermediate is in nature between an α-lithiocarbene (**D**) and the lithiated epoxide (**E**) (Figure 3).

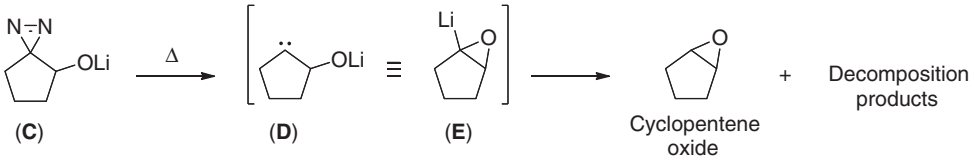
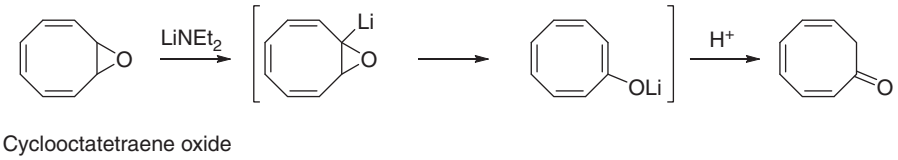


Figure 3 Experimental evidence of ambiphilic character (carbanionic/carbenoid) of oxiranyllithiums.

The existence of a metalated oxirane was first proposed by Cope and Tiffany[53] to explain the rearrangement of cyclooctatetraene oxide to cycloocta-2,4,6-trienone on treatment with $LiNEt_2$ (Figure 4). It was suggested that lithiated epoxide rearranged to enolate, which on protic workup furnished the ketone.

The first experimental evidence for the existence of metalated epoxides was reported by House and Ro in the lithiation-deuteration sequence carried out on *cis*- and *trans*-α-methyl-β-(phenylcarbonyl)acetophenone.[54] The intermediacy of the oxiranylanion was proved, and the issue of its configurational stability was also highlighted.

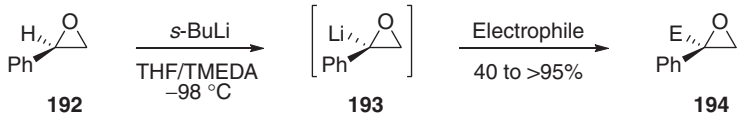


Cyclooctatetraene oxide

Figure 4 Isomerization of lithiated cyclooctatetraene oxide.

Due to such chameleon-like character α-lithiated epoxides undergo a variety of transformations; most simply, they can act as classical nucleophiles and react with a range of electrophiles to give more highly substituted epoxides, which constitute an attractive route to such compounds. When lithiated, the ring strain of the three-membered ring remains important and combined with the weakening of the α–C–O bond, due to its greater polarization, make lithiated epoxides a highly eletrophilic species. Therefore, they react with strong nucleophiles thus entering a variety of reactions including isomerization to enolates and carbonyl compounds, C–H and C–C insertions to give alcohols, cyclopropanation on suitably positioned C–C double bonds, reductive alkylation, and eliminative dimerizations.[51]

Treatment of optically active (*R*)-styrene oxide **192** with *sec*-Butyllithium at –98 °C in THF resulted in the smooth formation of **193**, a useful nucleophile that can be functionalized by reaction with alkyl halides, ketones or aldehydes to obtain more substituted arylepoxides **194**, thus leaving the absolute configuration at the benzylic carbon unaffected (**Scheme 59**) (*see* Chapter 1.16).[55]

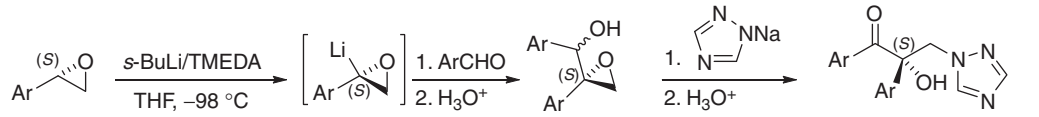


192 **193** **194**

Electrophile = D_2O, MeI, BnBr, $CH_2=C(CH_3)CH_2$, R_2CO, ArCHO

Scheme 59

The importance of such aryloxiranyl-anion methodology, developed by Florio and coworkers, was highlighted by employing the organolithium **196** as key intermediate in the construction of the quaternary carbinol center (**Scheme 60**) of the antifungal agent **198**. The straightforward synthesis started with the lithiation of the oxirane (*S*)-**195** and subsequent coupling with *p*-chlorobenzaldehyde to give a diastereomeric mixture of epoxy alcohols **197** (*dr* = 66/34); the ring-opening with 1,2,4-triazole sodium salt and Swern-oxidation furnished the α-hydroxy ketone (*S*)-**198** as a single enantiomer in 59% overall yield.



195 **196** **197** **198** (59% Overall yield)

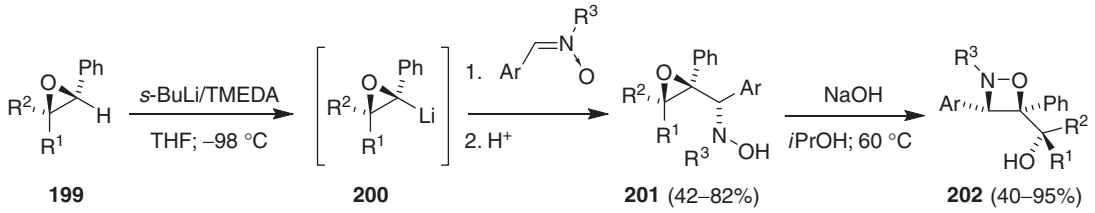
Ar = *p*-ClC_6H_4

Scheme 60

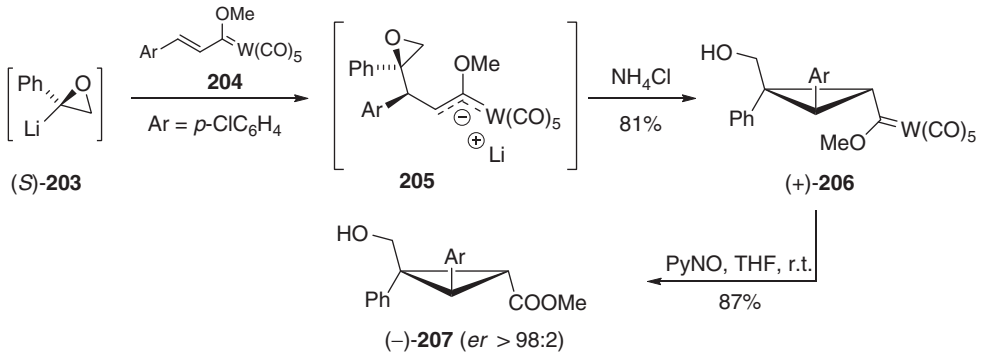
The aryloxiranyl-anion methodology was also applied to the stereospecific synthesis of 1,2-oxazetidines (**Scheme 61**).[56] Enantiopure α-lithiated aryloxiranes **200**, generated from **199**, reacted with aromatic nitrones to give epoxyhydroxylamines **201** which could be efficiently cyclized to the corresponding 1,2-oxazetidines **202** under basic conditions for NaOH/iPrOH.

The reaction of α-lithiated aryloxiranes **200** with aromatic nitrones represents a special case in the chemistry of such organolithiums since, in addition to the complete stereoretention at the lithiated carbon, a very high asymmetric induction at the newly formed stereogenic center was observed (**Scheme 61**). This result is noteworthy, considering that the addition of lithiated aryloxiranes to aldehydes and nonsymmetric ketones often results in nearly equimolar mixtures of diastereoisomers. A simple model for the explanation of the observed diastereoselectivity has been proposed by the authors:[56] a five-membered cyclic transition state, having minimized steric repulsions, should be the favored one on the reaction pathway. An asymmetric version of the above strategy, starting from enantioenriched aryloxiranes **199**, has been applied to the synthesis of both epoxyhydroxylamines **201** and hydroxyalkyl-1,2-oxazetidines **202** (98/2 *er*).

Lithiated epoxides can be employed as nucleophiles in MIRC (Michael Initiated Ring Closure) reactions, as demonstrated by the asymmetric synthesis of cyclopropanes **207** (**Scheme 62**).[57] Enantiomerically enriched lithiated styrene oxide (*S*)-**203** reacts with α,β-unsaturated Fischer carbene complexes **204** to afford, through a conjugate addition, intermediate **205** which cyclizes into functionalized cyclopropanes **206** in enantiopure form. The process is remarkable for its high diastereoselectivity (> 98/2 *dr*) and



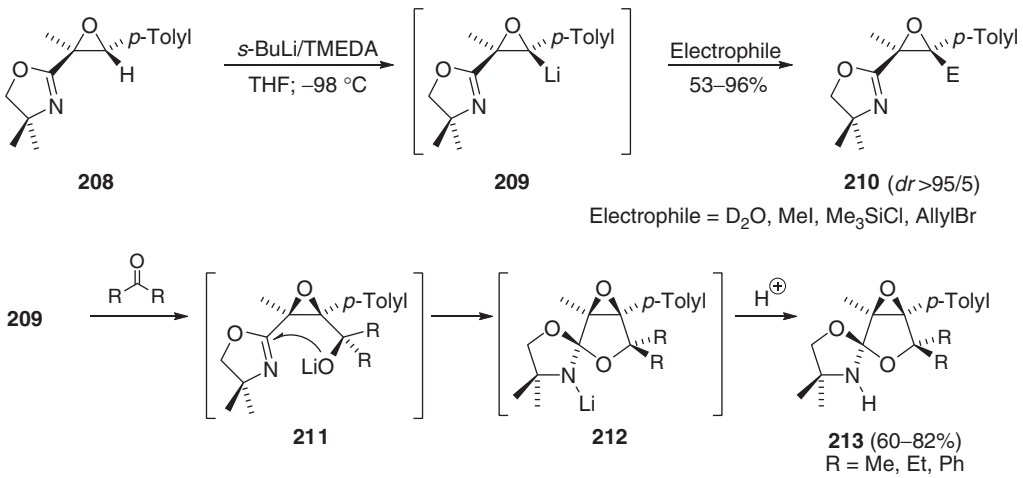
Scheme 61



Scheme 62

for the regioselective addition of the organolithium to C–C double bond rather than to carbonyl. The mild oxidation of the organometallic functionality with pyridine *N*-oxide at room temperature resulted in the formation of the corresponding methyl carboxylate **207**.

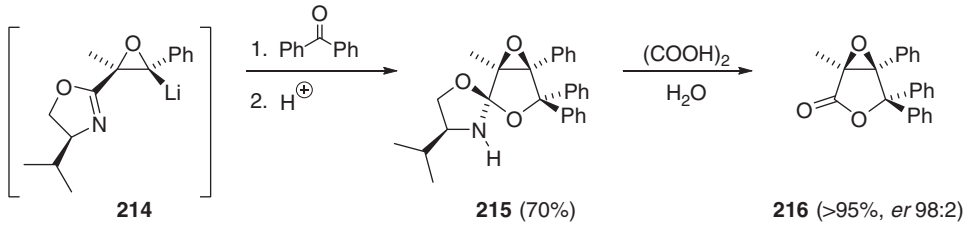
The synthetic utility of α-lithiated aryloxiranes increases very much when they bring functional groups on the three-membered ring. An example is represented by the α-oxazolinyl-substituted oxirane **208** that can be easily functionalized, in a stereospecific manner, on lithiation of the benzylic carbon to give **209** and trapping with electrophiles (Scheme 63).[58] Interestingly, such organolithium proved to be much more chemically stable at −98 °C (for several hours) than lithiated styrene oxide, whose decomposition started after one hour approximately. The presence of the oxazoline nitrogen atom in the lithium coordination sphere plays a role in the stabilization of the organolithium **209**.



Scheme 63

On treatment with alkyl halides or TMSCl, **209** was stereospecifically converted into the corresponding tetrasubstituted epoxides **210** (Scheme 63). When aliphatic and aromatic ketones were used as electrophiles in the coupling with **209**, a two-step process afforded spirocyclic compounds **213** with high diastereoselectivity, most likely resulting from an intramolecular nucleophilic addition of the lithium alkoxide **211** to the C – N double bond to give lithiated spirocyclic compound **212** (Scheme 63).

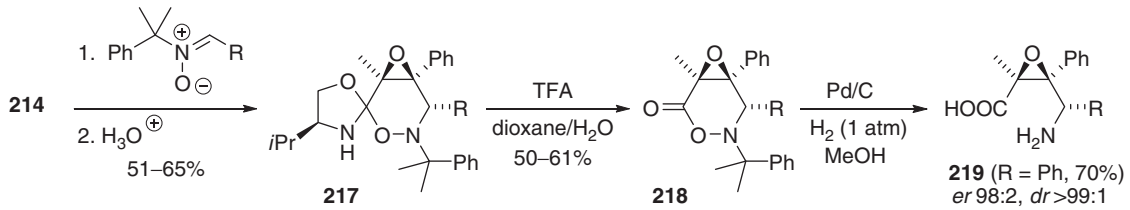
The 2-oxazoline ring played a crucial role as chiral auxiliary for the preparation of the enantiopure precursor of **214** utilized in the asymmetric version of the above reaction. In fact, treatment of enantiomerically enriched α-lithiated epoxide **214** with benzophenone resulted in the formation of spirocyclic compound **215** obtained as a single diastereoisomer with high enantiopurity (Scheme 64). Spiro-condensed 1,3-oxazolidine derivatives such as **215** can be easily hydrolyzed to the corresponding α,β-epoxy-γ-butyrolactones which are useful synthons for the synthesis of biologically active compounds such as (+)-cerulenine,[59] epolactaene[60] or in general α-methylenebis-γ-butyrolactones.[61]



214 **215** (70%) **216** (>95%, *er* 98:2)

Scheme 64

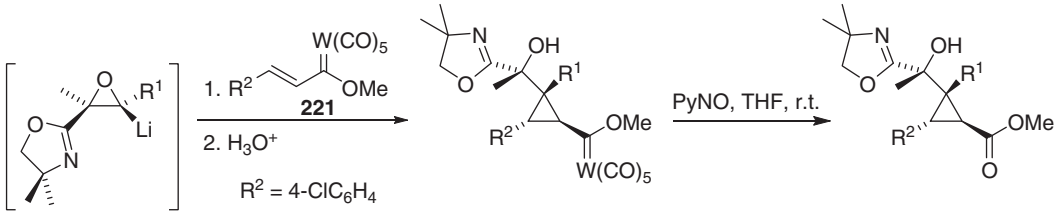
When the enantiomerically enriched organolithium **214** was coupled with aromatic nitrones, spirocyclic compounds **217** were obtained in moderate to good yields (Scheme 65).[62] Whereas the C – C bond formation occurred in a highly stereoselective manner, the closure to 1,2-oxazine derivative **217** gave a mixture of diastereomers. However, the removal of chiral auxiliary by hydrolysis with TFA resulted in the formation of 1,2-oxazin-3-one derivatives **218** in moderate yields and as sole enantiomers. The final reductive deprotection of the nitrogen atom was contextual to the reduction of the weak N – O bond and gave the rare α,β-epoxy-γ-aminoacids **219** in enantiopure form.



217 **218**

Scheme 65

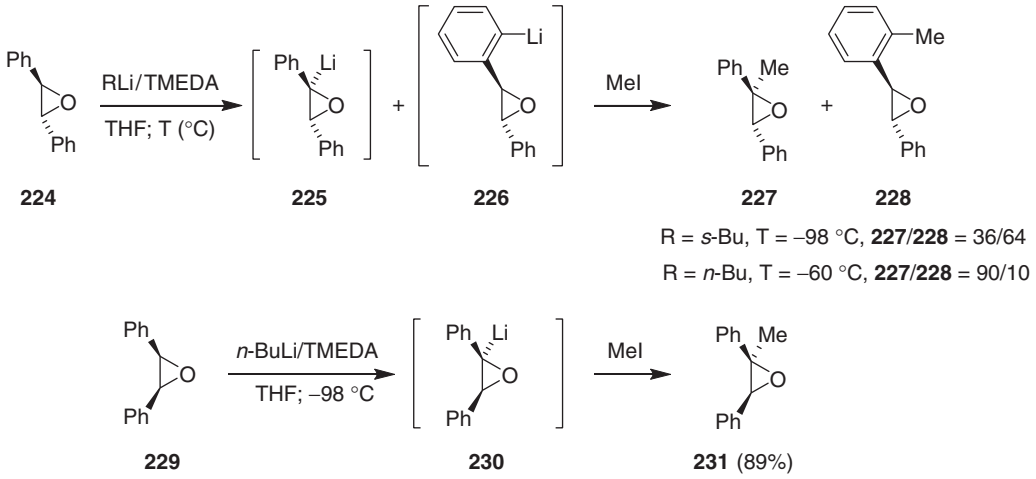
The coupling of the oxazolinyl-substituted oxiranyllithium **220** with the Fischer carbene complex **221** resulted in the formation of polyfunctionalized cyclopropane **222**, following an MIRC reaction (Scheme 66).[63] It's worthy of note that by combining the configurational stability of the organolithium to its highly stereoselective addition to the Michael acceptor it was possible to obtain only one of four possible diastereoisomers of the cyclopropane derivative **222**. The transformation of organo-tungsten compound **222** in the ester **223** was obtained with the mild oxidant pyridine–*N*–oxide (PyNO) in THF at room temperature.



220 **222** (63%, *dr* > 98:2) **223** (81%)

Scheme 66

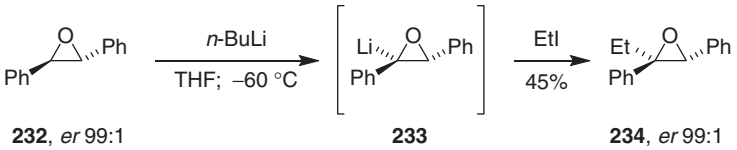
1,2-Disubstituted phenyloxiranes, such as *trans*- and *cis*-stilbene oxides **224** and **229** could be lithiated by *n*-BuLi (Scheme 67) at low temperature (– 98 °C).[64] In particular, treatment of **224** with alkyllithiums (*s*-BuLi or *n*-BuLi), followed by quenching with



Scheme 67

MeI, resulted in the formation of the expected α-methylated epoxide **227** (24–79%) from **225** together with the *ortho*-substituted epoxide **228** (9–43%) from **226**. A marked regioselectivity dependence on temperature and base was found. If the reaction is performed at −98 °C with *sec*-butyllithium as the base and TMEDA as the lithium-ligand, the metalation of the phenyl ring is preferred (*ortho*/*alpha* = 64/36). In contrast, the employment of *n*-BuLi at −60 °C in THF for 2 h favored α-lithiation (*ortho*/*alpha* = 10/90). In both cases the use of TMEDA was beneficial. Under the latter conditions, the benzylic position of **224** could be regioselectively functionalized with many electrophiles to obtain in good yields trisubstituted epoxides with *trans*-geometry. Organolithium **225** proved to be configurationally stable.

In contrast, *cis*-stilbene oxide **229**, when treated with *n*-butyllithium, was regioselectively lithiated at the benzylic position (Scheme 67); the coupling reaction of **230** with MeI furnished exclusively the product **231**. Moreover, the *cis* isomer underwent a complete deprotonation in 30 min at −98 °C, the *trans* isomer was lithiated in only 88% conversion after 2 h at −60 °C. An asymmetric version of the above methodology was accomplished by submitting optically active *trans*-(*R*,*R*)-**232** to the reaction conditions which favor α-deprotonation (Scheme 68); the coupling reaction of the configurationally stable (*R*,*R*)-**233** with EtI gave the highly enantiomerically enriched trisubstituted oxirane derivative **234**.[64]



Scheme 68

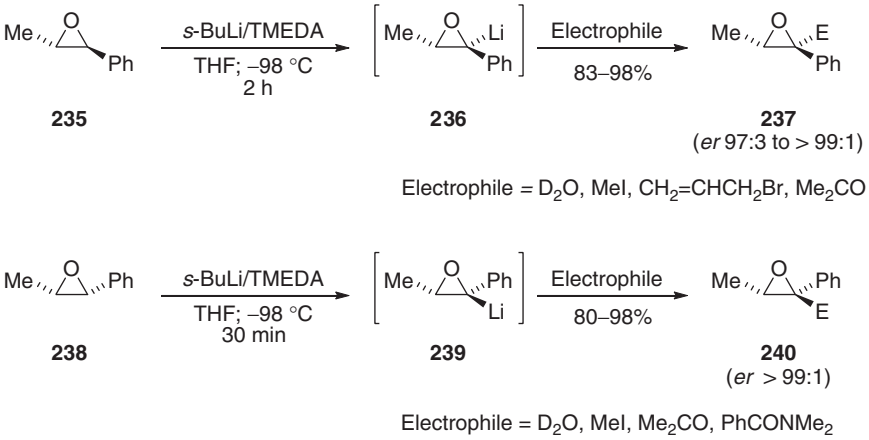
The influence of alkyl substituents in the lithiation of phenyloxiranes has been also studied. Treatment of **235** with *s*-BuLi and TMEDA at −98 °C furnished the expected oxiranyllithium **236** which was coupled with electrophiles with retention of configuration, thus allowing the stereospecific synthesis of trisubstituted epoxides **237** (Scheme 69).[65]

The reactivity of epimeric *cis*-(1*S*,2*R*)-**238** showed very similar results, since it could be lithiated by *sec*-butyllithium at −98 °C and the corresponding (1*S*,2*R*)-**239** trapped with electrophiles to give highly enantiomerically enriched epoxides **240** with retention of the configuration at the benzylic carbon. As observed in the case of other *cis*-epoxides (*vide supra*), *cis*-(1*S*,2*R*)-**238** was deprotonated faster than the epimeric *trans*-(1*S*,2*S*)-**235** (Scheme 69).

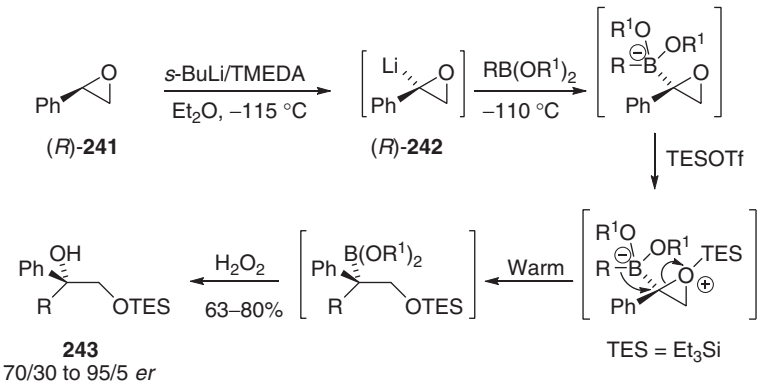
The configurational stability of these organolithiums can be dramatically influenced by the electrophile used to trap it. In fact, despite the fact that α-lithiated styrene oxide (*R*)-**242** retains its configuration when coupled with a large number of electrophiles, the stereochemical information was lost when it was added to boronic esters in THF at −98 °C, leading to racemic diols **243** (Scheme 70).[66] However, by performing the reaction in a less polar solvent (Et_2O) at −115 °C, and by using a less hindered and a more reactive neopentyl boronic ester, the enantioenriched diols **243** were obtained, after an oxidative work-up, in a very good enantiomeric ratio (up to 95/5).

The mechanism proposed for this reaction (Scheme 70), represents a useful homologation of boronic esters with lithiated epoxides and reflects both the carbanionic and carbenic reactivity of these intermediates.

The oxiranyl anion methodology applied to aryloxiranes has been exploited for the synthesis of substituted styrene oxides on a large scale, taking advantage of microflow technology.[67] The employment of such a microtechnology also represents a powerful tool for mechanistic studies.



Scheme 69



Scheme 70

Since their discovery, oxiranyllithiums have been extensively employed as key intermediates in organic synthesis but few studies were performed in order to clarify their stereoelectronic nature. A multinuclear magnetic resonance investigation, supported by DFT calculations, has been used to investigate the C–Li bond nature, reactivity and aggregation states of α-lithiated styrene oxide in THF at 173 K.[68] Such organolithium is mainly present as a THF-solvated monomer **244** as demonstrated by ^{13}C NMR analysis in which the most diagnostic signal was found at $\delta = 81.6$ ppm, as a broad 1:1:1:1 quartet, typical of a carbon coupled to only one lithium atom ($^{1}J_{C-Li} = 34$ Hz). The monomer (**244**) equilibrates in solution with smaller amounts of dimeric structures (**245**) (Figure 5). The NBO (Natural Bond Orbital) analysis indicates the carbenoid character showed by α-lithiated styrene oxide in some experimental conditions, such as temperatures higher than 173 K or higher concentrations, can be largely attributed to the presence of the *O*-coordinated bridged dimers **245**. This hypothesis, supported by Boche studies,[52] is based on the calculated energy gap between $\sigma^*_{O-C\alpha}$ and $\sigma_{O-C\alpha}$ that is significantly higher in dimeric species **245** than in monomeric trisolvated organolithium **244**.

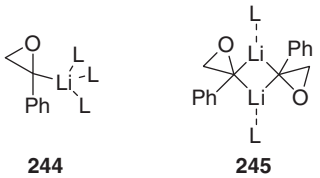
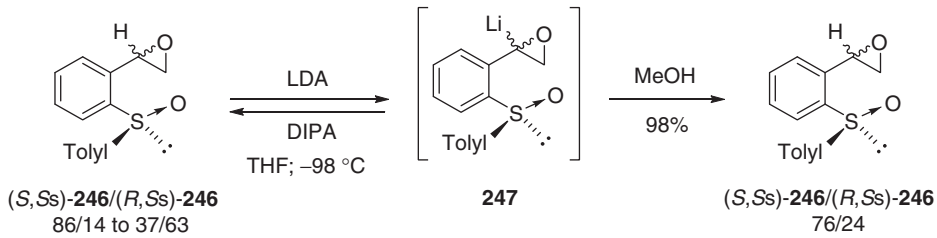


Figure 5 α-Lithiated styrene oxide: monomer and dimer.

α-Lithiated phenyl epoxides such as styrene[55] and stilbene[64] oxide derivatives showed configurational stability at low temperature in THF and were successfully employed as chiral synthons in asymmetric syntheses. The effect of the substitution on the

aryl group can influence the stereochemical integrity of α-lithiated aryloxiranes. Indeed, it has been reported that the *ortho*-positioned *p*-tolylsulfinyl group of α-lithiated styrene oxide induces fast epimerization.[69]

The benzylic deprotonation of **246** has been performed with LDA as the use of alkyllithiums causes desulfinylation. Oxiranyllithium **247** is configurationally unstable, in THF at −98 °C, as demonstrated by performing experiments using varied diastereomeric mixtures of the starting sulfinyloxirane and obtaining the same final ratio [*dr* (*S*,*Ss*)-**246**/(*R*,*Ss*)-**246** = 76/24] (Scheme 71).[69]



Scheme 71

Moreover, a low incorporation of deuterium (11–50%D) on the benzylic carbon, was found by performing lithiation-deuteration experiments on **246**. This result has been rationalized by considering an equilibrium between the starting epoxide/LDA and the lithiated intermediate/DIPA (*N*,*N*-diisopropylamine). To confirm such a hypothesis, an excess of *N*-deuterated DIPA was used as source of LDA and the amount of deuterium incorporation was checked into the final diastereomeric mixture. As expected, approximately 59% of the benzylic carbons was deuterated after quenching the reaction with MeOH.

The influence of fluorine as well as trifluoromethyl group on the configurational stability of lithiated styrene oxide derivatives has also been investigated. Lithiation/deuteration sequences starting from optically active substrates have shown that, in ethereal solvents, all the α-lithiated *ortho*-, *meta*-, and *para*-fluorostyrene oxides are configurationally stable in the reaction time scale, whereas α-lithiated *ortho*-, *meta*-, and *para*-trifluoromethylstyrene oxides are configurationally unstable. Kinetic experiments have been exploited to calculate the enantiomerization barriers: the *para*-CF_3 derivative racemizes very fast (half time of racemization: $t_{1/2}$ = 13.5 s at 157 K), whereas the inversion of *meta*-CF_3 isomer was much slower ($t_{1/2}$ = 272.4 min at 157 K).[70] The racemization of *ortho*-trifluoromethylated derivative resulted faster than *para*-CF_3 isomer, probably because of a synergistic cooperation of a 'conducted tour' mechanism ($t_{1/2}$ = 1.6 s at 157 K).

With the aim to rationalize the racemization mechanism, activation parameters for the enantiomerization process of lithiated epoxides, showed in Figure 6, were determined. A relatively small enthalpy of activation ($\Delta H^{\neq}$ = 5.5 ± 0.1 kcal mol^{-1}) beside a large entropy of activation ($\Delta S^{\neq}$ = −44 ± 1 calmol^{-1}K^{-1}) were attributed to the transformation of a contact ion pair into a solvent-separated ion pair (SSIP) as the rate-determining step.

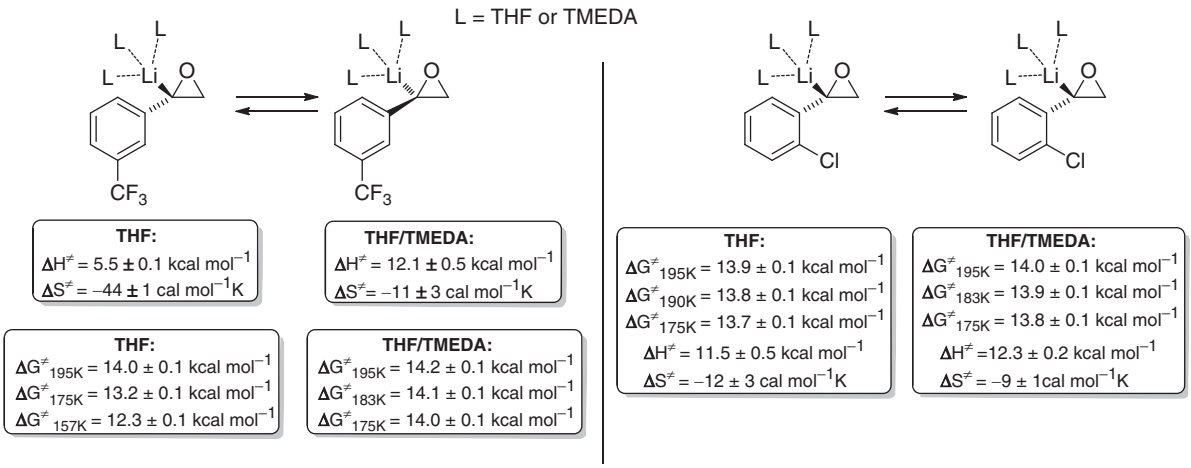
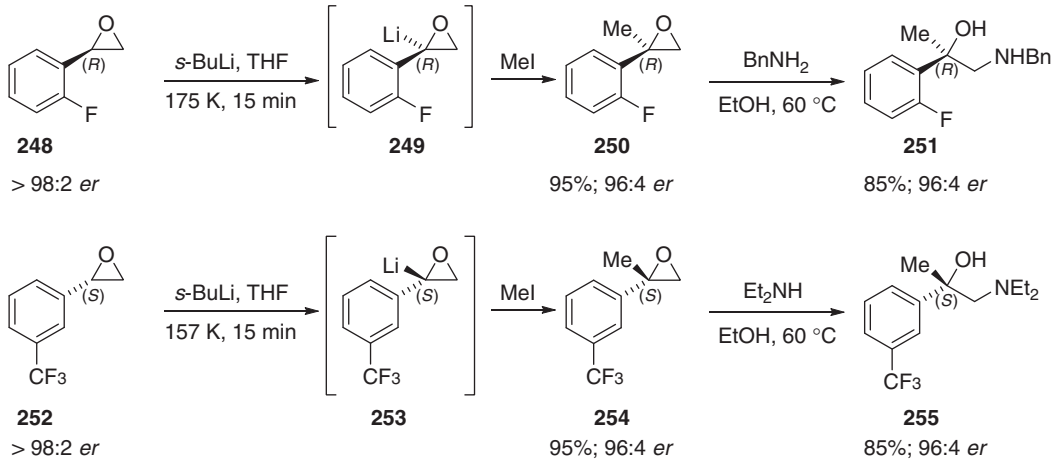


Figure 6 Activation parameters for the enantiomerization process of α-lithiated aryloxiranes in THF and THF/TMEDA.

Optically active oxiranyllithiums **249** and **253** were employed in the asymmetric synthesis of fluorinated β-amino alcohols with a stereodefined quaternary carbinol center: the two step methodology involves a stereospecific alkylation at the benzylic carbon, to obtain disubstituted epoxides **250** and **254**, followed by the regiospecific ring-opening reactions with amines to give aminoalcohols **251** and **255** (Scheme 72).



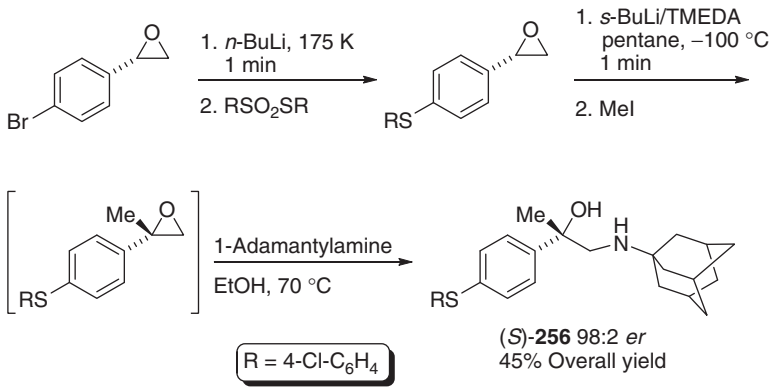
Scheme 72

The configurational stability of α-lithiated styrene oxides is strongly dependent not only on the electronic effect exerted by the substituents on the phenyl ring, but also by the reaction conditions, such as the nature of solvents and additives. Several aryl oxiranyllithiums have been investigated in both coordinating and noncoordinating solvents, and in the presence or absence of TMEDA (Figure 6).[71] While the electron-donating groups (e.g., methyl and methoxy) do not alter the configurational stability in THF at low temperatures, the electron-withdrawing groups (e.g., chloro, trifluoromethyl, and phenylthio) promote racemization in THF, at a rate that is dependent on their nature and their position on the phenyl ring.

The presence of TMEDA in THF often contributes to the slow down of the enantiomerization process of all those derivatives proven to be configurationally unstable on the timescale of their reactions, as demonstrated by the calculated barriers to inversion ($\Delta G^{\neq}$) and activation parameters ($\Delta H^{\neq}$ and $\Delta S^{\neq}$) for some oxiranyllithiums.

Surprisingly, the above organolithiums showed a remarkable configurational stability just when generated in hexane in the presence of TMEDA, and the importance of such a diamine was evidenced not only from a stereochemical point of view in the reaction, but also because the deprotonation process of all the studied aryloxiranes in hexane does not occur in the absence of TMEDA.

The use of the hexane/TMEDA combination to inhibit the racemization process, has allowed a short and straightforward asymmetric synthesis of an industrially important antifungal agent **256** (Scheme 73).[71,72]

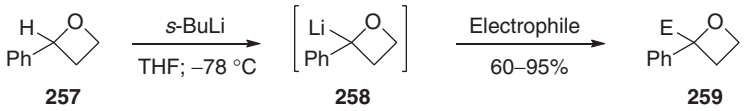


Scheme 73

1.14.2.3.2 α-Lithiated 2-phenyloxetane

Among the α-lithiated cyclic ethers, lithiated oxetanes represent a new class of organolithiums, recently discovered as useful intermediates for the synthesis of 2,2-disubstituted oxetanes. In particular, 2-lithiated-2-phenyloxetane **258** (Scheme 74) can be smoothly generated by treatment of 2-phenyloxetane **257** with *s*-butyllithium at −78 °C in THF and then functionalized with a wide range of electrophiles to give more substituted phenyloxetanes **259**.[73]

In contrast with α-phenyl-substituted oxiranyllithiums which proved to be configurationally stable, lithiated oxetane in ethereal solvents is configurationally labile. The deprotonation of (*R*)-**257** with *s*-BuLi in THF at − 78 °C, followed by quenching with MeOD, resulted in the racemic alfa deuterated **257** after just 5 min. Almost racemic silane **260** was obtained both in

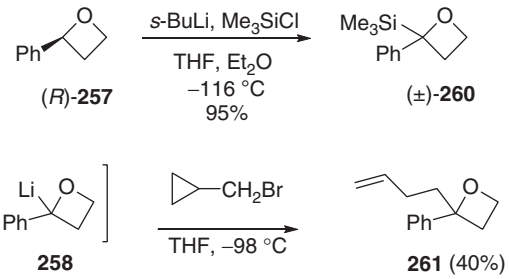


257 **258** **259**

Electrophile = RI, Me_3SiCl, Bu_3SnCl, $RCONMe_2$, R_2CO, RCHO

Scheme 74

THF/Et_2O (3:2) as the solvent mixture (95% yield) and in Et_2O in the presence of 1 equivalent of TMEDA (10% yield), by performing the *in situ* trapping experiments of lithiated (*R*)-**258** at very low temperature (− 116 °C) with Me_3SiCl as the electrophile (Scheme 75).



(*R*)-**257** (±)-**260**

258 **261** (40%)

Scheme 75

Again, in contrast to lithiated styrene oxides,[71] the use of hexane/TMEDA did not block the fast racemization of (*R*)-**258**.

A radical pathway for the lithiation-coupling reactions of 2-lithiated-2-phenyloxetane has been proposed. Lithiated oxetane **258** was reacted in THF at − 98 °C with cyclopropylmethylbromide, which is a very fast radical probe. The only product isolated by column chromatography (40% yield) was the linear butenyl-substituted oxetane **261**, resulting from coupling with the more stable butenyl radical further to the radical opening of the cyclopropyl ring (Scheme 75). The formation of **261** is consistent with a SET mechanism.

1.14.2.3.3 Non-stabilized oxiranyllithiums

An important manifestation of the carbenoidic character of oxiranyllithiums is represented by the isomerization reaction of cycloalkene oxides into bicyclic alcohols. In this contest, the asymmetric deprotonation of *meso*-epoxides with alkyllithiums and enantiopure ligands can lead to enantioenriched bicyclic alcohols as the final products.

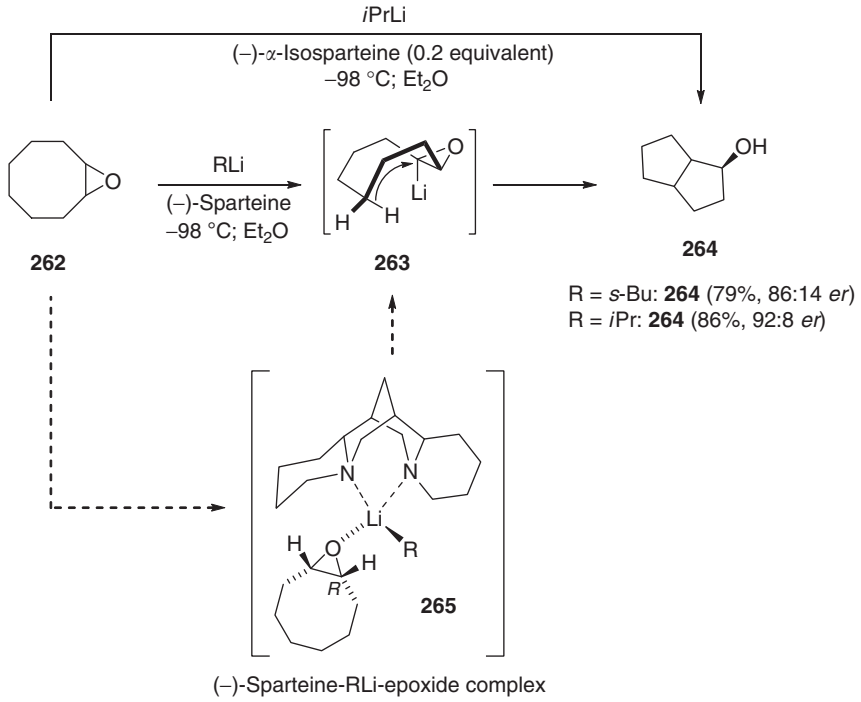
Hodgson et al. reported the enantioselective α-lithiation of cyclooctene oxide **262** in the presence of (–)-sparteine, followed by a stereospecific transanular C–H insertion within **263**[74]; the asymmetric synthesis of bicyclo[3.3.0]octanol **264** in 79% yield and 86:14 *er* was developed in this way (Scheme 76). By performing the same reaction with *i*-PrLi, instead of *sec*-BuLi, the alcohol **264** was obtained with an improved yield (86%) and higher enantioselectivity (92:8 *er*), whereas the alternative use of *n*-BuLi or *t*-BuLi gave poor or no enantioselectivity. A model for the observed stereoselectivity has been proposed: assuming the preliminary formation of the (–)-sparteine/RLi/epoxide complex **265** the RLi should approach the *R* proton of the epoxide preferentially for steric reasons.

A similar enantioselective deprotonation was also observed in the lithiation of **262** upon treatment with *i*-PrLi in the presence of a *sub*-stoichiometric amount (0.2 equivalent) of (–)-α-isosparteine (86%, *er* 92:8) (Scheme 76).[75] This result would encourage the deprotonation of *meso*-epoxides in the hitherto unreported catalytic asymmetric version.

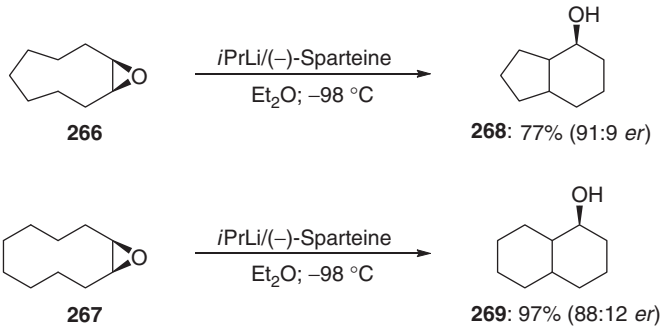
In a similar approach cyclononene **266** and cyclodecene oxides **267** were deprotonated with *i*-PrLi in the presence of (–)-sparteine to furnish bicyclic alcohols **268** and **269** in both cases with good yield and enantiomeric ratios (Scheme 77).[74]

The utility of lithiated epoxides was instrumental in the synthesis of natural compounds as, for example, the total synthesis of (–)-xialenon A **272** (Scheme 78).[76] The lithiation of the achiral cyclooctene oxide **270** with *i*-PrLi and (–)-α-isosparteine, leads to the formation of the bicyclic alcohol **271** in 55% yield and 90/10 *er*, as a result of a transannular insertion reaction. The so obtained skeleton of the alcohol **271** was further elaborated to (–)-xialenon A **272** in 12 steps. This study constitutes the first application of an epoxide transannular desymmetrization to the total synthesis of a natural product.

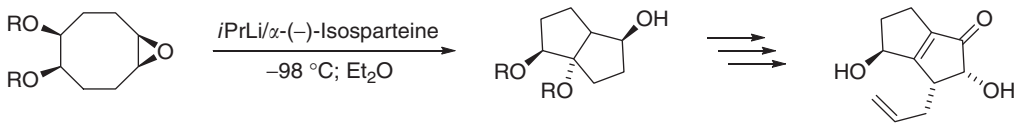
The C − H insertion reactions on α-lithiated epoxides can be affected by Lewis acids, as reported by Alexakis[77] who developed an enantioselective synthesis of cycloheptenyl alcohols starting from cycloalkene oxides. When bicyclic epoxide **273** was treated with *s*-BuLi and (–)-sparteine, the intermediate **274** is most likely formed, but in the presence of a strong Lewis acid such as $BF_3 \cdot Et_2O$, an insertion of the carbenoidic lithiated α-carbon into the allylic C–H bond occurred, leading to the chiral nonracemic cyclopropane derivative **275** (75% yield and 85/15 *er*) (Scheme 79).



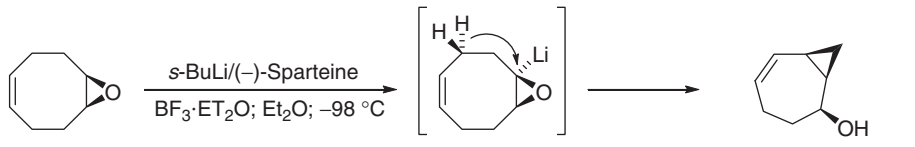
Scheme 76



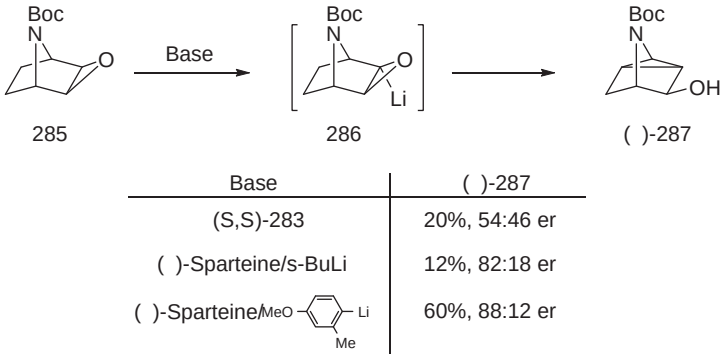
Scheme 77



Scheme 78

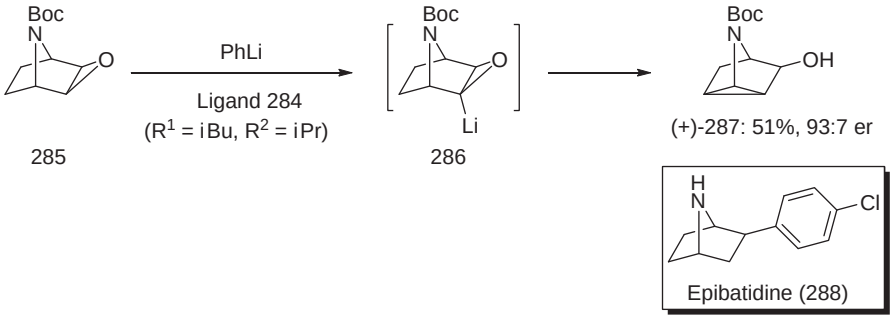


Scheme 79



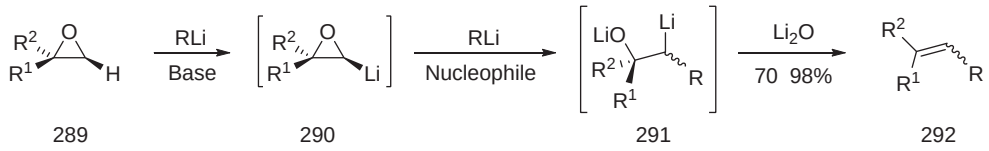
Scheme 82

The enantioselective synthesis of alcohol ( )-287 was performed by reacting the epoxide 285 with phenyllithium through the formation of the chiral organolithium 286 (Scheme 83). The presence of the oxazoline-based ligands 284 gave a high improvement of the final optical purity (93:7 er using ligand 284, R^1 = i-Bu, R^2 = i-Pr) (Scheme 83). Moreover, this approach was successfully applied to the synthesis of the analogs of the potent nonopioid analgesic epibatidine 288.[81]



Scheme 83

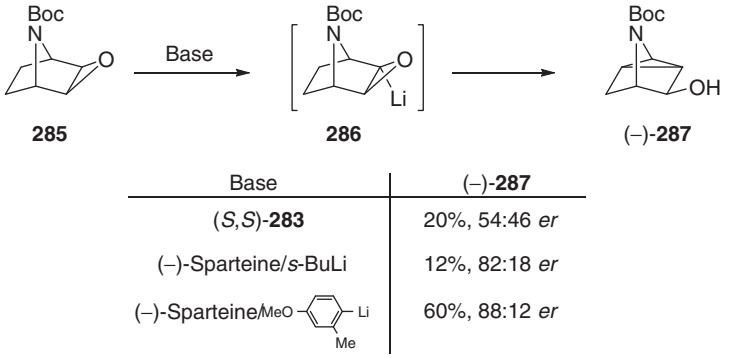
a-Lithiated epoxides exhibiting a carbene-like character can be coupled with organolithium in a reaction called 'reductive alkylation'; such a reaction represents a useful synthetic way to obtain alkenes. For example, the oxirane 289 can be transformed into the olefin 292 after reaction with two equivalents of the organolithium RLi, one acting as the base and the other one as a nucleophile (Scheme 84).[82,83] The proposed mechanism of the formation of the alkene 292 involves the deprotonation of the oxirane, followed by the nucleophilic addition of the alkyllithium at the lithiated carbon of 290 with formation of a bis-lithiated intermediate 291 which loses Li_2O with subsequent double bond formation in compound 292.



Scheme 84

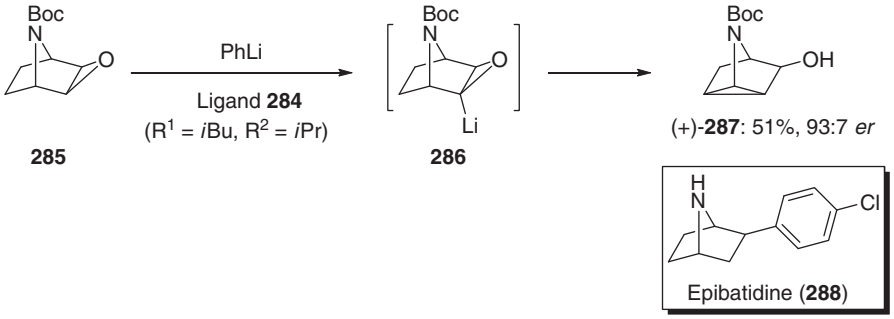
This methodology has been successfully applied to the synthesis of enantioenriched diols and aminoalcohols. The alkylated diol 295 was easily obtained in moderate yield (58%) and good enantioselectivity (86:14 er) from 294 which was obtained by the reaction of the epoxide 293 with an excess of i-PrLi in the presence of ( )-sparteine at 61 1C (Scheme 85).[84] Similarly, the a-lithiated epoxide 286 was the key intermediate in the synthesis of the bifunctionalized cyclohexene 296, obtained in high yield (78%) and enantiomeric enrichment (93:7 er) by the lithiation of azanorbornene oxide 285 with i-PrLi/( )-sparteine in Et_2O at 78 1C (Scheme 85).[85]

In the reductive alkylation methodology it is very common that the base and the nucleophile are the same molecule; by following this approach, alkyl or aryl units remain incorporated in the final product. An alternative is represented by the employment of lithium amides as recently reported by Hodgson: regioselective metalation of epoxide 297 proceeds smoothly, at the terminal carbon atom, when treated with lithium amides in THF at 25 1C (Scheme 86).[86] The relatively high temperature of the reaction medium accentuates the carbenoidic character of the oxiranyllithium 298 that readily undergoes nucleophilic attack



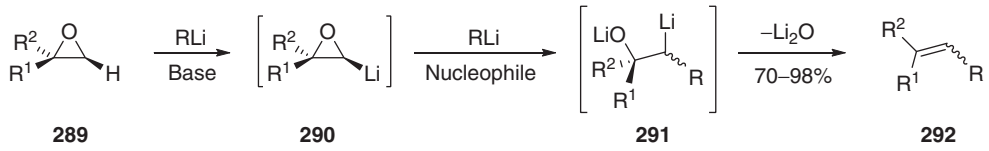
Scheme 82

The enantioselective synthesis of alcohol (+)-**287** was performed by reacting the epoxide **285** with phenyllithium through the formation of the chiral organolithium **286** (Scheme 83). The presence of the oxazoline-based ligands **284** gave a high improvement of the final optical purity (93:7 *er* using ligand **284**, $R^1 = i$-Bu, $R^2 = i$-Pr) (Scheme 83). Moreover, this approach was successfully applied to the synthesis of the analogs of the potent nonopioid analgesic epibatidine **288**.[81]



Scheme 83

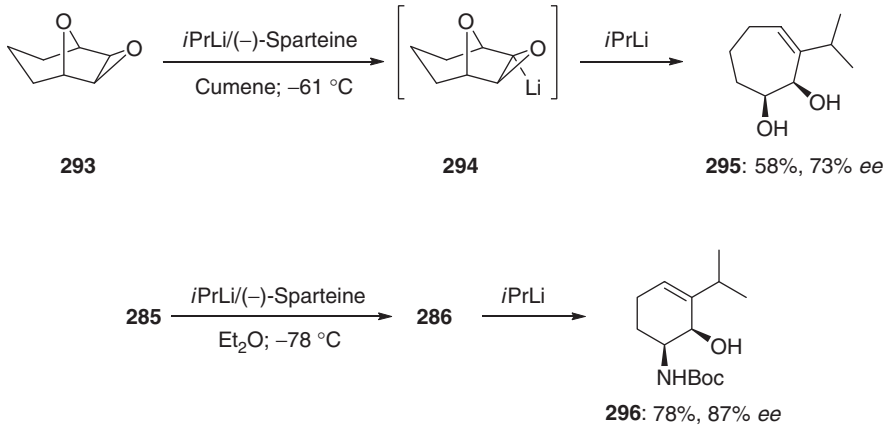
α-Lithiated epoxides exhibiting a carbene-like character can be coupled with organolithium in a reaction called 'reductive alkylation'; such a reaction represents a useful synthetic way to obtain alkenes. For example, the oxirane **289** can be transformed into the olefin **292** after reaction with two equivalents of the organolithium RLi, one acting as the base and the other one as a nucleophile (Scheme 84).[82,83] The proposed mechanism of the formation of the alkene **292** involves the deprotonation of the oxirane, followed by the nucleophilic addition of the alkyllithium at the lithiated carbon of **290** with formation of a bis-lithiated intermediate **291** which loses Li_2O with subsequent double bond formation in compound **292**.



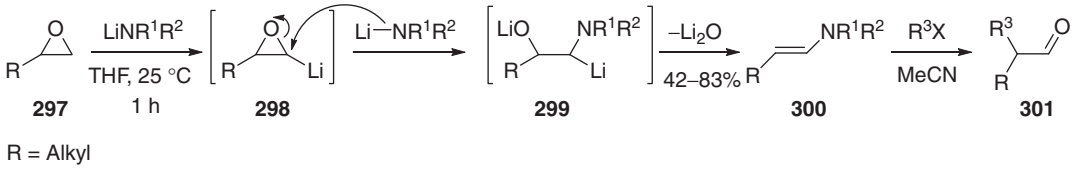
Scheme 84

This methodology has been successfully applied to the synthesis of enantioenriched diols and aminoalcohols. The alkylated diol **295** was easily obtained in moderate yield (58%) and good enantioselectivity (86:14 *er*) from **294** which was obtained by the reaction of the epoxide **293** with an excess of *i*-PrLi in the presence of (–)-sparteine at −61 °C (Scheme 85).[84] Similarly, the α-lithiated epoxide **286** was the key intermediate in the synthesis of the bifunctionalized cyclohexene **296**, obtained in high yield (78%) and enantiomeric enrichment (93:7 *er*) by the lithiation of azanorbornene oxide **285** with *i*-PrLi/(–)-sparteine in Et_2O at −78 °C (Scheme 85).[85]

In the reductive alkylation methodology it is very common that the base and the nucleophile are the same molecule; by following this approach, alkyl or aryl units remain incorporated in the final product. An alternative is represented by the employment of lithium amides as recently reported by Hodgson: regioselective metalation of epoxide **297** proceeds smoothly, at the terminal carbon atom, when treated with lithium amides in THF at 25 °C (Scheme 86).[86] The relatively high temperature of the reaction medium accentuates the carbenoidic character of the oxiranyllithium **298** that readily undergoes nucleophilic attack



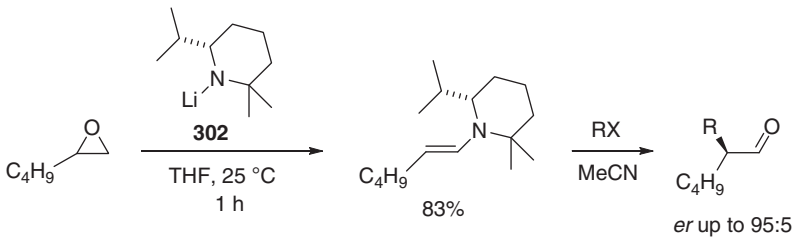
Scheme 85



Scheme 86

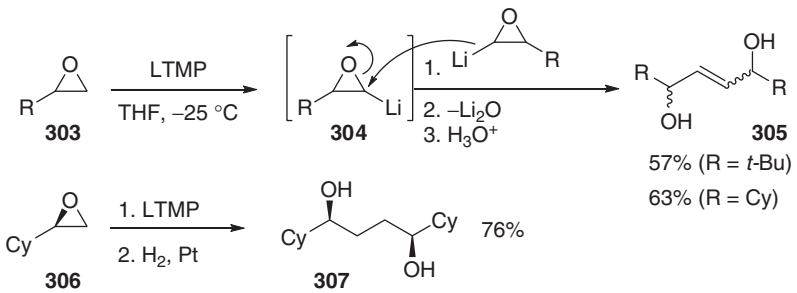
from a second molecule of the lithium amide giving the bis-lithiated species **299**. After Li_2O elimination the enamine **300** is obtained in moderate to good yields. The enamine **300** has been successfully employed as precursor of α-alkylated aldehydes **301**.

The methodology has been also applied to the asymmetric synthesis of α-alkylated aldehydes by using the lithioamide **302** as base and chiral auxiliary (Scheme 87).[87]



Scheme 87

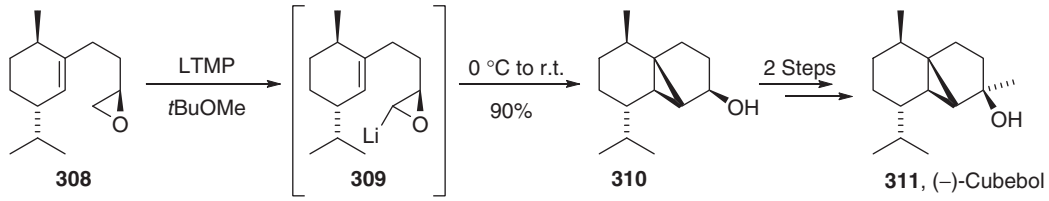
When alkyl substituted oxirane **303** was treated with LTMP in THF at − 15 °C and the reaction was allowed to warm to 25 °C over 2 h, the major product was not the expected enamine but rather a mixture of *E*/*Z* enediols **305** resulting from a dimerization process in which one lithiated epoxide **304** acts as a nucleophile and another one act as an electrophile (Scheme 88).[88]



Scheme 88

The above methodology was employed in the straightforward synthesis of enantiopure 1,4-diols **307** by treating enantiopure alkyloxiranes **306** with LTMP and subsequent reduction of C–C double bond (Scheme 88).

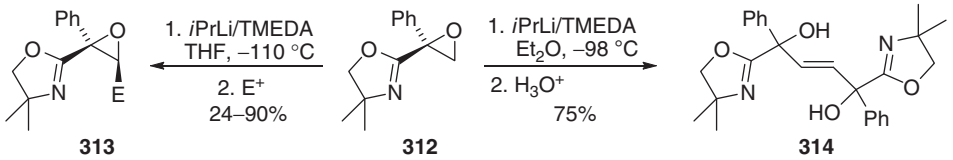
The reactivity of lithiated terminal epoxides can be very similar to those of carbenes as observed in the intramolecular cyclopropanation of intermediate **309** (Scheme 89). When treated with LTMP in *t*-BuOMe, epoxide **308** undergoes regioselective lithiation at methylene carbon. Subsequent insertion of the 'carbenoid' in the C – C double bond, promoted by heating from 0 °C to room temperature, resulted in the stereoselective formation of tricyclic compound **310**. Such transformation was employed as the key step in a concise synthesis of the natural product (–)-cubebol **311** (Scheme 89).[89]



308 **309** **310** **311**, (–)-Cubebol

Scheme 89

During the study on the stereoselective lithiation of terminal oxazolinyloxiranyl **312** in THF at very low temperature (– 110 °C), a small amount of dimeric ene-diol **314** was found (5–19%) beside the expected products of coupling with electrophiles **313** (Scheme 90).[90] Enediol **314** was obtained in a high yield and stereoselectivity (75%, $E/Z > 98{:}2$) by carrying out the deprotonation reaction in Et_2O at – 98 °C with LDA and TMEDA.



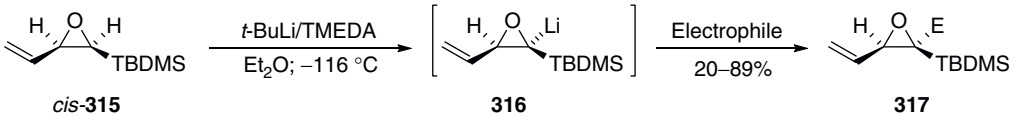
313 **312** **314**

Scheme 90

1.14.2.3.4 Silyl oxiranyllithiums

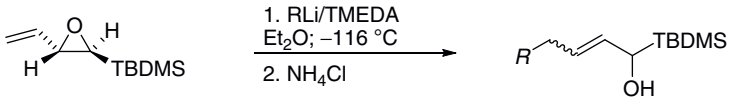
Among the oxiranyllithiums silylsubstituted derivatives were the first to be investigated. Courillon and Malacria[91] demonstrated that *cis*-α,β-epoxy-γ,δ-vinylsilanes **315** could be regioselectively α-lithiated with *t*-BuLi and TMEDA within 30 min in Et_2O at –116 °C and the resulting anion **316** could be trapped with external electrophiles to give trisubstituted epoxides **317** with complete retention of configuration at the oxiranyl ring (Scheme 91). In contrast, the *trans* epoxide **315** could not be deprotonated by *n*-BuLi, *s*-BuLi, or *t*-BuLi, an S_N2' reaction being observed instead with the addition of the organolithium to the double bond to give allylic alcohols **318** (Scheme 91).

It is noteworthy that, although the *cis* configuration of the three-membered ring is thermodynamically disfavored, the reaction occurs with complete retention of configuration at the lithiated carbon thus allowing the stereoselective functionalization of the epoxide **315** (Scheme 91).



cis-**315** **316** **317**

Electrophile = Me_3SiCl, CH_3I, PhCHO, $NCCO_2CH_3$, $ClCO_2CH_3$, $CH_2{=}CHCH_2I$



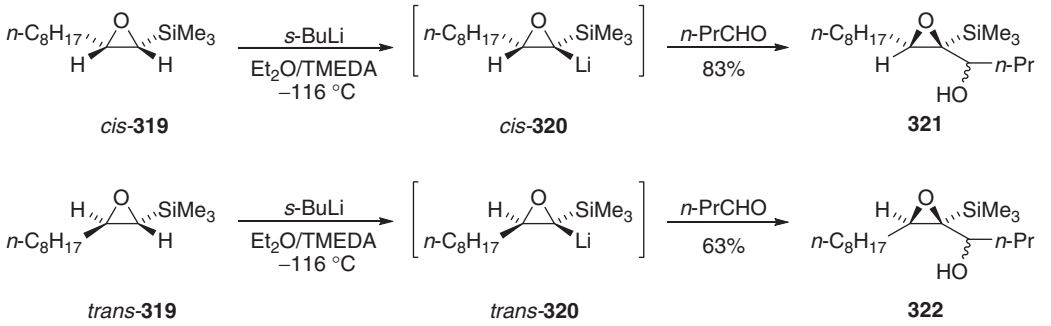
trans-**315** **318**

R = *n*-Bu (69%), *s*-Bu (99%), *t*-Bu (98%)

Scheme 91

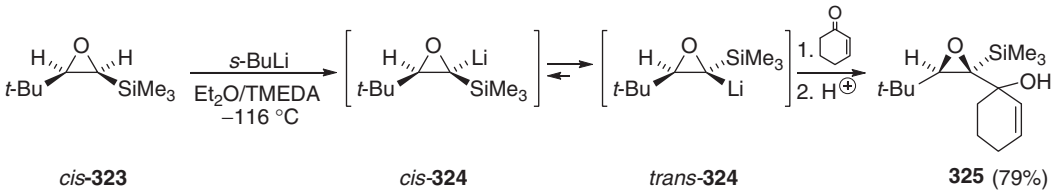
The examples above clearly support the hypothesis that the relative configuration at the epoxide stereogenic carbons plays a role in the control of the regioselectivity, as for the rate of the deprotonation reaction. A plausible explanation could be the formation of competitive prelithiation complexes between alkyllithium and the oxirane oxygen, with a different thermodynamic stability.

Similar results were previously obtained by Molander,[92] who studied the direct deprotonation of several *cis*- and *trans*-epoxysilanes. Lithiation of *cis*-α,β-epoxysilane **319** with *s*-BuLi and TMEDA was complete after just 10 min despite the very low temperature (− 116 °C), whereas the deprotonation of *trans*-α,β-epoxysilane **319**, under the same conditions, proved to be much slower requiring 4 h for completion (Scheme 92). Both the corresponding oxiranyl anions *cis*-**320** and *trans*-**320** are stable for hours at − 116 °C in Et_2O and can be trapped with aldehydes to give epoxyalcohols **321** and **322** in good yields and with retention of configuration at the lithiated carbon atom (Scheme 92).



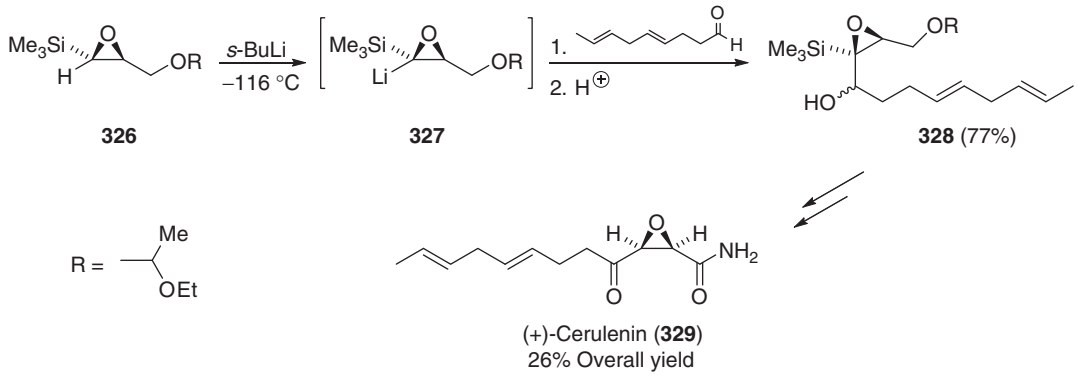
Scheme 92

An exception was represented by *cis*-oxirane **323**, because after lithiation and further reaction with 2-cyclohexen-1-one, the major product was the epoxyalcohol **325**, whose relative configuration was opposite with respect to the starting oxirane (Scheme 93). An isomerization from *cis*-**324** to *trans*-**324** is likely to occur before carbonyl addition. This behavior could be due to the strain between the *t*-butyl and the trimethylsilyl groups on the same side of the starting oxirane ring, which promotes the isomerization process after lithiation.



Scheme 93

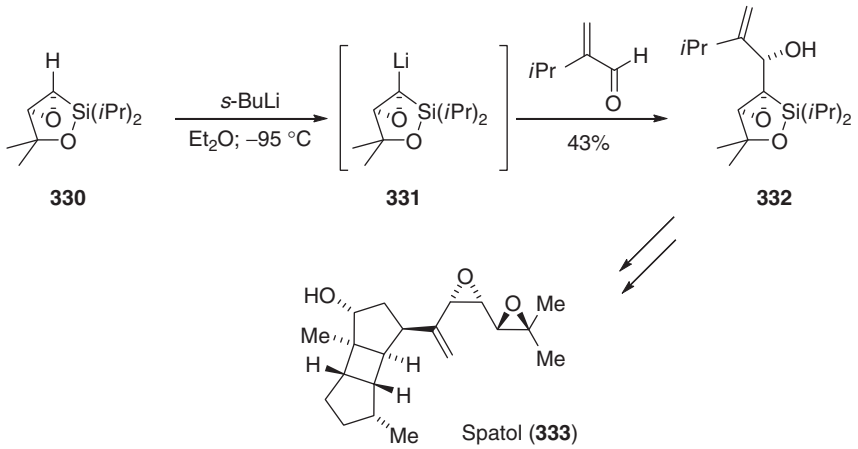
The importance of silicon-stabilized oxiranyl anions as key intermediates in stereoselective synthesis was investigated by Townsend, who used a chiral lithiated epoxysilane in the asymmetric synthesis of (+)-cerulenin **329**, a potent natural antimicrobial agent (Scheme 94).[59] Optically pure oxirane **326** (*ee* = 99%) was metalated with *s*-BuLi; the resulting lithiated



Scheme 94

intermediate **327** was then trapped with (4*E*,7*E*)-nonadienal to give the product **328** in 77% yield. Further elaboration in 12 steps led to the highly enantiomerically enriched target product **329** in 26% overall yield (Scheme 94).

In the course of the stereoselective synthesis of spatol **333**, a temporary tether was used by Salomon and Murthi[93] to circumvent the configurational instability of α-silylated epoxide **331**, obtained from deprotonation of **330** with *s*-BuLi (Scheme 95). Further elaboration of functionalized allylic alcohol **332** then leads to the target natural product **333**.



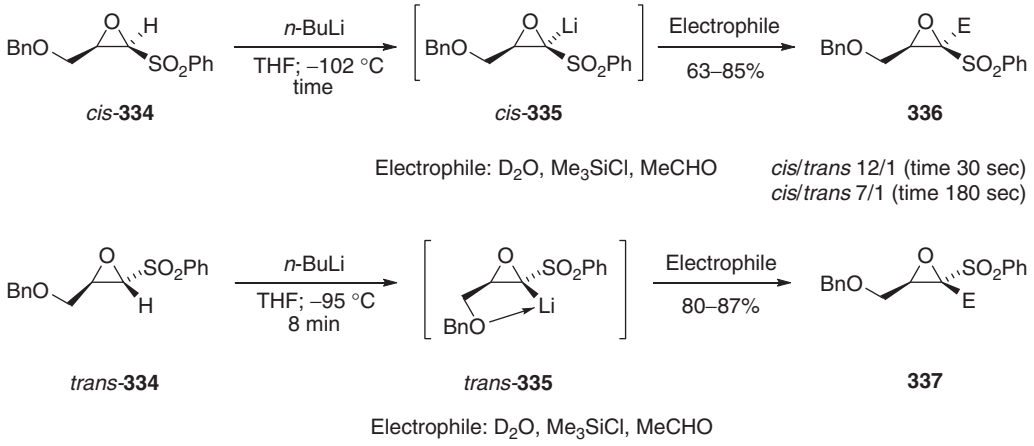
Scheme 95

In conclusion, lithiated epoxysilanes have a tendency to react with electrophiles with retention of configuration, thus allowing the transfer of the 'chirality' to the final products. However, further studies are necessary for the comprehension of the structural features that allow the observed configurational stability of such lithiated intermediates; a good rationalization of the known exceptions is also needed.

1.14.2.3.5 Sulfonyl oxiranyllithiums

Sulfonyloxiranyllithiums can be obtained by reaction of the corresponding sulfonyl epoxides with alkyllithiums at temperatures below −90 °C. The reactivity as well as the chemical and configurational stability of sulfonyloxiranyllithiums are strongly dependent on the stereoelectronic nature of the substrate and the reaction conditions, as demonstrated by Jackson[94] in the metalation studies of diastereomeric epoxides *cis*-**334** and *trans*-**334**.

Lithiated *cis*-**335** was quickly obtained from deprotonation of *cis*-**334** with *n*-BuLi at − 102 °C; its formation was complete in just 30 s (Scheme 96). Subsequent addition of several electrophiles afforded the corresponding *cis*-adducts **336**, together with a small quantity of the isomeric adduct **337** (*cis*/*trans* ratio 12:1), the epimerization process being influenced by the lithiation time. In fact, after treatment of *cis*-**334** with *n*-BuLi for 3 min followed by quenching with D_2O, a reduced overall yield of deuterated product was obtained, as well as a lower diastereomeric ratio (*cis*/*trans* 7/1) (Scheme 96).

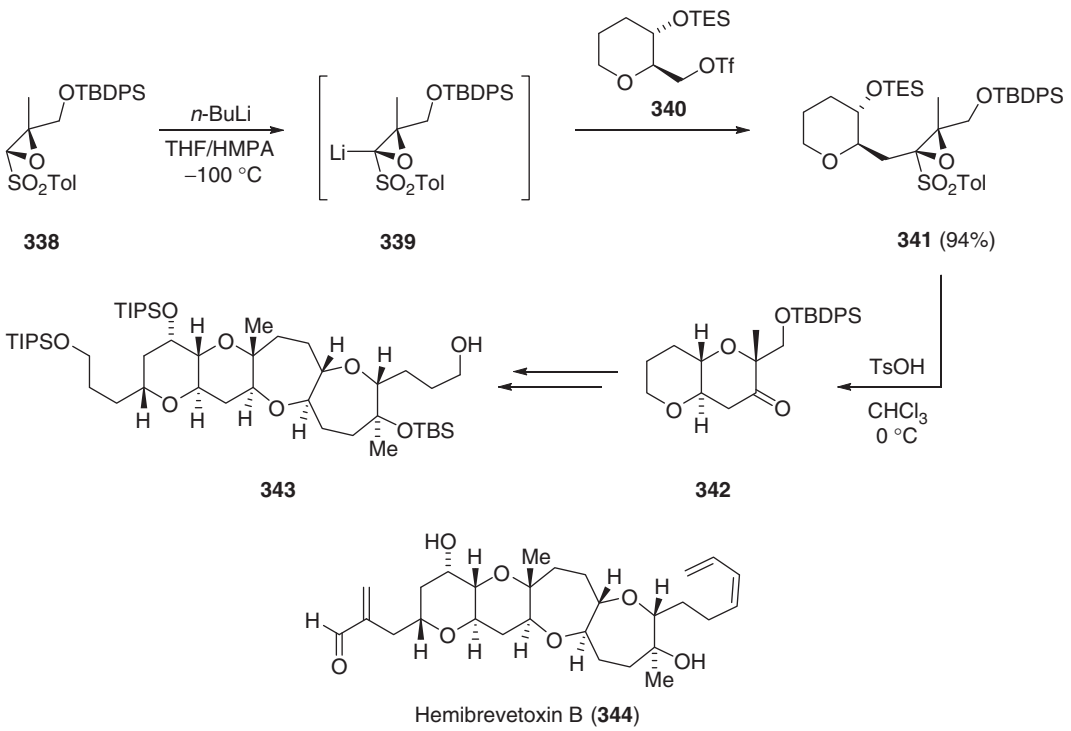


Scheme 96

These results imply that the sulfonyl group makes the oxirane moiety quite acidic, since deprotonation is very fast at − 102 °C; however, the corresponding oxiranyllithium turns out to be configurationally unstable, although the reason was not yet understood.

When *trans*-**334** was deprotonated with *s*-BuLi, longer reaction times (8 min) and higher temperatures (− 95 °C) were necessary to complete metalation. A *trans*-**335** intermediate was subsequently coupled with several electrophiles in a retentive stereospecific manner (Scheme 96). The configurational stability of the oxiranyllithium *trans*-**335** could be ascribed to an internal coordination of the lithium atom by the benzyloxy group, although this may not be the only contributing factor.

An attractive application of lithiated epoxysulfones was discovered by Mori,[95] who employed such oxiranyllithiums as key intermediates for the preparation of cyclic ethers and, in particular, for the total synthesis of natural polycyclic ethers such as marine toxins.[96] Since lithiated epoxysulfones such as **339** are known to be configurationally unstable even at a temperature of approximately −100 °C, optically pure oxirane **338**, once lithiated, was straightforwardly coupled with triflate **340** by an *in situ* trapping strategy (Scheme 97). Thus, the treatment of a **338** and **340** mixture with *n*-BuLi in the presence of HMPA in THF at − 100 °C, afforded the functionalized epoxide **341** in a stereospecific way.



Scheme 97

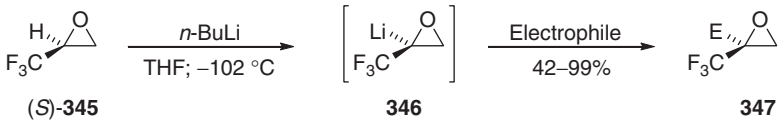
Treatment of **341** with TsOH at 0 °C resulted first in the removal of the triethylsilyl-group (TES) and subsequently in an intramolecular epoxide ring-opening. The regioselectivity of the process should be considered since the epoxyalcohol **341** might give, in principle, a tetrahydrofuran or a tetrahydropyran system *via* a 5-*exo* or 6-*endo* cyclization mode, respectively. However, the presence of a sulfonyl group, due to its electron-withdrawing ability, favors the *endo* mode pathway, thus leading to the *six*-membered ketone **342** (Scheme 97). The two-step sequence involving the coupling of lithiated epoxysulfones with triflates and subsequent oxirane-ring opening was iterated three times leading first to the stereoselective construction of the tetracyclic core of hemibrevetoxin B **343**, and finally to the total synthesis of the marine toxine **344**.[97]

In conclusion, despite their known configurational instability, lithiated epoxysulfones can be stereospecifically trapped with electrophiles under appropriate experimental conditions such as *in situ* trapping.

1.14.2.3.6 α-Trifluoromethyl- and ester-stabilized oxiranyllithiums

The lithiation reaction of trifluoromethyl epoxides has been investigated by Uneyama (*see* Chapter 1.07,[98] who developed a useful methodology for the α-functionalization of oxirane (*S*)-**345** with a wide range of electrophiles in a completely stereospecific manner (Scheme 98).

The metalation was performed by using *n*-BuLi at − 102 °C and resulted in the formation of the organolithium intermediate **346**, that showed a surprising chemical and configurational stability; the coupling of **346** with electrophiles led to the synthesis of optically active fluorinated epoxides **347** through the stereospecific formation of new C–C, C–Si, C–Sn, and C–P bonds.

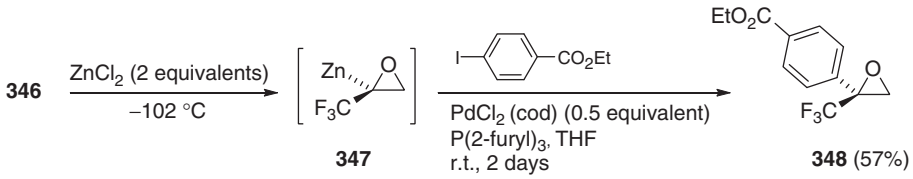


Electrophile = RCHO, R_2CO, PhCONMe(OMe), Ph_3SiCl, Ph_3SnCl, $(EtO)_2POCl$

Scheme 98

The configurational stability of enantiopure **346** is noteworthy since it is well-known that α-trifluoromethyl substituted carbanions frequently have an sp^2 hybridization, and their reactions lead to racemic mixtures.[99] Moreover, it was proved that α-lithiated trifluoromethyloxirane **346** retains its absolute configuration at −78 °C even for 1 h.

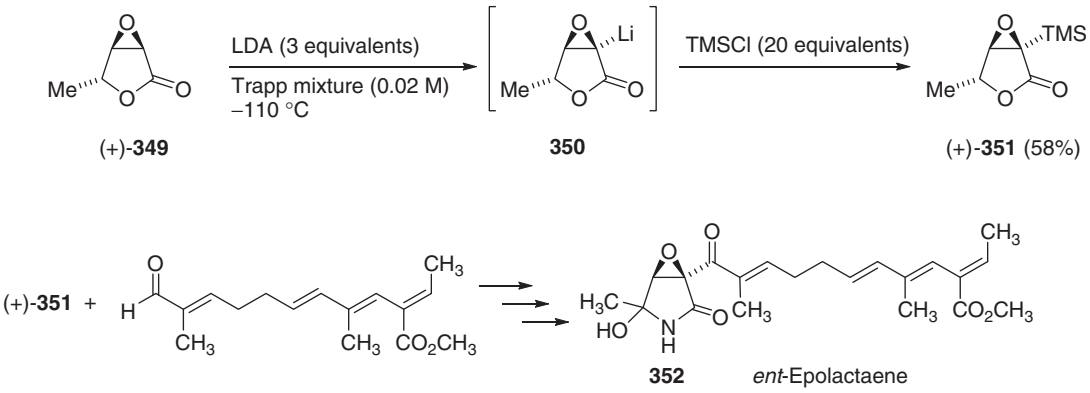
Thanks to Uneyama and coworkers's studies,[98] the possibility of using such oxiranyllithiums as precursors for the preparation of zinc-oxiranes to be used in Negishi cross-coupling reactions has been explored with the aim to develop a procedure for the direct arylation of the starting epoxide (Scheme 99).[98,100]



Scheme 99

In fact, lithiated epoxide **346**, generated as described above, reacted at −102 °C with $ZnCl_2$ to give the thermally stable zinc-species **347** whose structure, however, still remains unclear (Scheme 102). The zinc-oxirane **347** was then coupled with an aryl iodide in the presence of a substoichiometric amount of Pd (0.5 equivalent) to give the styrene oxide derivative **348** with retention of configuration at the α-carbon.

β-Angelica lactone epoxide (+)-**349** has been successfully lithiated and the oxirane ring was stereospecifically silylated by Kobayashi[60] to give (+)-**351** (Scheme 100). This functionalization represents one of the few examples employing an ester-containing oxiranyllithium as the key intermediate.[101] The reaction requires unusual experimental conditions: an excess of base and the Trapp mixture (THF/ether/pentane) as the solvent. Moreover, the *in situ* quenching technique and a low concentration of **349** (0.02 M) avoids undesired further transformations (such as dimerization) of the very reactive oxiranyl anion **350** (Scheme 100).



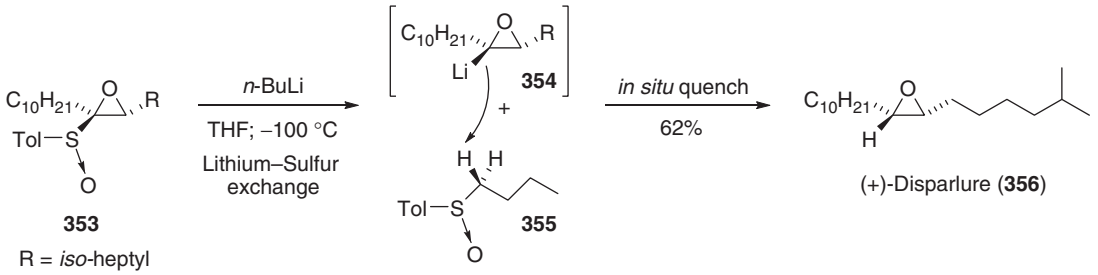
Scheme 100

This new synthetic approach provides the first example of the formation of a bridgehead oxiranyllithium. Furthermore, α-silylated epoxylactone (+)-**351** also represents an oxiranyl anion precursor; after reaction with a fluoride source, it has been successfully employed for the total synthesis of *ent*-epolactaene **352** and its substituted analogs (Scheme 100).[60]

1.14.2.3.7 Oxiranyllithiums by desulfinylation

Enantiopure oxiranyllithiums can be generated from the corresponding sulfinyl epoxides by treatment with alkyllithiums. This methododology is an important asymmetric tool for the synthesis of simple 1,2-disubstituted epoxides, as demonstrated by Satoh[102] in the total synthesis of (+)-disparlure, a pheromone of the female gypsy moth. After reaction with *n*-BuLi at −100 °C,

enantiomerically enriched sulfoxide **353** gives the oxiranylanion **354** as transient intermediate; the fast *in situ* quenching with *n*-butyl-*p*-tolylsulfoxide **355** afforded the *cis*-disubstituted epoxide (+)-disparlure **356** (Scheme 101).

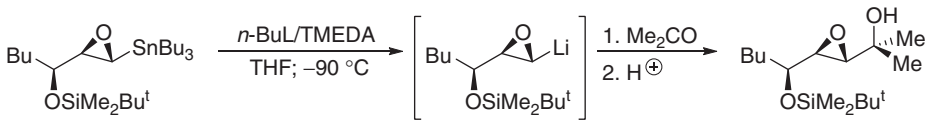


Scheme 101

Since the absence of a stabilizing group often caused the epoxide ring-opening, it is reasonable to guess that the unexpected chemical and configurational stability observed for the lithiated oxirane **354** derives from the *in situ* quenching process, promoted by reaction with the newly formed, acidic, alkyklsulfoxide (Scheme 101). For this reason, the methodology is limited to the stereospecific proto-desulfinylation of epoxysulfoxides.

1.14.2.3.8 Oxiranyllithiums by transmetalation

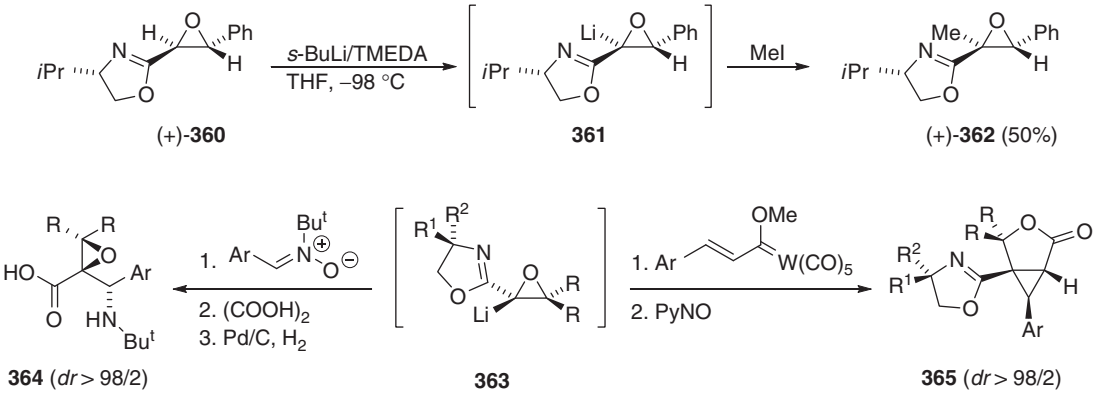
In 1991, Pfaltz[103] and coworkers have reported that tributylstannyl epoxide **357** can be lithiated to give **358** in only 5 min by reaction with *n*-BuLi at −90 °C in the presence of TMEDA. Subsequent quenching of **358** with acetone gave the hydroxyalkylated epoxide **359** in 77% yield as a single diastereoisomer, the whole process being highly stereoselective (Scheme 102). Furthermore, the authors have set the asymmetric version of the above reaction as the epoxide **357** can be prepared in enantiopure form by Sharpless epoxidation of the corresponding allylic alcohol.



Scheme 102

1.14.2.3.9 α-Lithiated oxazolinyloxiranes

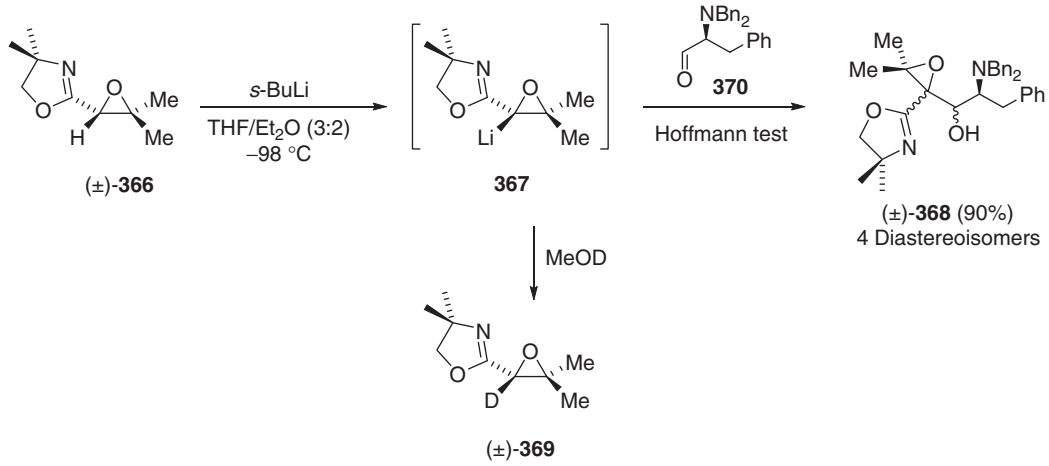
α-Lithiated oxazolinyloxiranes can be smoothly generated by deprotonation and then reacted with classical electrophiles, but, in general, they are configurationally unstable on the macroscopic time scale at low temperature.[104a,b] However, oxazolinyloxirane **361**, obtained by Li–H exchange from optically active oxirane (+)-**360**, was indeed methylated with retention of configuration to afford the epoxide (+)-**362** (Scheme 103).[58] The synthetic utility of oxazolinyloxiranyllithiums can be appreciated by considering



Scheme 103

that **363** has been successfully coupled with nitrones and Fischer carbene complexes for the highly stereoselective synthesis of α-epoxy-β-amino acids **364**[104c] and cyclopropane-γ-butyrolactones **365**,[63] respectively (Scheme 103).

In order to get a more detailed information regarding the configurational stability of α-lithiated oxazolinyloxiranes, a multinuclear magnetic resonance study on **367** has been recently reported, together with an *in situ* IR investigation.[105] Such an intermediate was generated in THF on treatment of **366** with *s*-BuLi at − 98 °C. At this temperature, **367** proved to be chemically stable for several hours and could be trapped quantitatively with a deuterium source to give **369** (Scheme 104).



Scheme 104

Preliminary information on the configurational stability of **367** was gathered by the Hoffman test,[106] performed by employing racemic **366** and the chiral aldehyde **370**: the oxiranyllithium **367** underwent enantiomer equilibration at –98 °C with a rate comparable to that of its addition to aldehyde **370** (Scheme 104). However, an enantiopure sample of (–)-**366**, once deprotonated, was found to racemize within 1 min at –130 °C in THF/Et_2O (3:2) ($t_{1/2}$ = 6 s). The application of the Eyring equation suggested a barrier to inversion for **367** of 8.8 kcal/mol at − 130 °C in THF/Et_2O (Figure 8).

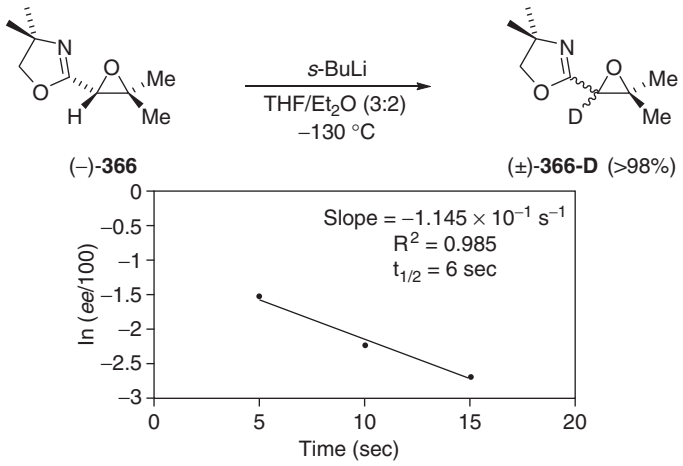
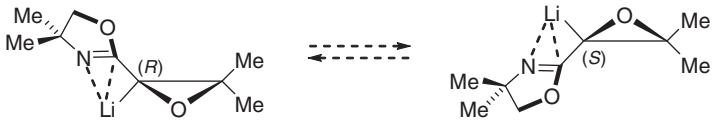


Figure 8 Plot of enantiomeric excess *vs* delay time.

Moreover, IR spectroscopic studies *in situ* showed that lithiation of **366** at − 98 °C in THF is accompanied by a decrease of the C═N wave numbers by only 60 cm^{-1}, thus supporting the idea that **367**, under the above conditions, mainly exists as a true organolithium and not as an azaenolate intermediate. Finally, a multinuclear magnetic resonance study suggested that several η^3-aza-allylic coordinated species might be involved in dynamic equilibria in a THF solution at − 103 °C. An indirect dynamic interconversion between two lithiated η^3-aza-allyl enantiomeric monomers, namely (*R*)-η^3–**367** and (*S*)-η^3–**367**, mediated by a

complex mixture of diastereomeric oxazoline-bridged dimeric species, has been proposed as a possible mechanism responsible for the fast racemization of **367** (Scheme 105).

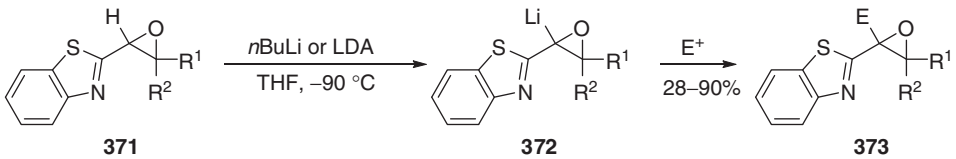


(*R*)-η^3-**367** (*S*)-η^3-**367**

Scheme 105

1.14.2.3.10 Heteroaryl substituted oxiranyllithiums

Among lithiated oxiranes α-heterosubstituted oxiranyllithiums are valuable synthons because of their great chemical stability in addition to their synthetic utility. The first example of such class of functionalized organolithiums, reported by Florio et al.,[107] is represented by α-benzothiazolyl α-lithiated oxirane **372** generated by treatment of epoxide **371** with *n*-BuLi at −90 °C in THF (Scheme 106). Trapping reactions of **372** with classical electrophiles gave polysubstituted oxiranes **373** in moderate to good yields. It is worth nothing that the deprotonation reactions of isomeric epoxides *cis*-**371** (R^1 = H, R^2 = Me) or *trans*-**371** (R^1 = Me, R^2 = Me), followed by coupling with benzaldehyde, led to the same (*Z*)-configured epoxyalcohol **373** (E = PhCHOH, R^1 = H, R^2 = Me); such stereoconvergency was explained by assuming that an equilibration between two isomeric oxiranyllithiums could occur and the attack of the benzaldehyde on the organolithium would take place from the less sterically hindered site.

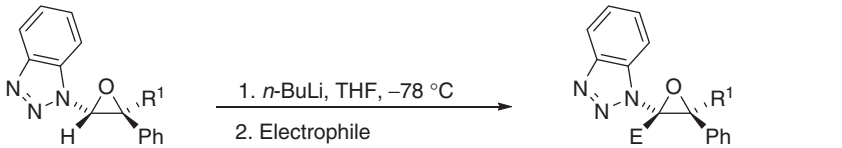


371 **372** **373**

E^+ = Me_3SiCl, MeI, ketones, aldehydes

Scheme 106

The benzotriazolyl moiety represents a valuable heteroaromatic anion-stabilizing group for lithiated epoxides, as recently demonstrated by Katritzky.[108] While arylepoxides are often generated and trapped at very low temperatures ($T \leq -98$ °C), benzotriazolyl oxirane **374** can be deprotonated at −78 °C with *n*-BuLi and trapped successfully with electrophiles to give tetrasubstituted oxiranes **376** (Scheme 107). The lithiation on the (*E*)-epoxide **375** (R^1 = Et) and the subsequent trapping with ethyl benzoate proceeds stereoselectively, leading to the α-benzoylated epoxide **377**.



374 (R^1=Ph)
375 (R^1=Et)

376 (72–92%, R^1=Ph)
377 (68%, R^1=Et, E=PhCO)

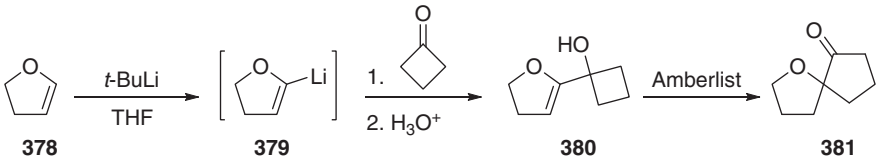
Electrophile = MeI, BuBr, PhCHO, Et_2CO, $PhCO_2Et$

Scheme 107

1.14.3 sp^2-Hybridized Organolithiums

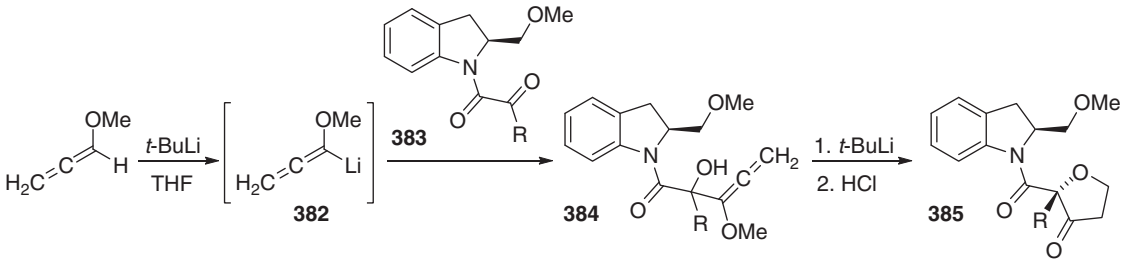
sp^2-Hybridized organolithiums α to oxygen have been extensively investigated and applications to the synthesis of molecules of varied complexity are countless. They can be easily generated mainly by deprotonation of cyclic and acyclic vinyl ethers, allenyl ethers using strong bases such as organolithiums, lithium amides, or mixed superbases (RLi and *t*-BuOK), sometimes by transmetalation, mainly Sn–Li exchange, or by halogen–lithium exchange. The structural features, stability, and reactivity of sp^2-α-O-organolithiums have been amply investigated either from the synthetic and mechanistic points of view so that they have been largely used in organic synthesis, in particular as acyl anion equivalents. Extensively reviewed by Yus and Najera,[1d,109] the present chapter focuses on some example cases and most recent achievements of this particular kind of heterosubstituted organolithiums.

Spiroketone **381** was prepared in a few steps the key one being the lithiation-trapping sequence of dihydrofuran **378** (Scheme 108). Indeed, lithiation of dihydrofuran **378** with *t*-BuLi in THF (− 78 to 0 °C) afforded lithiated intermediate **379**. Quench with cyclobutanone gave the adduct **380**, which after treatment with acidic ion-exchange resins furnished the spiroketone **381**.[110]



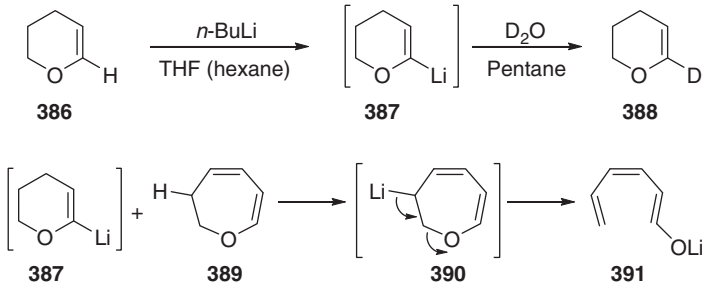
Scheme 108

The lithiation of 1-methoxyallene in ether or THF at − 30 to − 40 °C resulted in the formation of anion **382** which could be kept at − 30 °C for several days (Scheme 109). Spectroscopic data and *ab intio* calculations suggested a nonclassical 1,3-bridged structure for this lithiated species. It reacted efficiently with a variety of electrophiles under kinetically controlled conditions at the α-position.[111] Stereoselective addition to chiral α-keto amide **383** gave the hydroxy allenyl ether **384** that could be further transformed into dihydrofuranones **385**.[112]



Scheme 109

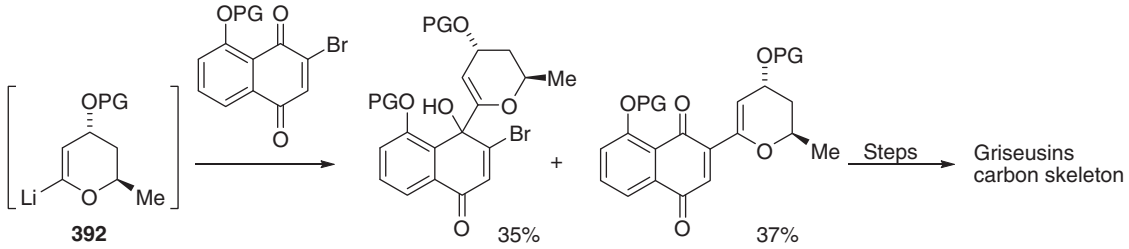
As mentioned above, cyclic vinyl ethers and their reactions with organic compounds have been extensively studied both experimentally and computationally because they are used as acyl anions synthons and precursors of cuprates. Dihydropyran **386** is smoothly lithiated to **387** by using *n*-BuLi in THF as proved by quenching with a source of deuterium to give **388** (Scheme 110). It is noteworthy that **387** is able to deprotonate the dihydrooxepin **389** at the allylic position. NMR investigation and deuteration



Scheme 110

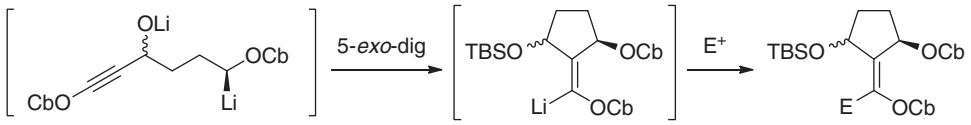
studies indicated that the resulting lithiated species **390** undergoes a ring-opening reaction ending up with the formation of the trienolate **391**.[113]

A very interesting application of functionalized lithiated dihydropyran such as **392** is the construction of the fully functionalized carbon skeleton of Griseusins based on a divergent-reconvergent approach (Scheme 111).



Scheme 111

As seen above sp^2-hybridized α-lithiated carbamate such as **180** is a key step in the synthesis of alkylidene cyclopentane derivative **182** (Scheme 112).[49]



Scheme 112

1.14.4 Conclusion

The understanding of the chemistry of α-oxygenorganolithiums, including α-lithiated ethers, acetals, carbamates, and epoxides has at present advanced to such a level that their use in organic synthesis has become almost routine. Indeed, several research groups have addressed the chemistry of α-oxygenated organolithiums over the last 20 to 30 years and still their work continues to unveil, on the basis of spectroscopic and computational studies, new aspects of their reaction pathways and to develop these into synthetically useful processes. The synthetic utility of α-lithiated ethers, carbamates, epoxides, boronates, based on trapping with electrophiles, stereoselective rearrangements, and asymmetric induction has been amply demonstrated, making them very useful building blocks for the synthesis of a variety of substances. What adds value to such lithiated species is that the adjacent stabilizing group is often amenable to useful synthetic elaborations, thus improving the synthetic potential. The current knowledge of the chemistry of α-oxygenated organolithiums allows it to be stated that they are not to be considered uncontrollable transient intermediates but deserve a place alongside any other organometallic species, ready to be used in organic synthesis.

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1.15 Olefination of Carbonyl Compounds by Main-Group Element Mediators

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Glossary

Horner–Wadsworth–Emmons reaction The transformation of an aldehyde or a ketone to an alkene by the action of a phosphonate-stabilized carbanion. The closely related Horner–Wittig reaction involves phosphine oxide-stabilized carbanions.

Julia olefination The transformation of an aldehyde or a ketone to an alkene by the use of sulfone-stabilized carbanions (metallated sulfones). Two variants exist, the multistage Julia–Lythgoe olefination employing simple aryl sulfones and the one-pot Julia–Kocienski olefination employing acceptor aryl sulfones.

Olefination A chemical process that leads to the connective synthesis of an alkene (olefin).

Peterson olefination The transformation of an aldehyde or a ketone to an alkene by the action of a silicon-stabilized carbanion. A similar process mediated by boron is also possible (the boron-Wittig reaction).

Wittig reaction The transformation of an aldehyde or a ketone to an alkene via reaction with a phosphorus ylide (phosphorane). The reaction proceeds via an oxaphosphetane intermediate (a 1-oxa-2-phosphacyclobutane).

1.15.1 Introduction

Before the advent of the Wittig reaction in 1953,[1] alkenes were typically prepared by comparatively harsh thermally driven elimination processes that lacked the finesse to effectively control either the location of the newly formed double bond or its stereochemical configuration. Thus, Saytzeff-type (i.e., most highly substituted) unsaturated products of *trans* configuration were easily targeted but access to *cis* configured olefins and less highly substituted examples was problematic (Hofmann elimination provided a solution in some cases). The Wittig reaction offered for the first time a mild connective alkene-forming method that circumvented these issues, being at once both regiospecific and often highly stereoselective with either (*E*)- or (*Z*)-alkenes being generated depending on the coupling partners and the reaction conditions employed. Today, a wide variety of related carbonyl olefination methods are available and a majority follow the same basic paradigm evident in the Wittig reaction, viz: reaction of a carbanion (or ylide) stabilized by an adjacent oxyphilic group (**1**) with a carbonyl component (**2**) initiates a cascade of fundamental steps that ultimately results in the formation of an alkene (located between the carbon atoms previously associated with the participating functional groups) with the concomitant extrusion of an oxidized form of the activating group (Scheme 1). Many powerful strategies are now available for alkene synthesis (e.g., transition metal-catalyzed cross-coupling, carbometallation of alkynes, etc.); however, carbonyl olefination methods remain indispensable because they provide the capability to splice fragments together while simultaneously generating a carbon–carbon double bond in a stereocontrolled fashion.

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

Group of activator	Activating unit X	Olefination method	Group of activator	Activating unit X	Olefination method
16	$PhSO_2$	Julia–Lythgoe	15	$(RO)_2P(=O)$	Horner–Wadsworth–Emmons (HWE)
16	$ActSO_2$	Julia–Kocienski			
15	R_3P^+	Wittig	14	R_3Si	Peterson
15	$R_2P(=O)$	Horner–Wittig	13	R_2B	Boron–Wittig

Scheme 1 Carbonyl olefination methods covered in this chapter.

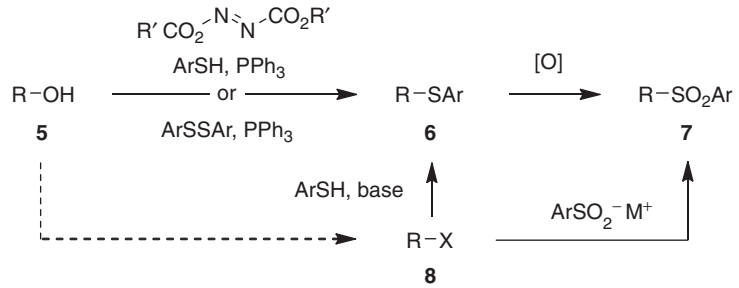
A selection of the most important main-group element-mediated carbonyl olefination methods will be covered herein (as indicated in Scheme 1), with an emphasis on recent developments that best highlight the synthetic utility of the process under consideration. For readers seeking more detailed information, within each section contemporary comprehensive reviews associated with the given method are cited first. Material is organized according to the group number of the atom center associated with the reactivity of the activating unit X, beginning with sulfur-based methods and progressing from right to left across the periodic table. Transition metal-mediated carbonyl olefination methods (e.g., the Cr-based Takai olefination and Ti-based Tebbe methylenation) are covered elsewhere in *Comprehensive Organic Synthesis II* (*see* Chapter 1.06).

1.15.2 Sulfur-Mediated Olefination Methods

Two significant olefination methods have emerged that involve the addition of α-metallated aryl alkyl sulfones to carbonyl compounds, herein referred to as the Julia–Lythgoe olefination and the Julia–Kocienski olefination. Beyond the initial addition step the two methods are quite distinct as in fact were the originators of each process: M. Julia introduced the 'classical' variant (the Julia–Lythgoe olefination) in 1973 while the 'modified' variant (the Julia–Kocienski olefination) was disclosed 18 years later by his brother S. A. Julia.[2,3] Both methods are capable of efficiently joining together fragments of great complexity about an olefinic linkage with a high degree of stereocontrol. The popularity of the Julia olefinations stems from their general effectiveness and the comparative ease of synthesizing the necessary sulfone precursors which are often simpler to prepare and purify than the phosphonium salts required for the Wittig reaction.

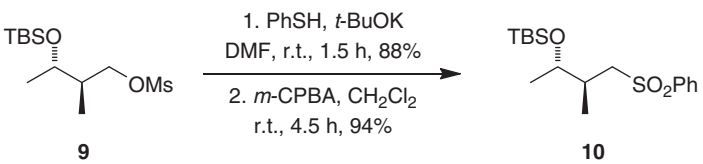
1.15.2.1 Synthesis of Sulfones for Julia Olefination Reactions

Sulfones for Julia olefination (**7**) are usually prepared by oxidation of the corresponding thioethers (**6**) which are commonly obtained by alkylation of the appropriate aryl mercaptan with either an alkyl halide/sulfonate ester (**8**) or with an alkanol (**5**) under phosphine activation conditions[4] (Scheme 2). Both steps are achievable in high yield and chemoselective oxidants are available that can convert thioethers **6** into sulfones **7** in the presence of other oxidizable functional groups. Sulfones can potentially be obtained more directly via alkylation of aryl sulfinates (**8** to **7**); however, sulfinate ester formation competes with sulfone formation in most cases unless the electrophile is allylic or benzylic.[5]

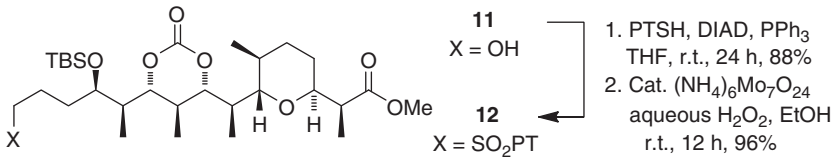


Scheme 2 Common approaches to sulfone synthesis.

The following equations exemplify methods for accessing Julia olefination precursors, typically phenyl sulfones for the Julia–Lythgoe variant and benzothiazol-2-yl (BT) or 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfones for the Julia–Kocienski variant. Simple aryl sulfones are most easily obtained via thioethers generated using reactive alkylating agents such as mesylate **9** (equation 1).[6] Complex aryl sulfones, such as zincophorin methyl ester fragment **12**, are best accessed from the corresponding alcohols by Mitsunobu reaction with the appropriate aryl thiol followed by oxidation (equation 2).[7] When applied to secondary alcohol substrates, the expected inversion of configuration is observed as seen in the synthesis of BT sulfone **14**, a precursor to vitamin D_2 (equation 3).[8] Alcohols have also been activated for direct substitution with BT and PT mercaptans using gallium(III) triflate[9] and *N*-(ethylsulfanylmethylene)-*N*,*N*-dimethylammonium tetrafluoroborate.[10]



(1)



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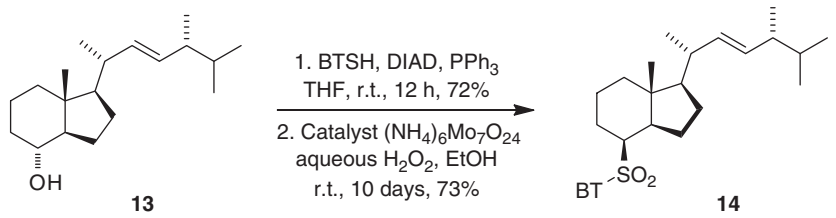
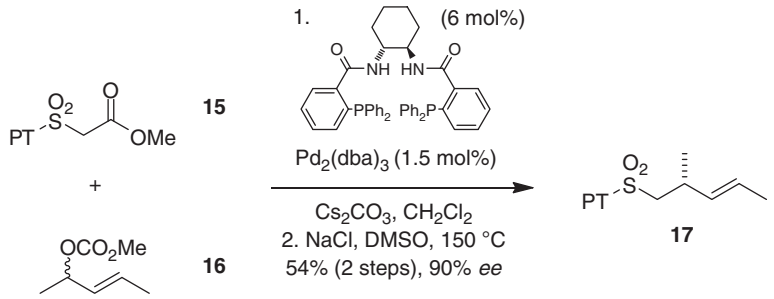


(3)

More inventive approaches to prepare sulfones for Julia olefination have been used on occasion. For example, an asymmetric allylic alkylation reaction using PT-sulfonylacetate **15** as nucleophile furnished enantioenriched branched PT sulfone **17** following Krapcho decarboalkoxylation en route to (+)-amphidinolide A (equation 4).[11] Alkylation of PhSCH(Li)SO_2Ph followed by reductive removal of the PhS moiety has also been used as a means to introduce an arylsulfonylmethyl unit.[12] Conjugate addition with vinyl sulfones provides another possibility for accessing Julia olefination precursors as seen in the diastereoselective synthesis of useful dioxanylmethyl BT sulfones (e.g., **19**, equation 5).[13] Requisite sulfones are also potentially available from thioethers generated by the addition of alkyl thiols to aryl chlorides capable of S_NAr reactions, such as 2-chlorobenzothiazole (BTCl, equation 6).[14]



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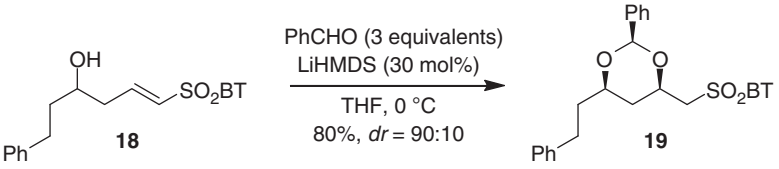

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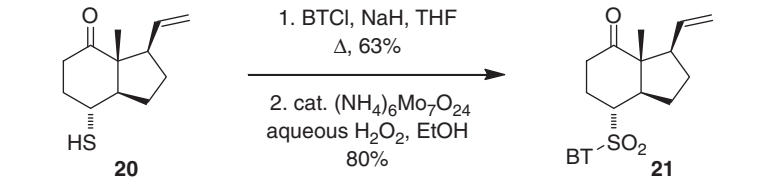


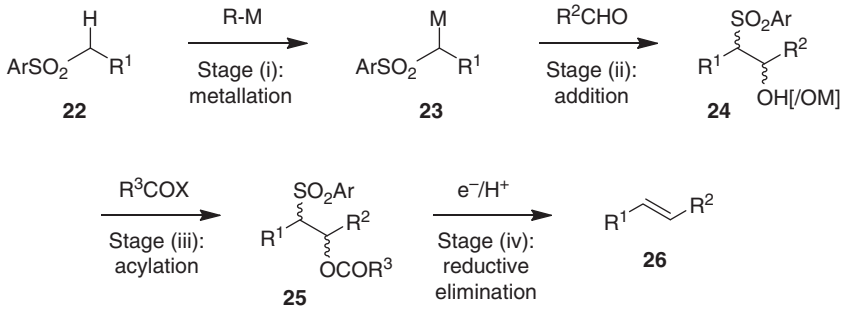
(6)

1.15.2.2 Multistep Alkene Formation With Aryl Alkyl Sulfone Anions: The Julia–Lythgoe Olefination

1.15.2.2.1 Overview and general considerations

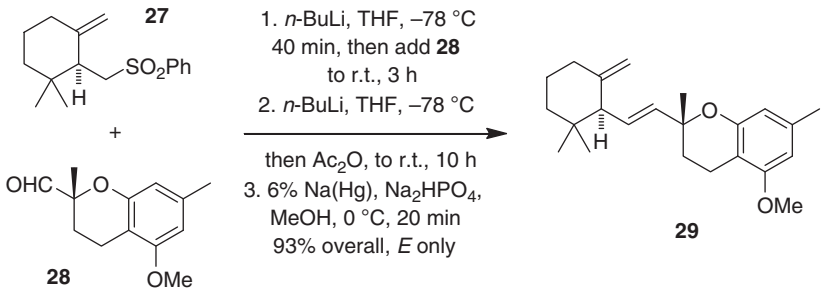
The Julia–Lythgoe olefination is a multistep process for the connective synthesis of alkenes based on the reductive elimination of β-acyloxysulfones generated by the addition of α-metallated alkyl aryl sulfones to carbonyl compounds.[15] It was first disclosed by Julia and Paris in 1973[2] and subsequently developed into a more general and useful transformation by Kocienski and Lythgoe.[16] Four distinct stages are involved in the olefination: (1) metallation of an aryl alkyl sulfone, (2) addition of the resulting carbanion

species to an aldehyde or ketone, (3) *O*-acylation (or sulfonylation) of the addition adduct, and (4) reductive elimination of the penultimate β-acyloxysulfone intermediate (Scheme 3, illustrated toward a 1,2-disubstituted alkene for the sake of simplicity). Although all stages can be conducted in a single reaction vessel, in practice, a higher overall yield is usually obtained if the penultimate intermediate is isolated before the reductive elimination step. The addition adduct **24** is typically generated as a mixture of all possible diastereoisomers; however, this is of no consequence because stereochemical information encoded in **24**/**25** is lost during the reductive elimination step. The distinguishing feature of the Julia–Lythgoe olefination is its high *trans* stereoselectivity, a facet of the various radical mechanisms that operate in the final stage (*vide infra*).



Scheme 3 The four stages of the Julia–Lythgoe olefination.

The most commonly adopted protocol for the Julia olefination remains that introduced by Kocienski and Lythgoe[16] and involves the addition of lithiated phenyl sulfones to the carbonyl component followed by acetylation or benzoylation and then reductive elimination mediated by 6% sodium amalgam in a phosphate-buffered MeOH-tetrahydrofuran (THF) solvent system. The acylation step mitigates against retroaddition that can occur during reductive elimination but it may sometimes be omitted without detriment to overall yield. The following highly optimized example, used in a recent synthesis of the mold metabolite siccanin, is representative (equation 7).[17]



(7)

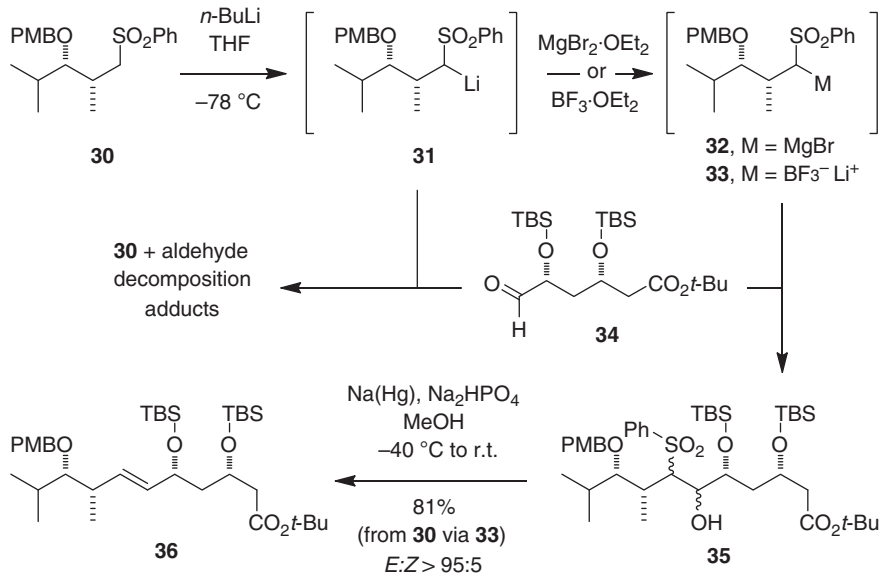
1.15.2.2.2 Factors affecting reaction efficacy and stereoselectivity

A successful outcome in the Julia–Lythgoe olefination is dependent on each of its four stages operating correctly. Problems are rarely encountered with the acylation step; however, the nature of the components to be coupled and the reaction conditions employed are a critical determinant of the efficacy of all other stages and the level of stereoselectivity that may be anticipated.

1.15.2.2.2.1 Sulfone metallation and addition to aldehydes and ketones

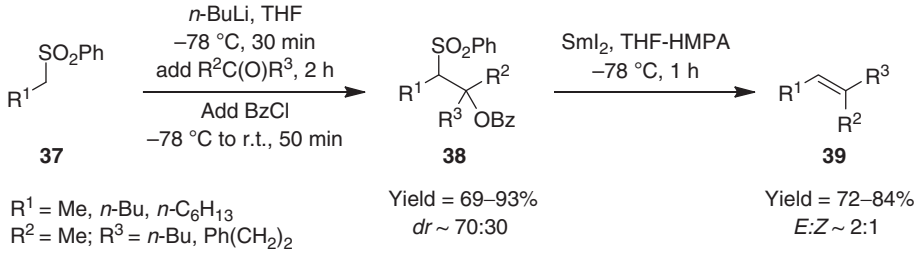
The α-protons of alkyl phenyl sulfones have an acidity comparable to those of esters ($pK_a \sim 30$ in DMSO)[18] and deprotonation can be conveniently achieved with *n*-butyllithium in THF solvent at low temperature. Alternatively, if the sulfone contains electrophilic sites that may be attacked by the alkyllithium reagent, a strong non-nucleophilic base like lithium diisopropylamide (LDA) can be employed instead to effect lithiation. Lithiated primary alkyl phenyl sulfones have good nucleophilicity and usually add to aldehydes to produce the expected β-alkoxysulfone intermediates in excellent yield; however, their intrinsic basicity can cause problems with readily enolizable aldehydes. Transmetallation from lithium to a less basic organometallic derivative offers a solution to this problem.[19] For example, the lithio derivative of sulfone **30** failed to add to α-oxygenated aldehyde **34** under all conditions examined, but transmetallation to the Grignard species **32** or trifluoroborate complex **33** led to the desired addition adduct **35** (Scheme 4).[20] Subsequent reductive elimination (without acylation of the alcohol) gave *trans*-alkene **36**, an intermediate in a synthesis of the antibiotic roxaticin, in greater than 80% overall yield.

Targeting of trisubstituted olefins must necessarily involve the use of either a secondary alkyl metallated sulfone or a ketone. Both component classes present potential problems that could result in a low yielding addition step. Addition of primary alkyl metallated sulfones to ketones introduces a heightened risk of retroaddition from β-alkoxysulfone adducts back into starting



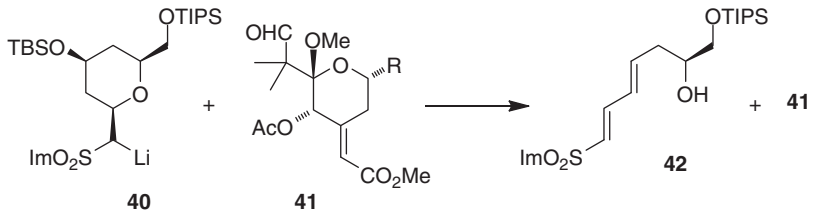
Scheme 4 Synthesis of (+)-roxaticin intermediate **36** by Julia–Lythgoe olefination.

materials. Conversely, proton transfer can dominate in the attempted addition of sterically hindered (and more basic) secondary alkyl metallated sulfones to enolizable aldehydes. Hart and Wu reported that the use of 1,2-dimethoxyethane (DME) as solvent lessens the extent of enolization,[21] although a general solution to the problem of adding primary alkyl metallated sulfones to ketones has been advanced by Markó et al.[22] The latter involves *in situ* trapping of the *β*-alkoxysulfone intermediate at low temperature by either benzoyl chloride (BzCl) or trimethylsilyl chloride. Use of BzCl for trapping combined with SmI_2-mediated reductive elimination conditions provides for a high yielding synthesis of trisubstituted olefins, albeit with low stereoselectivity (Scheme 5). Use of *in situ* trapping agents is also advocated when allylic (or other types of semistabilized) metallated sulfones are employed, again to guard against the specter of retroaddition.



Scheme 5 Synthesis of trisubstituted alkenes via *β*-benzoyloxysulfones.

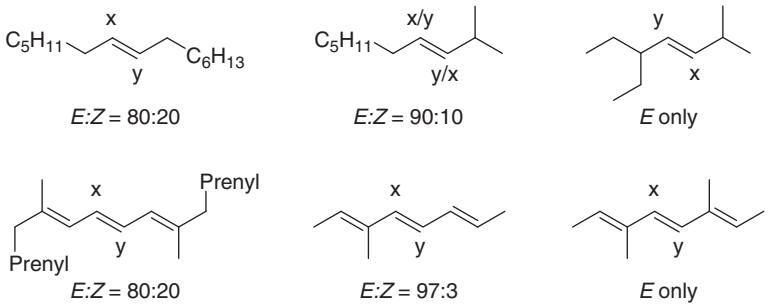
Sulfones with potential leaving groups in the *β*-position have been successfully employed on occasion;[23] however, problems with *β*-elimination are likely to be encountered if addition to the carbonyl component is not facile. For example, in an attempted synthesis of bryostatin 2, lithiated *N*-methylimidazol-2-yl (Im) sulfone **40** fragmented to diene **42** rather than adding to the hindered aldehyde **41** (equation 8).[24] This problem was overcome by reversing the nature of the components (see Table 1, entry 5 in Section 1.15.2.2.4).



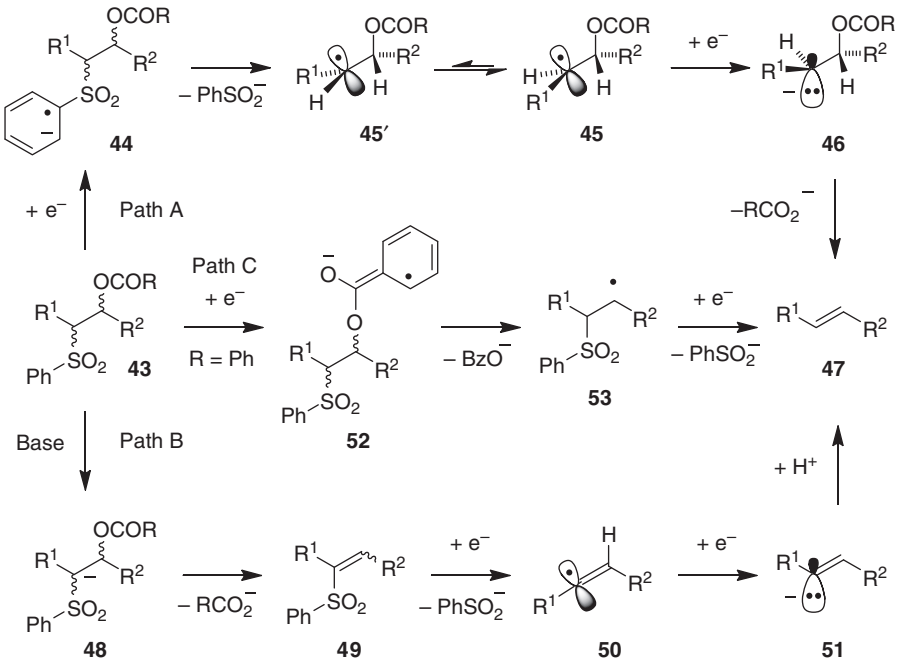
(8)

1.15.2.2.2.2 *Reductive elimination protocols and the effect of chain-branching on* trans *selectivity*

A marked improvement in *trans* selectivity is noted for the generation of 1,2-disubstituted alkenes by reductive elimination of β-acyloxysulfones as chain-branching elements are introduced into the substituents that will flank the new double bond (Scheme 6).[33] A mechanism accounting for this behavior (which is found for both nonconjugated and conjugated alkene products), and the fact that the *E*:*Z* ratio of the final product is independent of the diastereomeric composition of the β-acyloxysulfone starting material, was formulated by Kocienski and Lythgoe (path A, Scheme 7). Injection of a single electron into the phenyl sulfone followed by loss of sulfinate is proposed to lead to a radical intermediate **45** that conformationally relaxes before the addition of a second electron and elimination of oxygen nucleofuge from the incipient carbanion **46**. Later studies by Keck et al. cast doubt on the veracity of this mechanism for reductions mediated by Na(Hg) but supported its likely validity in reactions employing SmI_2 as an alternate electron source.[34] Keck put forth a second mechanistic hypothesis to better account for Na(Hg) reductions (path B) and Markó et al. later suggested yet another distinct possibility that potentially applies to the reduction of β-benzoyloxysulfones (path C).[22] The synthetic consequences of these alternate mechanisms are now briefly surveyed.



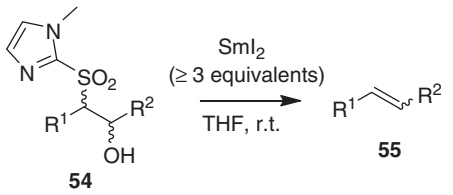
Scheme 6 Isomeric composition of alkenes generated by treatment of β-benzoyloxysulfones with 6% Na(Hg) in MeOH-THF at –20 °C (x = original site of $PhSO_2$ group, y = original site of BzO group).



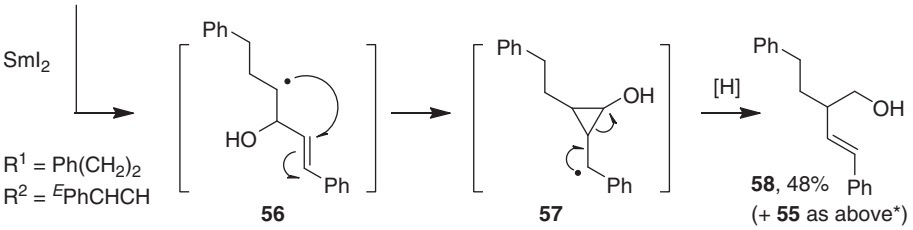
Scheme 7 Mechanistic manifolds for reductive elimination from β-acyloxysulfones.

Sodium amalgam is an inconvenient reagent to use for large-scale applications and alternative reductants have been sought for the final stage of Julia–Lythgoe olefination, among them a combination of mercuric chloride catalyst with magnesium metal as the stoichiometric electron source.[35] The use of samarium diiodide for the same purpose was introduced by Kende and Mendoza and applied to the reductive elimination of β-hydroxy-*N*-methylimidazol-2-ylsulfones (Scheme 8).[36] Such adducts are obtained in analogous fashion to comparable β-hydroxyphenylsulfones but are more easily reduced owing to the lower reduction potential of

the imidazolyl moiety (β-hydroxyphenylsulfones are not reduced at all by SmI_2 in THF alone). The method gives lower *trans* selectivity to that generally expected from the standard Na(Hg)-mediated Julia olefination proceeding via β-acyloxysulfones. Isolation of rearranged byproduct **58** from the reductive elimination of an hydroxysulfone **54** implicated the possible intermediacy of a radical species **56** (cf. **45**, Scheme 7).

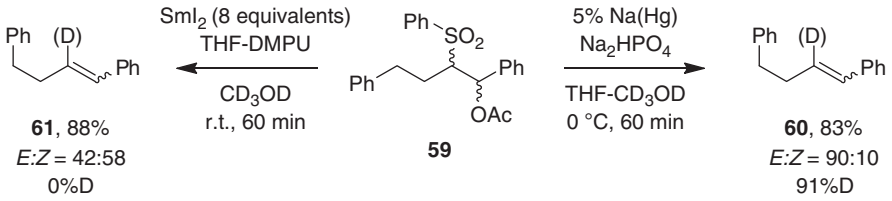


R^1	R^2	Yield **55**	*E*:*Z*
$Ph(CH_2)_2$	Ph	82%	88:12
$Ph(CH_2)_2$	Me_2CCH	84%	83:17
$Ph(CH_2)_2$	$Ph(CH_2)_2$	55%	75:25
Me_2CCH	^{E}PhCHCH	78%	> 95:05
Me_2CCH	Ph	87%	83:17
*$Ph(CH_2)_2$	^{E}PhCHCH	20%	82:18



Scheme 8 SmI_2-mediated reductive elimination from β-hydroxy-*N*-methylimidazolesulfones.

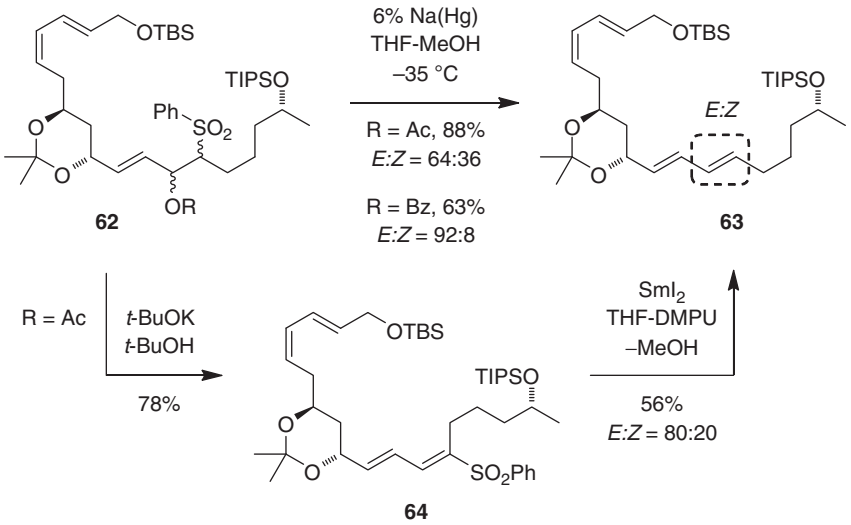
Independent work from Keck[34] and Ihara[37] later established that SmI_2 can be used to generate alkenes from less exotic β-hydroxy and β-acyloxy phenylsulfones in the presence of dipolar cosolvents such as hexamethylphosphoramide (HMPA) and 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU). Examination of the reductive elimination of acetoxysulfone **59** in solvent mixtures that included d_4-methanol revealed fundamental differences in the nature of the mechanism for Na(Hg) versus SmI_2-mediated reactions (Scheme 9).[34] The outcome of the reaction using Na(Hg) is incompatible with the original Kocienski–Lythgoe mechanism (path A, Scheme 7), which would not predict any deuterium incorporation into alkene **60**. Given the basic reaction conditions, Keck proposed instead that the first stage of the reaction involves E1cB elimination to give a vinyl sulfone **49** that is subsequently reduced by a pair of electron transfer events to produce an (*E*)-configured vinyl carbanion **51** that is quenched by proton to give the final olefin product (path B). By contrast, taken together with the earlier findings of Kende (Scheme 8),[36] the lack of deuteration found in **61** when the reduction of **59** was conducted with SmI_2 suggests that path A more likely operates under these conditions.



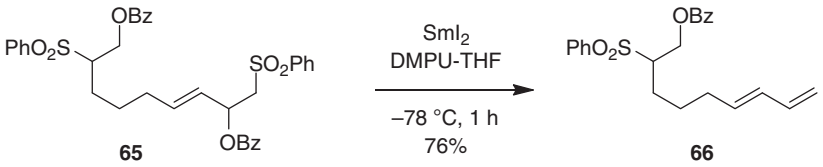
Scheme 9 Outcome of reductive elimination differs for Na(Hg) and SmI_2.

The third mechanistic possibility (path C) was introduced by Markó et al. to account for the large rate differences they observed in the SmI_2-mediated reductive elimination of β-hydroxy- versus β-benzoyloxysulfones in competition experiments.[22] The practical upshot of the various findings described above is that the outcome of reductive elimination can be fine-tuned by a judicious choice of electron source, aryl sulfone type, and acyl group. For example, in a total synthesis of macrolactin A, the *E*:*Z* ratio of advanced intermediate **63** was found to depend critically on the manner of the reductive elimination process used to access it (Scheme 10).[38] The conversion of vinyl sulfone **64** to **63** illustrates that SmI_2 can give good *trans* selectivity when applied to this substrate class.[34] Large differences in stereoselectivity and efficacy based on the use of acetyl or benzoyl groups were previously noted by Kocienski et al. in their syntheses of vitamin D_4[39] and milbemycin β_3.[40] One type of acyl group is not necessarily superior to the other and in challenging cases both AcO and BzO leaving groups should be evaluated. When a BzO leaving group is employed, the potential consequences of generating a carbon-centered radical at the β-position must be considered (e.g., potential geometrical isomerization of a preexisting γ,δ-unsaturated bond).[39]

Finally, it should be noted that the rate of reductive elimination is strongly influenced by the intrinsic structure of the β-hydroxysulfone derivative. Functional groups at benzylic or allylic sites are reduced faster than those located at unactivated positions, as illustrated by the chemoselective conversion of *bis*-benzoyloxysulfone **65** into diene **66** (equation 9).[41]



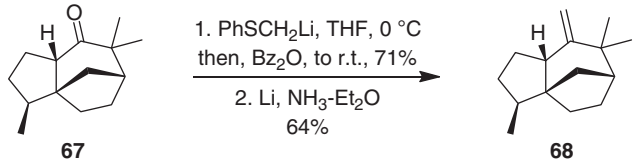
Scheme 10 Dependence of stereoselectivity on elimination protocol.



(9)

1.15.2.2.3 Notable reaction variants

A selection of the most synthetically useful variants of the Julia–Lythgoe olefination is collected together within this section. A process that has found few applications and yet deserving of mention is the methylenation reaction introduced by Coates and Sowerby in 1972.[42] This reaction is a direct antecedent of the Julia–Lythgoe olefination and involves the addition of phenylthiomethyllithium to ketones, benzoylation of the resulting β-alkoxysulfide anion, and then reductive elimination under dissolving metal conditions. The difficulty of generating α-lithiosulfides as compared to α-lithiosulfones effectively limits the scope of this transformation to methylenation. Nonetheless, the $PhSCH_2Li$-based process is capable of methylenating-hindered ketones that are prone to epimerization, as seen in the conversion of polycyclic ketone **67** to the sesquiterpene zizazene (**68**) (equation 10).[43]

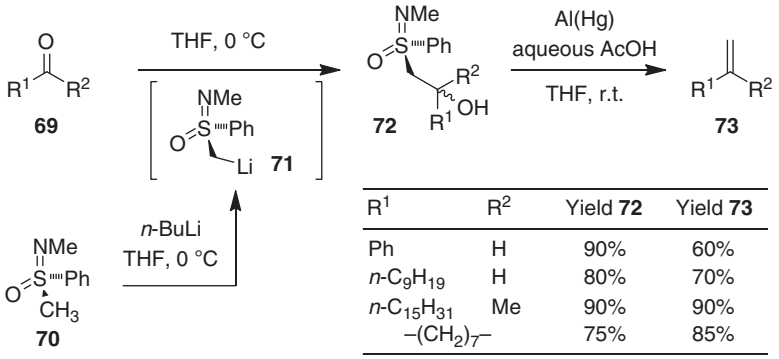


(10)

1.15.2.2.3.1 Sulfoximine-based variant: The Johnson methylenation

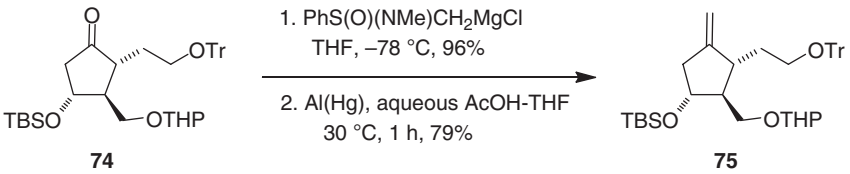
Contemporaneous with the introduction of the Julia–Lythgoe olefination, Johnson et al. disclosed an analogous reaction involving metallated phenylsulfoximines.[44,45] Initial experiments revealed that the process was not capable of generating stereogenic alkenes with synthetically useful levels of geometrical selectivity (e.g., 1,2-disubstituted alkenes are produced with $E{:}Z \sim 3{:}2$); however, this is of no consequence for methylenation, a transformation for which the Johnson protocol has found a special niche. Methylenation is achieved by the addition of lithiated *N,S*-dimethylphenylsulfoximine (**71**) to an aldehyde or ketone followed by reductive elimination of the resulting β-hydroxysulfoximine **72** with aluminum amalgam (Scheme 11).

As with the aforementioned Coates–Sowerby procedure, the Johnson methylenation is a useful tool to consider when contemplating the conversion of a readily epimerized ketone into a terminal alkene. The procedure has been applied successfully en route to eicosanoid TxA_2 receptor ligands such as 11*a*,9*a*-epoxymethanothromboxane A_2[46] and PgH_2 analogs, as illustrated by the preparation of methylidenecyclopentane **75** (equation 11).[47]



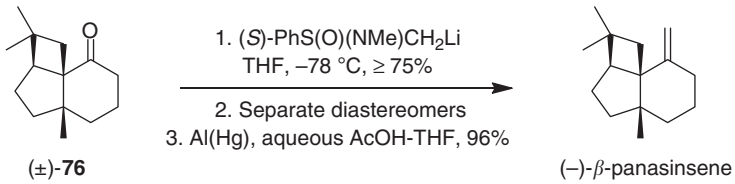
R^1	R^2	Yield **72**	Yield **73**
Ph	H	90%	60%
n-C_9H_{19}	H	80%	70%
n-$C_{15}H_{31}$	Me	90%	90%
–$(CH_2)_7$–		75%	85%

Scheme 11 The Johnson methylenation.



(11)

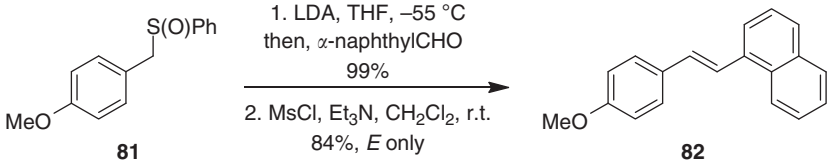
The sulfur atom within sulfoximines is stereogenic and compound **70** can be resolved into configurationally stable enantiomers. Deployment of this commercially available reagent in scalemic form enables methylenation to be achieved in concert with resolution of racemic substrates providing that the intermediate diastereomeric β-hydroxysulfoximines are separated into pure stereoisomers before reductive elimination. This strategy was demonstrated by Johnson and Meanwell in the denouement of their total synthesis of (–)-β-panasinsene (equation 12).[44c] Other potentially useful applications of sulfoximines in carbonyl olefination have appeared. For example, a general fluoromethylenation process has been achieved using *S*-(fluoromethyl)-*N*-methylphenylsulfoximine.[48]



(12)

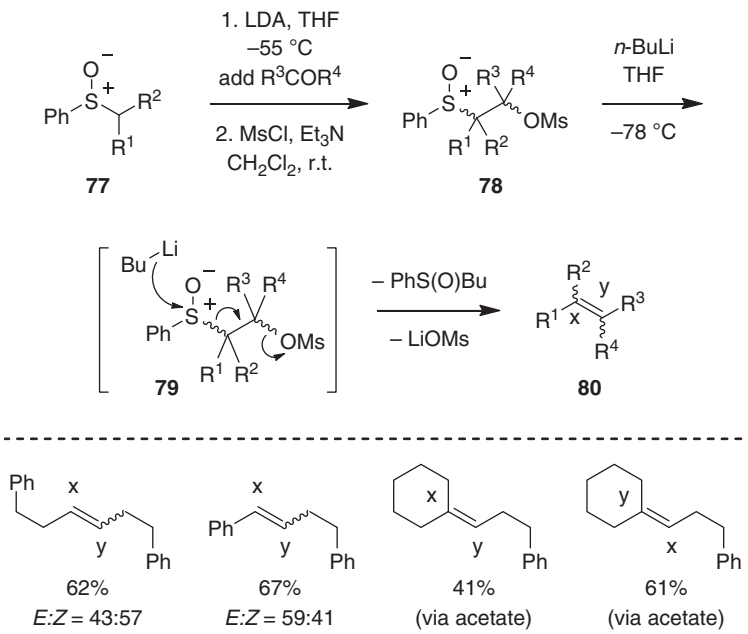
1.15.2.2.3.2 Sulfoxide-based variants

α-Metallated sulfoxides are more nucleophilic than the corresponding sulfone-stabilized carbanions and as such these reagents may offer advantages in the initial stage of Julia–Lythgoe type chemistry. Satoh et al. realized a viable sulfoxide-based Julia olefination and demonstrated that sulfoxide–metal exchange could be used as an alternative to single-electron reductants in the elimination step.[49,50] Generation of a lithiated sulfoxide is achieved with LDA (sulfoxide–metal exchange competes with deprotonation if *n*-BuLi is employed instead) and this species is added to an aldehyde or ketone to produce the expected isomeric mixture of β-hydroxysulfoxides (**Scheme 12**). Mesylation or acetylation of the hydroxyl group followed by sulfoxide–metal exchange (best achieved with *n*-BuLi) triggers a direct elimination that results in the formation of the desired alkene, a sulfoxide–ligand exchange byproduct (PhS(O)Bu), and a lithium salt. Disubstituted and trisubstituted olefins (including alkylidenecyclopropanes)[51] can be made in acceptable overall yield by the method but the formation of monosubstituted and tetrasubstituted examples is problematic. The breakdown of β-mesyloxysulfoxides to alkenes is not wholly stereospecific and this olefination process gives comparatively poor *E*:*Z* selectivity except when aromatic aldehydes are used as coupling partners. In this case, very high *trans* stereoselectivity is observed and elimination occurs spontaneously during the mesylation step via an E1-type mechanism. An effective synthesis of β-substituted styrenes and stilbenes is available from this approach (e.g., equation 13).[50]



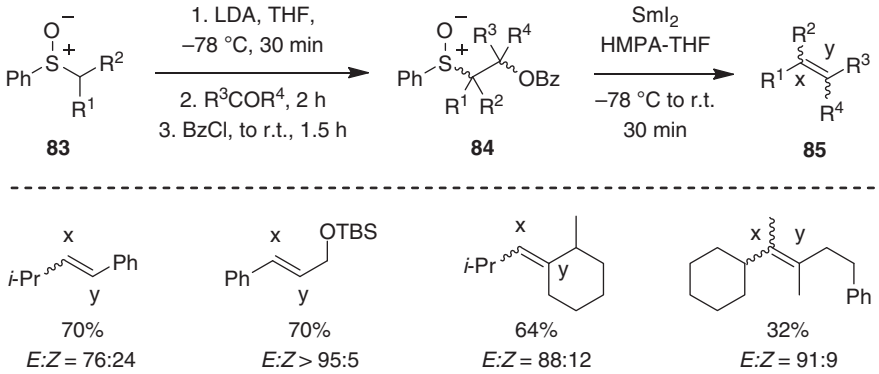
(13)

The characteristic general *trans* selectivity of the Julia olefination can be recovered in sulfoxide-based variants if the elimination stage is performed in the more usual reductive mode. Applying this principle, Markó et al. have demonstrated the *E*-selective



Scheme 12 Alkene formation from β-mesyloxy- and β-acetyloxy-sulfoxides initiated by sulfoxide–metal exchange. Overall yields from **77** are indicated for representative product olefins: x = original site of sulfoxide, y = original site of carbonyl group.

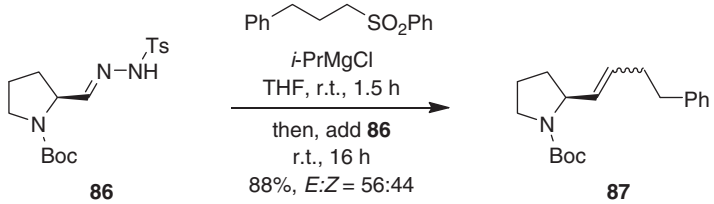
synthesis of 1,2-disubstituted, trisubstituted, and even tetrasubstituted, alkenes via SmI_2-mediated reductive elimination from diastereomeric mixtures of β-benzoyloxysulfoxides **84** (Scheme 13).[52]



Scheme 13 Alkene formation from β-benzoyloxy sulfoxides **84** by reductive elimination mediated by SmI_2. Overall yields from **83** are indicated for representative product olefins.

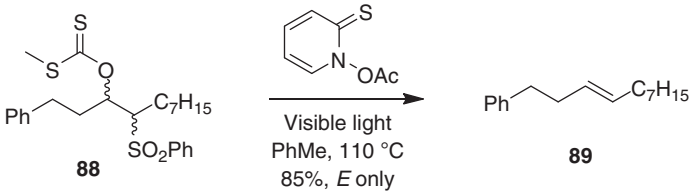
1.15.2.2.3.3 *Miscellaneous reaction variants*

Building on the precedent of Vedejs et al.,[53] Wicha and coworkers developed a two-step aldehyde olefination process based on the formation of the *N*-tosyl hydrazone derivative followed by treatment of this intermediate with a threefold excess of a magnesiated alkyl phenyl sulfone.[54] Organomagnesium reagents are favored over organolithium reagents for this purpose because they have a lower tendency to induce competing Shapiro fragmentation of the hydrazone. As illustrated by the following example (equation 14),[55] the method is high yielding and tolerates potential leaving groups in the α-position of the hydrazone but poor stereoselectivity is generally encountered.



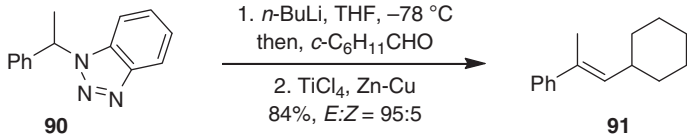
(14)

Barton and Tachdjian revisited a radical deoxygenation-based approach to the elimination stage of the Julia process[56] and succeeded in removing the requirement for an organotin hydride (equation 15).[57] A β-xanthylsulfone (e.g., **88**) replaces the usual β-acyloxysulfone and this compound is reduced with either the illustrated thiopyridone reagent or by a combination of diphenylsilane and dibenzoylperoxide. The requisite xanthate can be conveniently prepared by simply adding CS_2 followed by MeI to the β-alkoxyphenylsulfone intermediate generated in the initial addition stage of the olefination process.



(15)

A process conceptually related to the Julia–Lythgoe olefination but based on low valent titanium-mediated reductive elimination of β-hydroxybenzotriazoles has been described by Katritzky et al.[58] To date, investigation of this method has focused on the use of benzylic benzotriazoles but the data available suggest that it is highly *trans* selective for the generation of 1,2-disubstituted and trisubstituted alkenes (e.g., equation 16).



(16)

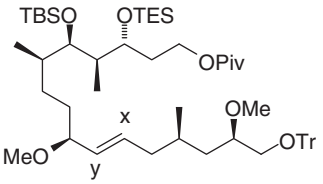
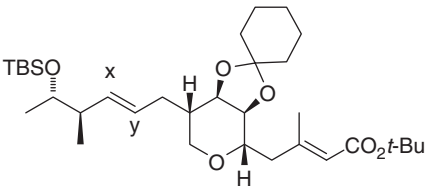
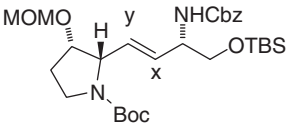
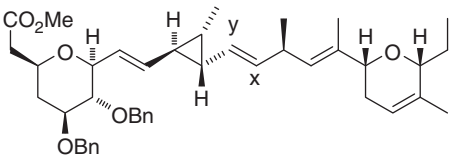
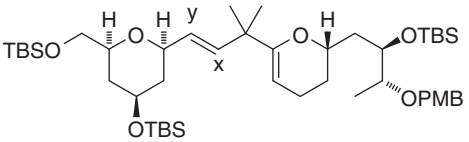
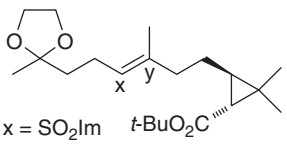
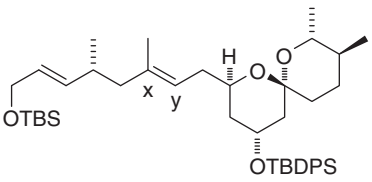
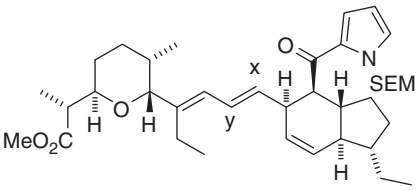
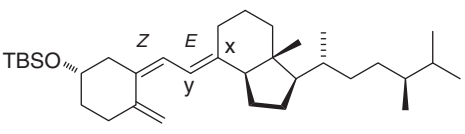
1.15.2.2.4 Illustrative examples in target-directed synthesis

Ten examples illustrating the use of the Julia–Lythgoe olefination as a fragment linkage tool in target-directed synthesis are depicted in **Table 1**. The selected examples include isolated and conjugated alkenes that are both 1,2-disubstituted and trisubstituted. The method is seen to be generally compatible with all major classes of protecting groups (including acetals, silyl ethers, benzyl ethers, esters, and carbamates) and shows good tolerance of potentially sensitive functionality such as cyclopropanes. As with simpler alkene targets, it is generally found that *trans* selectivity improves with increasing chain branching in the synthesis of 1,2-disubstituted alkenes. Thus, lesser branched targets leading to aplyronine A (entry 1)[25] and monic acid C (entry 2)[6] were generated with modest *E*:*Z*~5.5:1 (a related example is found in a synthesis of ionomycin),[59] whereas alkene targets with a greater degree of chain-branching and leading to slaframine (entry 3),[26] ambruticin (entry 4),[27] and bryostatin 2 (entry 5)[24] were obtained with significantly higher stereoselectivity. The last alkene was fashioned by Evans et al. using fairly conventional Julia olefination conditions; however, an initially attempted strategy using components of the opposite character failed due to β-elimination from the alternate sulfone anion (equation 8).[24] The successful component orientation was later applied in a more demanding context toward bryostatin 3 by Yamamura and coworkers.[60] Conjugated 1,2-disubstituted alkenes can generally be obtained with superlative *trans* selectivity without the need for such high levels of chain branching, as observed in the synthesis of an advanced indanomycin intermediate (entry 8).[30]

Synthesis of complex trisubstituted alkene targets presents the difficulties described above (see Section 1.15.2.2.2.1) and a good level of stereoselectivity is unlikely to be obtainable unless the olefin is conjugated. Thus, nonconjugated trisubstituted alkene-containing fragments of anthoplanone (entry 6)[28] and milbemycin β_3 (entry 7)[29] were obtained only as significant mixtures of *E* and *Z* isomers (*E*:*Z*~2:1). Addition of a primary alkyl sulfonyl anion to a ketone was used to prepare an alkene similar to the above milbemycin β_3 fragment en route to the related natural product avermectin B_{1a}.[61] Unusually, in this case, a single *E*-isomer was obtained, albeit in a significantly lower overall yield (16%).

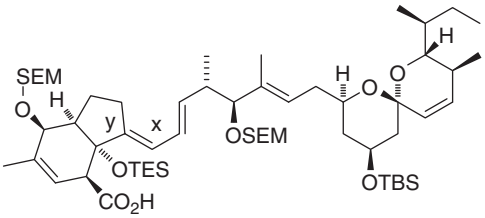
In a connective synthesis of the distinctive conjugated triene system of vitamin D_4 about the 7,8-trisubstituted olefin, it was discovered that the stereochemistry of a preexisting alkene within a dienal precursor was disturbed upon reductive elimination. Thus, the targeted vitamin D_4 silyl ether was obtained as a mixture of all four possible triene stereoisomers, albeit with good selectivity in favor of the desired 5*Z*,7*E*-isomer (entry 9).[31] Finally, White and Bolton's elaboration of the aglycon of avermectin B_{1a} exemplifies another conjugated alkene synthesis, this time via a Julia olefination utilizing the addition of an allylic phenylsulfone anion to a ketone (entry 10).[32] In this case, an ester moiety within the ketone substrate formed γ-lactone **93** during the course of usual operations circumventing the need for an exogenous acylating agent before reductive elimination (equation 17). The targeted trisubstituted olefin was generated as a single stereoisomer.

Table 1 A selection of complex alkene targets prepared by the Julia–Lythgoe olefination

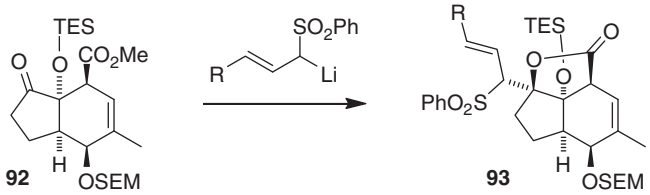
Entries	*Alkene target*[a]	*Reaction conditions and outcome*[b]	*References*
1		1. *n*-BuLi, THF, –78 °C 2. Ac_2O, DMAP, Py, r.t. 3. Na(Hg), Na_2HPO_4, MeOH, 0 °C 85%, *E*:*Z*=84:16	25
2		1. *n*-BuLi, THF, –65 °C 2. Ac_2O, Py, r.t. 3. Na(Hg), Na_2HPO_4, EtOAc-MeOH, 0 °C 62%, *E*:*Z*=85:15	6
3		1. *n*-BuLi, THF, –78 °C 2. Na(Hg), KH_2PO_4, MeOH, 0 °C 60%, *E* only	26
4		1. *n*-BuLi, Et_2O-hexane, –42 °C 2. Na(Hg), THF-MeOH, –35 °C 32%, *E*:*Z*=88:12	27
5		1. *n*-BuLi, THF, –78 °C 2. Ac_2O, DMAP, CH_2Cl_2 3. Mg, $HgCl_2$, EtOH 64%, *E* only	24
6		1. *n*-BuLi, THF, –78 °C, 1 h 2. SmI_2, THF 82%, *E*:*Z*=67:33	28
7		1. *n*-BuLi, THF, –78 °C 2. Ac_2O, DMAP, Py, to r.t. 3. Na(Hg), MeOH-THF, –20 °C 86%, *E*:*Z*=63:37	29
8		1. *n*-BuLi, HMPA, THF, –78 °C 2. BzCl, to r.t. 3. Na(Hg), MeOH-THF, –20 °C 53%, *E* only	30
9		1. *n*-BuLi, THF, –78 °C 2. AcCl, to r.t. 3. Na(Hg), Na_2HPO_4, MeOH-THF, –20 °C 68%, *ZE* (as shown):*ZZ*:*EE*:*EZ*=75:10:10:5	31

(*Continued*)

Table 1 Continued

Entries	Alkene target[a]	Reaction conditions and outcome[b]	References
10		i, *n*-BuLi, THF, −78 °C 2. NaOMe, Na_2HPO_4, MeOH, 0 °C 3. Na(Hg), Na_2HPO_4, MeOH, 0 °C 30%, *E* only	32

[a]Site of newly introduced alkene is located between x and y; x = original site of the arylsulfone ($PhSO_2$ unless otherwise indicated) and y = original site of β-substituent (OH, OAc, or OBz, as appropriate) in the reductive elimination precursor.
[b]Reaction conditions for all stages involved in generating the alkene from a sulfone precursor and an aldehyde or ketone; carbonyl component added after the sulfone was metallated; given yield is for overall process and ratio of isomers is about newly formed alkene unless otherwise indicated.

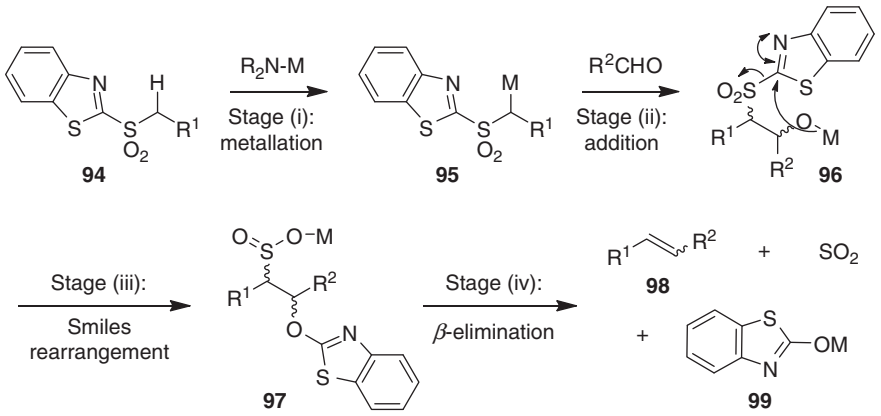


(17)

1.15.2.3 Direct Alkene Formation With Acceptor Aryl Alkyl Sulfone Anions: The Julia–Kocienski Olefination

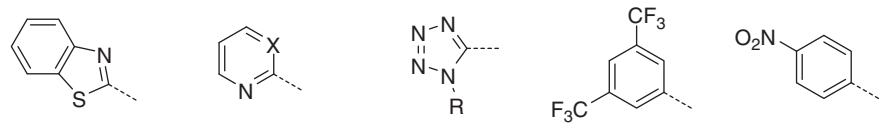
1.15.2.3.1 Overview and general considerations

In common with the Julia–Lythgoe olefination, the Julia–Kocienski olefination (also known as the 'modified' or 'one-pot' Julia olefination) forges alkenes via a process involving the addition of an α-metallated aryl alkyl sulfone to a carbonyl compound.[62] However, in this case the aryl group is an electron-acceptor (e.g., as in BT sulfone **94**) and the initially generated β-alkoxysulfone intermediate (**96**) experiences a spontaneous Smiles rearrangement (S→O migration of aryl group)[62c,63] which is followed by β-elimination of sulfur dioxide and an aryloxide anion to form an alkene directly (**Scheme 14**). The process as first disclosed by S. Julia and coworkers[3] utilized BT sulfones but since its introduction, numerous other aromatic activator groups have been similarly deployed, including pyrid-2-yl (PYR),[64,65] PT,[66] 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT),[67] and 3,5-bis(trifluoromethyl)phenyl (BTFP),[68] among others[69,70] (**Scheme 15**). The operational simplicity of the Julia–Kocienski olefination coupled with the facility it offers to fine-tune stereoselectivity on the basis of substrate selection and reaction conditions, and its excellent functional group tolerance, are all attributes that have contributed to this one-pot process gaining widespread acceptance as a generally applicable tool for advanced fragment linkage.



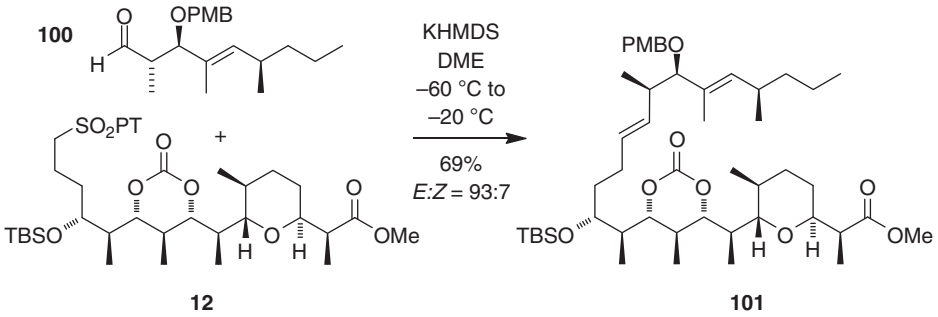
Scheme 14 Julia–Kocienski olefination employing a benzothiazol-2-yl (BT) sulfone.

Although the number of discrete stages involved in the Julia–Kocienski olefination equals that of the classical variant, in practice this is of little consequence because the entire process occurs as a spontaneous cascade once the α-metallated sulfone engages with the carbonyl coupling partner. The following example from a recent synthesis of zincophorin methyl ester is illustrative of the ease and power of the approach (preparation of PT sulfone **12** is shown above in equation 2). The protected



Scheme 15 A selection of aromatic activators used in the Julia–Kocienski olefination.

zincophorin adduct **101** was obtained in a good yield and with high stereoselectivity by the addition of aldehyde **100** to the potassium metallate of PT sulfone **12** at −65 °C followed by warming to −20 °C for 90 min (equation 18).[7]



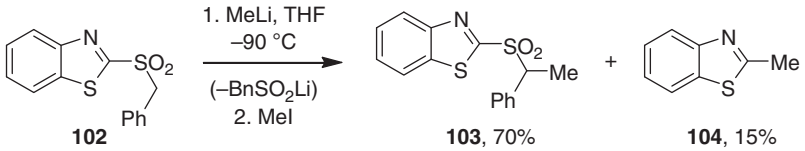
(18)

1.15.2.3.2 Factors affecting reaction efficacy and stereoselectivity

When applied in the proper context and with the appropriate choice of coupling partners and reaction conditions, the Julia–Kocienski olefination rarely fails to give acceptable results. Unlike the classical variant, the Julia–Kocienski olefination does not necessarily favor formation of the (*E*)-stereoisomer; however, scenarios where the (*Z*)-alkene product is likely to predominate, or where low stereoselectivity could be encountered, can often be predicted as described below.

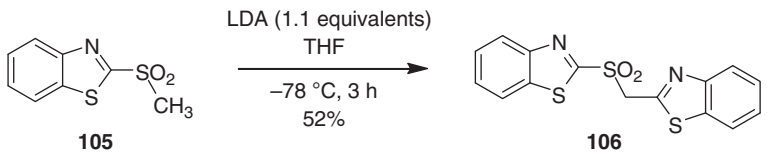
1.15.2.3.2.1 Base selection and premetallation versus Barbier protocols

The aryl sulfones used in the Julia–Kocienski olefination are by design electrophilic at the carbon–atom bearing the sulfonyl group; accordingly, the deprotonation step must be conducted with a non-nucleophilic base. LDA or the commercially available family of alkali metal hexamethyldisilazide bases (LiHMDS, NaHMDS, and KHMDS) are generally preferred for this purpose. Use of nucleophilic bases can induce side-reactions involving ipso substitution of a sulfinate nucleofuge, as indicated by the formation of a significant quantity of 2-methylbenzothiazole (**104**) during the attempted alkylation of BT sulfone **102** using methyllithium as base (equation 19).[64]



(19)

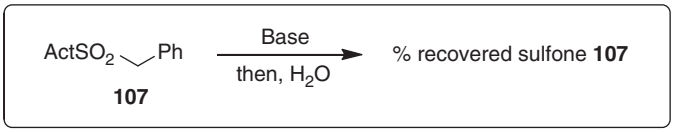
Assuming that a correct base selection is made, deleterious side-reactions caused by premature ipso substitution of sulfinate may still be encountered because the sulfone metallates are ambiphiles capable of pair-wise intermolecular self-condensation reactions. The propensity for such behavior is dependent on the type of aromatic activator and it is most likely to be exhibited by sulfone metallates bearing alkyl substituents of low steric demand. Unencumbered α-metallated BT sulfones are particularly susceptible to self-condensation, as evidenced by the formation of adduct **106** upon low temperature lithiation of methyl sulfone **105** (equation 20).[64]



(20)

The generality of previous assertions that metallated PT sulfones are less prone to self-condensation than related BT sulfone metallates[66] should now be regarded as suspect. Recent data indicate that many metallated BT and PT sulfones are of comparable stability and in some cases the former may actually be more stable.[71] A quantitative metallate stability study conducted by Nájera

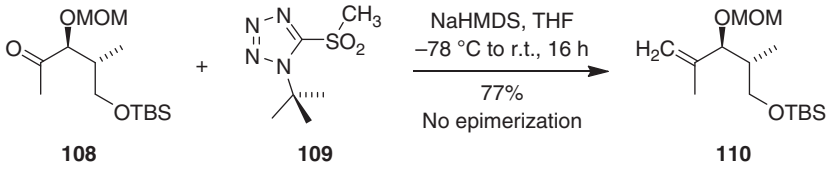
and coworkers revealed that TBT and BTFP sulfones are significantly more resistant to base-mediated decomposition than either BT or PT sulfones (Scheme 16).[68] The metallates of PYR sulfones are also known to be quite resistant to self-condensation.[64,65]



Conditions:	LDA, THF –78 °C, 24 h	KHMDS, DME –60 °C, 24 h	P4-*t*-Bu, THF –78 °C, 24 h	KOH, Bu_4NBr THF, r.t., 24 h
Activator: (Act)				
BT	> 95%	84%	73%	5%
PT	> 95%	50%	64%	0%
TBT	> 95%	99%	78%	0%
BTFP	> 95%	75%	88%	32%

Scheme 16 Recovery of sulfones **107** following treatment with base and reprotonation.

The heightened stability of TBT and BTFP sulfone metallates means that methyl sulfones bearing these particular aryl activators are optimal reagents for methylenation applications.[68,72] Aïssa examined methylenation of a wide variety of aldehydes and ketones with the easily prepared sulfone $TBTSO_2Me$ (**109**) using either NaHMDS in THF solvent at low temperature or a combination of Cs_2CO_3 in THF-DMF solvent at elevated temperature. Both procedures gave good to excellent yields of mono-substituted or 1,1-disubstituted alkenes; carbonyl compounds with α-stereogenic centers were not epimerized/racemized by the NaHMDS-mediated procedure (equation 21), but the alternate procedure results in some loss in stereochemical integrity (equation 22).[72] Aïssa also evaluated the Cs_2CO_3/THF-DMF procedure for the intramolecular condensation of ω-TBT-sulfonyl aldehydes and in doing so charted the first successful demonstration of intramolecular Julia–Kocienski reactions (6- (91%), 8- (32%, *E*:*Z*=50:50), and 14-membered (56%, *E*:Z=66:34) unsaturated carbocycles were prepared).[72] The monofluorinated analog of **109** (i.e., $TBTSO_2CH_2F$) is an effective fluoromethylenation reagent.[73]



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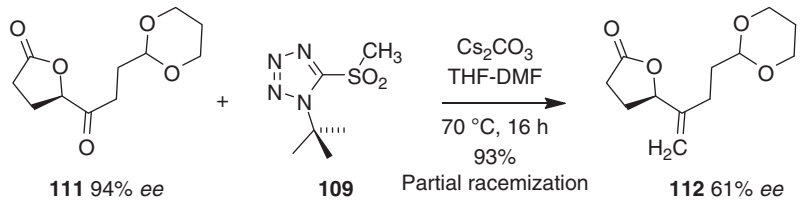
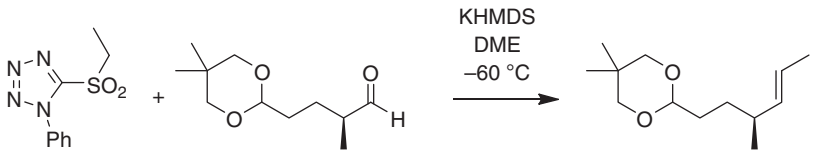


(22)

In Julia–Kocienski reactions where sulfone metallate self-condensation is a significant problem it can often be easily circumvented by adopting a Barbier addition protocol. Rather than first deprotonating the sulfone and then adding the carbonyl component (a premetallation protocol), the base is instead added to a mixture of the sulfone and carbonyl compound. In this manner, the sulfone carbanion reacts *in situ* with the carbonyl as soon as it is formed and the opportunity for self-condensation is minimized. Barbier protocols are often successful even in scenarios where the approach could be considered as potentially destructive to the aldehyde or ketone component. For example, during a synthesis of the polyketide herboxidiene (GEX1A) a Julia–Kocienski olefination between unencumbered PT sulfone **113** and enantioenriched aldehyde **114** results in only a 15% yield of *trans*-1,2-disubstituted olefin **115** via a premetallation protocol (equation 23). By contrast, adoption of a Barbier protocol produced the same target in 93% yield and without measurable loss in enantiomeric excess about the stereogenic center that originated in the enolizable aldehyde (presumably a consequence of sulfone **113** having higher kinetic acidity than **114**).[74] In general, it is recommended that a premetallation protocol be tested initially and then a Barbier protocol evaluated afterward only if significant self-condensation problems are noted with the first approach.



(23)

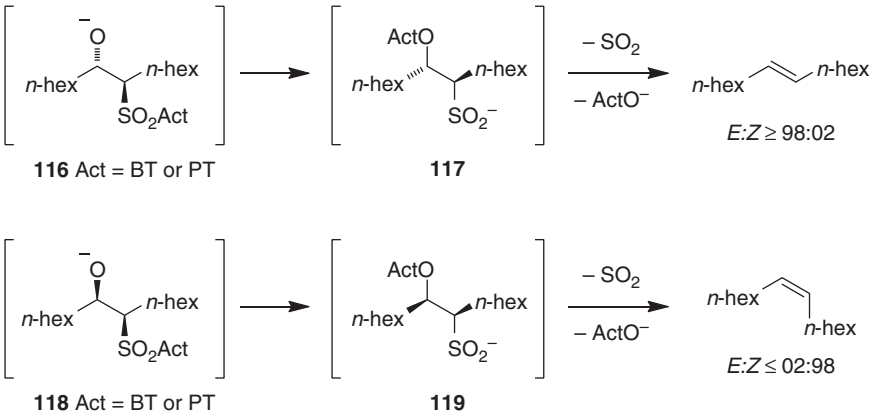
Premetallation (**113** + KHMDS, then **114**): 15%, *E:Z* > 90:10

Barbier (**113** + **114**, then KHMDS): 93%, *E:Z* = 93:07

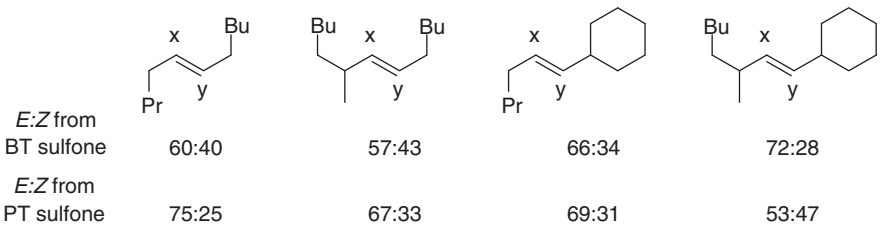
1.15.2.3.2.2 The effect of substrate structure on stereoselectivity

The electronic and steric character of substituents associated with the metallated sulfone nucleophile and the carbonyl electrophile strongly influences stereoselectivity in the Julia–Kocienski reaction. Stereochemical outcome is particularly sensitive to the presence of unsaturated bonds flanking the target carbon–carbon double bond and special attention must be given to sulfone and carbonyl component selection for the synthesis of conjugated alkenes. Discussion herein focuses on the generation of 1,2-disubstituted alkenes which can be prepared in a highly stereoselective manner. Similar mechanistic principles apply to the synthesis of trisubstituted and tetrasubsituted[75] alkenes, but high levels of stereocontrol are not generally realized when targeting these product classes via the Julia–Kocienski olefination.

In cases where the sulfone anion is not stabilized by resonance (i.e., no β,γ-unsaturation) and the carbonyl compound is not α,β-unsaturated, stereochemical outcome is determined by kinetic diastereoselectivity in the initial addition step. This fact was determined experimentally for several activator types (including BT,[76] PYR,[76] and PT[62a]) by the study of alkoxides derived from stereodefined β-hydroxysulfones which are observed to break down irreversibly and in a stereospecific manner to alkenes. For example, *anti*-β-alkoxysulfones **116** (Act = BT or PT) produced exclusively (*E*)-tetradec-7-ene upon their generation, whereas *syn* isomers **118** yielded (*Z*)-tetradec-7-ene instead (**Scheme 17**).[76,62a] The stereochemical outcome of these reactions indicates that electrofuge (SO_2) and nucleofuge ($ActO^-$) are antiperiplanar during the final β-elimination step of the Julia–Kocienski olefination (i.e., stage (iv), **Scheme 14**). By contrast to the Julia–Lythgoe olefination, there is no obvious relationship between overall stereoselectivity and the degree of chain-branching in the synthesis of nonconjugated 1,2-disubstituted alkenes via the one-pot variant (**Scheme 18**).[66] *Trans* selectivity can, however, be dramatically increased by variation in activator type, solvent, and base counter cation (Section 1.15.2.3.2.3).

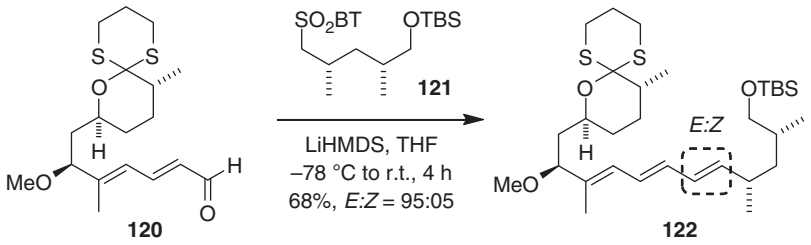


Scheme 17 Stereospecific breakdown of saturated β-alkoxysulfone anions.



Scheme 18 Isomeric composition of alkenes generated by addition of α-lithiated sulfones to aldehydes in THF at –78 °C (x = original site of SO_2Act, y = original site of CHO).[66]

The generation of alkenes from β-alkoxysulfone intermediates derived from addition reactions involving either β,γ-unsaturated α-metallated sulfones or α,β-unsaturated aldehydes, is not stereospecific.[62a] Thus, the net stereoselectivity of Julia–Kocienski olefinations that target conjugated alkenes is not a direct consequence of diastereoselectivity during the initial addition event. Reactions involving α,β-unsaturated aldehydes and nonconjugated α-metallated BT or PT sulfones generally exhibit high (*E*)-selectivity, for example as seen in an early application of the Julia–Kocienski olefination to fabricate the rapamycin triene system **122** (equation 24).[77] In the case of *para*-substituted benzaldehydes, preference for the *trans*-product positively correlates with the electron-donating ability of the substituent (equation 25).[64] In a rare exception to this common trend, Charette et al. discovered that the reactions of nonconjugated α-metallated PYR sulfones with (*E*)-configured α,β-unsaturated aldehydes in toluene solvent favor the formation of (*E,Z*)-dienes (equation 26).[65] Here it is noteworthy that PYR sulfone **126** could be premetallated at 25 °C without significant intervention of a self-condensation pathway; interestingly, use of lower temperatures resulted in decreased (*Z*)-selectivity for the newly introduced olefin.



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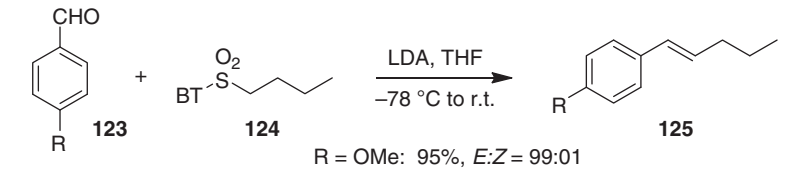

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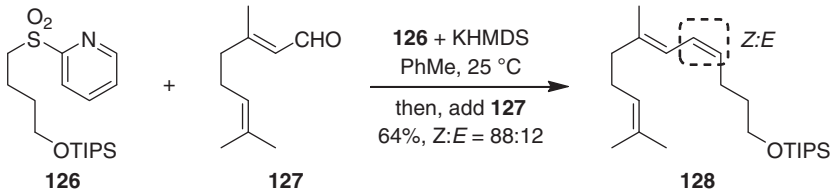
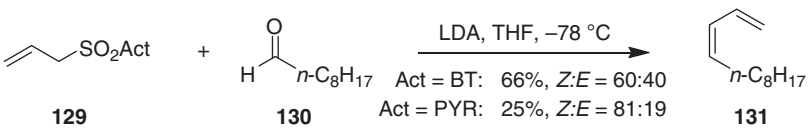


(26)

Reactions involving β,γ-unsaturated α-metallated sulfones (e.g., those derived from allylic, benzylic, or propargylic sulfones) and nonconjugated aldehydes typically show a preference for generation of the (*Z*)-configured alkene. The (*Z*)-selectivity observed in these cases is accentuated by the use of sulfones bearing less reactive aryl activators such as TBT and PYR (equations 27 and 28),[64,67] but it may become reduced or even reversed if significant chain-branching elements are present (equation 29).[64]



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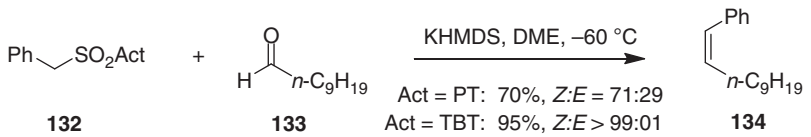

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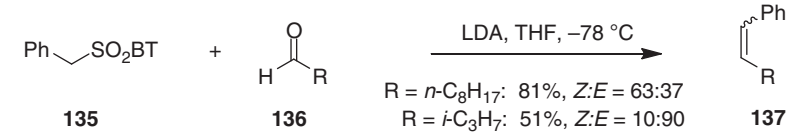
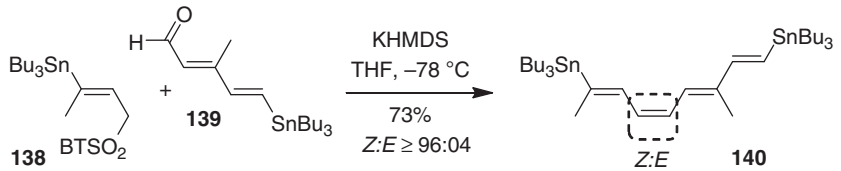


(29)

The stereochemical outcome of Julia–Kocienski reactions targeting 1,2-disubstituted alkenes wherein the reacting moieties of both coupling partners are conjugated cannot be predicted with complete confidence unless a very similar example has been previously examined. However, in the absence of significant chain-branching elements, such reactions have a tendency to favor formation of the (*Z*)-configured alkene. For example, an attempt to synthesize the (*E,E,E*)-trienyl rapamycin fragment **122** shown above (equation 24) via an alternative more convergent strategy involving formation of the central double bond gave the (*E,Z,E*)-triene preferentially instead (*vide infra*).[77] Brückner and coworkers took deliberate advantage of the same kind of stereoselectivity for the synthesis of conjugated bisvinylstannane synthons containing one (*Z*)-configured olefin in an otherwise all (*E*)-polyene (e.g., equation 30).[78] A counter-example exhibiting (*E*)-selectivity is seen in the synthesis of conjugated triene **143**; here the *α,β*-unsaturated aldehyde is *α*-branched (equation 31).[64]



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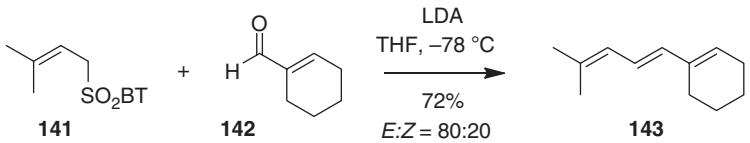
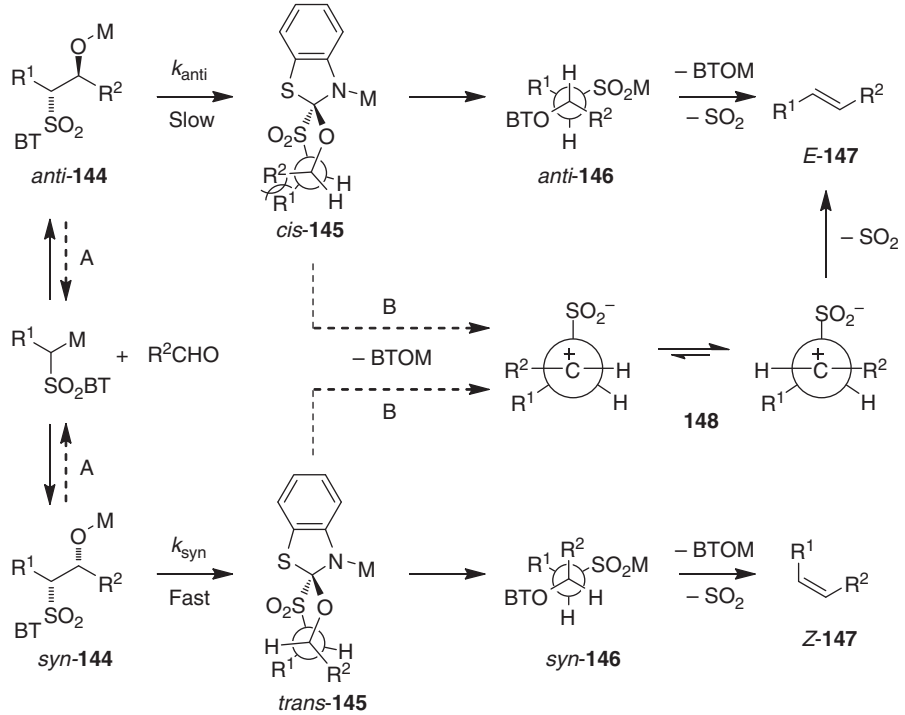


(31)

A mechanistic rationale to account for the stereochemical trends highlighted above was first proposed by Julia and coworkers based on their extensive seminal studies (**Scheme 19**).[64,76] The reality of the model has yet to be firmly established; however, it is of heuristic value and lies in broad agreement with a majority of the experimental findings made to date. As commented, for nonconjugated substrates initial addition is irreversible and *β*-alkoxysulfone intermediates **144** break down stereospecifically to alkene products: the observed *E:Z* ratio is then an artifact of any kinetic diastereoselectivity encountered during the generation of *anti*-**144** and *syn*-**144**. All other cases deviate from this simple scenario. When the sulfone metallate is stabilized (R^1 unsaturated), the initial addition step is reversible (pathway A available) and the final *E:Z* ratio is potentially determined by which *β*-alkoxysulfone intermediate experiences faster Smiles rearrangement. *Syn*-**144** avoids serious eclipsing interactions during the formation of spirocycle *trans*-**145** and therefore undergoes a faster net Smiles rearrangement than its



Scheme 19 A mechanistic proposal accounting for the origin of stereoselectivity in the Julia–Kocienski olefination (illustrated for a BT sulfone): $k_{syn} > k_{anti}$; pathway A (retroaddition) available if R^1 is unsaturated; pathway B (via zwitterion **148** to *E*-**147**) available if R^2 is unsaturated.

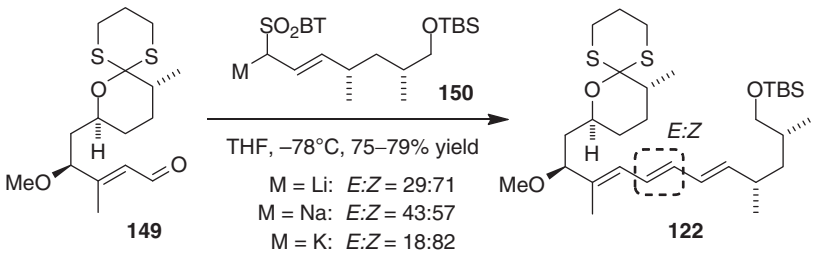
epimer *anti*-**144**. Thus, in cases where the rate of equilibration between *anti*-**144** and *syn*-**144** is significantly faster than Smiles rearrangement, a preference for formation of the (*Z*)-alkene product is anticipated on the basis of the Curtin–Hammett principle. Smiles rearrangement is retarded for less reactive/hindered aryl activators such as PYR and TBT and this accounts for the heightened (*Z*)-stereoselectivity of Julia–Kocienski reactions involving β,γ-unsaturated α-metallated TBT or PYR sulfones with nonconjugated aldehydes. The possibility of retroaddition from β-alkoxysulfones **144** where $R^1 = Ph$ has been verified by crossover experiments.[62a]

To account for the (*E*)-selectivity of olefination reactions involving α,β-unsaturated aldehydes (R^2 unsaturated) and nonconjugated sulfone metallates, an E1-type elimination pathway involving a putative zwitterionic species was proposed by Julia.[64] In this scenario, direct loss of an aryloxide anion from spirocycles **145** (pathway B), or a similar event from **146** following conclusion of the Smiles rearrangement, produces a zwitterion (**148**) that experiences conformational relaxation before loss of sulfur dioxide and the preferential formation of an (*E*)-alkene. For this pathway to be completely viable R^2 must be unsaturated (and electron donating) to offer conjugative stabilization to the carbocation center of **148**. Given the comparatively low nucleofugality of aryloxide anions, this hypothesis should be regarded as contentious; nonetheless, it does account for the observed increase in *E*:*Z* ratio for the Julia–Kocienski reactions of benzaldehydes **123** (equation 25) as the aromatic ring becomes more electron-rich.

Finally, in those examples where both R^1 and R^2 are unsaturated, there may be a confluence of pathways A and B and a delicate balance of effects will determine which geometrical isomer of the alkene product is ultimately favored.

1.15.2.3.2.3 The effect of base counter-cation and solvent on stereoselectivity

Early efforts to optimize the Julia–Kocienski reaction for applications in target-directed synthesis first indicated the profound effect that solvent polarity and base counter-cation exert on stereochemical outcome.[77,79,80] The influence of counter-cation was investigated by Kocienski and coworkers during their synthesis of a C10-C26 fragment of rapamycin (equation 32).[77] Variation between Li, Na, and K counter-cations for sulfone metallate **150** (prepared using HMDS metal amide bases) affected stereoselectivity in the formation of the central alkene of triene **122** but not in any obvious manner and none of the conditions surveyed favored the desired (*E*,*E*,*E*)-stereochemistry (the result of substrate effects, see Section 1.15.2.3.2.2). During study of a model reaction to identify optimal conditions to generate the cyclopropane flanked 1,2-disubstituted alkene of the anti-fungal agent U-106305, Charette and Lebel encountered wide variation in product *E*:*Z* ratio for the reaction between BT sulfone **151** and aldehyde **152** as different base and solvent combinations were surveyed (**Scheme 20**).[80] Subsequent reports now summarized have somewhat clarified which solvent and base combinations are preferred for a given alkene synthesis; however, investigation of these variables should continue to figure prominently in any optimization study for a given Julia–Kocienski olefination.



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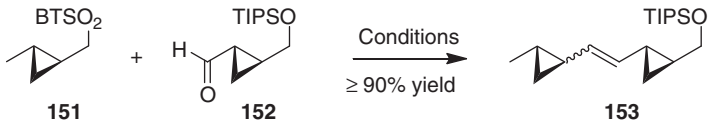
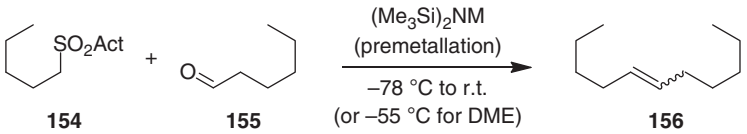


Reaction conditions	*E*:*Z* ratio of **153**
NaHMDS, DMF, –60 °C	78:22
NaHMDS, DME, –60 °C	71:29
KHMDS, THF, –78 °C	55:45
KHMDS, PhMe, –78 °C	21:79
NaHMDS, Et_2O, –78 °C	11:89
NaHMDS, PhMe, –78 °C	09:91

Scheme 20 Synthesis of a U-106305 model alkene.

The study of a variety of new possible aromatic activators by Kocienski and coworkers led to the important finding that PT sulfones offer generally superior (*E*)-selectivity for the synthesis of nonconjugated 1,2-disubstituted alkenes.[66] It was reasoned that

innate heightened diastereoselectivity in the initial addition step was the origin of improved stereocontrol and that this property could likely be accentuated by counter-cation and medium polarity effects. This hypothesis was borne out by experiments that showed a marked increase in *trans* selectivity in the synthesis of simple disubstituted alkenes from PT sulfones as solvent polarity and cation electropositivity were systematically increased (e.g., Scheme 21).[66] Comparable BT sulfones were found to be less responsive to the same changes in reaction conditions and the PT system has emerged as an optimal activator class for the synthesis of nonconjugated 1,2-disubstituted alkenes. All subsequent work with PT sulfones has reaffirmed that conditions favoring maximum dissociation of ion pairs (e.g., large cation, high polarity medium, and/or metal complexation agents) result in the highest level of *trans* selectivity in the synthesis of nonconjugated alkenes.



154 155 156

E:*Z* of **156** for Act = PT

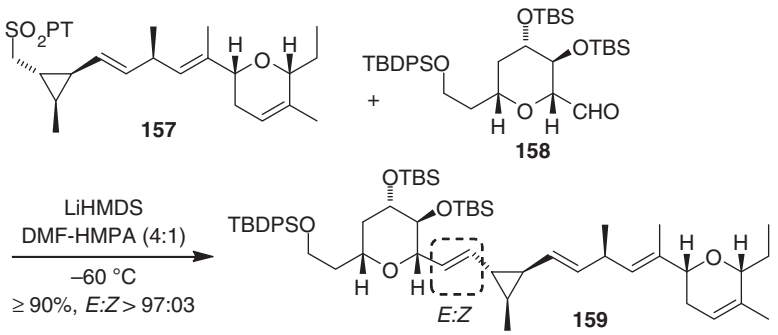
M	PhMe	Et_2O	THF	**DME**
Li	57:43	73:27	75:25	77:23
Na	59:51	57:43	76:24	86:14
K	64:36	72:26	86:14	**94:06**

E:*Z* of **156** for Act = BT

M	PhMe	Et_2O	THF	DME
Li	40:60	43:57	60:40	55:45
Na	51:49	53:47	–:–	77:23
K	47:53	51:49	55:45	75:25

Scheme 21 Dependence of stereoselectivity on solvent and base counter-cation in the synthesis of 5-undecene (**156**) from BT and PT sulfones **154.**

Following the introduction of PT sulfones, Jacobsen and Liu found that *trans* selectivity in the synthesis of the C8-C9 alkene of ambruticin could be increased significantly by conducting the Julia–Kocienski olefination in a very polar medium (DMF) that included strong dipolar aprotic cosolvent additives such as HMPA or DMPU with LiHMDS as base (equation 33).[81] In this case, Kocienski's preferred conditions of KHMDS base and DME solvent gave **159** in excellent yield but with no stereoselectivity. Since its introduction, the Jacobsen solvent and base system has been occasionally adopted by others and found to boost (*E*)-selectivity in those cases where the standard KHMDS/DME conditions failed to give satisfactory results.[82,83] More recently, Pospisil has demonstrated that the use of crown ether additives as metal ion complexation agents also results in increased (*E*)-selectivity.[84] Reagent combinations of either LiHMDS/12-crown-4 or KHMDS/18-crown-6 in THF solvent are effective and in many cases these conditions give superior yields to comparable reactions conducted in the absence of the crown ether (equation 34). Significantly, the LiHMDS/12-crown-4 protocol also gives excellent yields for the synthesis of trisubstituted alkenes (75–97% yield, employing either ketones or 2° alkyl PT sulfones), albeit with the low stereoselectivity (*E*:*Z*≤72:28) that characterizes a majority of the attempts to target such olefins via the Julia–Kocienski reaction.



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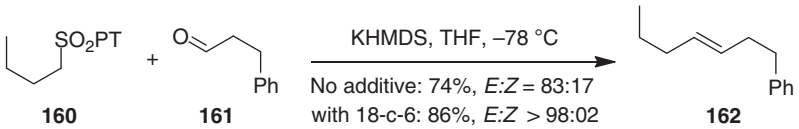
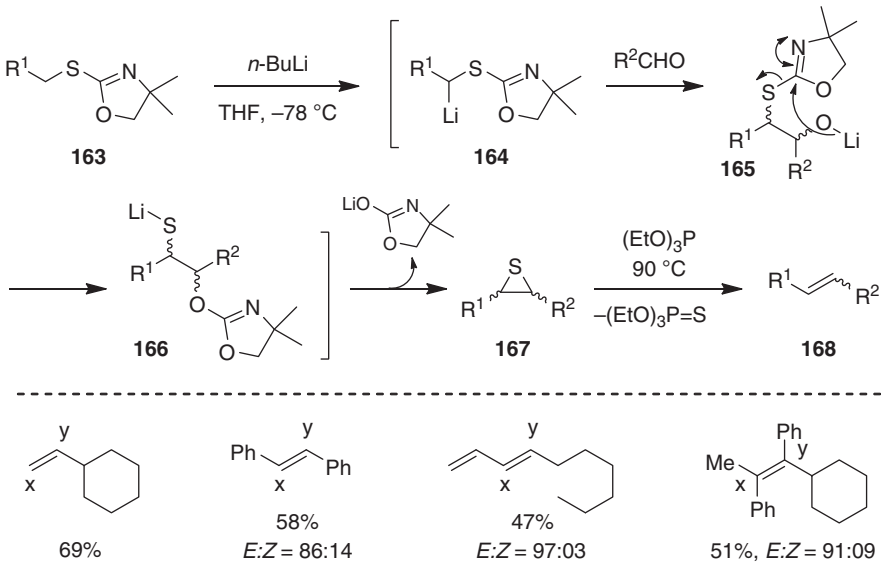


160 161 162

(34)

1.15.2.3.3 Notable reaction variants and specialized applications

The reaction manifold of the Julia–Kocienski olefination can be applied to produce numerous useful types of alkenes and also extended to generate other types of compounds. Collected together here is a selection of methods that either enable the synthesis of special types of alkenes and/or engage acceptor aryl sulfone anions with less common classes of electrophile. Before beginning, it should be noted that the Julia–Kocienski olefination can be considered to have an antecedent in an indirect carbonyl olefination procedure also based on the Smiles rearrangement described by Meyers and Ford in 1975.[85] The Meyers–Ford olefination involves the connective generation of a thiirane followed by sulfur extrusion via pyrolysis or by the action of a thiophile-like triphenylphosphine or triethylphosphite. Thirane formation involves the addition of an α-metallated 2-(alkylthio)-2-oxazoline (**164**) to an aldehyde or a ketone followed by S→O migration of the oxazoline and displacement of an oxazolidinyl anion by the resulting thiolate (**166**). Reaction mechanism and some representative examples are shown in Scheme 22.



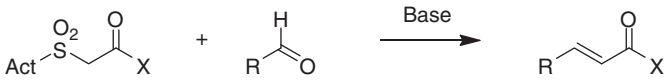
Scheme 22 Carbonyl olefination involving α-lithio-2-(alkylthio)-2-oxazolines. Overall yields from **163** are indicated for representative product olefins: x = original site of thiooxazoline, y = original site of carbonyl group.

1.15.2.3.3.1 Julia–Kocienski olefination reactions involving β-oxosulfones

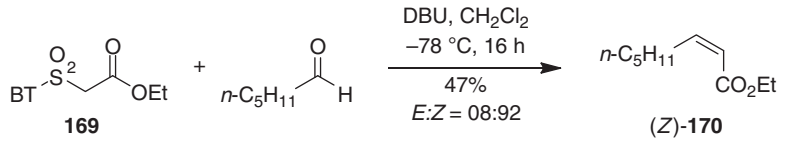
Sulfone analogs of the phosphonoacetate reagents commonly used in the Horner–Wadsworth–Emmons (HWE) olefination (Section 1.15.3.2) have recently emerged as viable alternatives to their better known counterparts for the synthesis of α,β-unsaturated carbonyl compounds. The first such reagent, ethyl (benzothiazol-2-ylsulfonyl)acetate (**169**),[86] was introduced by Blakemore and coworkers and numerous related $ActSO_2CH_2COX$ species were subsequently disclosed that incorporated alternative aryl activators and/or contained different types of carbonyl group, including: Act = BT, X = N(OMe)Me (**178**);[87] Act = NP, X = OEt (**179**);[69] Act = BTFP, X = O*t*Bu (**180**);[88] and Act = BTFP, X = N(OMe)Me (**181**).[88] These reagents can be prepared quite simply via alkylation of the appropriate aryl thiolate with an α-halocarbonyl compound followed by oxidation of the resulting thioether. Pospísil et al. have recently demonstrated an alternative approach based on the acylation of α-metallated BT sulfones.[89] Given the double activation afforded to the α-C–H bonds in these β-oxosulfone reagents, strong bases are not needed to effect deprotonation; however, the resulting anions are weak nucleophiles and heating is sometimes required to effect Julia–Kocienski olefination (Table 2). A majority of these reactions generate the (*E*)-configured α,β-unsaturated carbonyl product with high stereoselectivity. Similar base-mediated reactions of β-arylketo BT and PT sulfones leading to (*E*)-chalcone derivatives have also been reported.[90]

BT sulfonyl acetate **169** was found to engage successfully with aryl aldehydes of varying steric demand and electronic character to give (*E*)-enoate products selectively by the action of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) base in dichloromethane solvent at ambient temperature (entries 1–6).[86] Nonbranched enolizable aliphatic aldehydes gave significantly lower yields with a preference for the (*Z*)-enoate product; however, (*E*)-selectivity was restored and yield increased by the introduction of chain-branching in the carbonyl component (entry 7; cf. entries 8 and 9). The stereoselectivity observed here conforms with the general expectation for stabilized sulfone anions (see Section 1.15.2.3.2.2). In the reaction of **169** with *n*-hexanal, the inherent kinetic (*Z*)-selectivity of the process could be enhanced by conducting olefination at −78 °C (equation 35), while coupling the same components instead at 67 °C in THF solvent with NaHMDS as base gave the (*E*)-enoate **DD6** preferentially (equation 36). It was established that *trans* selectivity in the second case was not the result of (*Z*)- to (*E*)-isomerization of product **170** under the reaction conditions and as such the observation may reflect the operation of a different stereodetermining step in the elimination mechanism (*vide infra*).

Table 2 Synthesis of α,β-unsaturated esters and amides using β-oxosulfone reagents



Entries	*Sulfone*	*Act*	*X*	*R*	*Reaction conditions*	*Yield (%)*	E:Z	*References*
1	169	BT	OEt	Ph	DBU, CH_2Cl_2, r.t., 16 h	78	>98:02	86
2	169	BT	OEt	4-$(NO_2)C_6H_4$	DBU, CH_2Cl_2, r.t., 16 h	89	>98:02	86
3	169	BT	OEt	4-$(MeO)C_6H_4$	DBU, CH_2Cl_2, r.t., 16 h	93	92:08	86
4	169	BT	OEt	2-ClC_6H_4	DBU, CH_2Cl_2, r.t., 16 h	72	95:05	86
5	169	BT	OEt	2,6-$Cl_2C_6H_3$	DBU, CH_2Cl_2, r.t., 16 h	83	>98:02	86
6	169	BT	OEt	1-Naphthyl	DBU, CH_2Cl_2, r.t., 16 h	86	96:04	86
7	169	BT	OEt	*n*-C_5H_{11}	DBU, CH_2Cl_2, r.t., 16 h	41	19:81	86
8	169	BT	OEt	*c*-C_6H_{11}	DBU, CH_2Cl_2, r.t., 16 h	80	80:20	86
9	169	BT	OEt	$PhCH_2$	DBU, CH_2Cl_2, r.t., 16 h	80	>98:02	86
10	169	BT	OEt	*t*-Bu	DBU, CH_2Cl_2, r.t., 16 h	21	>98:02	86
11	178	BT	N(OMe)Me	Ph	NaH, THF, r.t., 24 h	67	>98:02	87
12	178	BT	N(OMe)Me	1-Furyl	NaH, THF, r.t., 24 h	52	>98:02	87
13	178	BT	N(OMe)Me	*n*-C_3H_7	NaH, THF, r.t., 24 h	48	>98:02	87
14	179	NP	OEt	4-$(NO_2)C_6H_4$	Cs_2CO_3, DMF, r.t., 18 h	41	>98:02	69
15	179	NP	OEt	4-$(MeO)C_6H_4$	Cs_2CO_3, DMF, 60 °C, 6 d	40	>98:02	69
16	180	BTFP	O*t*-Bu	Ph	K_2CO_3, Bu_4NBr, DMF, 120 °C, 18 h	95	96:04	88
17	180	BTFP	O*t*-Bu	4-$(CF_3)C_6H_4$	K_2CO_3, Bu_4NBr, DMF, 120 °C, 18 h	74	>98:02	88
18	180	BTFP	O*t*-Bu	4-$(MeO)C_6H_4$	K_2CO_3, Bu_4NBr, DMF, 120 °C, 18 h	45	>98:02	88
19	180	BTFP	O*t*-Bu	*n*-C_9H_{19}	K_2CO_3, Bu_4NBr, DMF, 120 °C, 18 h	14	68:32	88
20	180	BTFP	O*t*-Bu	*c*-C_6H_{11}	K_2CO_3, Bu_4NBr, DMF, 120 °C, 18 h	15	75:25	88
21	181	BTFP	N(OMe)Me	Ph	K_2CO_3, Bu_4NBr, DMF, 120 °C, 18 h	66	>98:02	88
22	181	BTFP	N(OMe)Me	4-$(CF_3)C_6H_4$	K_2CO_3, Bu_4NBr, DMF, 120 °C, 18 h	82	>98:02	88
23	181	BTFP	N(OMe)Me	4-$(MeO)C_6H_4$	K_2CO_3, Bu_4NBr, DMF, 120 °C, 48 h	20	>98:02	88
24	181	BTFP	N(OMe)Me	2-Naphthyl	K_2CO_3, Bu_4NBr, DMF, 120 °C, 18 h	30	>98:02	88
25	181	BTFP	N(OMe)Me	2-Furyl	K_2CO_3, Bu_4NBr, DMF, 120 °C, 18 h	50	>98:02	88



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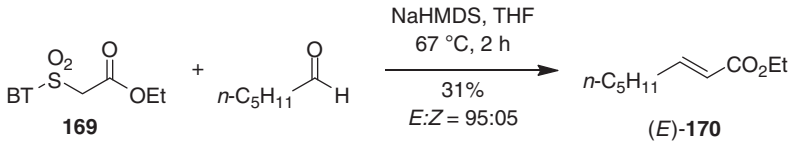
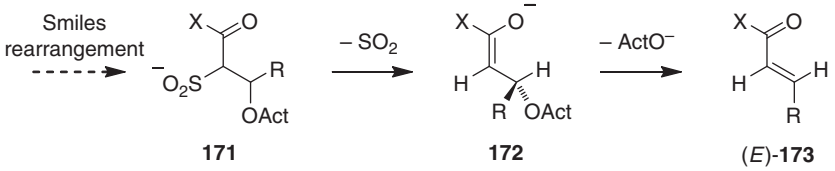


(36)

An acetamide reagent analogous to **169** (**178**) was introduced by Aidhen and coworkers for the synthesis of (*E*)-configured α,β-unsaturated Weinreb amide derivatives. In addition to the reactions illustrated (entries 11–13), it was found to successfully generate enamides from suitably protected aldosugars.[87] Exchange of the BT moiety in **169** for a 4-nitrophenyl activator (NP) was investigated by Zhu and coworkers; however, the resulting reagent (**179**) is significantly less reactive than **169** and extended reaction times were necessary for engagement with electron-rich aryl aldehydes (entry 15).[69] Nájera and coworkers studied the reactivity of two 3,5-bis(trifluoromethyl)phenyl (BTFP) sulfones of related structure, *t*-butyl acetate **180** and Weinreb-type acetamide **181**.[88] The ester derivative failed to react with aldehydes in the presence of DBU base at room temperature, but gave good to excellent yields of (*E*)-enoate products with aryl aldehydes by using a convenient reagent combination of potassium carbonate base with a phase-transfer catalyst (Bu_4NBr) in DMF solvent at elevated temperature (entries 16–18). Aliphatic aldehydes failed to react appreciably under the same conditions (entries 19 and 20) and decomposition pathways were evident for reactions with certain other carbonyl compounds. The Julia–Kocienski reactions of acetamidyl BTFP sulfone **181** were less problematic (entries 21–25); however, electron-rich aryl aldehydes gave low yields of enamide products even after protracted reaction times (entry 23).[88]

Computational work by Nájera and coworkers focused on deriving an explanation for the (*E*)-selectivity encountered in the olefination reactions of reagent **180**,[88] indicated that loss of SO_2 and $ActO^-$ is not concerted in this case and that an E1cB-like elimination mechanism is a possibility. Thus, following Smiles rearrangement, SO_2 loss from **171** could be accompanied by enolate formation rather than direct generation of the alkene. Conformational relaxation of the enolate (**172**) to minimize 1,3-allylic strain

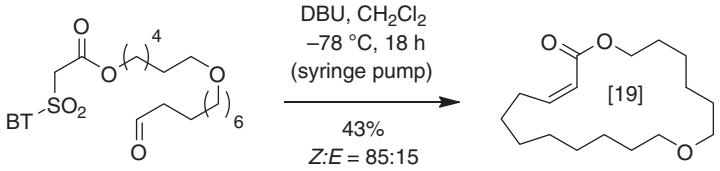
before ejection of the $ActO^-$ nucleofuge would lead preferentially to the (*E*)-alkene product regardless of stereochemical information encoded in **171** (Scheme 23). This elimination mechanism is extendable to the wider class of β-oxosulfone reagents and it may account for the selective formation of (*E*)-**170** during the high temperature reaction of BT sulfone **169** with *n*-hexanal (equation 36).



171 **172** (*E*)-**173**

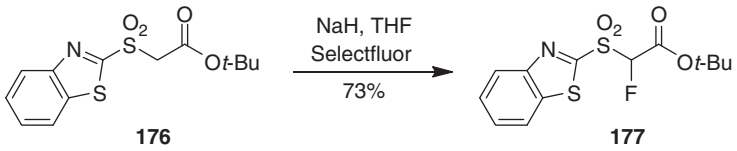
Scheme 23 E1cB-like elimination following Smiles rearrangement.

Surprisingly few intramolecular Julia–Kocienski olefination reactions have been disclosed to date. Among these rare reports, Blakemore and coworkers described the generation of macrocyclic lactones and diolides by DBU-mediated cyclization of ω-sulfonyl aldehydes derived from esters of (benzothiazol-2-ylsulfonyl)acetic acid and ω-alkenols or α,ω-diols.[91] Care must be taken during the preparation of this acid to avoid its decarboxylation (which happens spontaneously in polar solvents), but if properly handled, the formation of esters via DCC coupling with alcohols is straightforward. The following example of intramolecular olefination to yield a 19-membered cyclic enoate is representative (equation 37) and shows the expected (*Z*)-selectivity based on an earlier precedent from comparable intermolecular reactions with **169**. Aldehyde **174** was prepared via ozonolysis of the corresponding terminal alkene and added via a syringe pump for 18 h to a 0.04 M solution of DBU at −78 °C to give the macrolide **175** in reasonable yield. The method is stereocomplementary to a comparable (*E*)-selective Wittig reaction-based macrocyclization strategy,[92] and similar results were achieved contemporaneously by Ando and coworkers using their powerful HWE variant.[93]



174 **175** (37)

α-Fluorinated reagents of the type $ActSO_2CHFCOX$ have been successfully employed for the synthesis of α-fluoroacrylate and α-fluoroacrylamide derivatives. The first of these reagents, BT sulfonyl fluoroacetate **177**, was prepared by Zajc and Kake (equation 38) and was shown to be far more reactive than its nonfluorinated congener (**169**) in the Julia–Kocienski olefination of aldehydes.[94] By contrast to **169**, the fluorinated reagent **177** favors formation of *cis*-like ((*E*)-configured) products in DBU-mediated reactions with all types of aldehydes (Table 3, entries 1–3). Lequeux and coworkers later demonstrated that (*Z*)-α-fluoroacrylate products could be obtained selectively from the same class of reagent by using $DBU/MgBr_2$/THF reaction conditions (entries 4 and 5).[95] Fluorinated analogs of BTFP sulfonyl acetate **180** and acetamide **181** have also been investigated and again found to be more reactive than their nonfluorinated progenitors.[96] In this case, (*E*)- or (*Z*)-α-fluoroacrylates (entries 6–8) and (*Z*)-α-fluoroacrylamides (entries 9 and 10) were generated at ambient temperature and good yields were obtained for both aryl and aliphatic aldehydes (cf. Table 2, entries 16–25).



176 **177** (38)

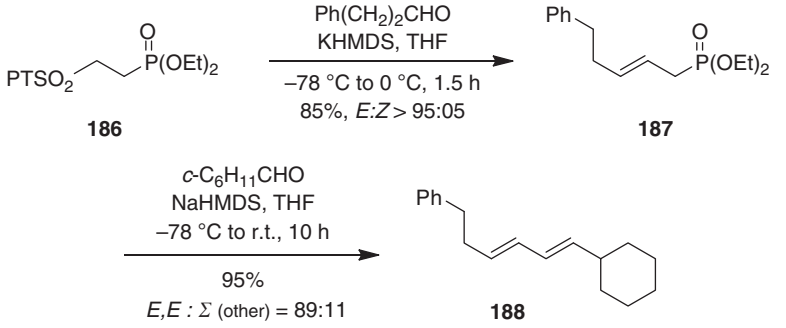
Table 3 Synthesis of α-fluoroacrylates and α-fluoroacrylamides using α-fluoro-β-oxosulfone reagents fx143

Entries	*Sulfone*	*Act*	*X*	*R*	*Reaction conditions*	*Yield (%)*	Z:E	*References*
1	**177**	BT	O*t*-Bu	Ph	DBU, CH_2Cl_2, r.t., 30 min	78	25:75	94
2	**177**	BT	O*t*-Bu	(*E*)-PhCH=CH	DBU, CH_2Cl_2, r.t., 25 min	93	24:76	94
3	**177**	BT	O*t*-Bu	*n*-C_7H_{15}	DBU, CH_2Cl_2, r.t., 3 h	75	17:83	94
4	**182**	BT	OEt	Ph	DBU, $MgBr_2$, THF, r.t., 2 h	71	92:08	95
5	**182**	BT	OEt	*n*-C_8H_{17}	DBU, $MgBr_2$, THF, r.t., 2 h	87	88:12	95
6	**183**	BTFP	OMe	Ph	K_2CO_3, Bu_4NBr, DMF, r.t., 18 h	95	93:07	96
7	**183**	BTFP	OMe	$Ph(CH_2)_2$	K_2CO_3, Bu_4NBr, DMF, r.t., 18 h	66	48:52	96
8	**184**	BTFP	O*t*-Bu	$Ph(CH_2)_2$	K_2CO_3, Bu_4NBr, DMF, r.t., 18 h	92	23:77	96
9	**185**	BTFP	N(OMe)Me	Ph	K_2CO_3, Bu_4NBr, DMF, r.t., 18 h	83	>98:02	96
10	**185**	BTFP	N(OMe)Me	$Ph(CH_2)_2$	K_2CO_3, Bu_4NBr, DMF, r.t., 18 h	57	>98:02	96

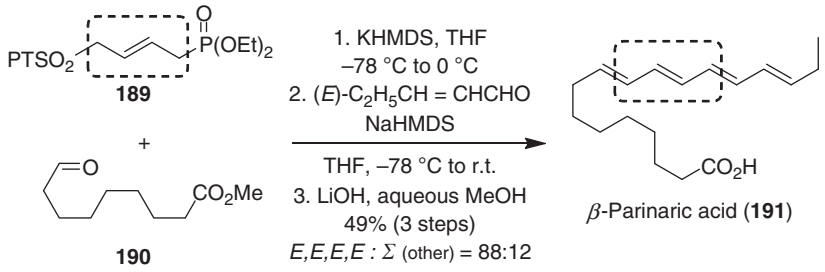
An extension to the synthesis of α-fluoroacrylonitriles has been reported.[97] Readers interested in broader applications of the Julia–Kocienski olefination to the synthesis of fluorinated alkenes are referred to a recent comprehensive review of this specific topic.[98] A selection of other reactions of β-oxosulfones with alternate types of electrophiles is covered in Section 1.15.2.3.3.3.

1.15.2.3.3.2 Specialized sulfone reagents for the synthesis of useful structural motifs

In addition to the methylenation reagent introduced by Aïssa ($TBTSO_2Me$ (**109**), equations 21 and 22),[72] numerous other cleverly designed sulfone reagents have been developed for special purpose niche applications. For example, Nagorny and Cichowicz recently introduced useful sulfonylphosphonate reagents (**186** and **189**) for the synthesis of conjugated polyenes by sequential Julia–Kocienski and HWE reactions with aldehydes.[99] Metallation of **186** initially occurs adjacent to the sulfone moiety with complete selectivity reflecting the higher kinetic and thermodynamic acidity of the C–H bonds activated by the PT sulfonyl group; the first stage Julia–Kocienski reaction is not complicated by HWE reactivity or double condensation. As illustrated, all *trans* dienes can be easily accessed in high overall yield (**Scheme 24**). Extended reagent **189** behaves in an analogous manner and enabled the rapid assembly of β-parinaric acid in high overall yield and with excellent stereoselectivity for the all *trans* tetraene (equation 39).

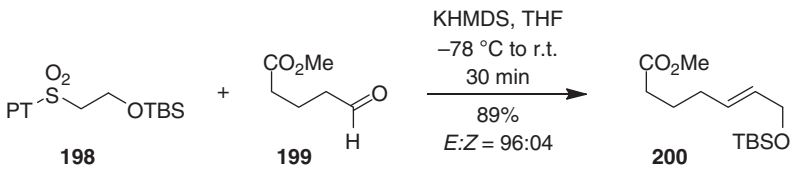


Scheme 24 Synthesis of an all *trans*-conjugated diene using sulfonylphosphonate **186.**



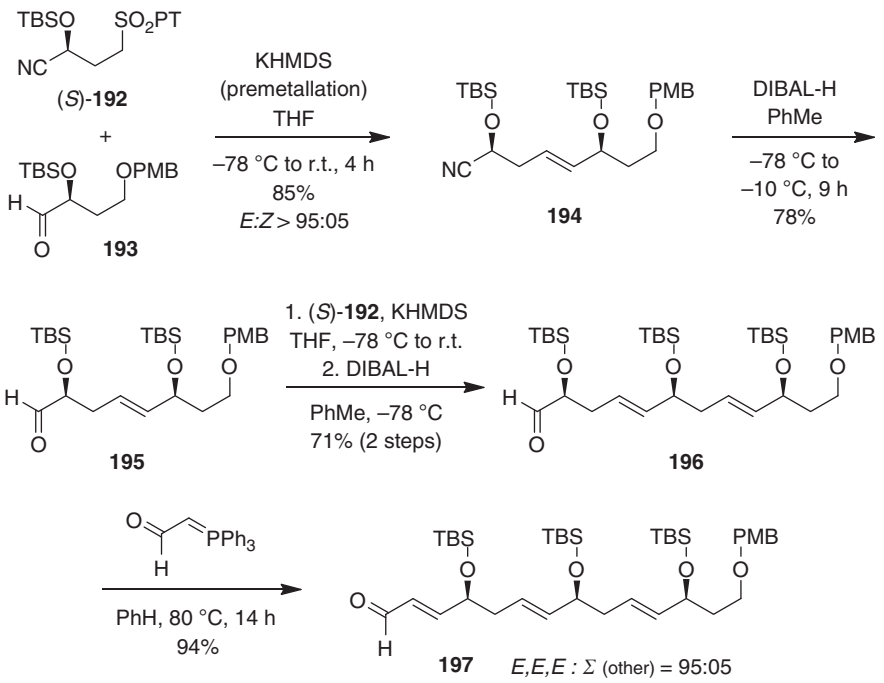
(39)

Another conjunctive reagent (**192**) has been introduced by Friestad and Sreenilayam for the stereocontrolled iterative assembly of all *trans*-unsaturated 1,5-polyols.[100a] The iteration consists of two steps: an (*E*)-selective Julia–Kocienski olefination between **192** and an appropriate aldehyde, followed by DIBAL-H-mediated conversion of nitrile to aldehyde. A streamlined synthesis of the C27-C40 fragment of tetrafibricin illustrates the method (**Scheme 25**). Since either enantiomer of PT sulfone **192** is readily available (via catalytic enantioselective silylcyanation of the conjugate addition adduct formed from PTSH and acrolein), the programmed installation of any array of stereogenic centers is trivial to achieve. A related simpler reagent for the synthesis of allylic alcohols was reported by Markó and Pospísil: condensation of the potassium metallate of PT sulfone **198** with aldehydes gives intermediate allylic TBS ethers which may be desilylated to unsaturated carbinols (e.g., equation 40).[100b]



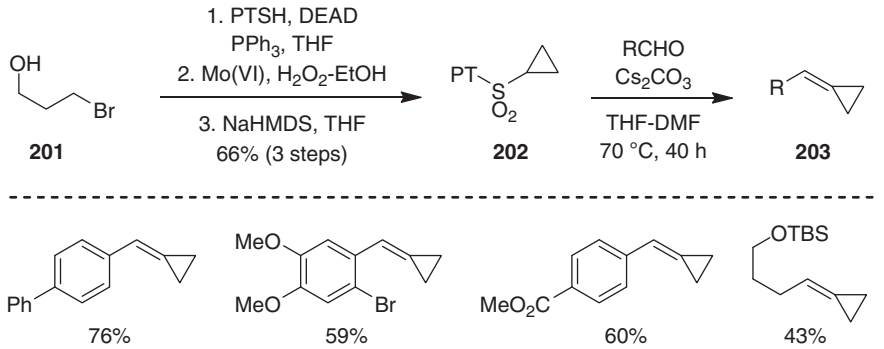
(40)

Fürstner and Aïssa have described a convenient synthesis of methylenecyclopropanes by base-mediated condensation of PT sulfone **202** with aldehydes.[101] Reagent **202** is easily prepared from PTSH and 3-bromopropanol and acceptable yields of



Scheme 25 Iterative synthesis of 1,5-polyols with reagent **192.**

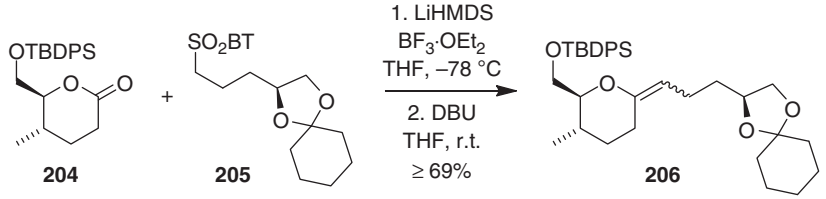
methylenecyclopropanes are generally obtained from both aryl and aliphatic aldehyde substrates (Scheme 26). The same transformation has also been achieved with a pentachlorophenylsulfone analogous to **202**.[70]



Scheme 26 Examples of methylenecyclopropane synthesis using $PTSO_2c\text{-}C_3H_5$ (**202**).

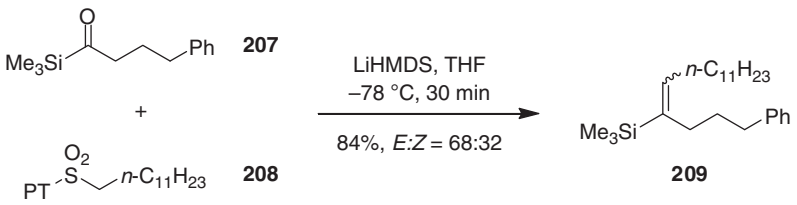
1.15.2.3.3.3 Addition of acceptor aryl sulfone anions to other types of electrophiles

The synthetic utility of acceptor aryl sulfone anions is not limited to their addition reactions with aldehydes and ketones. For example, Gueyrard and coworkers have shown that α-metallated BT sulfones will convert lactone carbonyl groups to exocyclic enol ethers via a two-step coupling/elimination process.[102] The following transformation (equation 41) is representative and was used to prepare a spiroketal fragment of bistramide A.[103] Enol ethers have also been generated more conventionally by the addition of metallated alkoxymethyl PYR sulfones derived from carbohydrates to aldehydes.[104]



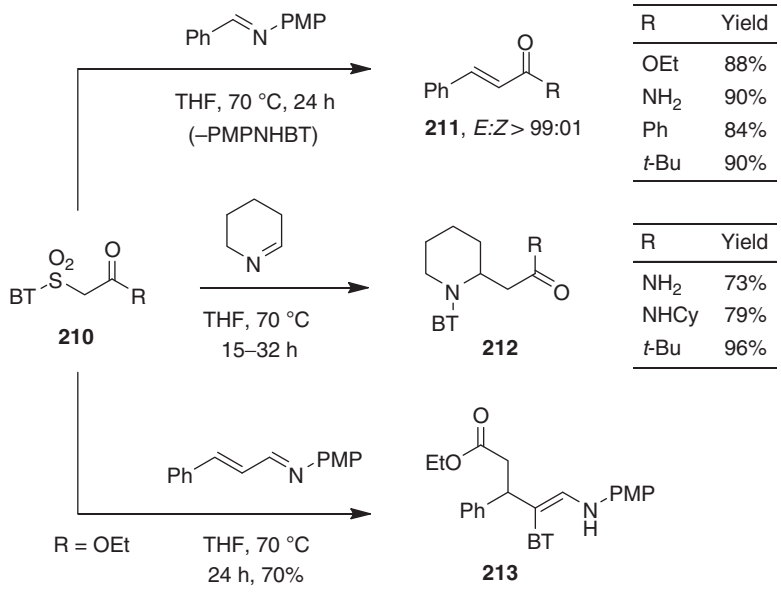
(41)

Wicha and coworkers reported that vinylsilanes that are otherwise difficult to prepare are available from Julia–Kocienski olefination of PT sulfones with acylsilane electrophiles.[105] A competing Brook rearrangement process from the intermediate β-alkoxysulfone leads to minor quantitites of enol ether side-products, but for the most part good to excellent yields of vinylsilanes are realized albeit with only low (*E*)-stereoselectivity (e.g., equation 42).



(42)

Tian and coworkers have disclosed a number of interesting transformations involving the reactions of all manner of β-oxo BT sulfones with imines (Scheme 27).[106] For example, aryl aldimines react with the BT sulfonyl acetate **210** (and its amide or ketone congeners) in the absence of exogenous base to give α,β-unsaturated carbonyl products **211** via essentially the same mechanism as the usual Julia–Kocienski olefination (with the basic imine substrate effecting the intial deprotonation step). When the same process is applied to cyclic aldimines, the resultant pendant amino leaving group re-engages with the initially generated α,β-unsaturated carbonyl adduct via an intramolecular conjugate addition reaction to produce a cyclic amine as the ultimate product (e.g., **210**–**212**). Reaction with α,β-unsaturated aldimine substrates commences with conjugate addition of the sulfone **210** followed by a Truce–Smiles rearrangement that transports the benzothiazolyl unit from sulfur to the carbon atom of the enamine previously generated. Tautomerization and desulfonylation yield the illustrated product type (**213**) reflecting a net vicinal difunctionalization of the imine.

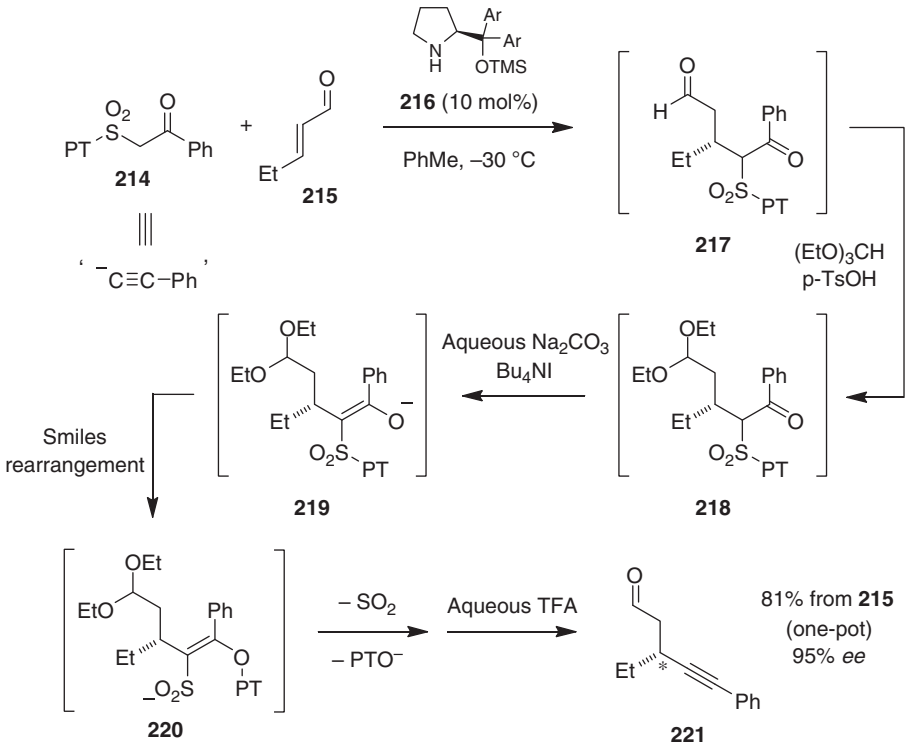


Scheme 27 Reactions of α-sulfonyl carbonyl compounds with imines.

Jørgensen and coworkers have developed enantioselective processes involving conjugate addition of β-keto PT sulfones to enals.[107] The net alkynylation of pentenal shown below using PT sulfone **214** as an acetylide anion equivalent is representative of what can be achieved and shows the utility of the Smiles rearrangement in yet another guise (Scheme 28).[108] Thus, following an organocatalyzed conjugate addition reaction of PT sulfone **214** to the enal (the comparable BT sulfone fails to add under these conditions), temporary protection of the aldehyde in the resulting Michael adduct **217** followed by its enolization results in S→O transfer of the tetrazole with subsequent elimination of sulfur dioxide and aryloxide leading now to an alkyne rather than the more usual alkene. A final *in situ* deprotection stage reveals the net result of β-alkynylation of the enal in high overall yield and with excellent enantioselectivity. None of the intermediates need to be isolated and if desired the Michael addition adduct can be reduced to a β-alkoxy PT sulfone to initiate alkene formation instead of alkyne formation. A related process leading to enantioenriched 2,4-disubstituted cyclopentenones has also been reported.[109]

1.15.2.3.4 Illustrative examples in target-directed synthesis

Fifteen examples illustrating use of the Julia–Kocienski olefination as a fragment linkage tool in contemporary target-directed synthesis are collated in Table 4. Trends in stereoselectivity largely reflect the expected substrate, activator, base, and solvent effects

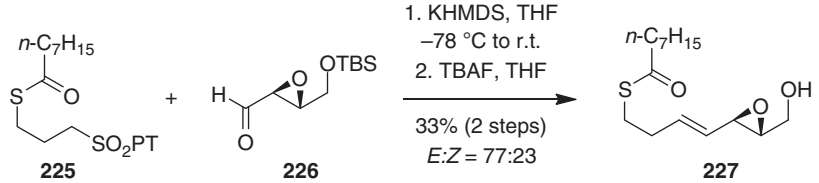


Scheme 28 Enantioselective alkynylation of an enal.

discussed above but the great complexity of the components being coupled together provides for some surprises. Immediately evident is the excellent functional group tolerance of the process. The reaction is not only compatible with standard protecting groups, such as silyl ethers, acetals, and esters, but also tolerant of sensitive functionality intrinsic to the substrates, including epoxides, α-stereogenic centers in the carbonyl component, β-alkoxy substituents in the sulfone, and alkyl or alkenyl halides.

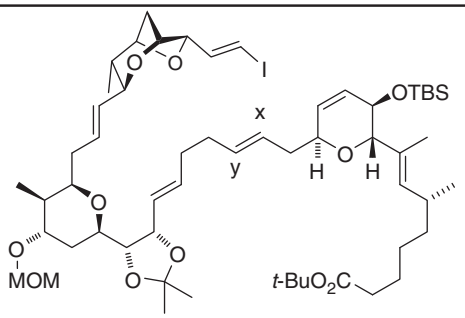
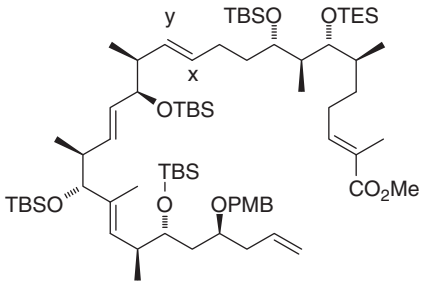
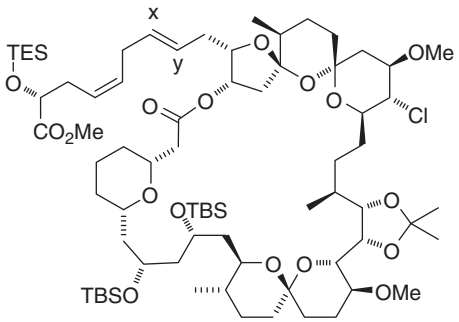
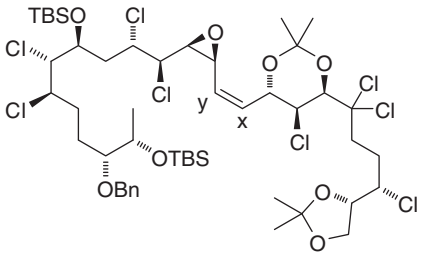
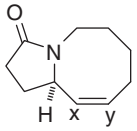
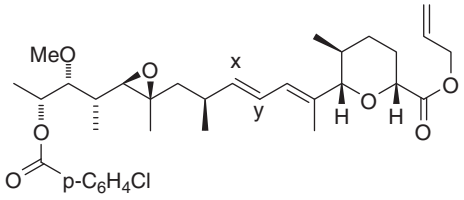
The first three entries show the elaboration of complex nonconjugated 1,2-disubstituted alkene targets en route to the polyketide natural products sorangicin A (entry 1),[110] oasomycin A (entry 2),[111] and spirastrellolide F methyl ester (entry 3).[112] PT sulfones are typically optimal for this kind of application, particularly if *trans* selectivity is desired. Smith and coworkers originally targeted the sorangicin A precursor shown (entry 1) with sulfone and aldehyde moieties residing in the opposite fragments; however, this coupling strategy gave only a 28% yield of the desired alkene. Reversing the orientation of the activating functional groups to that illustrated resulted in a 51% higher yield, also with complete (*E*)-selectivity. It was hypothesized that having multiple chelating THP ring-associated oxygen atoms in the sulfone component was detrimental to the efficiency of the metallation step. The C15-C16 of the same target was later successfully assembled via a PT sulfone-mediated Julia–Kocienski reaction by Crimmins et al.[123] In their synthesis of oasomycin A, Evans et al. observed the formation of an unusual sultone side-product **224** accompanying the desired alkene (entry 2). The aldehyde component in this case contained a β-siloxy substituent and it was presumed that the usual course of the olefination process was partially subverted by silyl migration after the initial addition event (**222** to **223**) followed by sulfonylation of the resulting alkoxide (**Scheme 29**).

Carreira and coworkers described an unusual application of the Julia–Kocienski olefination during their preparation of undecachlorosulfolipid A (entry 4).[113] This example is notable for the fact that the alkene target was obtained successfully from a PT sulfone bearing a β-alkoxy group and that the carbonyl component was an α,β-epoxyaldehyde. Also of interest is the unusual base and solvent combination which preferentially produced the (*Z*)-stereoisomer. Forsyth and coworkers recently reported the following related example en route to the depsipeptide largazole (equation 43); notable in this case is the presence of a thioester moiety in the PT sulfone **225**.[124] BT and PT sulfones with proximal epoxide moieties have also been successfully used in Julia–Kocienski olefination reactions.[74,125] The final synthesis of a nonconjugated 1,2-disubstituted alkene shown in **Table 4** is a rare example of an intramolecular Julia–Kocienski olefination employed by Dixon and coworkers to prepare a nakomarin A precursor via Aïssa's protocol (entry 5).[114]



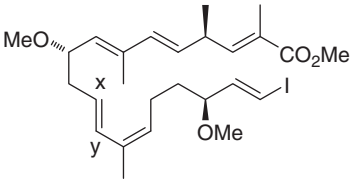
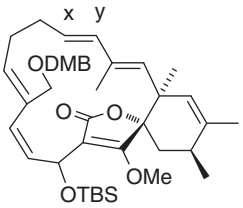
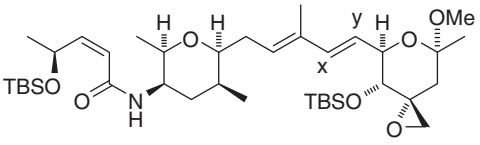
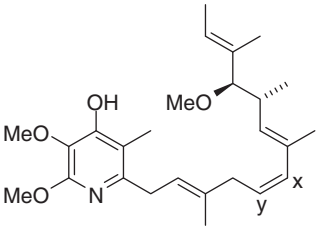
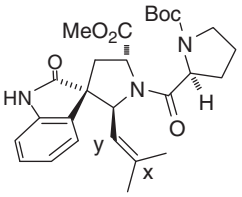
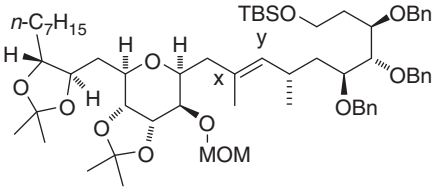
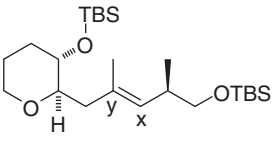
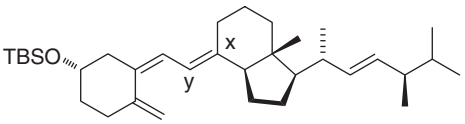
(43)

Table 4 A selection of complex alkene targets prepared by the Julia–Kocienski olefination

Entries	*Alkene target*[a]	*Reaction conditions and outcome*	*References*
1		PT sulfone; premetallation KHMDS, DME, −72 °C 79%, *E* only	110
2		PT sulfone; premetallation KHMDS, DME, −46 °C 57%, *E*:Z = 88:12 (+ 15–25% **Y6**; Scheme Y2)	111
3		PT sulfone; premetallation KHMDS, THF, −78 °C to −60 °C 76%, *E* only	112
4		PT sulfone: Barbier NaHMDS, PhMe, −78 °C 67%, *E*:Z = 25:75	113
5		TBT sulfone; Barbier Cs_2CO_3, wet THF-DMF 70 °C, 10 h 56%, *Z* only	114
6		BT sulfone; premetallation LDA, THF, −78 °C to −20 °C 81%, *E*:*Z* = 91:9	74

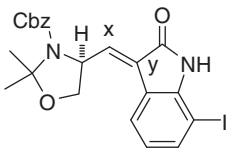
(*Continued*)

Table 4 Continued

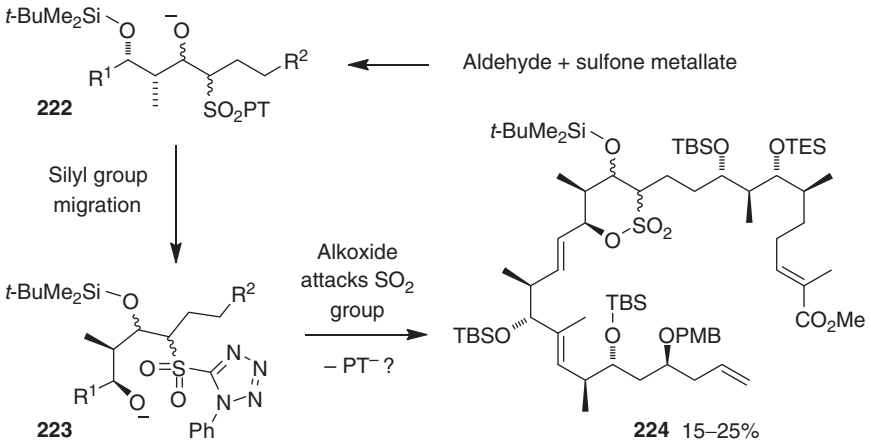
Entries	*Alkene target*[a]	*Reaction conditions and outcome*	*References*
7		BT sulfone; Barbier LiHMDS, THF, −78 °C 70%, *E* only	115
8		PT sulfone; Barbier KHMDS, THF-PhMe, −78 °C to r.t. 15%, *E* only	116
9		BT sulfone; premetallation LiHMDS, THF, −78 °C to r.t. 68%, *E* only	117
10		PT sulfone; Barbier KHMDS, THF, −78 °C 43%, *Z* only	118
11		PT sulfone; premetallation LiHMDS, THF, −78 °C 78%	119
12		PT sulfone; premetallation LDA, THF, −78 °C to −40 °C 78%, *E:Z* = 60:40	120
13		PT sulfone; premetallation LDA, $CeCl_3$, THF, −78 °C to 0 °C 80%, *E:Z* = 62:38	121
14		BT sulfone; premetallation NaHMDS, Et_2O, −100 °C to r.t. ≥70%, *E:Z* = 72:28	8

(*Continued*)

Table 4 Continued

Entries	*Alkene target*[a]	*Reaction conditions and outcome*	*References*
15		BT sulfone LiHMDS, DMF-DMPU, 0 °C 79%, *E:Z* = 83:17	122

[a]Site of newly introduced alkene is located between x and y; x = original site of the aryl sulfone and y = original site of the carbonyl group in the other coupling partner.



Scheme 29 An unusual competing pathway encountered during the synthesis of oasomycin A.

In the preparation of conjugated 1,2-disubstituted alkenes, intrinsic substrate traits play a major role in determining the sense of stereoselectivity (Section 1.15.2.3.2.2). *Trans* olefins of this type are accessed with excellent stereocontrol in virtually all cases if the double bond is assembled from a nonconjugated 1° alkyl sulfone and an α,β-unsaturated aldehyde. The Kocienski synthesis of the rapamycin triene system (equation 24 above) is representative as are alkenes made en route to herboxidiene (GEX1A; entry 6)[74] and iejimalide B (entry 7).[115] Choice of base and solvent is often less critical in such cases and BT or PT sulfones are usually equally effective. In a related reaction, Burkart and coworkers prepared the macrocyclic ring of spirohexenolide B via the most complex intramolecular Julia–Kocienski olefination yet reported (entry 8).[116] As previously discussed, the stereochemical outcome of reactions involving allylic (or benzylic) sulfone anions is variable and depends on the degree of conjugation in the aldehyde component and the presence or absence of chain-branching elements. Thus, the conjugated diene prepared in this manner en route to cell cycle inhibitor FR901464 was produced as a single (*E*)-isomer (entry 9),[117] whereas a (*Z*)-isomer was generated from a similar reaction intended to yield piericidin B_1 in which the aldehyde was not α-branched (entry 10).[118] High *cis* stereoselectives have also been observed during the synthesis of carotenoid polyene systems using allylic BT sulfones.[126]

Nonconjugated trisubstituted alkenes can be successfully prepared from both 1° and 2° alkyl sulfones via respective Julia–Kocienski reactions with either ketone or aldehyde coupling partners; however, good stereocontrol is not generally to be expected. Of course, where either the 2° alkyl sulfone or the ketone employed is symmetrical, stereocontrol is not an issue. Notable in this regard is the reagent $PTSO_2i$-Pr which was introduced by Carreira and coworkers for the expression of prenyl groups from aldehydes during natural product synthesis.[119] The reagent was first used for the synthesis of a spirotryprostatin B precursor (entry 11); attempts to prepare the same compound via the Julia–Lythgoe olefination gave only a 11% overall yield. This prenylation tactic has since also been successfully employed in the syntheses of fumagillol,[127] aplykurodinone-1,[128] and heliespirone B.[129] In their synthesis of a fragment of symbiodinolide, Takamura et al. prepared a stereogenic trisubstituted alkene in excellent yield using a 2° alkyl PT sulfone (entry 12); the low stereoselectivity shown by this reaction is typical.[120] Sakaki and coworkers' synthesis of a trisubstituted alkene en route to the gambieric acids (entry 13) likewise shows that use of ketones does not lead to improved stereoselectivity.[121] This example is notable for the use of a $CeCl_3$ additive which supressed unwanted enolization of the ketone coupling partner and also resulted in improved (*E*)-selectivity (without $CeCl_3$: 38% yield, *E:Z* = 50:50). Attempts to prepare the same alkene using Wittig, HWE, or the Julia–Lythgoe olefination were wholly unsuccessful. Conjugated trisubstituted alkenes can generally be prepared with higher stereoselectivity. For example, Kocienski and coworkers generated the C7-C8 trisubstituted alkene of the vitamin D_2 triene system with reasonable (*E*)-selectivity by condensing a 2° alkyl lithiated CD-ring BT sulfone with a conjugated dienal coupling partner (entry 14).[8] The outcome of this process compares favorably with the use of the Julia–Lythgoe olefination for essentially the same purpose (see entry 9, **Table 1**). Vitamin D analogs have since also been successfully prepared by

forging the C6-C7 trisubstituted alkene via Julia–Kocienski olefinations involving ketones and allylic BT sulfones.[130] Finally, Albrecht and Williams successfully employed an isatin derivative in a Julia–Kocienski reaction to afford a conjugated trisubstituted α,β-unsaturated oxindole en route to proteasome inhibitors TMC-95 A/B (entry 15).[122] High stereoselectivity ($E{:}Z = 83{:}17$) was obtained by using Jacobsen-type conditions at 0 °C.

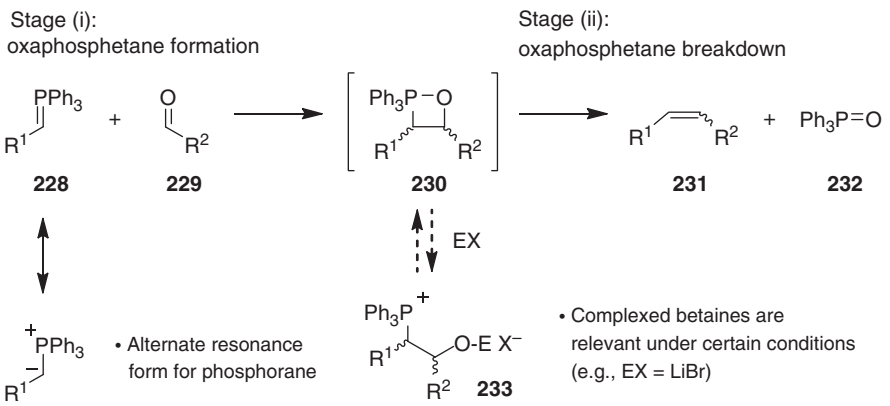
1.15.3 Phosphorus-Mediated Olefination Methods

The high oxophilicity of phosphorus coupled with the ready availability of organophosphorus compounds has facilitated the invention of numerous synthetically useful carbonyl olefination processes driven by the formation of strong P–O bonds. Phosphorus-mediated olefination methods have been extensively reviewed;[131–133] accordingly, a comprehensive treatment will not be attempted here and this section will instead focus on recent progress in the synthetic practice of these methods with an emphasis on examples that best illustrate their proper implementation and scope together with overview of a selection of the most useful reaction variants.

1.15.3.1 Alkene Formation With Phosphorus Ylides: The Wittig Reaction

1.15.3.1.1 Overview and general considerations

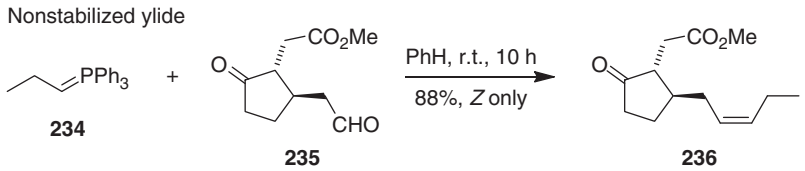
Addition of phosphorus ylides (phosphoranes) to carbonyl compounds results in the connective formation of an alkene and the generation of a phosphine oxide by-product (Scheme 30). It is difficult to overstate the importance of this process, known universally as the Wittig reaction and rooted in the discoveries of Staudinger,[134] to the field of synthetic organic chemistry. Since its disclosure in 1953,[1] an event that precipitated the award of the Nobel prize to Georg Wittig some 26 years later,[135] the Wittig reaction has been applied to the synthesis of literally thousands of different alkene products belonging to all major olefin classes.[131] Furthermore, investigation of the mechanism of the Wittig reaction has stimulated much debate and has led to innovations in the practice and theory of physical organic chemistry. There is now broad consensus that standard Wittig reactions under 'salt-free' conditions (i.e., absence of lithium salts) occur via a two-stage mechanism: (1) direct formation of an oxaphosphetane intermediate (**230**) by an asynchronous cycloaddition between the phosphorane (**228**) and carbonyl component (with P–O bond development lagging behind C–C bond formation) and (2) breakdown of the oxaphosphetane to an alkene and a phosphine oxide by-product by a syn cycloreversion process (Scheme 30).[136] Betaine species, once thought to play a significant role in all Wittig reactions and erroneously depicted as the *de facto* intermediates en route to alkenes in many undergraduate textbooks, may be generated in complexed form by the interception of oxaphosphetanes by electrophiles (EX) under certain conditions. For example, lithium-complexed betaines (**233**, E = Li) are formed reversibly from oxaphosphetanes when Wittig reactions are conducted in the presence of lithium salts.[137] Seminal ^{31}P NMR studies by Vedejs et al. established oxaphosphetanes as the sole observable intermediates in typical Wittig reactions involving nonstabilized ylides.[138] These findings were supported by early computational investigations that identified oxaphosphetanes as viable intermediates while failing to locate free betaines along the reaction coordinate.[139] The most recent theoretical and experimental work supports the hypothesis that oxaphosphetanes are in fact the pivotal intermediates in the Wittig reactions of all types of ylides (in the absence of lithium salts).[136,140]



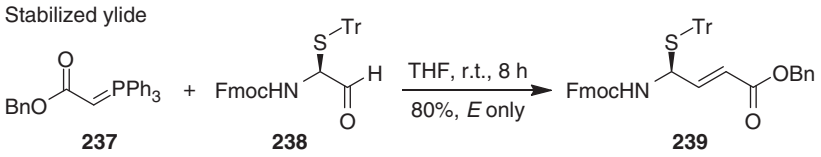
Scheme 30 The Wittig reaction of phosphorus ylides (**228**) proceeds via oxaphosphetane intermediates (**230**); complexed betaine species (**233**) may form by interception of the oxaphosphetanes with electrophiles under certain conditions.

One of the most striking features of the Wittig reaction is the high (Z)-selectivity that is observed in the synthesis of 1,2-disubstituted alkenes from 'nonstabilized' ylides **228** (e.g., R^1 = alkyl) and aldehydes. 'Stabilized' ylides **228** (e.g., R^1 = COR, CO_2R, etc.) on the contrary generally result in the stereoselective generation of (E)-olefins, whereas 'semistabilized' ylides **228**

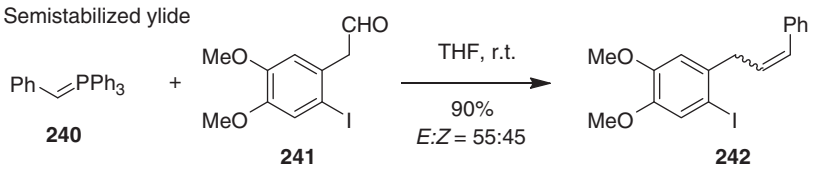
(e.g., R^1 = vinyl, aryl) give mixtures of (*E*)- and (*Z*)-stereoisomers. The equations below exemplify these well-known selectivity traits (equations 44–46),[141–143] although as we shall see (Section 1.15.3.1.3), there are notable instances of stark exceptions to these guidelines. The choice of reaction conditions and the type of spectating ligands found on phosphorus also have a profound impact on stereocontrol.



(44)

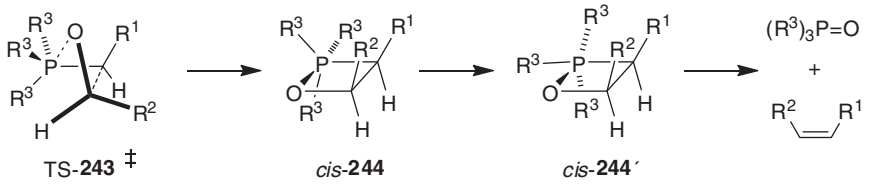


(45)



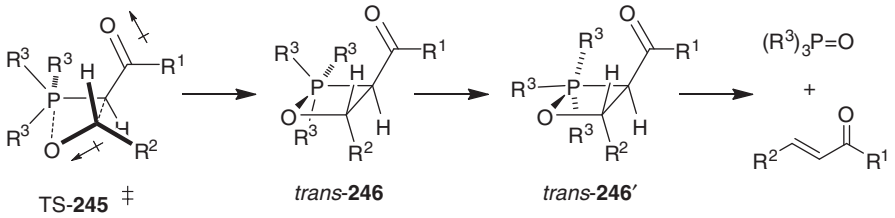
(46)

Studies of the conversion of stereodefined oxaphosphetanes into alkenes have revealed that a majority of such intermediates break down irreversibly and in a stereospecific manner.[144,145] Net stereoselectivity observed in Wittig reactions is therefore generally the result of kinetic diastereoselectivity in the initial cycloaddition step leading to the oxaphosphetane. Building on transition state models developed by Vedejs,[145] recent high-level computational work by Harvey and coworkers has clarified the origin of the (*Z*)-selectivity of Wittig reactions involving nonstabilized ylides and the characteristic (*E*)-selectivity of Wittig reactions involving stabilized ylides.[140] Detailed discussion of the Vedejs–Harvey stereocontrol model is beyond the scope of the present account; however, salient points are summarized. In the case of nonstabilized ylides, oxaphosphetane generation is exothermic and the transition state leading to this intermediate is early on the reaction coordinate (**Scheme 31**). The four-centered cyclic transition state (TS-**243**) is highly puckered with a pseudo-tetrahedral coordination geometry about phosphorus; minimization of 1,2 (R^1 and R^2) and 1,3 (R^2 and R^3) interactions favors the illustrated diastereoisomeric configuration for bulky R^3 (e.g., Ph) in which substituents R^1 and R^2 are on the same face. The resulting *cis* oxaphosphetane (**244**) is initially generated with an apical O-atom and its ensuing decomposition to the *cis* alkene requires a low barrier pseudorotation step (C-atom about to leave phosphorus becomes apical, **244′**) followed by rate-limiting cycloreversion.



Scheme 31 Preferred transition state for nonstabilized ylides leading to *cis* alkene products.

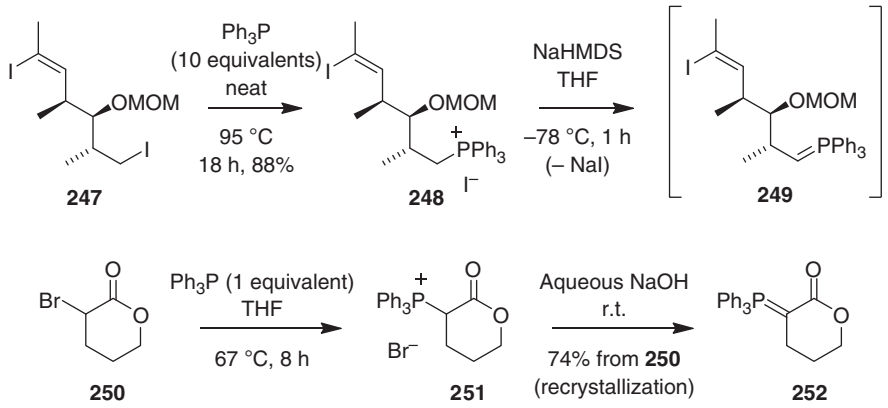
By contrast, in the case of stabilized ylides, oxaphosphetane generation is endothermic and the relevant transition state (TS-**245**) is as expected now relatively late with pseudo-trigonal bipyramidal geometry about phosphorus; however, the cyclic TS assembly is not flat as originally proposed in the Vedejs model (**Scheme 32**). Significantly, in this case, the sense of puckering is opposite to that seen in TS-**243** and such that steric (R^2 and R^3) and dipole–dipole interactions are minimized. Further conversion of the resulting *trans* oxaphosphetane (**246**) to the *trans* alkene again requires a pseudorotation event (**246** to **246′**) before cycloreversion; however, in this case the barrier to fragmentation is low and cycloreversion is not rate-limiting. Further details concerning this model and illuminating notes charting its historical development have been cogently summarized by Byrne and Gilheany.[136]



Scheme 32 Preferred transition state for stabilized ylides leading to *trans*-alkene products.

1.15.3.1.2 Synthesis of phosphonium salts and phosphorus ylides

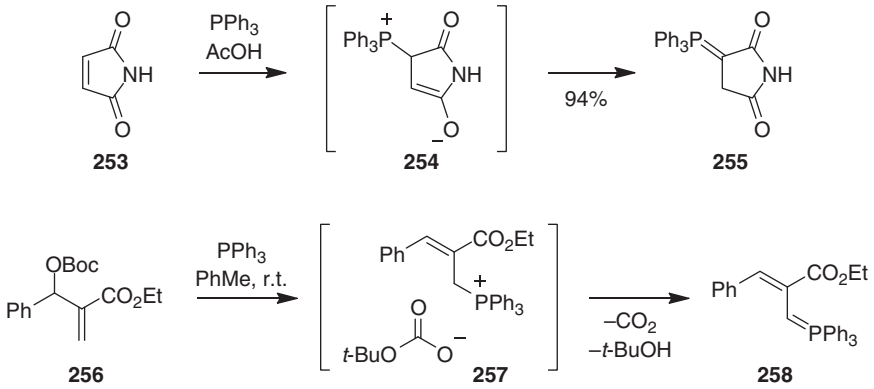
Phosphorus ylides are routinely generated by the deprotonation of phosphonium salts, themselves typically produced via quaternization of a phosphine with an alkyl halide. Triphenylphosphine is an overwhelmingly favorite starting material because it is easy to handle (air-stable crystalline solid), inexpensive, of comparatively low toxicity, and the resulting alkyltriphenylphosphonium salts have only one site for subsequent deprotonation during their conversion to ylides. The choice of base depends on the acidity of the phosphonium salt. For simple alkyltriphenylphosphonium salts a comparatively strong base such as NaHMDS is required to generate the corresponding nonstabilized ylide (nb. lithium amide bases compromise (*Z*)-selectivity and are best avoided for this reason, see Section 1.15.3.1.3.1). An illustrative example, albeit a fairly complex one, is seen in the preparation of 1° alkyl phosphonium salt **248** and its conversion to an ylide (**249**) representing a C9-C14 fragment of discodermolide (Scheme 33).[146] To facilitate phosphonium salt formation from the branched iodide **247**, this compound was heated neat with excess PPh_3; more conventionally, the phosphine and alkyl halide are combined in a solvent such as toluene or THF (at reflux). The red-orange ylide **249** (nonstabilized phosphoranes are often a red color) was generated from the purified salt by deprotonation with NaHMDS base in THF solvent at low temperature to avoid competing β-elimination of the vinyl iodide. As is typical for nonstabilized ylides, **249** was used immediately in a Wittig reaction without isolation. By contrast, stabilized ylides are usually isolated before use and they are easily generated using much weaker bases such as alkoxides or inorganic hydroxides in aqueous media. For example, the phosphorane **252** derived from α-bromovalerolactone (**250**) was formed from the corresponding phosphonium bromide salt **251** by deprotonation in alkaline solution and then isolated as a crystalline solid following extraction into chloroform, evaporation of organic solvent, and recrystallization.[147]



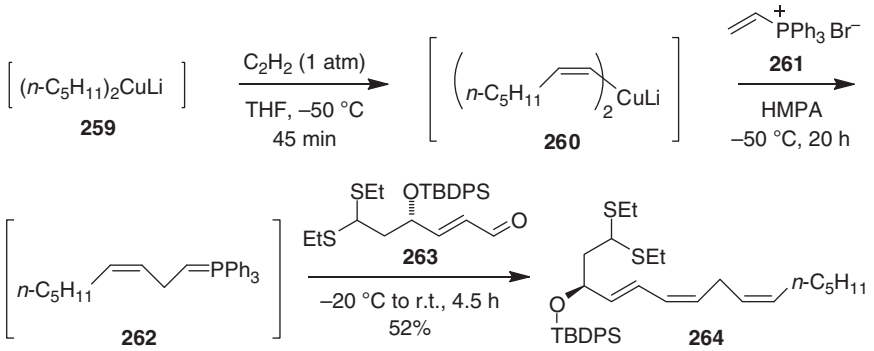
Scheme 33 Representative examples of traditional syntheses of nonstabilized (**249**) and stabilized (**252**) phosphorus ylides via deprotonation of phosphonium salts.

A less commonly exploited route to stabilized ylides involves conjugate addition of Ph_3P to maleic acid derivatives followed by tautomerization, as shown by the synthesis of succinimidyl phosphorane **255** (Scheme 34).[148] A related method for the *in situ* generation of semistabilized ylides was recently reported involving addition of PPh_3 to *O*-Boc Baylis–Hillman adducts (e.g., **256**) followed by β-elimination and deprotonation of the resulting phosphonium salt (**257**) by the liberated *tert*-butoxide base.[149] Zwitterionic enolates derived from Michael acceptors and PPh_3 have also been used as bases for the *in situ* generation of stabilized ylides from α-bromoacetates.[150]

Conjugate addition reactions of a different nature can be employed to access nonstabilized ylides via nucleophilic addition to vinyl phosphonium salts. Cuprates react in the desired manner to form new C–C bonds with concomitant emergence of useful ylides. This process has been utilized by Just and coworkers in a convergent approach to eicosanoids (e.g., HETE precursor **264**) involving acetylene carbocupration, vinyl cuprate conjugate addition to vinyltriphenylphosphonium bromide (**261**), and a terminating Wittig reaction (Scheme 35).[151] Deployment of heteroatom nucleophiles is particularly useful and leads to ylides that would be otherwise difficult to access. For example, a dihydropyridazine precursor to a piperazic acid needed for the synthesis of

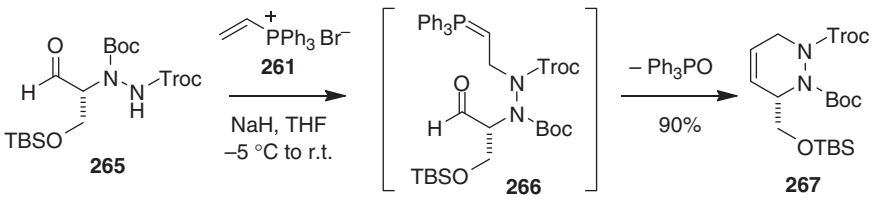


Scheme 34 Synthesis of stabilized phosphorus ylides via conjugate addition.



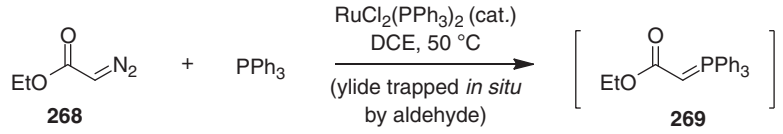
Scheme 35 Ylide generation via cuprate addition to a vinyl phosphonium salt.

the cyclohexapeptide chloptosin was prepared via a reaction cascade involving the addition of hydrazine **265** to vinyl phosphonium salt **261** followed by intramolecular Wittig reaction of the resulting phosphorane **266** (Scheme 36).[152]



Scheme 36 Ylide generation via addition of a heteronucleophile to a vinyl phosphonium salt.

Trapping of carbene and carbenoid intermediates with phosphines allows for a mild synthesis of phosphorus ylides that is potentially applicable to the synthesis of both traditional and less conventional types of ylides. Early examples are provided by the synthesis of halo- and dihalomethylidene phosphoranes from halocarbene species generated by base-mediated alpha elimination.[153] Contemporaneous studies by Wittig and Schlosser established that phosphoranes can also be generated from transition metal alkylidenes with their successful realization of ylide formation via Cu(I) catalyzed decomposition of diazo compounds in the presence of PPh_3.[154] Wider adoption of this broadly applicable paradigm for the synthesis of phosphoranes has not occurred until relatively recently. The formation of stabilized ylides from α-diazoacetates and PPh_3 using Ru(II) catalysis was reported by Fujimura and Honma (equation 47)[155] and a similar approach employing FeTPP was more recently disclosed by Woo and coworkers.[156] A related methylenation protocol using TMS diazomethane and Rh(I) catalysis has been demonstrated by Lebel et al.[157] Aggarwal et al. achieved the first synthesis of phosphite-derived ylides by tetraphenylporphyrin iron chloride (ClFeTPP) catalyzed decomposition of tosyl hydrazone anions in the presence of trimethylphosphite (equation 48).[158] In this case, the usual approach to ylides cannot be applied because phosphite esters engage in the Michaelis–Arbuzov phosphonate synthesis when heated with alkyl halides (see Section 1.15.3.2.2).



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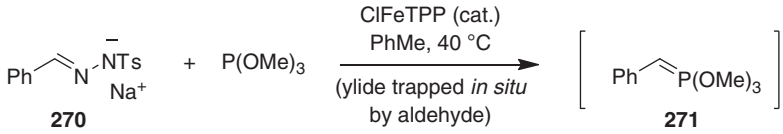
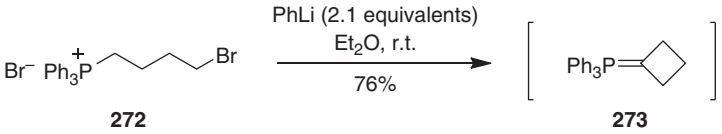


(48)

Finally, it should be noted that ylides are nucleophilic species and consequently they can be readily derivatized to more complex examples by reactions with appropriate electrophiles. Alkylation of nonstabilized ylides can be used to access quite exotic Wittig reagents; for example, the ylide initially formed from phosphonium salt **272** experienced intramolecular alkylation to give a cyclobutyl phosphonium salt that was deprotonated *in situ* to give cyclobutylidene ylide **273** (equation 49).[159] Acylation of simple ylides is a preferred route to β-keto ylides because quaternization of PPh_3 with α-bromoketones can be problematic. An example is seen in the preparation of an ylide (**276**) of interest by Christie and Heathcock during their elaboration of halichlorine (equation 50).[160] Acylation of stabilized ylides can likewise be achieved with acid chlorides, carboxylic anhydrides, or more conveniently by carbodiimide-mediated coupling with carboxylic acids, as shown by the synthesis of arginine-derived phosphorane **279** (equation 51).[161] The reaction of stabilized ylides with conjugate addition acceptors likewise leads to new ylides; Hong et al. recently achieved this feat in an enantioselective fashion using a chiral thiourea as catalyst (equation 52).[162] A description of yet further methods for the preparation phosphoranes can be found in Johnson's excellent monograph.[131c]



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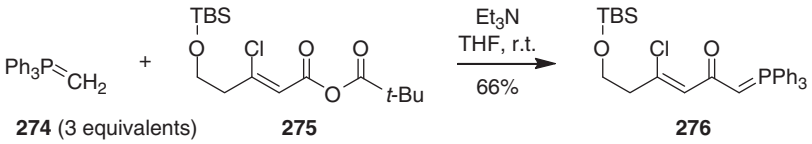

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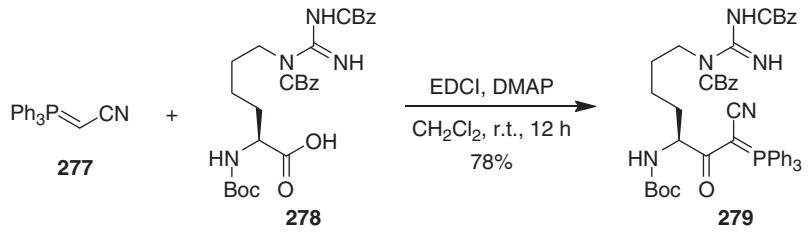

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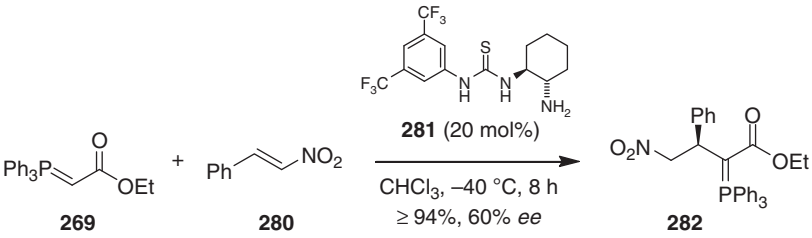


(52)

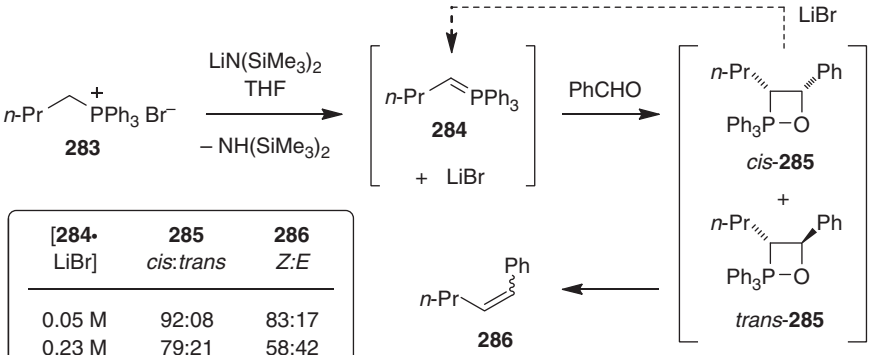
1.15.3.1.3 Factors affecting reaction efficacy and stereoselectivity

The well-known dependence of stereoselectivity on the type of ylide as stated in the introductory comments (Section 1.15.3.1.1) is certainly true, but this is also a gross simplification. The factors affecting efficacy and stereocontrol in the Wittig reaction are finely

balanced and among the wealth of examples found in the literature are observations that run counter to the familiar maxim that nonstabilized ylides are (*Z*)-selective whereas stabilized ylides are (*E*)-selective. These issues, including the role played by additivies and reaction media, are described in considerable detail in the Maryanoff and Reitz review[131d] and they will be summarized here only quite briefly along with delineation of more recent relevant findings.

1.15.3.1.3.1 The effect of lithium salts and solvent on stereoselectivity

From the earliest investigations of the Wittig reaction it was recognized that additives, be they intentionally introduced or formed *in situ* as the result of ylide generation from phosphonium salts, can have a major effect on the yield and stereoselectivity of olefination.[163] Of special concern is the presence of lithium salts and many optimized Wittig olefination procedures call for 'salt-free' conditions: a misnomer really indicating that dissolved *lithium* salts should not be present (other ionic species such as sodium or potassium salts are in fact present in most 'salt-free' procedures). Salt effects are less relevant for stabilized ylides, which are typically purified before their deployment, but they are an important consideration for most reactions involving nonstabilized ylides which are found to give lower levels of (*Z*)-selectivity in the presence of lithium cations. In a revealing study, Maryanoff and coworkers observed that the (*Z*)-selectivity of the Wittig reaction between benzaldehyde and butylidene phosphorane **284** decreased significantly as substrate concentration was increased but only when the ylide was generated using a lithium amide base (**Scheme 37**).[164] On the contrary, if the ylide were instead generated using NaHMDS as base (not illustrated), (*Z*)-selectivity was very high (*Z*:*E* ≥ 94:06) and did not show any strong dependence on substrate concentration. The key distinction between the two sets of findings, and the cause of the errosion in observed stereoselectivity as verified by subsequent control experiments, is the presence of LiBr in the first case, a by-product of ylide generation from phosphonium salt **283** and LiHMDS, but not in the second case where the less Lewis acidic (and less soluble) salt NaBr is the only by-product. Of further interest, these workers also tracked the correlation between the diastereomeric ratio of the initially generated *cis*- and *trans*-oxaphosphetane intermediates **285** with the final *Z*:*E* ratio of the alkene product **286**. At higher concentrations of LiBr it can seen that there is a considerable discrepancy between the two ratios indicating an apparent move away from stereospecific conversion of oxaphosphetane into alkene. The lack of stereochemical fidelity is actually a consequence of the faster rate of conversion of *trans*-**285** to (*E*)-**286** and selective LiBr promoted retroaddition of *cis*-**285** back into the phosphorane and aldehyde. This effect, termed 'stereochemical drift' by Maryanoff and Reitz,[144b] discriminates disproportionately against advancement of *cis*-oxaphosphetanes into (*Z*)-alkene products and is associated with heightened levels of the (*E*)-alkene being generated. Oxaphosphetanes derived from aliphatic aldehydes and nonstabilized ylides are rarely susceptible to stereochemical drift; nonetheless, since this phenomenon is not the sole cause of reduced (*Z*)-selectivity in the presence of lithium salts, 'salt-free' protocols are recommended for all reactions targeting (*Z*)-alkenes from nonstabilized ylides. The effect of lithium cation on the reactions of semistabilized[165] and stabilized[166] ylides is typically the reverse of that observed for nonstabilized ylides: i.e., the amount of (*Z*)-olefin generated is often increased. However, since many of these reactions intrinsically favor the (*E*)-alkene product, the presence of Li^+ is usually also deleterious, eroding net stereoselectivity.

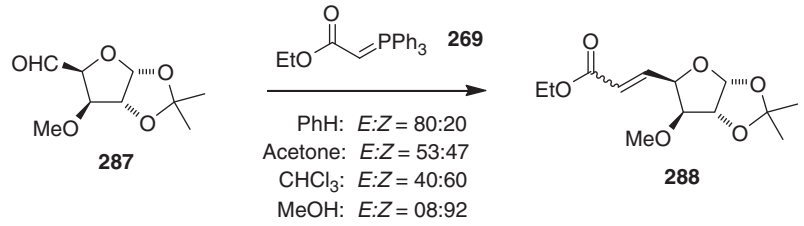


[**284**• LiBr]	**285** *cis*:*trans*	**286** *Z*:*E*
0.05 M	92:08	83:17
0.23 M	79:21	58:42
1.00 M	72:28	36:64

Scheme 37 Dependence of stereochemical outcome of Wittig reaction and the extent of stereochemical drift on LiBr concentration.

The choice of solvent is somewhat limited in the case of nonstabilized ylides, which are basic and so may be prematurely quenched in protic media. Little variation in stereoselectivity is noted for reactions conducted in ethereal (e.g., THF) or hydrocarbon (e.g., toluene) solvents,[167] but (*Z*)-selectivity is reduced in DMSO[168] and significantly so if EtOH is added after aldehyde addition.[169] The Wittig reactions of stabilized ylides show dramatically reduced (*E*)-selectivity if conducted in alcohols.[166] This effect can be usefully exploited to maximize (*Z*)-selectivity in the anomalous reactions of stabilized ylides with highly oxygenated aldehydes (*vide infra*) as illustrated in equation 53.[170] Solvent effects are less pronounced for the reactions of semistabilized ylides.[131e] For example, Pandolfi and coworkers noted that stilbene **290** was formed with optimal stereoselectivity using the *trans*-selective Boden protocol (potassium base and 18-crown-6)[171] in toluene solvent but that the *E*:*Z* ratio was only slightly reduced in

methanol (equation 54).[172] Interestingly, the same rarely applied reaction conditions enabled a simple nonstabilized alkylidene phosphorane to be coupled with a benzaldehyde in aqueous media and this also resulted in *trans* selectivity (*E*:*Z*=73:27).[172]



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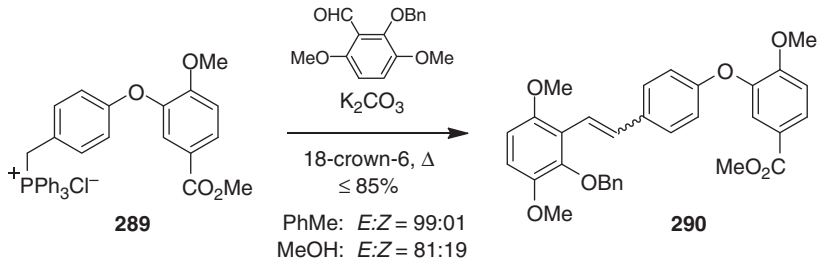
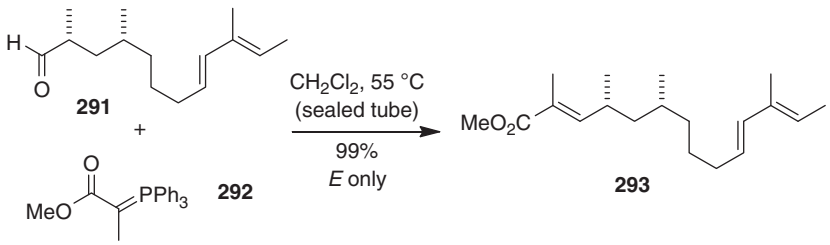


(54)

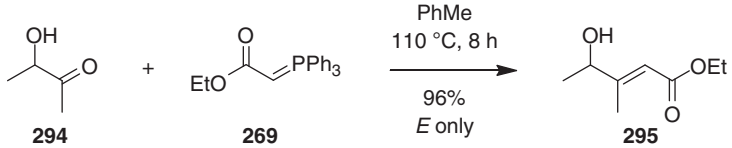
1.15.3.1.3.2 *The effect of substrate structure on stereoselectivity (anomalous outcomes)*

The intrinsic nature of substructure found within the phosphorane and carbonyl components has the most obvious effect on stereoselectivity. The common trends were noted previously above and are exemplified further in Section 1.15.3.1.5; accordingly, this section will focus on Wittig reactions wherein an outcome contrary to that usually expected has been noted. Before turning to such ostensibly 'anomalous' examples, it is worth emphasizing that the high (*E*)-selectivity observed in the reactions of stabilized ylides extends to those examples wherein the ylidic carbon atom is fully substituted. This finding is strongly supportive of the Vedejs–Harvey stereocontrol model (i.e., importance of minimizing dipole–dipole interactions in TS-**245**, **Scheme 32**),[140] and enables an efficient synthesis of trisubstituted (*E*)-alkenes. Most other carbonyl olefination methods fail to give superlative stereoselectivity in the synthesis of higher substituted alkenes because steric factors alone do not adequately distinguish between the pathways leading to (*E*)- and (*Z*)-isomers in such cases. The following example from a recent synthesis of okilactomycin D is illustrative (equation 55); α,β-unsaturated methylester **293** was obtained in quantitative yield as a single (*E*)-isomer and with no trace of epimerization at the stereogenic center that originates in the α-position of the aldehyde.[173]



(55)

Significant deviations from conventional outcomes for a given ylide type are usually associated with substrates that present polar functional groups in close proximity to the reacting atom centers.[131d] These effects can be advantageous when resulting in higher than expected stereoselectivity or problematic if otherwise. Apropos to the aforementioned comments about trisubstituted alkene synthesis, it is generally observed that the reactions of stabilized ylides with simple ketones do not result in good stereocontrol (e.g., *E*:*Z*=60:40 to 70:30 for methyl ketones with **269**).[174] By contrast, it was discovered by Garner et al. that α-hydroxyketones react with such phosphoranes with complete stereoselectivity in favor of the isomer in which the hydroxyl group-bearing side-chain is *trans* to the newly introduced carbonyl group (i.e., in most cases this would be designated as the (*E*)-isomer).[175] The following examples involving acyclic and cyclic α-hydroxyketones are representative (equations 56 and 57).[176,175]



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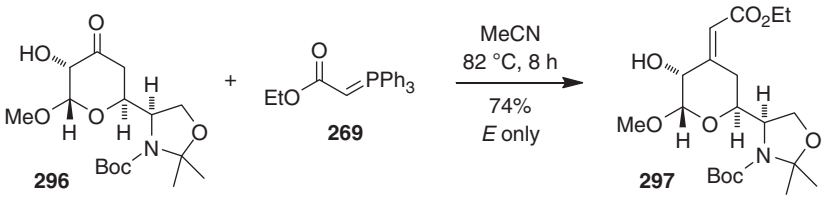

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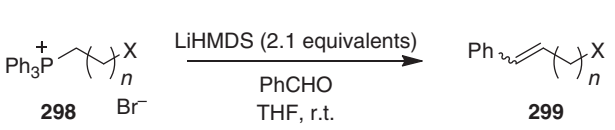
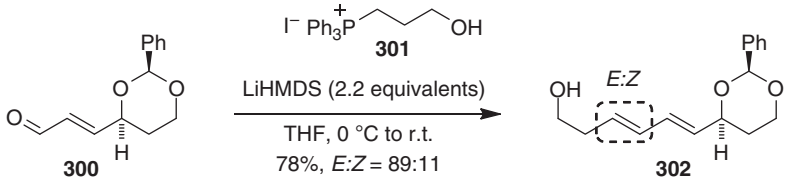
Exaggerated (*E*)-selectivity was also charted by Maryanoff et al. for the reactions of aromatic aldehydes with nonstabilized ylides bearing anionic heteroatoms in their side-chains in the presence of lithium salts (**Scheme 38**).[177] Alkoxide, carboxylate, or amide (not illustrated) anionic sites located in close proximity to the ylidic carbon in phosphoranes derived from phosphonium salts **298** caused styrene derivatives **299** to be generated with high (*E*)-selectivity. If the side-chain of the ylide bore no such anionic group (e.g., **298**, X=H, *n*=3), or if the anion was too far away from the ylidic carbon atom, no significant boost in (*E*)-selectivity was observed under otherwise identical reaction conditions. Maryanoff et al. attributed the origin of the effect to enhanced equilibration between *cis*- and *trans*-oxaphosphetanes ('stereochemical drift') facilitated by those anionic side-chain substituents that were capable of attacking the phosphorus atom in these intermediates.[177] High stereoselectivity can also be obtained from *α*,*β*-unsaturated aldehydes, as demonstrated by the preparation of (*E*,*E*)-dienol **302** en route to the lepadin alkaloids by Kibayashi and coworkers (equation 58).[178] The anionic effect has been recently duplicated by associating the alkoxide anions with the spectating ligands on phosphorus (see Section 1.15.3.1.3.3).[179] *Trans* alkenols are also available via the *β*-oxido ylide species utilized in the Wittig–Schlosser reaction variant (Section 1.15.3.1.4.1).[180]



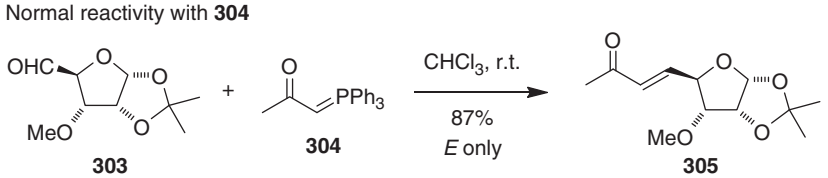
	E:*Z* ratio for **299**	
n	X = OH	X = CO_2H
1	72:28	90:10
2	96:04	93:07
3	85:15	87:13
4	74:26	-:-
5	41:59	69:31

Scheme 38 Dependence of stereoselectivity on anionic groups in ylide side-chain.



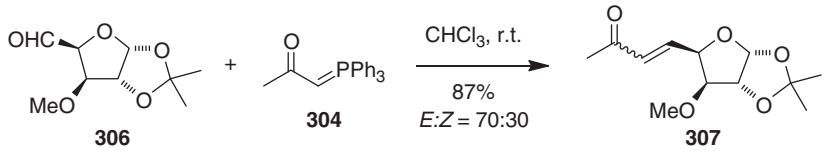
(58)

Perhaps the best known of the atypical Wittig reactions are those involving the addition of stabilized ylides to aldehydes that bear alkoxy groups (or other donor heteroatoms) in close proximity to the carbonyl group.[131d] In such cases, the exquisite (*E*)-selectivity usually offered by stabilized ylides is significantly eroded under standard conditions (e.g., *E*:*Z*~80:20) and completely reversed in alcohol solvents (e.g., equation 53 above). Examples of this kind abound in the field of carbohydrate chemistry where aldehydes with *α*- and *β*-oxygen substituents (and particularly 2,3-isopropylideneglyceraldehyde derivatives) are commonplace.[181] For the effect to operate, an *α*-alkoxyaldehyde is usually required but there must also be another alkoxy group or some alternate donor atom in the *β*- or *γ*-position that is capable of a close approach to the carbonyl group.[170] For example, D-ribose-derived aldehyde **303** showed no anomalous effect in its Wittig reaction with stabilized ylide **304** (*E*:*Z*>99:01; equation 59), but the comparable D-xylose-derived aldehyde **306** gave an alkene product with substantially reduced *E*:*Z* ratio (*E*:*Z*=70:30) upon its treatment with the same phosphorane under otherwise identical conditions (equation 60).[170] When the effect is deliberately accentuated by the use of MeOH as solvent, or by the presence of a carboxylic acid additive, it can be very useful, as seen in the conversion of lactol **308** to (*Z*)-enoate **309** en route to the cladospolides (equation 61).[182]

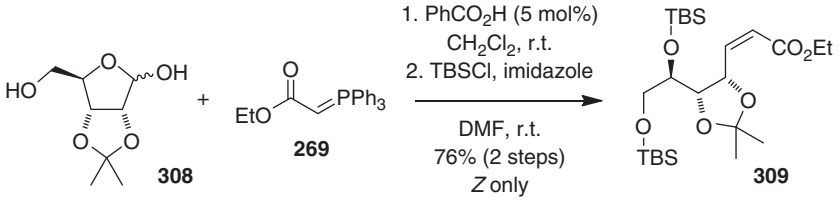


(59)

Abnormal reactivity with **304** (reduced stereoselectivity)

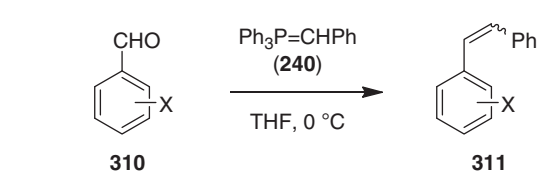


(60)

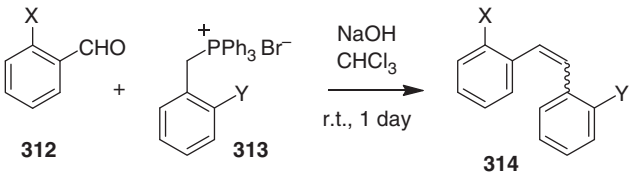


(61)

A related heteroatom effect has been encountered in the Wittig reactions of semistabilized benzylidene phosphoranes with benzaldehydes. The parent ylide belonging to this class (**240**) gives notoriously poor stereocontrol (e.g., equation 46); however, in its reactions with substituted benzaldehydes, Yamataka et al. observed good (*Z*)-selectivity in the formation of stilbenes **311** from aldehydes that possessed ortho heteroatoms (data set A, Scheme 39).[183] Gilheany and coworkers later discovered that the reactions of ortho halosubstituted benzylidenes **313** (Y=F, Cl, or Br (not illustrated)) with benzaldehyde instead modestly favor generation of the corresponding (*E*)-configured stilbenes **314** (data set B).[184] However, when the ortho halosubstituted benzylidene ylides were combined with ortho-substituted benzaldehydes a counterintuitive cooperative effect led to the highest levels of (*Z*)-selectivity yet found. This effect has synthetic utility and was exploited by Harrowven et al. in an efficient approach to helicenes.[185] For example, the double Wittig reaction of dialdehyde **316** with the benzylidene ylide generated *in situ* from phosphonium salt **315** gave (*Z,Z*)-bis(stilbene) **317** which was subsequently converted to a [5]helicene by radical cyclization (equation 62).

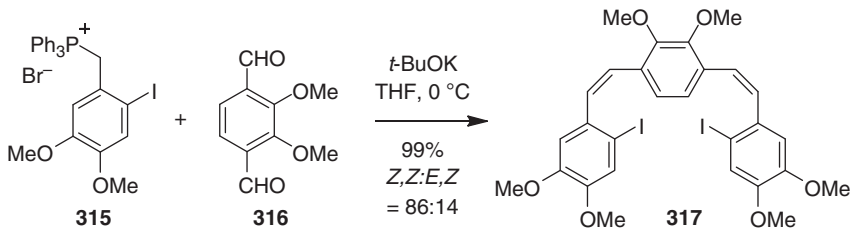


A: X	**311** *Z:E*
2-MeO	**84:16**
3-MeO	46:54
2-Me	37:63
3-Me	38:62
2-Cl	**86:14**
3-Cl	44:56



B: X	Y	**314** *Z:E*
F	H	70:30
H	F	26:74
F	F	90:10
Cl	H	77:23
H	Cl	23:77
Cl	Cl	87:13

Scheme 39 Ortho substituent effects in the reactions of benzylidene ylides with benzaldehydes.



(62)

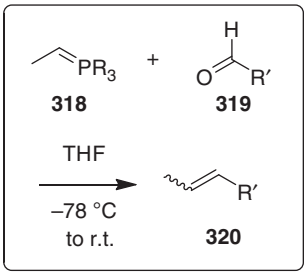
Extending their earlier work, Gilheany and coworkers made the significant discovery that the lithium salt-free Wittig reactions of all classes of ylide (nonstabilized, semistabilized, and stabilized) with ortho heteroatom substituted benzaldehydes show the

same increased selectivity for the (*Z*)-alkene product.[136] Furthermore, these workers have posited that the (*Z*)-selectivity in these reactions has the same mechanistic origin as the (*Z*)-preference of Wittig reactions involving stabilized ylides and aliphatic aldehydes possessing proximal alkoxy substituents. Taken together, these findings bolster the argument that there is in fact a common mechanism in operation for all types of 'salt-free' Wittig reactions. The proximal heteroatom effect was accommodated within the framework of the Vedejs–Harvey model by invoking an interaction of the aldehyde-associated heteroatom with phosphorus in the cycloaddition transition state.[136]

From the foregoing discussion, it is evident that one should contemplate Wittig reactions involving substrates that incorporate donor or polar functionality with some trepidation because the normal guidelines for predicting stereochemical outcome may not be sufficient for reliable strategic planning.

1.15.3.1.3.3 The effect of the spectating ligands on phosphorus

For reasons of practicality and the already dominant literature precedent, a vast majority of Wittig reactions are conducted with phosphorus ylides prepared from triphenylphosphine. However, the nucleophilicity of ylides and their characteristic stereoselectivity preferences are modulated by the spectating ligands bound to phosphorus. Formal exchange of one or more of the phenyl groups found in a given $Ph_3P{=}CRR'$ type ylide for an alternate ligand may boost reactivity and/or result in a welcome increase in stereoselectivity. In some cases, changes of this kind will wholly reverse the usual stereochemical bias imposed by the intrinsic nature of the components being spliced together. Use of trialkylphosphines in place of triarylphosphines for ylide generation has dramatic effects on stereoselectivity and gives phosphoranes with enhanced nucleophilicity. For example, in experiments designed to probe Schlosser's 'leeward approach' stereocontrol model for the Wittig reaction, Schlosser and Schaub compared the outcome of transformations involving a series of ethylidene phosphoranes derived from either PPh_3 or Et_3P in the absence of lithium salts; a marked switch from (*Z*)- to (*E*)-selectivity was noted (data set A, Scheme 40).[186] Vedejes et al. likewise examined stereoselectivity in the salt-free reactions of a series of ethylidenes $Ph_{3-n}Et_nP{=}CHCH_3$ ($n=0$ to 3) with aldehydes including the bulky substrate $BnCMe_2CHO$ (data set B).[145b] The observed decreases in *Z:E* ratio with an increasing number of sterically nondemanding alkyl spectator ligands on phosphorus is typical and is accommodated by the Vedejs–Harvey stereocontrol model (viz, reduced significance of 1,3-interactions between R^2 and R^3 favors transition state wherein positions of R^2 and H are reversed in TS-**243** to minimize 1,2-interactions between R^1 and R^2, Scheme 31).[140] Other factors may also be important: for



A:

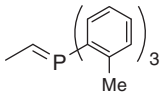
Yield **320** (Z:*E* ratio)		
R′	R = Ph	R = Et
n-C_6H_{13}	95% (86:14)	94% (33:67)
t-Bu	92% (98:02)	92% (10:90)
Ph	94% (87:13)	99% (17:83)
4-ClC_6H_4	88% (88:12)	89% (04:96)

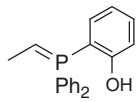
B:

Ylide (**318**):	PPh_3	PPh_2Et	$PPhEt_2$	PEt_3
Yield **320**:	98%	85%	90%	97%
Z:E **320**:	> 99:01	85:15	57:43	10:90

(R′ = CMe_2Bn)

C:

R′ Ylide (**318**):	PPh_3	*Z:E* **320**		*Z:E* **320**
n-C_5H_{11}	96:04		99:01	
c-C_6H_{11}	98:02		-:-	
Ph	92:09		95:05	
(*E*)-*n*-PrCH=CH	90:10		97:03	
n-BuC≡C	84:16		96:04	

D:* R′		*Z:E* **320**
n-C_9H_{19}	38:62	
3-$MeOC_6H_4$	10:90	
4-$MeOC_6H_4$	08:92	

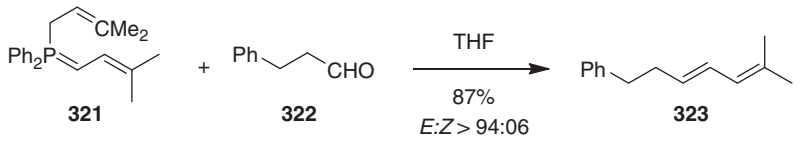
*ylide generated with *s*-BuLi, reaction in THF-HMPA

Scheme 40 Effect of spectating ligands on phosphorus in the Wittig reactions of ethylidene phosphoranes **318** generated with $NaNH_2$ base except where noted.

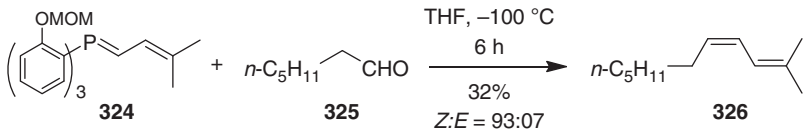
example, stereochemical drift effects (equilibration between oxaphosphetane diastereoisomers) contributed significantly to the high (*E*)-selectivity of the reaction between nonstabilized ylide $Et_3P{=}CHCH_3$ and $BnCMe_2CHO$.

By the same token that smaller spectator ligands on phosphorus can promote (*E*)-selectivity, the intrinsic preference for the (*Z*)-alkene isomer to be generated from nonstabilized ylides can be accentuated by equipping the phosphorane with more sterically demanding substituents. Schlosser and coworkers established that ylides derived from fully ortho-substituted triaryl phosphines give superior *cis* selectivity in the synthesis of 1,2-disubstituted olefins from aldehydes that result in poor stereoselectivity using traditional PPh_3-based ylides (data set C).[187] Interestingly, (*E*)-selectivity is instead induced by using quite similar aryl spectator ligands that possess free hydroxyl groups. Thus, McNulty et al. recently demonstrated that the intramolecular alkoxide *trans*-selectivity effect (**Scheme 38**, Section 1.15.3.1.3.2) can be realized in ylides derived from triarylphosphonium salts in which one of the spectating ligands on phosphorus is an orthophenol moiety (data set D).[179] This approach requires that a lithium base be used to generate the ylide (lithium salt must be present) and it has the obvious advantage over the Maryanoff procedure in that (*E*)-selectivity can be obtained from nonstabilized ylides without the need for any particular intrinsic functionality in the side-chain.

The use of modified phosphoranes is particularly advantageous in the reactions of semistabilized ylides that might otherwise give poor stereocontrol with the canonical PPh_3-based reagents. Again, the presence of alkyl spectator ligands can promote (*E*)-selectivity[188] whereas bulky aryl spectator ligands have the opposite effect. For example, Vedejs and Fang showed that ylide **321** with one alkyl and two aryl spectator ligands (produced by $NaNH_2$-mediated deprotonation of the corresponding symmetrical phosphonium salt) reacted with an aliphatic aldehyde to give an (*E*)-diene product **323** with high stereoselectivity (equation 63).[189] By contrast, Schlosser and coworkers showed that semistabilized ylides derived from bulky tris(2-methoxymethoxyphenyl)-phosphonium salts by deprotonation with $NaNH_2$ (e.g., **324**) give (*Z*)-configured alkene products instead (equation 64).[190]

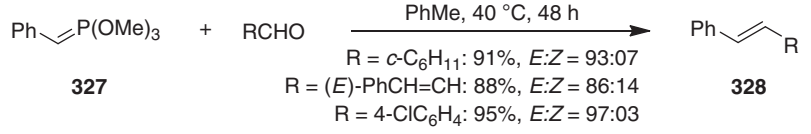


(63)

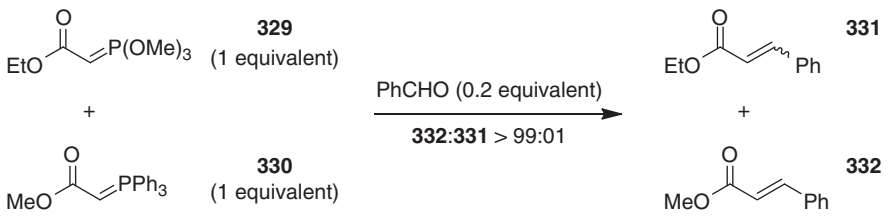


(64)

More recently, Aggarwal et al. have demonstrated the *in situ* generation of a new class of phosphoranes by the trapping of metal carbenoids with trimethylphosphite (see Section 1.15.3.1.2, equation 48).[158] The spectating substituents on these phosphate-based ylides are small but electron-withdrawing and this leads to some unique stereoselectivity and reactivity traits. Significantly, it was found that benzylidene phosphoranes of this type (e.g., **327**) give high (*E*)-selectivity in their reactions with aliphatic, α,β-unsaturated, and aryl aldehydes (equation 65). The *trans* selectivity observed here is of course much higher than would ordinarily be expected from the comparable semistabilized ylide derived from PPh_3. Interestingly, the reaction of a phosphite ylide obtained from ethyl diazoacetate (**329**) reacted with benzaldehyde to give much lower (*E*)-selectivity (**331**, 57% yield, *E:Z* = 69:31) than can be obtained from the analogous PPh_3 ylide. In competition experiments it was found that phosphite ylides are substantially less reactive than phosphine ylides, presumably reflecting the higher stability conferred on them by the electron-withdrawing alkoxy spectator ligands on phosphorus (equation 66).[158]



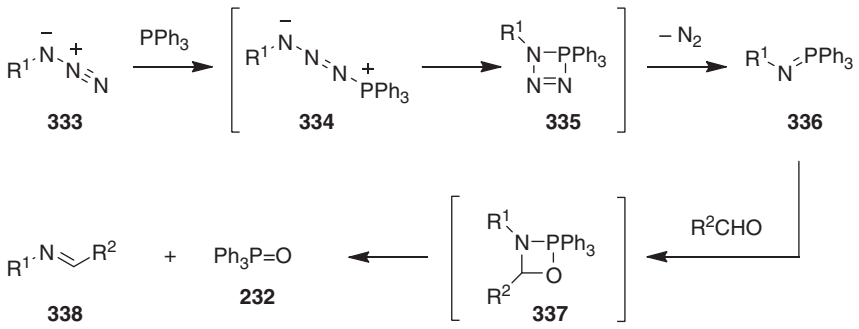
(65)



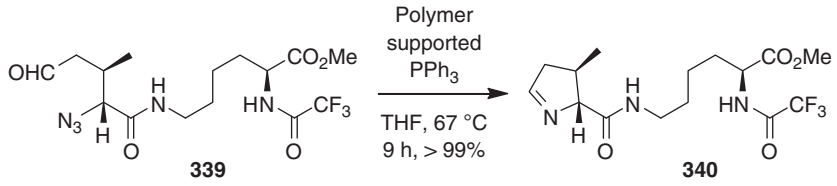
(66)

1.15.3.1.4 Notable reaction variants and specialized applications

Surveyed here are a selection of useful variants of the Wittig reaction and a number of ylide reagents with specialized synthetic applications. To begin with it is noted that the reactions of phosphorus ylides with carbonyl compounds were actually first described by Staudinger and Meyer in 1919,[134] some 34 years before Wittig's inaugural paper on the same subject opened the way for their practical implementation.[1] The most well known of these contributions today are Staudinger's studies concerning the addition of iminophosphoranes to carbonyl groups to generate imines but it should not be forgotten that Staudinger also reported the formation of a carbon–carbon double bond from the reaction of diphenylmethylidenephosphorane with diphenylketene and proposed an oxaphosphetane as the intermediate.[134] The Staudinger method for phosphorus ylide generation from diazo compounds and phosphines is impractical for the synthesis of carbon-based phosphoranes unless metal catalyzed (see Section 1.15.3.1.2); however, it produces iminophosphoranes from organic azides in high yields at ambient or only slightly elevated temperatures (Scheme 41).[191] Azides are conveniently converted to amines via hydrolysis of iminophosphoranes prepared in this manner and heterocycles are formed directly from the reaction of azidocarbonyl compounds with phosphines, as seen in the synthesis of pyrroline **340** (equation 67).[192] Understandably, the latter type of transformations are frequently referred to as 'aza Wittig' reactions; however, given the chronology of the relevant contributions, this practice is discouraged. More recently, the *in situ* generation of iminophosphoranes from azides in cellular environments has formed the basis of numerous important bioorthogonal chemical ligation methods.[193] For example, the biotinylated phosphinylbenzoate derivative **341** is capable of capturing azide-tagged glycoproteins obtained from the cell lysates of bioengineered organisms (equation 68).[194]



Scheme 41 Formation of iminophosphoranes (**336**) from organoazides and triphenylphosphine and their reactions with carbonyl compounds to generate imines.



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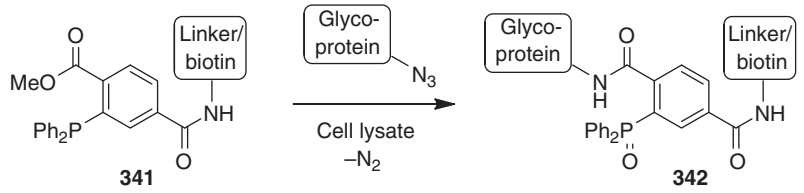
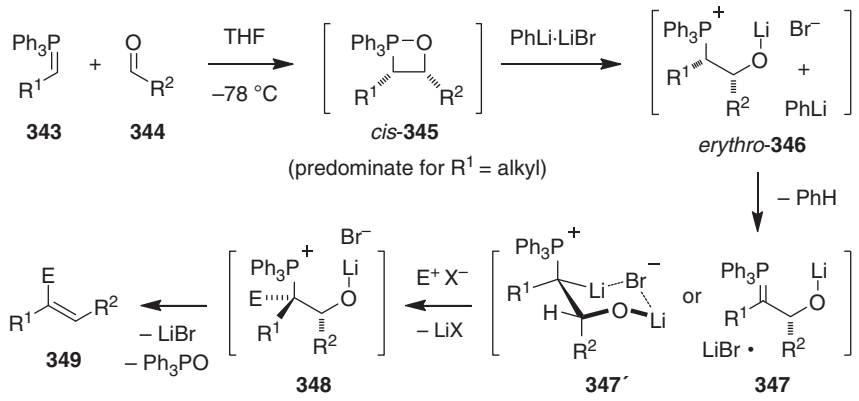


(68)

1.15.3.1.4.1 Generation and reactions of β-oxido ylides: The Wittig–Schlosser reaction

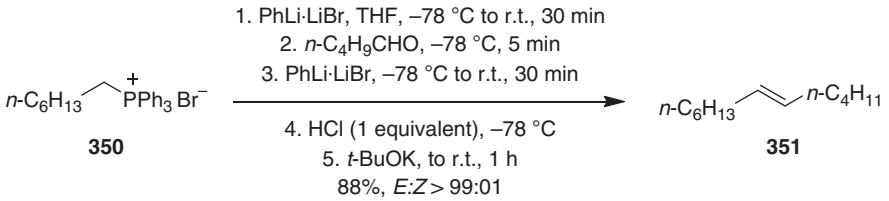
Schlosser and coworkers have demonstrated that oxaphosphetane intermediates **345** can be converted to synthetically useful β-oxido ylide species **347**/**347′** by the combined action of LiBr and phenyllithium via deprotonation of LiBr betaine complexes **346** (Scheme 42).[131e] Necessarily generated in the presence of LiBr, these ylides can be regarded as either α-lithiated phosphonium salts **347′** or LiBr complexed phosphoranes **347**. Whatever their true nature, the β-oxido ylide LiBr complexes are intercepted by a range of electrophiles in an highly diastereoselective manner leading to the production of LiBr betaine complexes **348** that collapse to alkenes in which the original R^1 and R^2 substituents are disposed in an *anti* fashion. The procedure was initially reported as a means to access (*E*)-configured 1,2-disubstituted alkenes: in this case, the electrophile employed is simply proton (i.e., $E^+ = H^+$,

usually one equivalent of anhydrous ethereal HCl) and *t*-BuOK is added in the last stage to decomplex LiBr from the betaine to facilitate its further evolution to the alkene.[195] Schlosser and coworkers recently clarified how to conduct this useful procedure to obtain high *trans* selectivity in a reproducible manner.[196] The use of homemade PhLi•LiBr (prepared from PhBr and 2Li) is advocated because commercially available solutions of PhLi contain too little LiBr for the Wittig–Schlosser reaction to function properly. Preparing the initial ylide from a triiphenylphosphonium bromide salt (e.g., **350**) and PhLi•LiBr helps to ensure a high concentration of the critical LiBr additive throughout (e.g., equation 69).[196]



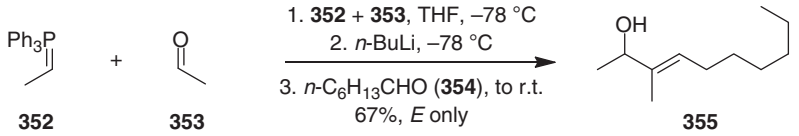
343 **344** *cis*-**345** (predominate for R^1 = alkyl) *erythro*-**346** **349** **348** **347´** **347**

Scheme 42 Generation of β-oxido ylide LiBr complexes (**347**/**347′**) from oxaphosphetanes (**345**) and their stereoselective conversion to alkenes.

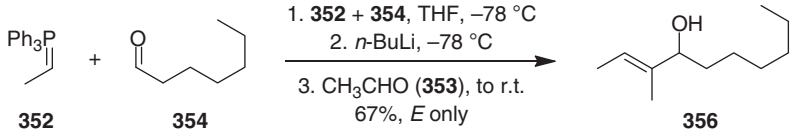


350 **351** (69)

Use of nontrivial electrophiles in place of proton affords the possibility of generating trisubstituted alkenes via so-called 'SCOOPY' (α-substitution plus carbonyl olefination via β-oxido phosphorus ylides) or 'three-dimensional' Wittig reactions.[197] Some of the highest yielding reactions of this nature are those involving a second aldehyde as the electrophile (nb. reactions involving alkyl halides fail in most cases). In this case there is an interesting regioselectivity issue to content with since a β,β′-dioxido phosphonium salt species is involved as an intermediate. Corey and Yamamoto discovered that the second aldehyde added is typically the component involved in alkene formation and that (*E*)-configured trisubstituted allylic alcohols are available in this fashion, as demonstrated by equations 70 and 71.[198] Reactions involving formaldehyde fare differently, however, and give (*Z*)-configured hydroxymethyl-bearing alkenes regardless of the order of addition of aldehydes. Mechanistic models accounting for the origin of the interesting regio- and stereo-selectivity attributes of these kinds of reactions have been put forth by Corey et al.[199]



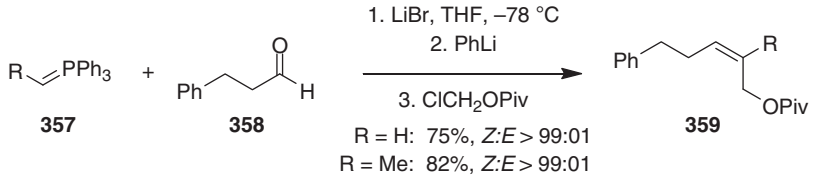
352 **353** **355** (70)



352 **354** **356** (71)

More recently, Hodgson and Arif demonstrated a high yielding synthesis of (*Z*)-configured allylic esters by employing acyloxy halomethanes as electrophiles in the SCOOPY process.[200] The method can be used to prepare 1,2-disubstituted or trisubstituted products by commencing with either methylenetriphenylphosphorane or a longer chain nonstabilized phosphorus ylide (equation 72).[200a] Hodgson's procedure complements the synthesis of comparable 1,2-disubstituted (*E*)-configured products using the Julia–Kocienski reaction.[100b] Vinylhalides are also conveniently prepared by the SCOOPY process; however, in this case

stereochemical outcome is dependent on the size of the alkylidene and usually opposite to that commonly encountered in more conventional SCOOPY reactions.[197b,201–203] Thus, (*E*)-configured trisubstituted vinylhalides were obtained from all but ethylidene ylides in SCOOPY reactions involving 1,2-dibromotetrafluoroethane or molecular iodine as the oxidant (e.g., equation 73).[203]



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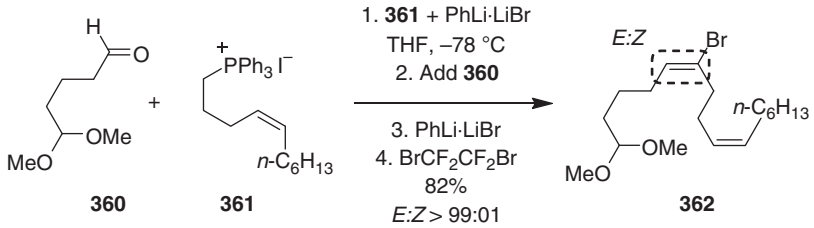
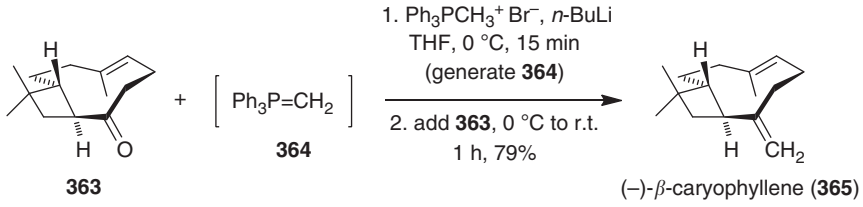


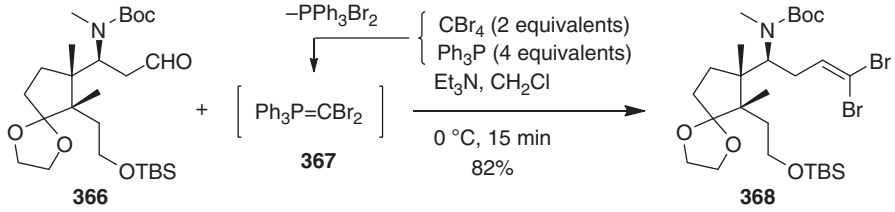
(73)

1.15.3.1.4.2 Specialized phosphorane reagents for the synthesis of useful structural motifs

Featured in this section is a selection of phosphoranes that are uniquely suited to the introduction of structural motifs of common occurrence and/or of general synthetic utility. One such widely used species is methylenetriphenylphoshorane (**364**) which is an efficient reagent for the methylenation of aldehydes and ketones; a representative example is seen in the final step of a recent synthesis of *β*-caryophyllene (equation 74).[204] The basicity of this reagent (and nonstabilized phosphorus ylides in general) can cause problems with readily epimerizable substrates and it fails to react with hindered ketones. The latter problem has been solved by generation of a putative metallated form of the phosphorane ($Ph_3P{=}CHLi$),[205] or by use of the Tebbe reagent instead.[45] Geminal dibromoalkenes utilized in the Corey–Fuchs alkyne synthesis,[206] or employed in cross-coupling procedures,[207] are obtained from the Wittig reaction of aldehydes with dibromomethylenetriphenylphoshorane (**367**).[208ab] The ylide in this case is conveniently generated in the presence of the aldehyde by *in situ* reduction of CBr_4 by excess PPh_3 (or alternatively by a combination of equal parts of CBr_4, PPh_3, and zinc metal if the substrate is sensitive to the Ph_3PBr^+ Br^- by-product of the first procedure). The synthesis of dibromoalkene **368** from aldehyde **366** en route to hederacines A and B by Aoyagi and coworkers is illustrative (equation 75).[208c] Alkene **368** was subsequently transformed into the corresponding terminal alkyne by the Corey–Fuchs procedure (treatment with *n*-BuLi followed by protonolysis).



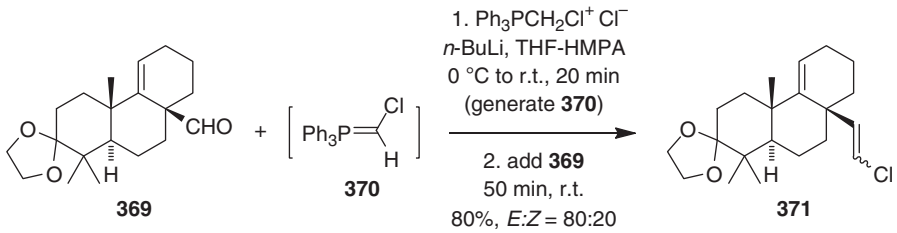
(74)



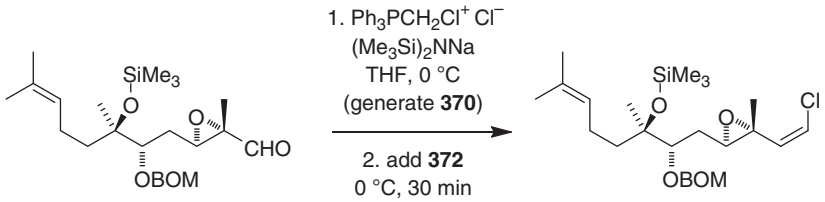
(75)

Stereogenic vinyl halides are likewise available by the reactions of aldehyde and ketones with halomethylene phosphoranes.[209] Due to the decreasing electronegativity of X in the series of $Ph_3P{=}CHX$ from X = Cl, Br, to I, the character of these ylides changes from semistabilized to nonstabilized. Accordingly, chloromethylenetriphenylphosphine (**370**) gives variable results and mixtures of (*E*)- and (*Z*)-isomers are obtained under most circumstances. For example, vinyl chloride **371** was obtained with modest (*E*)-selectively (*E*:*Z* = 80:20) from hindered aldehyde **J7** in the presence of lithium salts (equation 76),[209a] whereas (*Z*)-vinyl chloride **373** was generated as a single isomer from *α*,*β*-epoxyaldehyde **372** using NaHMDS to generate the ylide

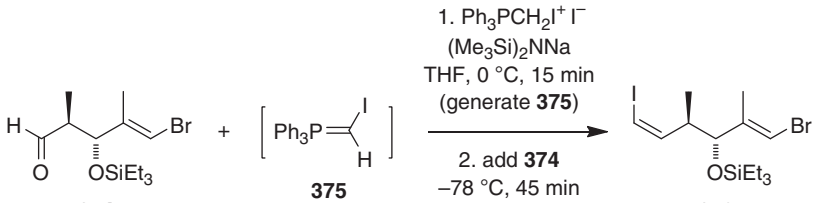
(equation 77).[209b] High *cis* selectivity in the second case is presumably accentuated by the presence of lone-pair donor atoms in close promixity to the carbonyl group of the aldehyde (see Section 1.15.3.1.3.2). Stork and Zhao established that excellent (*Z*)-selectivity can generally be obtained in the synthesis of 1-iodo-1-alkenes by the use of iodomethylenetriphenylphosphine (**375**) generated *in situ* with a sodium base.[209c] The following recent example from Paterson and coworkers is illustrative (equation 78).[209d] A stereocomplementary result is available using the Cr-based Takai olefination which consistently delivers (*E*)-1-iodo-1-alkenes from aldehydes with equally high selectivity.[210] The behavior of $Ph_3P{=}CHBr$ is intermediate between that of **370** and **375** and it typically gives a mixture of stereoisomers, as does its fluorinated congener.[211]



369 **370** **371** (76)



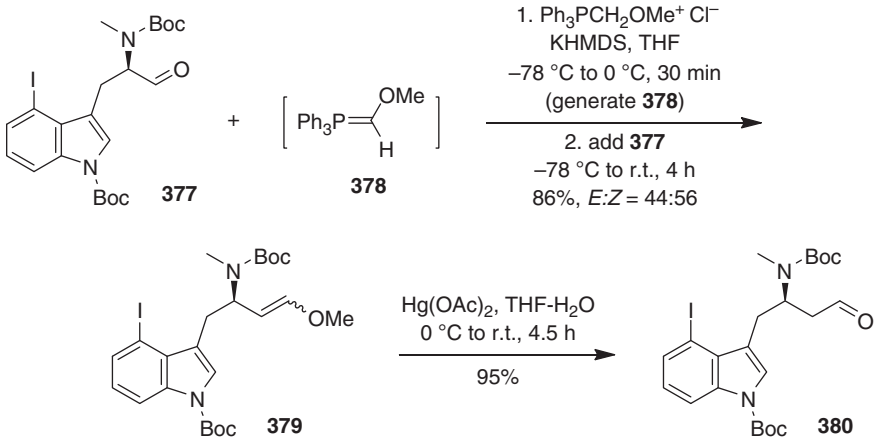
372 **373** (77)



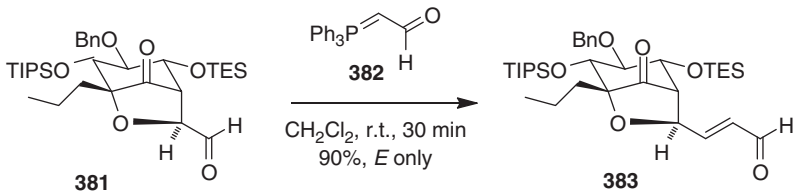
374 **375** **376** (78)

A one-carbon-atom homologation of aldehydes and ketones is achieved by acidic hydrolysis of enol ethers derived from them by the Wittig reaction with methoxymethylenetriphenyl-phosphorane (**378**) and related alkoxymethylidene ylides.[212] The enol ether is typically formed with almost no stereochemical bias, a fact of little consequence if the intention is to generate the homologous carbonyl compound. The following reaction sequence, used to homologate an iodotryptophan-derived aldehyde (**377**) in a total synthesis of lyseric acid by Liu and Jia, is exemplary (**Scheme 43**).[213] Acyloxymethylene phosphorus ylides have been similarly used to make *O*-acyl enol ethers.[214]

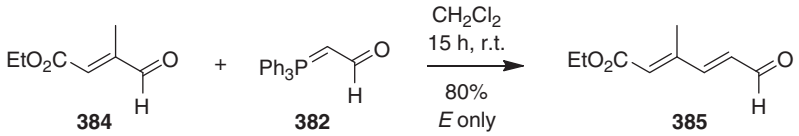
Finally, this section highlighting specialized Wittig reagents concludes with a brief mention of formyl- (**382**) and acetylmethylenephosphorane (**387**) reagents.[215] This remarkable family of stabilized ylides contains aldehyde or ketone functionality within them and yet do not spontaneously polymerize. Furthermore, such reagents engage with nonconjugated cabonyls to give α,β-unsaturated enals and enones that show sufficiently attenuated electrophilicity not to react further. As stabilized ylides, these compounds are isolable and give the expected high level of (*E*)-selectivity in their reactions with aldehydes. Many are commericially available but easily prepared by the acylation of alkylidene ylides with formyl or acetyl donors. The following examples are representative and reveal some interesting chemoselectivity traits: discrimination between aldehyde and ketone sites (equation 79);[216] reaction of an α,β-unsaturated enal starting material (**384**) but not continued reaction from the product enal (**385**) owing to slightly higher electrophilicity of substrate (equation 80);[217] and olefination of ketone in ethyl pyruvate (**386**) but not continued reaction from enone product (**388**) which is again less electrophilic than its precursor (equation 81).[218] The last example further exemplifies that high stereoselectivity in the synthesis of trisubstituted alkenes from stabilized ylides cannot be generally expected with ketone substrates. By contrast, the formylethylidene ylide variant ($Ph_3P{=}CMeCHO$) gives trisubstituted α,β-unsaturated enals with very high (*E*)-stereoselectivity in its reactions with aldehydes: an example is given in **Table 5** (entry 7) in Section 1.15.3.1.5.



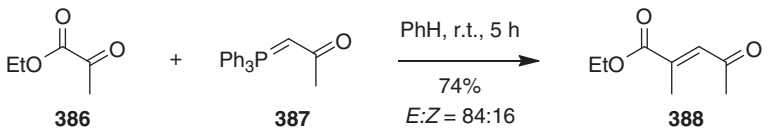
Scheme 43 Aldehyde homologation via an enol ether generated using methoxymethylene-triphenylphosphorane (**378**).



(79)



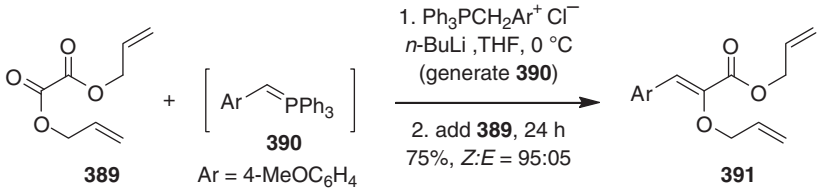
(80)



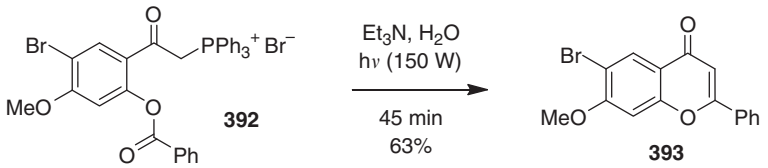
(81)

1.15.3.1.4.3 *Wittig reactions with electrophiles other than aldehydes and ketones*

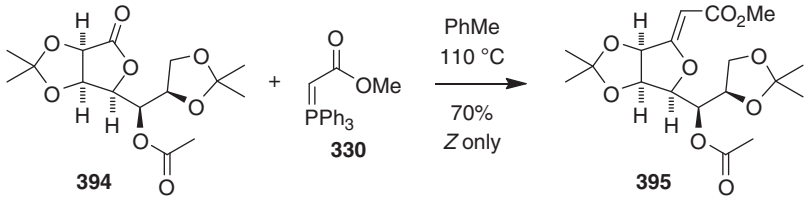
The formation of alkenes with phosphorus ylides is not necessarily limited to aldehyde and ketone substrates and in certain circumstances esters or even amide type carbonyl compounds will react in the desired manner to give enol ether and enamine products, respectively.[228] The intermolecular reactions of phosphoranes with esters typically result in acyl substitution and the formation of stabilized ylides (see Section 1.15.3.1.2); by contrast, perfluoroalkanoates,[229] formate esters,[230] and other types of unusually reactive esters (e.g., oxalate diesters, equation 82)[231] can give enol ethers instead. Simple esters do, however, engage in the Wittig reaction in an intramolecular sense, as seen in a recent synthesis of flavones based on a rarely exploited photochemical activation method (equation 83).[232] Lactones are more reactive than acyclic esters and have been converted to enol ethers via both intramolecular and intermolecular Wittig reactions. Equation 84 is representative of the latter and illustrates chemoselective reaction at the lactone carbonyl group rather than at the less hindered acetate moiety.[233] The formation of dichloromethylene enol ethers from both simple acyclic esters and lactones has been achieved with a reagent combination of PPh_3 and CCl_4,[234] a related process is available for comparable dibromomethylenation reactions of lactones.[235]



(82)

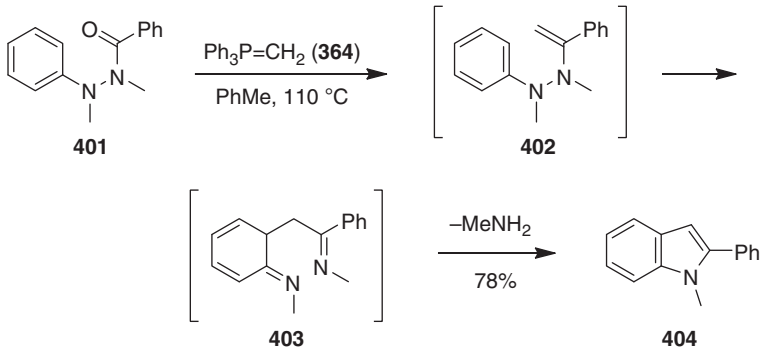


(83)

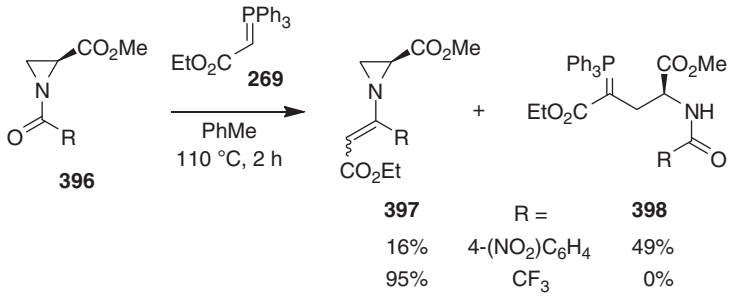


(84)

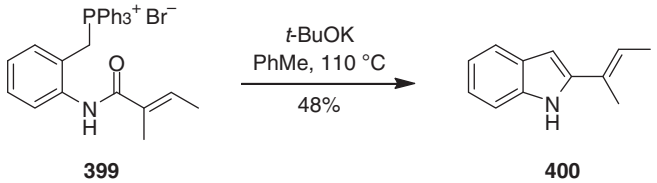
Amide carbonyl groups are far less reactive than those of esters; however, again it is possible to olefinate them with phosphorus ylides providing some sort of special activation is available. Thus, trifluoroacetamide derivatives are converted to enamines under fairly standard conditions[236] and amides lacking proper conjugation between the nitrogen–atom lone-pair and the carbonyl group are also potentially olefinated. For example, the conversion of aziridinyl benzamide **396** (R=4-$(NO_2)C_6H_4$) to the desired ring-opened adduct **398** with phosphorane **269** was complicated by the formation of a significant quantity of vinylogous carbamate **397** (equation 85).[237] Performing the same reaction from trifluoroacetamide **396** (R=CF_3) under otherwise identical conditions gave the Wittig product **397** (R=CF_3) as the sole product as a single stereoisomer (configuration not determined). Intramolecular Wittig reactions of amides en route to indoles have been charted;[238] these important heterocycles are available via base-mediated cyclization of benzylidene ylides derived from anilides such as **399** (equation 86).[239] An alternative indole synthesis involving the Wittig olefination of hydrazides was recently described by Murphy and coworkers (Scheme 44).[240] In this case, olefination cleverly intersects on the familiar intermediates of the classical Fisher indole synthesis (e.g., **401** to **402**); unfortunately, the basicity of nonstabilized ylides limits the process to nonenolizable hydrazides.



Scheme 44 Alkylidenation of hydrazides to intersect on Fisher indole synthesis.

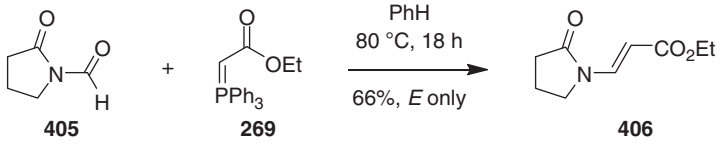


(85)

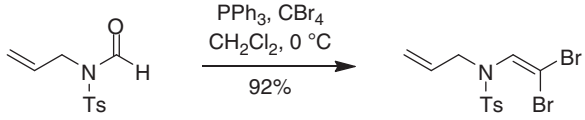


(86)

Wittig reactions have also been described from other types of nontraditional carbonyl compound substrates, such as anhydrides, imides, and thioesters.[228] For example, the Wittig reactions of *N*-formylimides have been usefully exploited in a synthesis of enamides reported by Marquez and coworkers (e.g., equation 87).[241] *N*-Sulfonyl amides have imide-like reactivity and are also susceptible to the Wittig olefination. Thus, Brückner has demonstrated the olefination of *N*-tosyl formamides with dibromomethylenephosphorane generated *in situ* from PPh_3 and CBr_4 (equation 88).[242] Valuable *N*-tosyl ynamines were subsequently obtained from the products via the Corey–Fuchs procedure.[206]

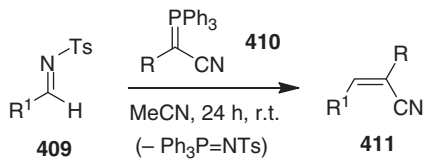


405 + **269** → **406** (87)



407 → **408** (88)

Finally, Tian and coworkers have recently documented olefination of *N*-sulfonyl imines with stabilized ylides via an aza analog of the classical Wittig reaction that produces iminophosphorane by-products rather than phosphine oxides.[243] The reactions of carbonyl stabilized ylides with tosyl imines offer no advantage over their conventional counterparts; however, acrylonitrile products **411** derived from the reactions of cyanomethylenetriphenyl-phosphorane (**410**, R=H) with imines **409** were obtained with higher stereoselectivity (in favor of the (*Z*)-isomers) than that expected from comparable reactions involving aldehydes (Scheme 45). The substituted cyano-stabilized ylide **410** (R=Me) failed to react effectively with aldehydes and gave the opposite acrylonitrile stereoisomer preferentially.



R^1	R	Yield **411**	*Z*:*E*
Ph	H	97%	95:05
(*E*)-PhCH=CH	H	78%	93:07
c-C_6H_{11}	H	80%	85:15
Ph	Me	32%	30:70

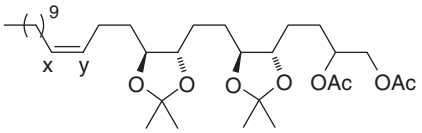
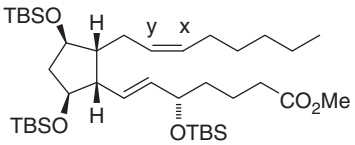
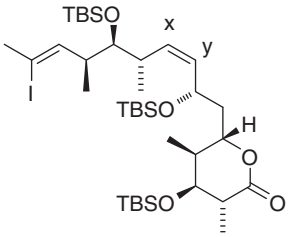
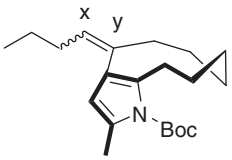
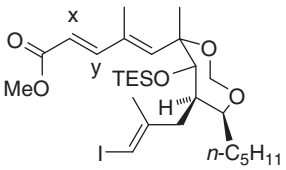
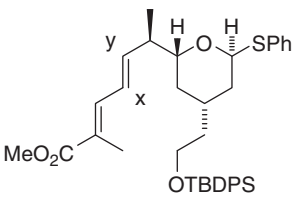
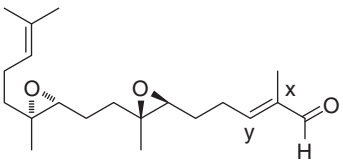
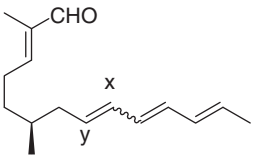
Scheme 45 Olefination of *N*-tosyl imines **409** with cyanomethylidene ylides **410**.

1.15.3.1.5 Illustrative examples in target-directed synthesis

The Wittig reaction has been applied to the synthesis of hundreds of complex target molecules in its 60-year history and a handful of illustrative examples culled from the more recent literature are collected together in Table 5. Although it can be used to generate all types of alkenes, the unique advantage that the Wittig reaction holds over alternative carbonyl olefination methods is the facility that it offers to directly access nonconjugated (*Z*)-configured 1,2-disubstituted alkenes in a stereocontrolled fashion (from nonstabilized ylides in the absence of lithium salts). It is also an excellent tool for the preparation of various kinds of (*E*)-configured olefins (including trisubstituted examples) using stabilized ylides. The phosphorane reagents of the Wittig reaction are usually compatible with complex molecular fragments, although on occasion the heightened basicity of nonstabilized ylides can cause epimerization and other problems associated with proton transfer. As is evident from Table 5, complex aldehydes are commonly used as components in Wittig reactions but the phosphoranes deployed to olefinate them are rarely as elaborate; of course, this is not without some notable exceptions.[244]

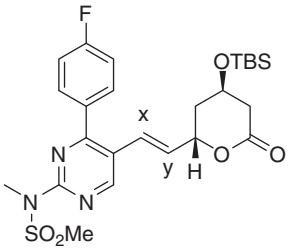
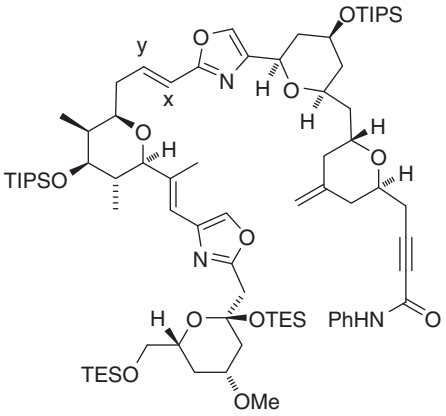
The first three entries of the table exemplify the synthesis of nonconjugated (*Z*)-configured 1,2-disubstituted alkenes from nonstabilized ylides en route to the annonaceous acetogenin sylvaticin (entry 1),[219] 5-F_{2t}-isoprostane (entry 2),[220] and the polyketide discodermolide (entry 3).[146] The phosphorane involved in the synthesis of 5-F_{2t}-isoprostane (entry 2) was generated using Schlosser's 'instant ylide' technique[245] whereby the phosphonium salt and metal amide base are premixed in a Schlenk tube and then the solvent is added to the mixture of solids. Prostaglandin-unsaturated side-chains have also been appended using ylides containing carboxylate anions (e.g., $Ph_3P{=}CH(CH_2)_3CO_2^-$).[246] Smith and coworkers' gram-scale synthesis of discodermolide is notable for the fact that a complex nonstabilized ylide was employed (entry 3); the synthesis of the phosphorane in this case is described above (Section 1.15.3.1.2). By contrast to transformations involving aldehydes, the reactions of nonstabilized ylides with ketones are seldom highly stereoselective, as encountered by Fürstner and coworkers during the installation of a four-carbon-atom side-chain en route to a prodigiosin derivative (entry 4).[221] Fortunately, in this case alkene stereochemistry was of no consequence (the olefin was hydrogenated in next step), and the Wittig reaction was being used as a convenient generic coupling tool.

Table 5 A selection of complex alkene targets prepared by the Wittig reaction

Entries	*Alkene target*[a]	*Reaction conditions and outcome*	*References*
1		Ylide precursor: Ph_3P^+ Br^- KHMDS, PhMe, –78 °C to r.t., 16 h 100%, *Z* only	219
2		Ylide precursor: Ph_3P^+ Br^- KHMDS, THF-CH_2Cl_2, –78 °C to r.t., 8 h 80%, *Z* only	220
3		Ylide precursor: Ph_3P^+ I^- NaHMDS, THF, –78 °C 62%, *Z* only	146
4		Preformed PPh_3 ylide PhMe, 110 °C, 1.5 h 75%, *E:Z* ~ 50:50	221
5		Preformed PPh_3 ylide PhH, 65 °C, 18 h 91%, *E* only	222
6		Preformed PPh_3 ylide THF, 67 °C, 16 h 77%, *E* only 77%, *E* only	223
7		Preformed PPh_3 ylide PhH, 80 °C, 24 h 64%, *E:Z* > 95:05	224
8		Ylide precursor: Ph_3P^+ Br^- *n*-BuLi, THF, –78 °C, 2 h 61%, *E:Z* = 60:40	225

(*Continued*)

Table 5 Continued

Entries	*Alkene target*[a]	*Reaction conditions and outcome*	*References*
9		Ylide precursor: $Bu_3P^+ CF_3CO_2^-$ NaHMDS, PhMe, 110 °C, 5 min 67%, *E:Z* = 93:07	226
10		Ylide precursor: $Bu_3P^+ MsO^-$ DBU, DMF, r.t. 81%, *E:Z* > 95:05	227

[a]Site of newly introduced alkene is located between x and y; x = original site of the phosphonium salt (or preformed ylide) and y = original site of the carbonyl group.

The use of stabilized ylides in target-directed synthesis, and particularly phosphoranes conjugated with carbonyl groups, is widespread owing to the dependable nature of their reactions which typically favor the (*E*)-alkene (aside from the exceptional cases noted in Section 1.15.3.1.3.2). Table entries 5–7 typify such reactions and show alkenal and alkenoate intermediates prepared en route to formamicin (entry 5),[222] rhizoxin D (entry 6),[223] and dioxepandehydrothyrsiferol (entry 7).[224] As remarked above (Section 1.15.3.1.3.2), even carbonyl-stabilized ylides derived from 2° alkyl halides strongly favor generation of the (*E*)-configured olefin and provide one of the most reliable ways to prepare trisubstituted alkenes (e.g., equation 55). The conjugated enal precursor to a thyrsiferol congener prepared from a diepoxyaldehyde by Jamison and coworkers shows that this principle extends to the use of formylphosphorane reagents (entry 7).[224]

The Wittig reactions of semistabilized ylides are more variable in their outcome than those of the nonstabilized or stabilized kind and special conditions are typically required to obtain the desired level and sense of stereoselectivity. Simple PPh_3-derived semistabilized ylides often lead to poor stereocontrol as observed by Theodorakis and coworkers in their synthesis of a conjugated triene en route to fusarisetin A (entry 8).[225] This example is notable for the fact that the preformed semistabilized ylide discrimated between two carbonyl groups in the dialdehyde substrate with reaction occurring at the more reactive nonconjugated aldehyde site. The same chemoselectivity was not obtainable with either HWE or Julia–Kocienski olefinations.[225] Semistabilized ylides equipped with alkyl spectator ligands on phosphorus boost (*E*)-selectivity (see Section 1.15.3.1.3.3). Thus, Kosmrlj and coworkers were able to obtain a direct precursor to the HMG-CoA reductase inhibitor rosuvastatin with good (*E*)-selectivity by employing a heterobenzylic tributylphoshonium salt as ylide precursor (entry 9).[226] The carefully optimized reaction conditions minimized β-elimination of a silyloxy substituent found in the lactone ring of the sensitive aldehyde component and also avoided epimerization at the α-stereocenter. The final example in **Table 5** highlights one of the most complex Wittig reactions ever attempted and was documented by Evans et al. in their successful elaboration of phorboxazole B (entry 10).[227] Again, use of a trialkyl phosphonium salt ylide precursor was critical for the realization of high stereoselectivity. Smith et al. later used the same tactic to prepare the related target molecule phorboxazole A.[247]

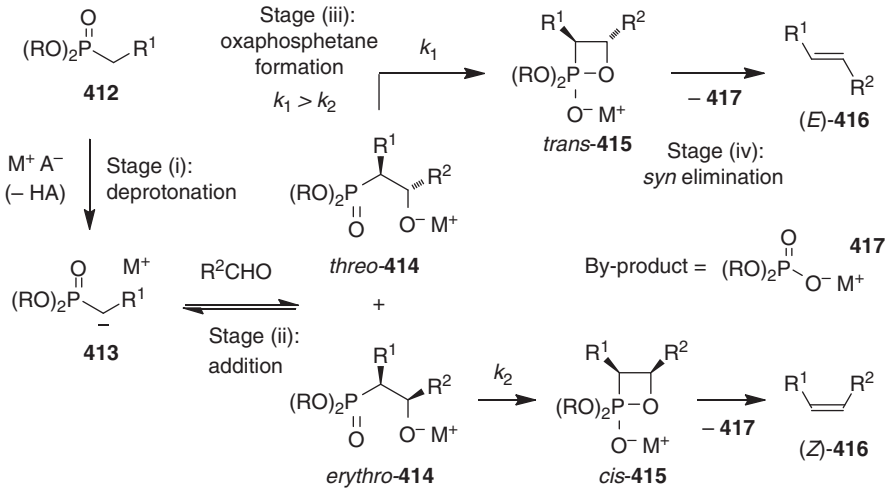
1.15.3.2 Alkene Formation With Phosphoryl-Stabilized Carbanions: The Horner–Wadsworth–Emmons Reaction and Related Processes

1.15.3.2.1 Overview and general considerations

Two significant connective olefination methods are based on the addition of phosphoryl-stabilized carbanions to carbonyl compounds, herein referred to as the Horner–Wittig and the HWE reactions. Seminal results from Horner et al. established that

carbanions generated by the deprotonation of either phosphine oxides or organophosphonates engage with aldehyde and ketone electrophiles to deliver alkene products.[248] The second process (HWE reaction), which was more thoroughly investigated by Wadsworth and Emmons soon after Horner's disclosure,[249] has the greater practical value and will be the focus of this section. The phosphine-oxide-based method (Horner–Wittig reaction) is treated in less detail within Section 1.15.3.2.4.1. Both methods have been reviewed previously.[132,133]

In its usual guise, the HWE reaction involves phosphonate reagents **412** bearing an anion-stabilizing group on the α-carbon-atom (e.g., $R^1 = COR'$, CO_2R', CN, aryl, etc.). The reaction is initiated by deprotonation of the phosphonate with a suitable base (e.g., NaH, or *t*-BuOK, or milder concoctions like DBU/LiCl) and followed by the addition of the resulting carbanion (**413**) to the carbonyl component of choice (**Scheme 46**). In the commonly accepted, albeit still controversial, mechanism, the reaction progresses via a β-alkoxyphosphonate intermediate (**414**) that break downs to the desired alkene product and a dialkylphosphate anion by-product (**417**) by way of an oxephosphetane (**415**) stage reminescent of the Wittig reaction.[250] Unlike the Wittig reaction, however, the initial addition phase of the HWE reaction is generally reversible and the *threo* and *erythro* forms of the β-alkoxyphosphonate intermediate **414** may equilibrate before alkene formation.[251] This accounts for the observation of high (*E*)-selectivity from most HWE reactions under standard conditions because the activation barrier to access *trans*-oxaphosphetane **415** is significantly lower than that to access *cis*-oxaphosphetane **415**.

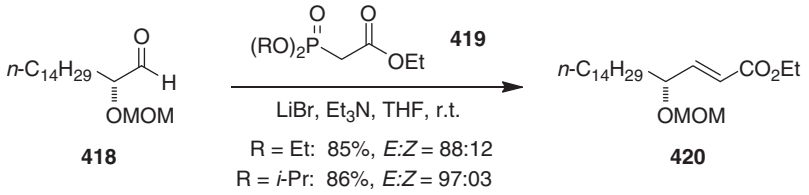


Scheme 46 The Horner–Wadsworth–Emmons reaction of phosphonates illustrated toward 1,2-disubstituted alkene products for the sake of clarity.

It is a popular misconception that alkenes cannot be obtained from phosphonates that lack the anion-stabilizing group; in fact they can, but HWE reactions involving such substrates are problematic. Phosphonates substituted by only trivial groups on the α-carbon-atom (**412**, R^1 = alkyl or H) are difficult to deprotonate and the resulting carbanions have a tendency to self-condense above cryogenic temperatures to give 'dimeric' adducts of the form $(RO)_2P(=O)CHR^1P(=O)(OR)CH_2R^1$.[252] More significantly, the β-alkoxyphosphonate intermediates derived from the addition of these anions to aldehydes or ketones do not spontaneously evolve to give alkenes.[253] Rather, β-hydroxyphosphonates are isolated instead that can only be made to eliminate phosphate under more forcing basic conditions (e.g., aq. K_2CO_3, DMF, 100 °C).[254] For the above reasons, and the comparative ease of making simple nonconjugated alkenes with other carbonyl olefination methods, the usual practice of the HWE reaction is limited to the synthesis of alkenes conjugated to anion-stabilizing moieties such as carbonyl and cyano groups. Fortunately, a wealth of desirable target molecules contain the readily accessible functional groupings and typical HWE products are themselves versatile synthetic intermediates amenable to further transformations (e.g., conjugation, addition, etc.).

Although restricted in its effective target range, the HWE reaction has a number of well-recognized advantages over the Wittig reaction: (1) phosphonate anions are more nucleophilic than comparable phosphorus ylides[255] and have less difficulty adding to hindered or deactivated carbonyl groups such as ketones; (2) the by-product of the HWE reaction is a water-soluble dialkyl phosphate salt that is trivial to remove upon aqueous work-up; and (3) simple phosphonate starting materials are readily obtained from inexpensive trialkylphosphites via the Michaelis–Arbusov reaction and more elaborate substrates are available by subsequent high yielding derivatization chemistry (see Section 1.15.3.2.2). Furthermore, as with the Wittig reaction, it has proved possible to fine-tune the stereochemical outcome of the HWE reaction by varying reaction conditions and spectator ligands on phosphorus. The following two examples are illustrative of these practices and indeed the HWE method in general, which is perfectly suited to the preparation of all kinds of α,β-unsaturated esters in particular. In the first example, the usual (*E*)-selectivity of the HWE reaction has been accentuated by the use of a lithium salt additive and bulky isopropoxy spectator ligands on phosphorus

(equation 89).[256] In the second transformation, the use of an Ando-type (i.e., diaryl) phosphonate (**422**) along with other special conditions (including low temperature) enabled the synthesis of a (*Z*)-enoate precursor (**423**) to the tubulin binding agent pironetin (equation 90).[257] The origin of these effects and other significant attributes of the venerable HWE olefination method will now be elaborated.



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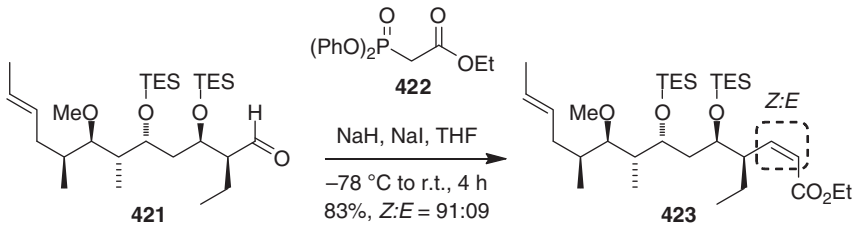
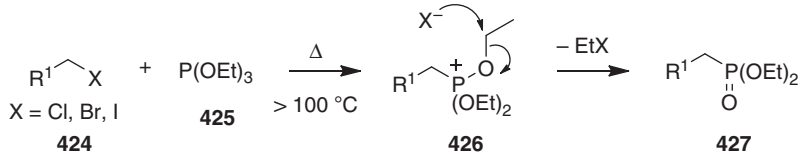


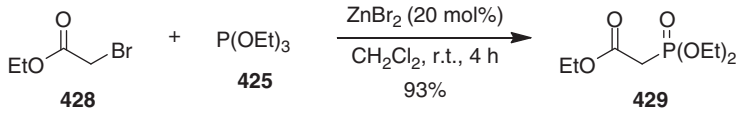
(90)

1.15.3.2.2 Synthesis of phosphonates for the Horner–Wadsworth–Emmons reaction

Simple phosphonates are readily accessed by the Michaelis–Arbuzov reaction of trialkyl phosphites with alkyl halides (Scheme 47).[258,259] The reaction works well for 1° alkyl halides, including α-bromoacetates, but it is less effective for 2° alkyl halides and branched 1° alkyl halides. The classical method involves strong heating of the alkyl halide and phosphite ester without solvent but more recently Mohanakrishnan and coworkers have demonstrated efficient room temperature Michaelis–Arbuzov reactions of benzylic (and heterobenzylic) halides, α-bromoacetates, and α-bromoketones, mediated by Lewis acid additives such as $ZnBr_2$ and $InBr_3$ (e.g., equation 91).[260] This method is extendable to benzylic alcohols but fails to convert 1° alkyl bromides to phosphonates which in any event are easily made via the traditional pyrolysis route.

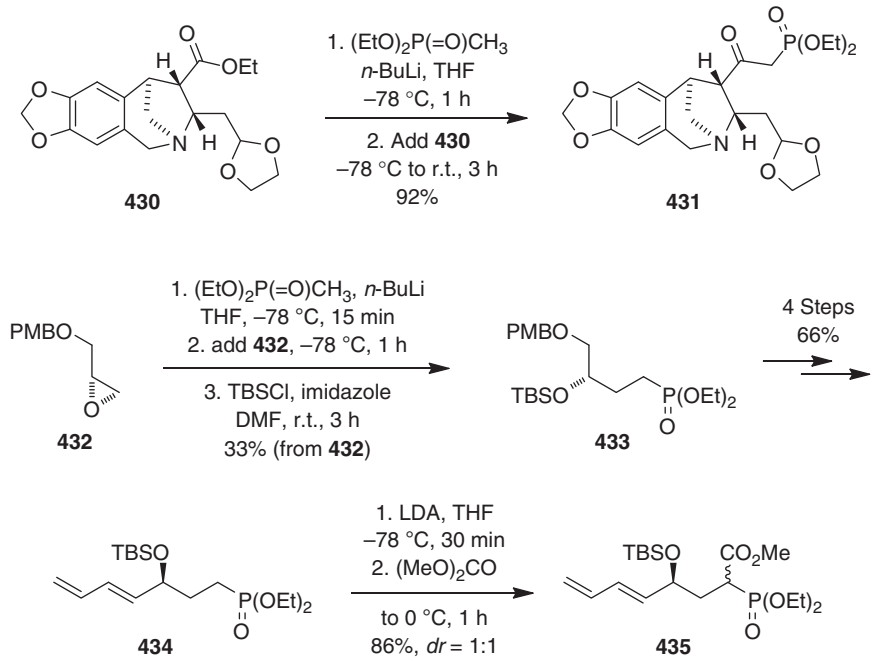


Scheme 47 The Michaelis–Arbuzov reaction of triethylphosphite with alkyl halides.



(91)

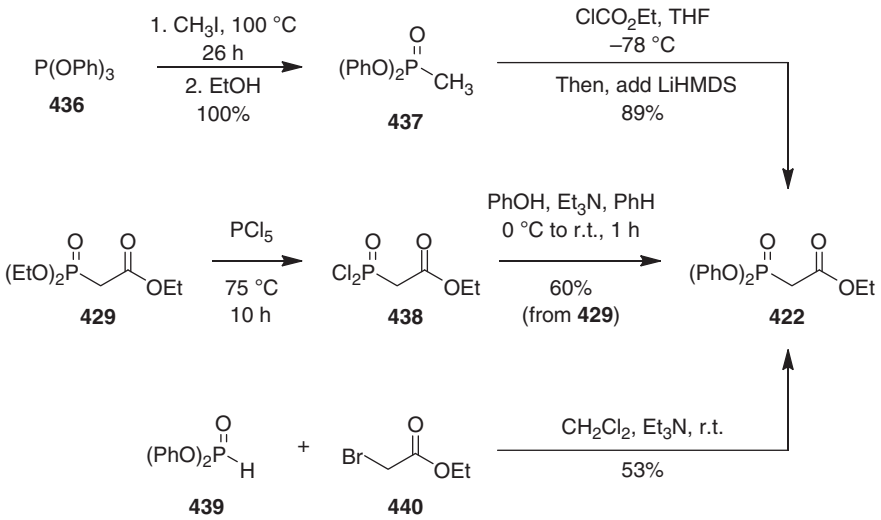
At low temperatures simple α-metallated alkyl phosphonates are well-behaved nucleophiles that can be readily derivatized by reactions with alkyl electrophiles (e.g., alkyl halides, alkyl sulfonate esters, epoxides, etc.) or via acylation with various types of acyl donors (e.g., esters, dialkylcarbonates, etc.).[261] The latter chemistry provides for a synthesis of β-ketophosphonates which are not generally available by the conventional Michaelis–Arbuzov reaction from α-haloketones due to competing Perkow reactions (enol phosphate generation).[258] For example, Pandey and coworkers achieved a high yielding synthesis of a complex β-ketophosphonate (**431**) during the total synthesis of pancracine by adding an excess of the lithiated form of diethyl methylphosphonate to ester **430** (equation 92).[262] An alternative synthesis of the same phosphonate via the addition of a methyl ketone enolate to diethyl chlorophosphate ($ClP(=O)(OEt)_2$) resulted in only a 12% yield. Both phosphonate alkylation and acylation chemistry were employed to good effect by Heathcock and Ott in their synthesis of a complex phosphonoacetate (**435**) representing the side-chain of spongistatin 2 (Scheme 48).[263] This sequence aptly demonstrates that phosphonates are tolerant of many standard functional group interconversions and that their anion chemistry can be used to build up complex fragments before HWE olefination reactions.



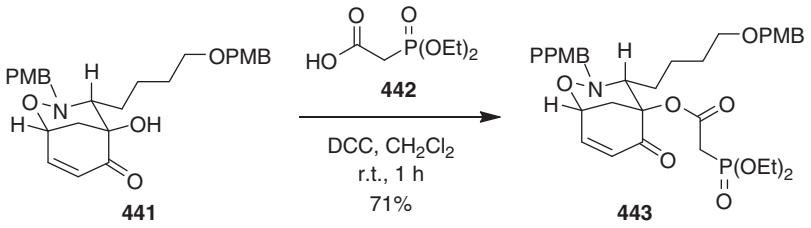
(92)

Scheme 48 Illustrative synthetic manipulations of phosphonate anions en route to a spongistatin 2 fragment (**435**).

Many of the more desirable small α-phosphonocarbonyl building blocks (e.g., **429**) are commericially available and these present a convenient starting point for the elaboration of HWE reagents of greater complexity or examples that contain unusual ligands on phosphorus. Net transesterification of alkoxy groups on phosphorus can be achieved via alcoholysis of dichlorophosphonates generated by treatment of (dialkylphosphono)acetates with PCl_5. For example, Ando prepared the modified HWE reagent ethyl (diphenylphosphono)acetate (**422**) from inexpensive triethyl phosphonoacetate (**429**) in this manner by quenching phosphoryl dichloride **438** with phenol (Scheme 49).[264] The same reagent is also available via acylation of the phosphonate anion derived from **437** under Barbier conditions, or via the Michaelis–Becker reaction between ethyl bromoacetate (**440**) and diphenylphosphite (**439**).[265] Incorporating a phosphonoacetate moiety into a complex molecule is perhaps most easily achieved by ester formation between an alcoholic substrate and diethylphosphonoacetic acid (**442**) or a related compound. Acylation proceeds under standard conditions with carbodiimide reagents providing arguably the most straightforward means to effect the desired coupling. Using this method Kerr and Carson adorned hindered 3° alcohol **441** with a phosphonoacetate moiety to prime the substrate for a subsequent intramolecular HWE reaction en route to the *Securinega* alkaloid phyllantidine (equation 93).[266]

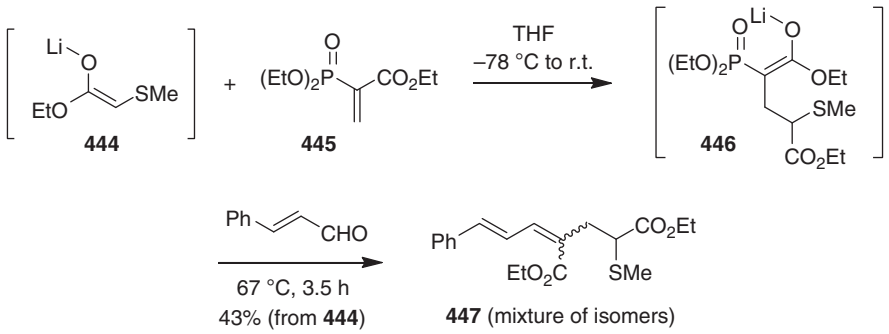


Scheme 49 Three syntheses of ethyl (diphenylphosphono)acetate (**422**).

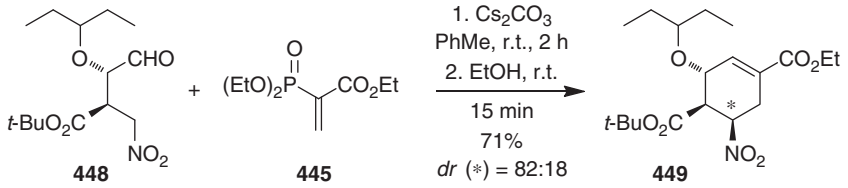


(93)

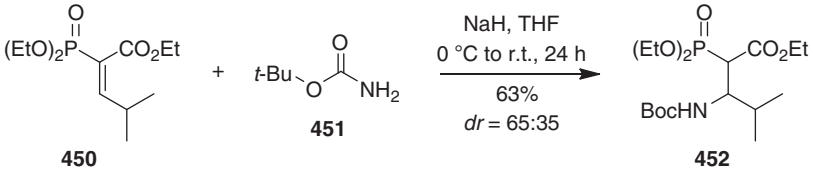
Conjugate addition to vinyl phosphonates provides another derivatization tactic potentially amenable to the synthesis of complex substrates for HWE reactions. The concept can be applied via conventional anionic chemistry or via the addition of radical species,[267] but for the product phosphonates to be of direct use in olefination the usual electron-withdrawing substituent must be present. A Michael acceptor such as ethyl α-(diethylphosphono)acrylate (**445**) is particularly useful in this regard and was used by Minami et al. as a linchpin in a multicomponent coupling process involving carbon-centered nucleophiles and aldehyde electrophiles (e.g., **Scheme 50**).[268] The same kind of process can also be terminated by an intramolecular HWE reaction. For example, Hayashi and coworkers recently achieved a concise synthesis of the anti-influenza drug oseltamivir (Tamiflu) by intermolecular addition of nitroaldehyde **448** to vinyl phosphonate **445** followed by spontaneous intramolecular HWE reaction of the resulting phosphonate anion with the pendant aldehyde to yield cyclohexene **449** in high yield (equation 94).[269] Heteroatom nucleophiles can be similarly employed to access other useful phosphonoacetate derivatives for HWE reactions. This tactic was utilized by Janecki and coworkers for the preparation of phosphonates (e.g., **452**) needed for the synthesis of α-alkylidene-β-amino acids (equation 95).[270]



Scheme 50 Phosphonate anions generated *in situ* via conjugate addition can be used directly in HWE reactions.

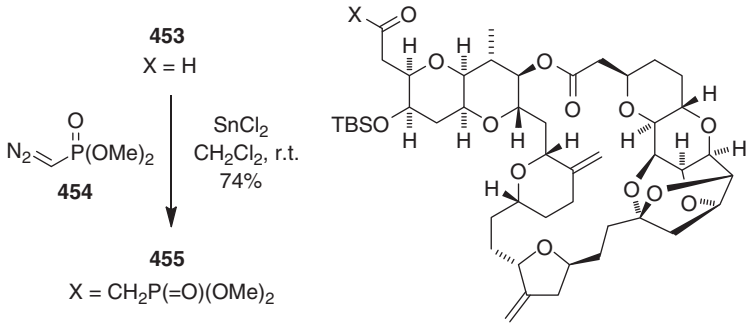


(94)



(95)

Finally, we note an important direct synthesis of β-ketophosphonates from aldehydes using the Gilbert–Seyferth reagent (**454**). Thus, Roskamp and coworker disclose that aldehydes are converted into HWE olefination ready phosphonates by treatment with dimethyl diazomethyl-phosphonate (**454**) in the presence of stannous chloride.[271] The illustrated synthesis of an advanced norhalichondrin B fragment (**455**) by Phillips and coworkers exemplifies the method (equation 96).[272] An enantioselective variant of the Roskamp phosphonate synthesis was recently reported.[273]



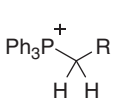
(96)

1.15.3.2.3 Factors affecting reaction efficacy and stereoselectivity

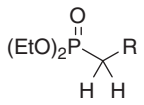
A majority of HWE reactions involve very similar types of phosphonates and standard reactions conditions (e.g., NaH, THF) will often lead to the successful production of an (*E*)-configured alkene target. Nonetheless, in certain scenarios suboptimal stereoselectivity may be encountered with conventional procedures or else side-reactions such as epimerization or unwanted β-elimination may accompany olefination. In other situations, access to the contrathermodynamic (*Z*)-configured alkene may be desired. Fortunately, as with the Wittig reaction, the outcome of the HWE reaction can often be altered to one's liking by a judicious selection of reaction variables. In this section, the role that base, media, and substrate effects play in controlling the yield and stereoselectivity of the HWE reaction is outlined. Readers wishing for a more detailed treatment are directed to the Maryanoff–Reitz review.[131d] A selection of illustrative examples of (*E*)- and (*Z*)-selective HWE reactions is found in Section 1.15.3.2.5.

1.15.3.2.3.1 Choice of base for phosphonate anion generation: Milder alternatives to traditional ionic bases

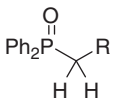
Phosphonates are significantly less acidic than comparable phosphonium salts and their conversion to phosphonate anions therefore requires proportionately stronger bases than those needed for phosphorane generation (**Scheme 51**).[274] Fortunately, since phosphonates involved in conventional HWE reactions possess anion-stabilizing groups, very strong bases like alkyl lithiums are not required to effect the olefination and simple metal hydrides (e.g., NaH) or metal alkoxides (e.g., *t*-BuOK) in ethereal or aromatic solvents will usually suffice. Weaker ionic bases such as $Ba(OH)_2$,[275] K_2CO_3,[276] and $(CF_3)_2CHOLi$[277] have also been successfully employed for HWE reactions using stabilized phosphonates, sometimes under phase-transfer conditions. Solvent-free intermolecular HWE olefinations employing DBU (3 mol%) as a homogenous base catalyst in the presence of stoichiometric heterogenous K_2CO_3 at ambient temperature were more recently disclosed.[278]



R	pK_a (DMSO)
Ph	17.4
CO_2Et	8.50
CN	6.93



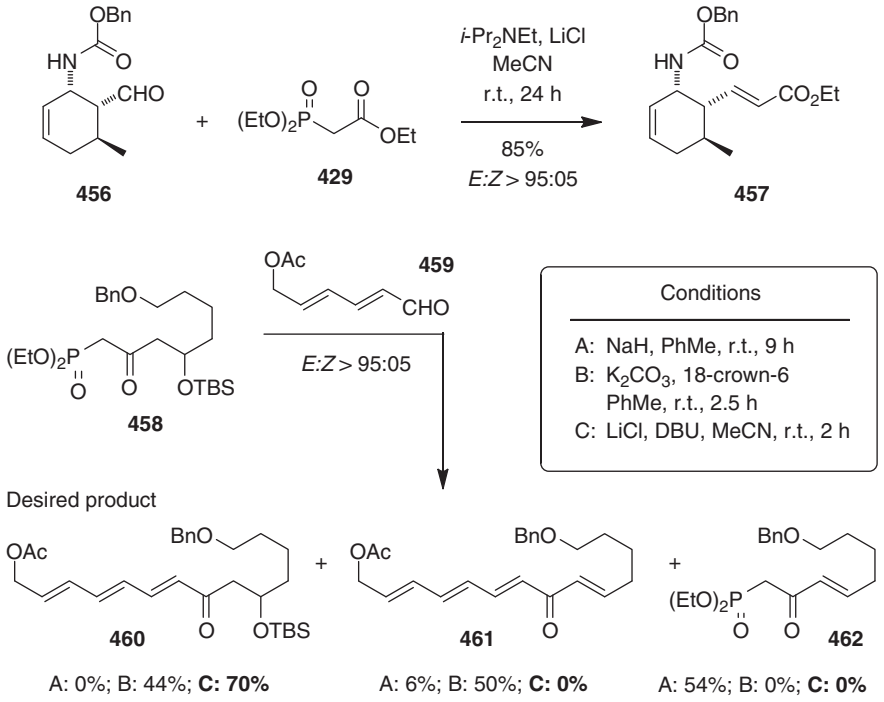
R	pK_a (DMSO)
Ph	27.6
CO_2Et	18.6
CN	16.4



R	pK_a (DMSO)
– –	– –
– –	– –
CN	16.9

Scheme 51 Comparison of equilibrium acidities for some phosphonium salts, phosphonates, and phosphine oxides in DMSO solvent.

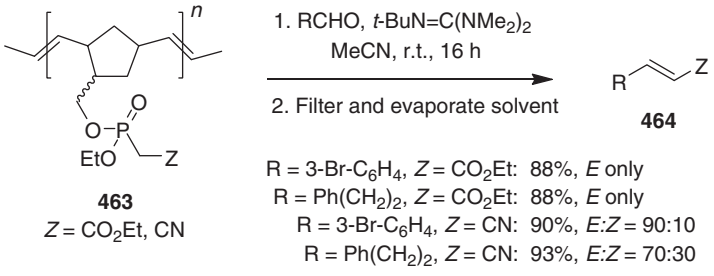
Although most substrates will tolerate anionic bases, particularly sensitive compounds may not and for this reason HWE reaction protocols that obviate the need for any kind of ionic base have been developed. The best known and most commonly employed such procedure was introduced by Masamune and Roush and their coworkers and calls for a combination of anhydrous LiCl and a neutral nitrogenous base, typically diisopropylethylamine or DBU.[279] Carbanion generation is the result of a 'soft' enolization whereby complexation of Lewis basic sites within the carbonylphosphonate by Li cation results in sufficient acidification of α-C–H bonds to allow for their deprotonation by the amine/amidine base. Masamune–Roush conditions have been found to be superior to more conventional protocols in a number of HWE reactions involving base-sensitive phosphonates and aldehydes. For example, significant epimerization of aldehyde **456** occurred upon its conversion to enoate **457** using the sodium salt of phosphonate **429** (prepared with NaH in benzene).[280] By contrast, the transformation was accomplished in high yield and without compromising stereochemical integrity using LiCl/*i*-Pr_2NEt (equation 97).[279] The same conditions were also successfully applied to the olefination of dienal **459** with a base-sensitive ketophosphonate (**458**). In this case, traditional protocols resulted in competing β-elimination and failed to give satisfactory yields of the desired product **460** (**Scheme 52**).[279] The intriniscally mild Masamune–Roush conditions are particularly advantageous for intramolecular HWE reactions because in such cases the aldehyde or ketone electrophile is necessarily present at the same time that the phosphonate is deprotonated (see Sections 1.15.3.2.3.2 and 1.15.3.2.5).



(97)

Scheme 52 Comparison of HWE reaction protocols for the olefination of **459** by **458**.

Other neutral bases have also been successfully used in the HWE reaction.[132] For example, Barrett et al. reported use of the Barton guanidine base (*tert*-butyltetramethyl-guanidine) to promote the HWE reactions of ROMPGEL polymer-supported phosphonate reagents **463** (equation 98).[281] In this case, a number of ionic bases (e.g., KHMDS, NaOEt, LDA) gave only complex mixtures, although Masamune–Roush conditions (LiCl, DBU) resulted in slow conversion. As expected, the phosphonoacetate reagent **463** ($Z=CO_2Et$) resulted in highly (*E*)-selective reactions, whereas its cyano congener **463** ($Z=CN$) gave significant mixtures of (*E*)- and (*Z*)-configured *β*-substituted acrylonitriles (cyanophosphonates generally give lower stereoselectivity in HWE reactions). More recently, Verkade and coworkers have demonstrated the successful execution of a wide variety of HWE reactions using the strongly basic proazaphosphatrane neutral base **466** ($pK_{aH}=33.5$).[282] Reactions promoted by **466** were generally cleaner than otherwise identical couplings conducted with traditional bases and the olefination of ketones occurred with significantly higher than average (*E*)-stereoselectivity (**Scheme 53**). In common with HWE reactions using conventional bases, phosphonates lacking the usual electron-withdrawing *α*-substituent (e.g., $(EtO)_2P(=O)Et$) also failed to give alkene products under these more exotic conditions. A useful summary of all of the types of bases that have been employed in the HWE reaction to date has been compiled by Verkade and coworkers.[282]



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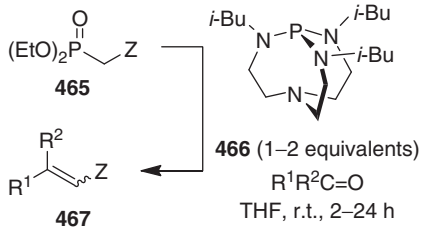
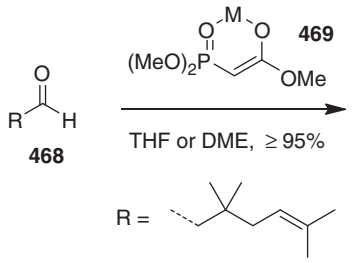


R^1	R^2	Z	Yield	*E*:*Z*
Ph	H	CO_2Et	86%	99:01
n-C_6H_{13}	H	CO_2Et	91%	96:04
c-C_6H_{11}	H	CO_2Et	78%	83:17
Ph	Me	CO_2Et	67%	99:01
2-(MeO)C_6H_4	H	CN	84%	54:46
Ph	Me	CN	89%	> 99:01

Scheme 53 HWE reactions with proazaphosphatrane **466**.

1.15.3.2.3.2 Effect of base counter-cation, phosphonate spectator ligands, and solvent on stereoselectivity: (E)- and (Z)-selective HWE reactions

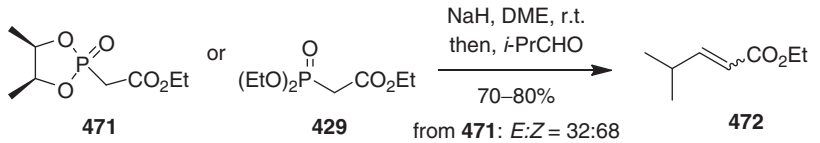
The HWE reactions of carbonyl group-stabilized phosphonate anions are generally found to produce α,β-unsaturated esters and ketones with excellent (*E*)-selectivity.[283] This behavior extends to α-substituted phosphonates and allows for an effective stereoselective synthesis of trisubstituted alkenes from aldehydes; however, the reactions of cyano or aryl stabilized phophonates typically show reduced (*E*)-selectivity.[132] As outlined above (Section 1.15.3.2.1), the origin of (*E*)-selectivity is attributed to Curtin–Hammett kinetics wherein the possibility of retroaddition from β-alkoxyphosphonates **414** enables indirect equilibration between *threo* and *erythro* isomers with the former being preferentially siphoned off to the *trans*-oxaphosphetane and thence the (*E*)-alkene. Substituents and reaction conditions that hinder oxaphosphetane formation and in this, or other ways, generally promote equilibration between *threo*-**414** and *erythro*-**414**, have a tendency to accentuate the usual (*E*)-selectivity of HWE reactions. Thus, (*E*)-selectivity is usually maximized by, amongst other factors, the use of bulky spectator alkoxy ligands on phosphorus (e.g., *i*-PrO groups), the presence of a strongly coordinating counter-cation (e.g., Li^+), a polar reaction solvent to stabilize charged intermediates, and the use of comparatively high (e.g., ambient) rather than low temperatures (e.g., −78 °C). The HWE reaction between trimethyl phosphonoacetate and β-branched aliphatic aldehyde **468** as studied by Heathcock and Thompson is exemplary of some of these effects (**Scheme 54**).[284] As illustrated, the highest (*E*)-selectivity was obtained by condensing Li metallate **469** with the aldehyde in DME solvent at room temperature. α-Branching in the aldehyde was also found to promote (*E*)-selectivity; thus, reactions between the same phosphonate reagent and pivaldehyde (**468**, R=*t*-Bu) produced only the *trans*-enoate product **470** (R=*t*-Bu, *E*:*Z*>98:02) for all of the same 12 reaction condition variations.[284]



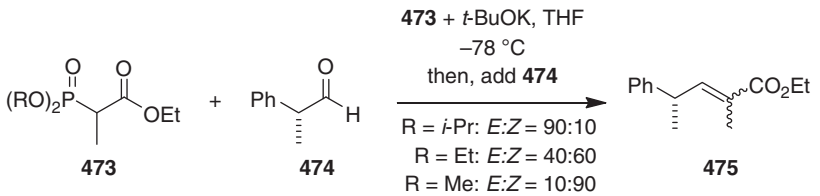
M	Temperature	*E*:*Z* in THF	*E*:*Z* in DME
Li	−78 °C	58:42	88:12
Li	23 °C	92:08	**95:05**
Na	−78 °C	87:13	87:13
Na	23 °C	88:12	90:10
K	−78 °C	83:17	83:17
K	23 °C	87:13	83:17

Scheme 54 Dependence of HWE reaction stereoselectivity on solvent and counter-cation.

Accentuating the 'natural' stereoselectivity preference of a given process is useful; however, having the ability to completely reverse its usual stereochemical outcome will lend the method significantly increased scope. Such a reversal in stereoselectivity has proved possible with the HWE olefination and a number of (*Z*)-selective variants are now available. The requirements to maximize (*Z*)-selectivity are the reverse of those stated above for optimal (*E*)-selectivity: i.e., conditions that disfavor equilibration between *threo* and *erythro* β-alkoxyphosphonates **414** while promoting the kinetic diastereoselective generation of *erythro*-**414** are needed. These prerequisites are ostensibly best met by the use of phosphonate anions that have heightened susceptibility toward oxaphosphetane formation (small and/or Lewis-acidity increasing spectator ligands on phosphorus) matched with noncoordinating counter-cations in reactions with aldehydes at low temperature. Thus, in the early development of (*Z*)-selective HWE reactions, Breuer et al. employed ring-strain induced Lewis-acidity effects inherent in five-membered cyclic phosphonates to successfully obtain modest *trans*- to *cis*-stereoselectivity reversals (e.g., equation 99).[285] Contemporaneous studies by Seyden-Penne and coworkers revealed the validity of related effects in the synthesis of substituted acrylonitriles.[286] During their pursuit of some polyketide target molecules, Kishi and coworkers later uncovered the profound influence of phosphonate ester steric effects in low temperature HWE reactions involving a potassium base (equation 100).[287]



(99)



(100)

Building on insights gained from the aforementioned precedent and related work,[288] Still and Gennari introduced the first generally applicable highly (*Z*)-selective HWE protocol based on the low temperature reactions of 'naked' bis(trifluoroethyl) phosphonoacetate anions (prepared by deprotonation with KHMDS in the presence of 18-crown-6) with aldehydes (Table 6).[289] Of note, it was found that the method is just as (*Z*)-selective, and in many cases more so, for the synthesis of trisubstituted alkenes using α-substituted phosphonoacetate **476** (R^1 = Me) as for the synthesis of 1,2-disubstituted alkenes with its lesser substituted congener **476** (R^1 = H). Given that conjugated (*Z*)-enoates (and related enones) are not generally accessible by Wittig reactions involving stabilized ylides, the Still–Gennari HWE reaction has enjoyed considerable popularity and some representative examples of its use in target-directed synthesis are summarized in Table 7 in Section 1.15.3.2.5.

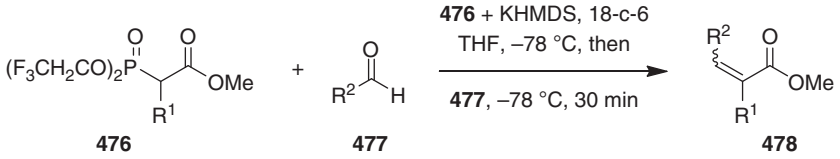
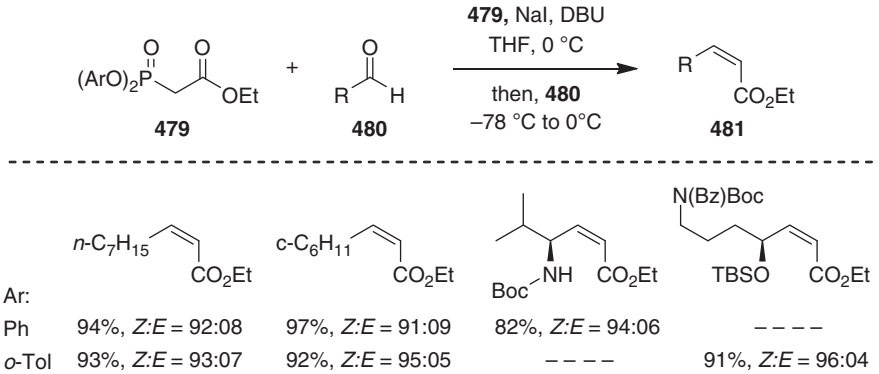


Table 6 The Still–Gennari HWE reaction of bis(trifluoroethyl)phosphonoacetates **476** with aldehydes for the stereoselective formation of (*Z*)-configured enoates **478**

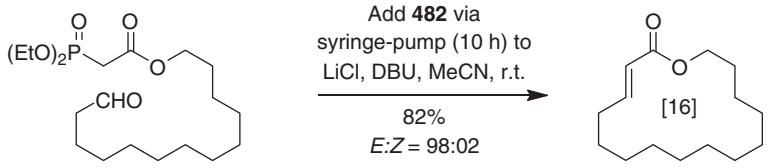
Entry	R^1	R^2	*Yield 478 (%)*	*478* Z:E
1	H	*n*-C_7H_{15}	90	92:08
2	H	*(E)*-*n*-$C_3H_7CH{=}CH$	87	>98:02
3	H	(*E,E*)-$CH_3CH{=}CHCH{=}CH$	76	95:05
4	H	*c*-C_6H_{11}	74	80:20
5	H	Ph	>95	>98:02
6	CH_3	*n*-C_7H_{15}	88	98:02
7	CH_3	*(E)*-*n*-$C_3H_7CH{=}CH$	79	>98:02
8	CH_3	*c*-C_6H_{11}	80	>98:02
9	CH_3	Ph	>95	97:03

More recently, Ando et al. have developed an alternative (*Z*)-selective HWE method utilizing diarylphosphonoacetates that rivals the stereoselectivity of the Still–Gennari protocol but that occurs under reaction conditions not requiring an expensive crown ether additive.[310] The reaction as initially reported was mediated by ionic bases (Triton B or NaH),[264,310a] but it can also be performed very conveniently via sodium salt Masamune–Roush conditions (NaI, DBU) in THF solvent.[310b] Excellent results are obtainable with simple diphenylphosphonoacetates (e.g., **479**, Ar = Ph); however, slightly higher (*Z*)-selectivity is available by replacing the phenoxide groups with *ortho*-methylphenoxide ligands (Scheme 55). A Rhodia group later established that the reaction can be conducted at 0 °C without compromising (*Z*)-selectivity by employing phosphonoacetates derived from *ortho-tert*-butylphenol.[311] In this case, remarkably simple reaction conditions (K_3PO_4 in MeCN) can be employed making the procedure potentially amenable to large-scale applications.

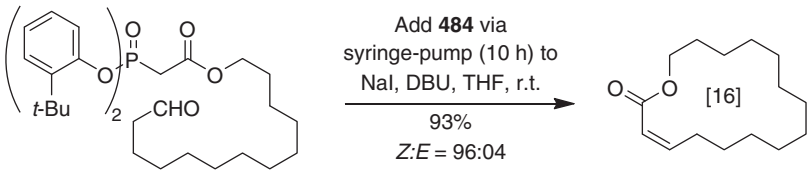


Scheme 55 Synthesis of (*Z*)-enoates **481** using ethyl (diarylphosphono)acetates **479**.

The substrate and media effects discussed in this section extend to intramolecular HWE reactions provided that the cyclic compounds being generated are sufficiently large to freely accommodate both (*E*)- and (*Z*)-alkenes. For example, Ando and coworkers recently demonstrated the stereoselective formation of either (*E*)- or (*Z*)-configured *α,β*-unsaturated macrocyclic lactones in high yield by matching the appropriate phosphonate reagent class with optimal Masamune–Roush-type reaction conditions.[93] Syringe-pump techniques were required to obtain the desired macrocycles in high yield from the conformationally unbiased precursors that were employed, equations 101 and 102 are representative. Several examples of significantly more complex intramolecular HWE reactions are found in Table 7 in Section 1.15.3.2.5.



482 (*E*)-**483** (101)



484 (*Z*)-**483** (102)

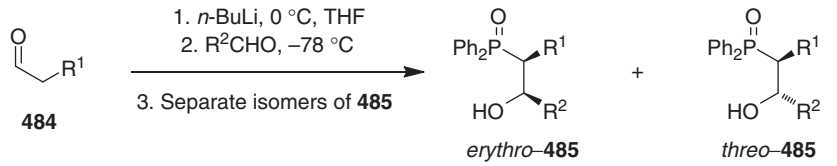
1.15.3.2.4 Notable reaction variants, related methods, and specialized applications

Surveyed here are a selection of useful variants of the HWE reaction and other olefination methods that are closely related to it, beginning with the Horner–Wittig reaction.

1.15.3.2.4.1 Alkene formation with phosphine oxide anions: The Horner–Wittig reaction

Carbonyl group olefination using metallated phosphine oxides was disclosed by Horner et al. just a few years after the Wittig reaction was itself introduced.[248] The Horner–Wittig reaction is closely related to the now better known HWE olefination but with a diphenylphosphoryl moiety taking the role usually played by the phosphonate group.[133] At an essential mechanistic level the two processes are virtually indistinguishable and the pathway laid out in Scheme 46 if viewed with $Ph_2P(=O)$ in place of $(RO)_2P(=O)$ would constitute an accurate depiction of the broader aspects of the Horner–Wittig reaction. Diphenylphosphoryl alkanes are of comparable acidity to phosphonates (see Scheme 51 above) and they can be deprotonated with the same types of bases for structurally related examples. The Horner–Wittig olefination is similarly recalcitrant to the HWE reaction in progressing from the initial addition adduct (cf. **414**) on to the alkene unless R^1 is an anion-stabilizing group. Nonstabilized lithiated phosphine oxides do not directly generate alkenes upon their treatment with carbonyl compounds and the Horner–Wittig olefination of such substrates is accomplished via two distinct steps: viz, *β*-hydroxyphosphine oxides are produced and isolated from an initial addition reaction and then subsequently converted to alkenes via treatment with a sodium or potassium base in a second separate reaction. The inefficiency of this protocol is offset by the possibility of separating *erythro* and *threo* diastereoisomers of the intermediate *β*-hydroxyphosphine oxides before their respective stereospecific elimination to geometrically pure (*Z*)- and (*E*)-alkenes. This holds a practical advantage over simply separating the isomers of the ultimate olefin product because *erythro* and *threo* forms of *β*-hydroxyphosphine oxides are typically much easier to separate from each other by standard chromatographic (or crystallization) techniques than the corresponding less polar *cis*- and *trans*-alkene isomers.

Warren and coworkers have extensively developed the two-step Horner–Wittig olefination method and described optimized protocols for the indirect stereocontrolled synthesis of 1,2-disubstituted (*Z*)- and (*E*)-alkenes (Scheme 56).[312] The addition of lithiated phosphine oxides derived from primary alkyl substrates **484** to aldehydes at low temperature in THF solvent favors generation of *erythro β*-hydroxyphosphine oxides **485** unless significant chain-branching is present in the phosphoryl lithium (e.g., $R^1 = i\text{-Pr}$).[313] Diastereomerically pure addition adducts **485** break down with complete stereospecificity in the second stage only in cases where R^1 is not an anion-stabilizing group; otherwise, stereofidelity is lost because of competition between retroaddition and elimination pathways. In the case of *threo* adducts **485** this is not a problem because all possible pathways favor the (*E*)-alkene; however, the same phenomenon severely compromises the generation of (*Z*)-alkenes from *erythro β*-hydroxyphosphine oxides **485**. The diastereomeric ratios of *β*-hydroxyphosphine oxides can be altered before elimination via oxidation to the corresponding ketones (e.g., with pyridinium chlorochromate in DMF) followed by stereocontrolled reduction. Adding useful flexibility to the method, it is observed in some cases that $NaBH_4$-mediated reduction of *β*-keto phosphine oxides **487** occurs with *threo* stereoselectivity whereas a low-temperature Luche modification ($NaBH_4$, $CeCl_3{\cdot}nH_2O$) offers *erythro* selectivity instead (Scheme 57).[313]

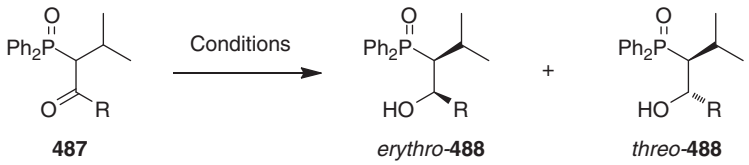


Addition stage			
R^1	R^2	Yield **485**	*erythro:threo*
Me	Me	93%	75:25
Me	*c*-C_6H_{11}	86%	79:21
Me	Ph	88%	88:12
i-Pr	Me	85%	42:58
i-Pr	*c*-C_6H_{11}	78%	45:55
i-Pr	Ph	79%	67:33
Ph	Me	97%	72:28
Ph	Ph	88%	83:17

Elimination of *erythro-**485***			
R^1	R^2	Yield **486**	*Z:E*
Me	*c*-C_6H_{11}	79%	> 99:01
Me	Ph	75%	95:05
Ph	Me	78%	50:50
Ph	Ph	61%	95:05

Elimination of *threo-**485***			
R^1	R^2	Yield **486**	*E:Z*
Me	*c*-C_6H_{11}	80%	> 99:01
Me	Ph	81%	> 99:01
Ph	Me	86%	> 99:01
Ph	Ph	95%	> 99:01

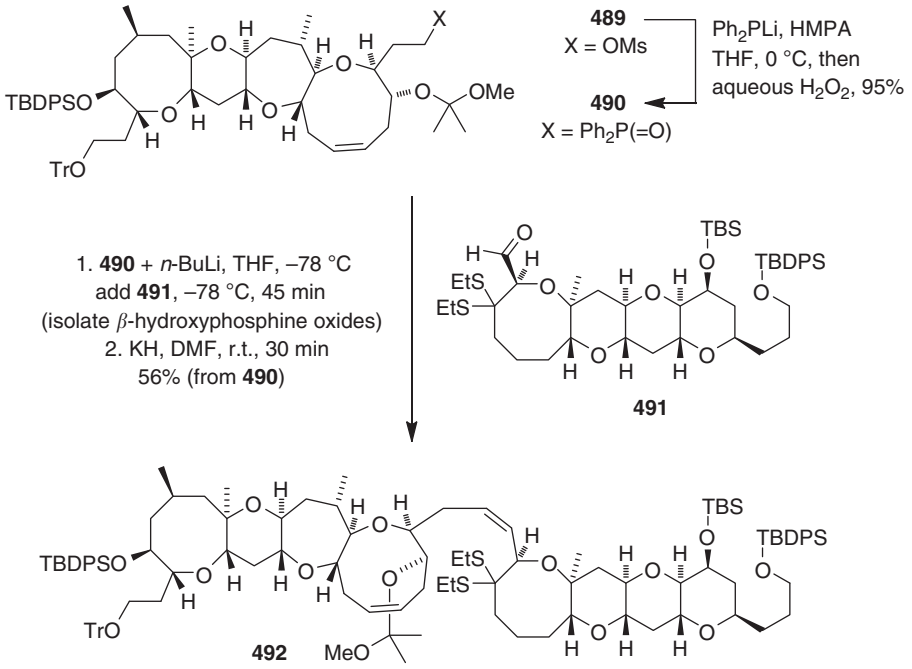
Scheme 56 The two-step Horner–Wittig olefination.



	$NaBH_4$, EtOH, r.t.		$NaBH_4/CeCl_3$, EtOH, –78 °C	
R	Yield (%) **488**	*erythro:threo*	Yield **488**	*erythro:threo*
Et	93	40:60	81%	> 91:09
n-Pr	74	38:62	84%	> 96:04
i-Pr	56	19:81	52%	88:12
Ph	71	24:76	100%	> 99:01
2-Furyl	100	18:82	98%	97:03

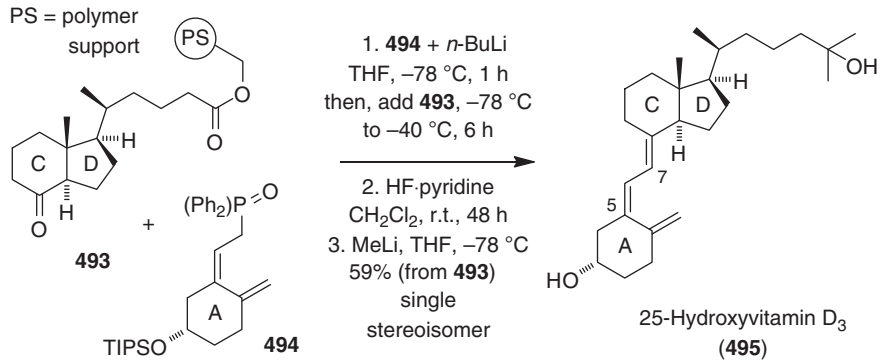
Scheme 57 Diastereoselective reduction of β-keto phosphine oxides **487**.

A two-step Horner–Wittig olefination was used to good effect by Nicolaou et al. at a late stage in their total synthesis of the polyether ladder compound brevetoxin A.[314] Phosphine oxide **490** representing the BCDE rings of the target was prepared from the corresponding mesylate **489** via displacement with Ph_2PLi followed by oxidative work-up (Scheme 58). The addition phase of olefination was achieved by treating the lithiated form of **490** with GHIJ-ring aldehyde fragment **491** to yield a pair of *erythro* β-hydroxyphosphine oxides (not illustrated). Subsequent potassium base-induced elimination gave a *cis* olefin (**492**) containing all but one of the skeletal carbon atoms of brevetoxin A in a 56% overall yield from **490**. In this instructive complex example,[315] the Horner–Wittig olefination was selected as a fragment linkage tool only after it was discovered that the nonstabilized Ph_3P-based ylide analogous to **490** failed to add to the hindered aldehyde **491**. Use of the more nucleophilic phosphine oxide anion solved the reactivity problem and due to the inherent *erythro* selectivity of the Horner–Wittig addition reactions of nonstabilized diphenylphoshoryl alkyllithiums to aldehydes, the desired 1,2-disubstituted (*Z*)-configured alkene was obtained without resort to more circuitous tactics.



Scheme 58 Synthesis of a brevetoxin A precursor via a two-step Horner–Wittig olefination.

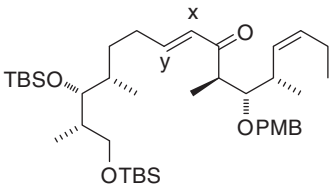
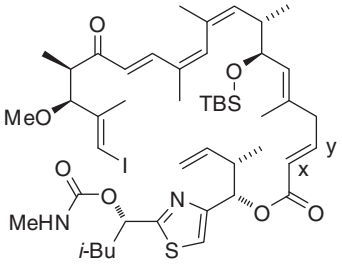
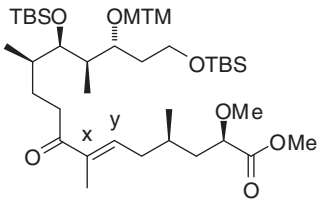
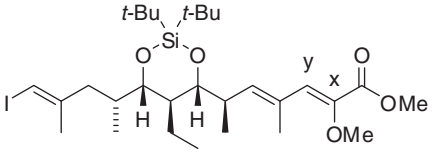
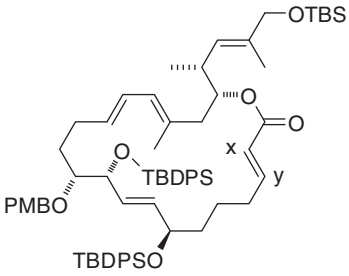
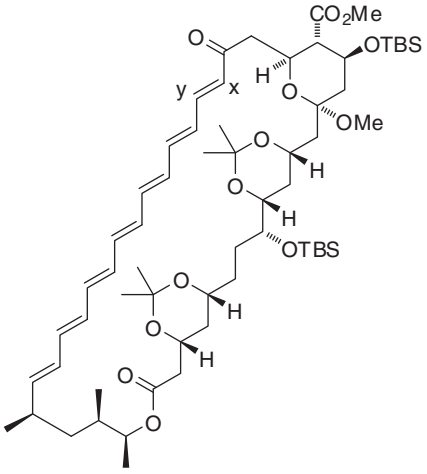
Direct one-pot Horner–Wittig olefination is achievable provided that the phosphine oxide is equipped with an anion-stabilizing group (vinyl, aryl, CN, etc.) and it is facilitated by adopting conditions that disfavor counter-cation coordination (e.g., use of dipolar cosolvents and/or avoidance of lithium bases). In such cases, spontaneous breakdown of β-alkoxy phosphine oxide intermediates occurs to yield alkene products which are generally formed with a preference for the (*E*)-isomer for the same reasons that conventional HWE reactions likewise favor *trans* products (see Section 1.15.3.2.3.2). Horner–Wittig reactions employing allylic or benzylic phoshine oxides have proved to be particularly useful in the stereocontrolled synthesis of conjugated alkenes, including trisubstituted examples. Seminal work from Lythgoe and coworkers established the suitability of the method for elaboration of the vitamin D triene system with their finding that the C7-C8 trisubstituted double bond of calciferol (vitamin D_3) can be formed from a Grundmann's ketone CD-ring fragment and a diphenylphosphoryl diene A-ring fragment with complete stereoselectivity in favor of the natural (5*Z*,7*E*)-configuration.[316] Given its efficiency, the Lythgoe protocol, which was subsequently improved upon by a Roche group,[317,318] continues to enjoy considerable popularity in the vibrant vitamin D synthetic field.[319] A solid phase approach to 25-hydroxyvitamin D_3 (**495**) by Torneiro and coworkers illustrates the Lythgoe–Roche method (equation 103).[320]



(103)

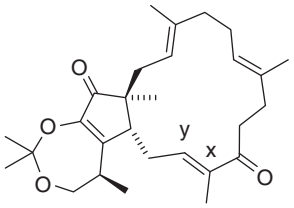
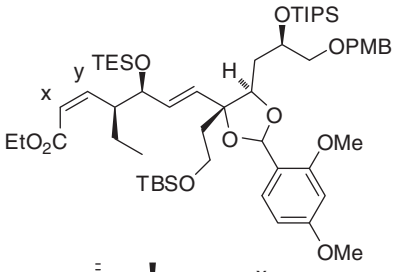
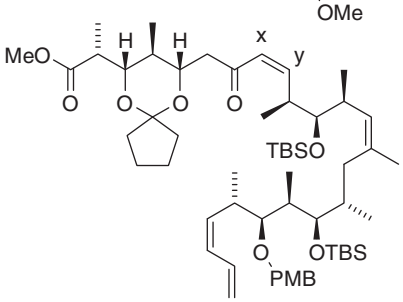
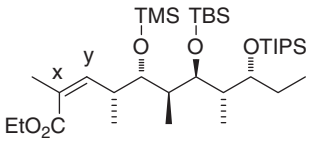
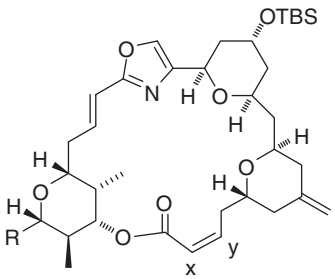
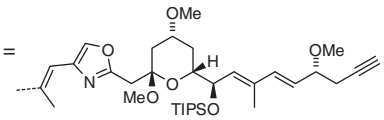
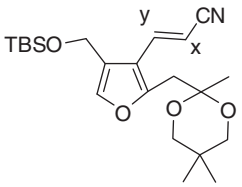
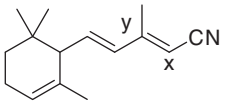
Further examples of the synthesis of complex alkenes via the Horner–Wittig reaction are collated below in **Table 7** (Section 1.15.3.2.5). Other applications for the diphenylphosphoryl moiety in stereocontrolled synthesis, of which there are many, and methods that may be used to prepare these types of compounds, are detailed in the review by Clayden and Warren.[133] Additional types of phoshoryl carbanions used in olefination reactions (e.g., phosphoramidyl systems such as **497**) are well covered in the Maryanoff and Reitz review.[131d]

Table 7 A selection of complex alkene targets prepared by the HWE (entries 1–15) and Horner–Wittig (entries 16–20) olefination reactions

Entries	*Alkene target*[a]	*Reaction conditions and outcome*	*References*
1		Phosphonate: $P(=O)(OMe)_2$ $Ba(OH)_2$, $THF\text{-}H_2O$, r.t., 12 h 91%, *E* only	290
2		Phosphonate: $P(=O)(OEt)_2$ NaH, THF, −20 °C, 30 min 66%, *E* only	291
3		Phosphonate: $P(=O)(OEt)_2$ $(CF_3)_2CHOLi$, DME, r.t., 48 h 66%, *E* only	292
4		Phosphonate: $P(=O)(O\text{-}i\text{-}Pr)_2$ KHMDS, 18-crown-6, THF, 0 °C, 4.5 h 98%, *Z*:*E* = 94:06	293
5		Phosphonate: $P(=O)(OEt)_2$ *i*-Pr_2NEt, LiCl, MeCN, r.t., 12 h 73%, *E* only	294
6		Phosphonate: $P(=O)(OEt)_2$ K_2CO_3, 18-crown-6, PhMe, 60 °C, 12 h [0.002 M] 52%, *E* only	295

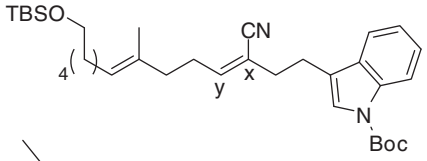
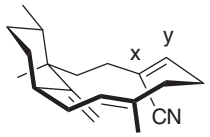
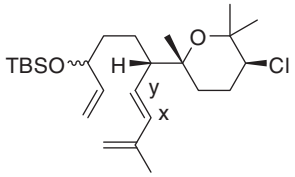
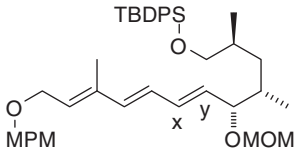
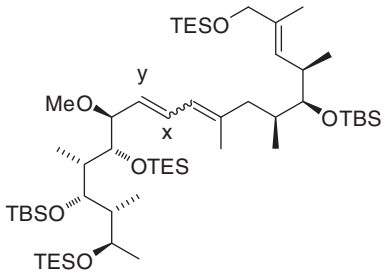
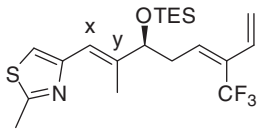
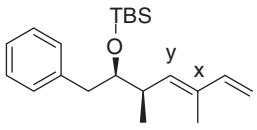
(*Continued*)

Table 7 Continued

Entries	*Alkene target*[a]	*Reaction conditions and outcome*	*References*
7		Phosphonate: $P(=O)(OEt)_2$ *i*-Pr_2NEt, LiCl, MeCN, r.t., 45 h 70%, *E* only	296
8		Phosphonate: $P(=O)(OPh)_2$ NaHMDS, THF-HMPA, –78 °C to –20 °C, 5 h 97%, *Z* only	297
9		Phosphonate: $P(=O)(OCH_2CF_3)_2$ NaH, THF, –10 °C to r.t. 81%, *Z*:*E* = 91:09	298
10		Phosphonate: $P(=O)(OCH_2CF_3)_2$ KHMDS, 18-crown-6, THF, –78 °C to r.t., 8 h 60%, *Z* only	299
11		Phosphonate: $P(=O)(OCH_2CF_3)_2$ K_2CO_3, 18-crown-6, PhMe, r.t., 1 h 77%, *Z*:*E* = 80:20 R = 	300
12		Phosphonate: $P(=O)(OEt)_2$ NaH, THF, r.t. 97%, *E*:*Z* = 92:08	301
13		Phosphonate: $P(=O)(OEt)_2$ NaH, *t*-BuOMe, r.t. 74%, *E*:*Z* = 75:25	302

(*Continued*)

Table 7 Continued

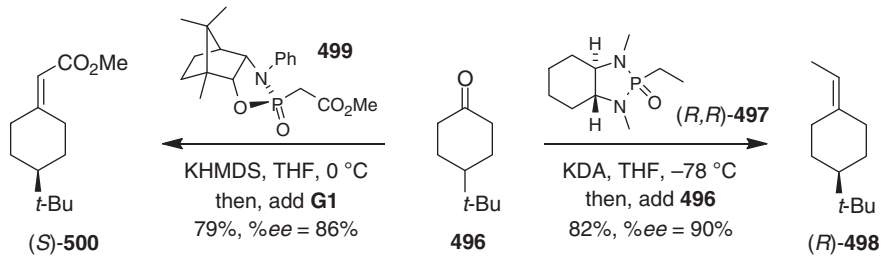
Entries	*Alkene target*[a]	*Reaction conditions and outcome*	*References*
14		Phosphonate: $P(=O)(OEt)_2$ KHMDS, PhMe, −78 °C, 2 h 83%, *Z:E* > 95:05	303
15		Phosphonate: $P(=O)(OEt)_2$ K_2CO_3, 18-crown-6, PhMe, 20 °C, 24 h 38%, *Z* only	304
16		Phosphine oxide: $P(=O)Ph_2$ *n*-BuLi, THF-HMPA, −78 °C to r.t., 2 h ≥ 78%, *E* only	305
17		Phosphine oxide: $P(=O)Ph_2$ *n*-BuLi, THF-HMPA, −78 °C to r.t., 1.5 h 92%, *E:Z* > 94:06	306
18		Phosphine oxide: $P(=O)Ph_2$ NaHMDS, THF, −78 °C to r.t. 51%, *E:Z*=91:09	307
19		Phosphine oxide: $P(=O)Ph_2$ *n*-BuLi, THF, −78 °C to r.t., 4 h 83%, *E* only	308
20		Phosphine oxide: $P(=O)Ph_2$ *n*-BuLi, THF-HMPA, −78 °C, 15 min 73%, *E:Z* = 75:25	309

[a]Site of newly introduced alkene is located between x and y; x = original site of the phosphonate or phosphine oxide and y = original site of the carbonyl group.

1.15.3.2.4.2 Enantioselective and other stereocontrolled HWE reactions using chiral phosphonic acid derivatives

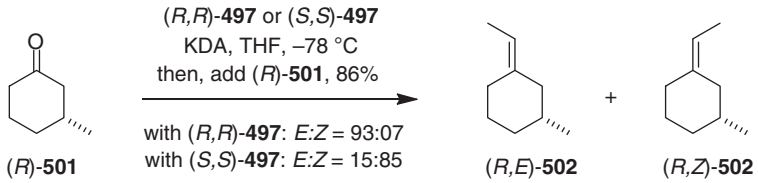
Use of chiral spectator ligands on phosphorus opens the possibility of net enantioselective carbonyl olefination and also provides for an additional means to influence geometrical stereoselectivity for reactions involving chiral carbonyl components.[321] Implementation of this paradigm has been explored with both Wittig and HWE reactions but greater successes have generally been charted using chiral phosphonic acid derivatives associated with the latter. For enantioselectivity to be relevant to the synthesis of a double bond moiety from a simple achiral monocarbonyl compound, the substrate must be prochiral and the targeted alkene stereogenic and chirotopic in nature. Olefinations of 4-substituted cyclohexanones are the most commonly encountered examples of this kind and provide a useful bench mark for the evaluation of new chiral HWE reagents.[322] Hanessian et al. demonstrated the first examples of highly (>90% *ee*) enantioselective olefination of 4-*tert*-butylcyclohexanone (**496**) using C_2-symmetric phosphonic bisamide **497** (Scheme 59).[323] Building on earlier work by Koizumi and coworkers,[324] Denmark and Rivera later achieved

excellent enantioselecitivity olefinating the same carbonyl substrate using chiral phosphonamidate reagents (e.g., **499**) stereogenic at phosphorus.[325]

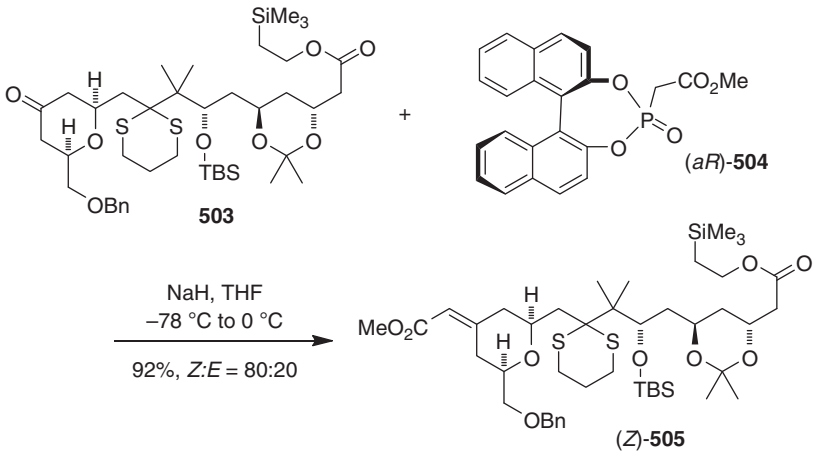


Scheme 59 Enantioselective olefination of 4-*tert*-butylcyclohexanone (**496**).

Subtle diastereomeric interactions between homochiral HWE reagents and homochiral carbonyl components can be exploited to effect the controlled synthesis of stereogenic alkenes that might be otherwise difficult to obtain in a stereoselective fashion. Thus, Hanessian et al. shrewdly demonstrated that (*R*)-3-methylcyclohexanone **501** could be selectively converted to (*E*)-configured alkene **502** using the potassium metallate of (*R,R*)-**497**, but instead to (*Z*)-**502** by an otherwise identical reaction employing (*S,S*)-**497** (equation 104).[323] Using enantiopure chiral reagents to influence *geometrical* selectivity in this kind of context is rare[326] and the approach has been employed to impressive effect in total syntheses of the bryostatin family of natural products.[24,60] For example, by deploying Fuji's BINOL-derived chiral phosphonate (*aR*)-**504**,[327] Yamamura and coworkers were able to obtain (*Z*)-**505** with good stereoselectity (*Z:E* = 80:20) in a model study directed toward bryostatin 3 (equation 105).[60] Using the enantiomeric reagent (*aS*)-**504** also gave (*Z*)-**505** but with significantly reduced stereoselectivity (*Z:E* = 70:30).

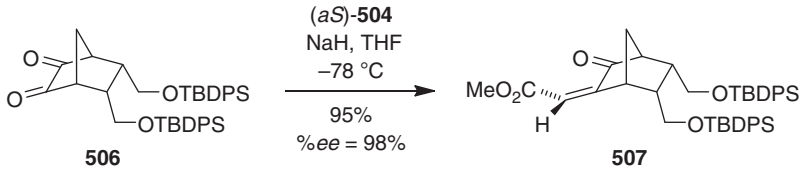


(104)

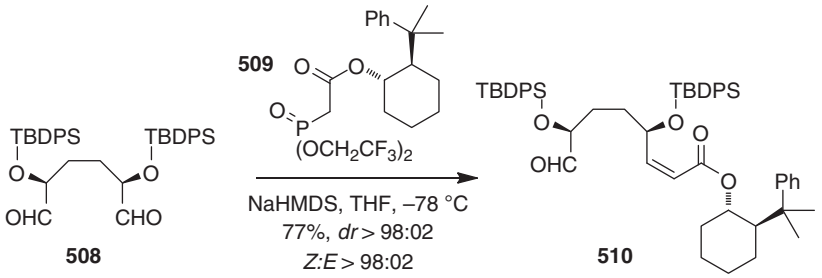


(105)

Enantioselective HWE olefination can be usefully exploited to access other product classes. The target olefin need not necessarily be stereogenic if one considers desymmetrization of an achiral symmetrical dicarbonyl substrate wherein the chiral phosphorus reagent selects between two enantiotopic reactive sites. A successful demonstration along these lines is seen in Fuji and coworkers' conversion of meso 1,2-diketone **506** to enone **507** by the action of BINOL-derived phosphonate reagent (*aS*)-**504** (equation 106).[327b] Desymmetrization of meso substrates has also been achieved in a net diastereoselective manner using phosphonates bearing an intrinsic chiral substructure. Thus, Rein et al. recently achieved stereocontrolled total syntheses of the annonaceous acetogenins pyranicin and pyragonicin using the nor-8-phenylmenthyl-derived Still–Gennari-type phosphonate **509** which effected the efficient conversion of meso dialdehyde **508** to (*Z*)-enoate **510** with high diastereoselectivity (equation 107).[328]

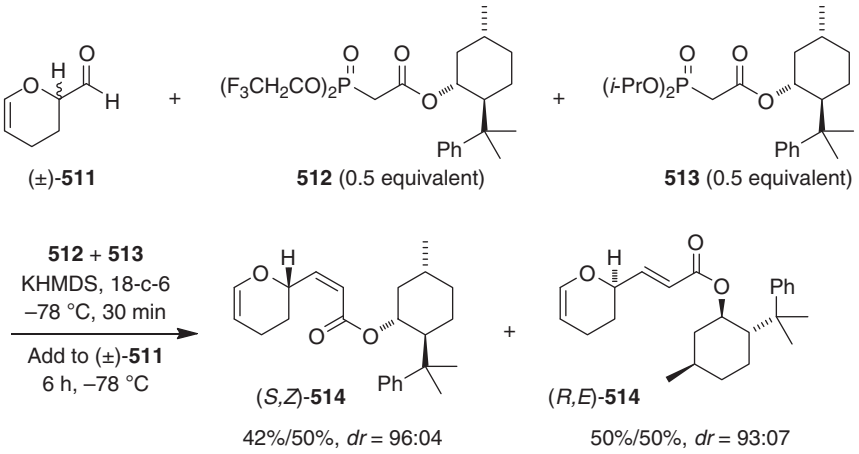


(106)



(107)

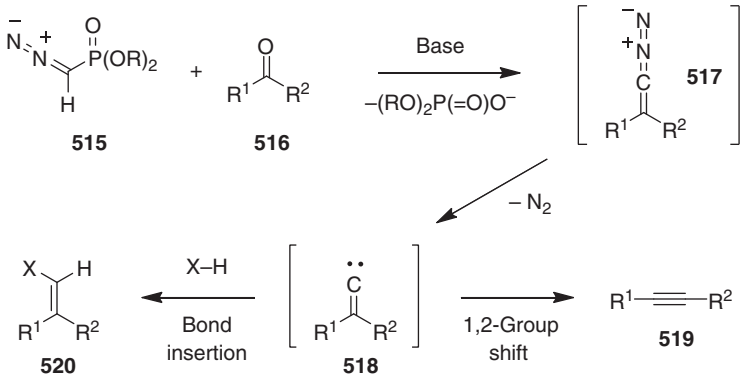
The kinetic resolution of racemic chiral carbonyl substrates affords additional opportunities for enantioselective olefination. Besides dynamic kinetic resolution,[329] another less prosaic way to implement this approach concerns parallel kinetic resolution (PKR) whereby both enantiomers of the racemic substrate actually react but such that each antipode is converted to an intrinsically different type of alkene product. Significantly, it was discovered by Rein and coworkers that (*E*)- and (*Z*)-selective phosphonoacetate reagents equipped with identical 8-phenylmenthyl chiral auxiliaries have opposite substrate enantiomer preferences.[330] PKR of a racemic carbonyl compound can therefore be affected by simultaneous HWE reactions with a pair of chiral phosphonate reagents, one of a conventional type and the other of Still–Gennari type. This curious method is exemplified by the stereodivergent conversion of racemic aldehyde **511** into enoate products (*S*,*Z*)-**514** and (*R*,*E*)-**514** via respective transformations with phosphonates **512** and **513** (equation 108).[331] Other enantioselective Wittig-type olefination reactions, including those involving the use of achiral phosphorus reagents in the presence of chiral modifiers, are detailed in a recent review.[321]



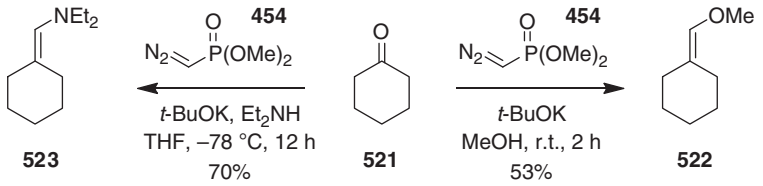
(108)

1.15.3.2.4.3 Formation of enol ethers, enamines, and alkynes using α-diazophosphonoacetates

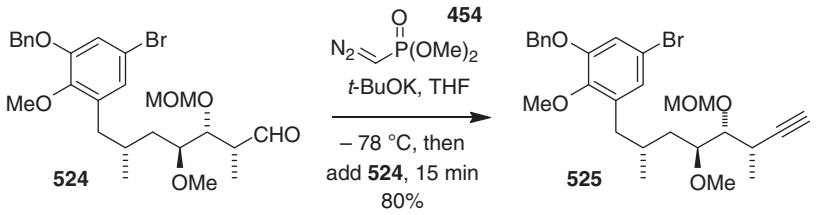
α-Diazophosphonoacetates **515** react with carbonyl compounds under the usual basic conditions of the HWE reaction to give diazoalkylidenes **517** and thence transient alkylidene carbene species **518** that experience synthetically useful bond insertion reactions leading to alkenes or 1,2-group shifts affording alkyne products (Scheme 60).[332] Gilbert and Weerasooriya demonstrated that dimethyl (diazomethyl)phosphonate (**454**), a compound first investigated by Seyferth,[333] converts aliphatic ketones to enol ethers in the presence of *t*-BuOK and an alcohol solvent, or to enamine products in the presence of *t*-BuOK and an amine in THF solvent (Scheme 61).[334] These workers also showed that aldehydes and aromatic ketones are instead transformed to alkynes under similar conditions via the facile 1,2-hydride or 1,2-aryl shifts of the corresponding intermediate alkylidenes. The preparation of a reblastatin intermediate (**525**) by Panek et al. exemplifies this so-called Seyferth–Gilbert homologation method (equation 109).[335]



Scheme 60 HWE reactions of α-diazophosphonoacetates **515** lead to synthetically useful transient alkylidene carbenes **518**.

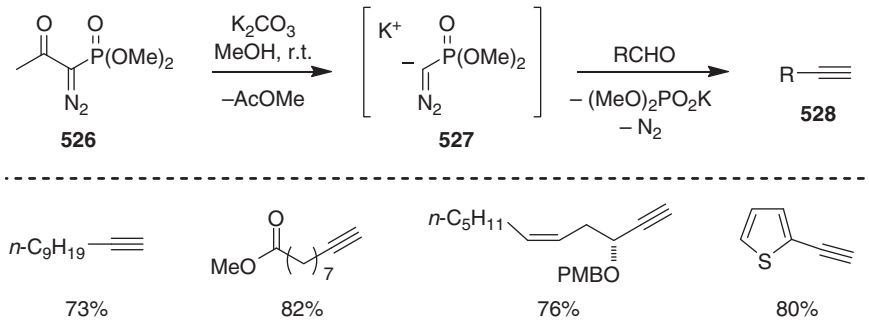


Scheme 61 Enol ether and enamine formation using the Seyferth–Gilbert reagent (**454**).

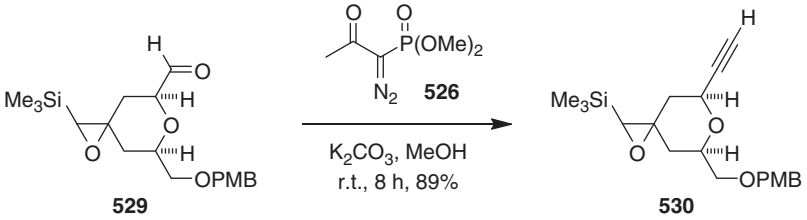


(109)

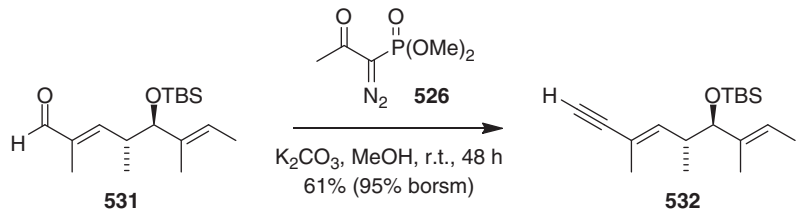
The above process is a valued transformation for alkyne synthesis but the limited stability of the Seyferth–Gilbert reagent (**454**) and its noncommercial availability reduces the general appeal of the method. Fortunately, seminal work from Ohira,[336] subsequently greatly expanded on by Bestmann and coworkers,[337] established that the anion of **454** (**527**) is conveniently generated *in situ* via the retro-Claisen reaction of commericially available dimethyl (1-diazo-2-oxopropyl)-phosphonate (**526**) in basic methanol. Deacetylation of **526** by the action of K_2CO_3 in methanol when conducted in the presence of an aldehyde substrate leads directly to terminal alkyne products in good yield (**Scheme 62**). Alkynylation with the Ohira–Bestmann reagent (**526**) occurs without epimerization at α-stereogenic centers (e.g., equation 110),[338] and it can be applied to access enynes from substituted α,β-unsaturated aldehydes (e.g., equation 111),[339] but less bulky enals may give homopropargylic ethers due to concomitant conjugation addition of solvent before alkyne formation (i.e., RCH=CHCHO to RCH(OMe)CH_2CCH).[337]



Scheme 62 Synthesis of alkynes with the Ohira–Bestmann reagent (**526**).



(110)

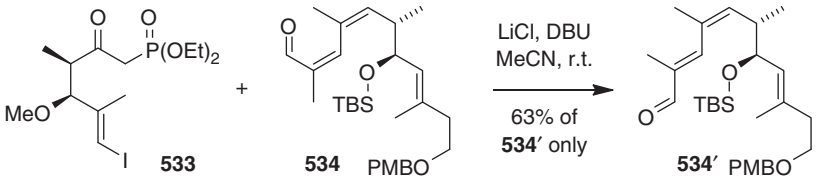


(111)

1.15.3.2.5 Illustrative examples in target-directed synthesis

The comparatively mild reaction conditions needed to promote the HWE olefination are often compatible with complex multifunctional molecules and the method is widely used as a late stage fragment linkage tool in target-directed synthesis. Fifteen examples giving some idea of the impressive scope of the HWE reaction are collected together in Table 7 (entries 1–15). As with the other sulfur and phosphorus-based olefination methods surveyed herein, the HWE process is seen to be generally tolerant of all major classes of common protecting groups (including silyl ethers, alkyl ethers, esters, carbamates, and acetals) and it can also be applied in both intermolecular and intramolecular contexts with essentially equal facility. Furthermore, (*E*)- or (*Z*)-stereoselectivity (for 1,2-disubstituted or trisubstituted olefins) is usually obtainable by matching reaction protocols with the appropriate type of spectating alkoxy ligands on phosphorus: i.e., simple dialkyl phosphonates for most (*E*)-selective reactions (bulkier to accentuate) or Still–Gennari/Ando type phosphonates for most (*Z*)-selective reactions (see Section 1.15.3.2.3.2).

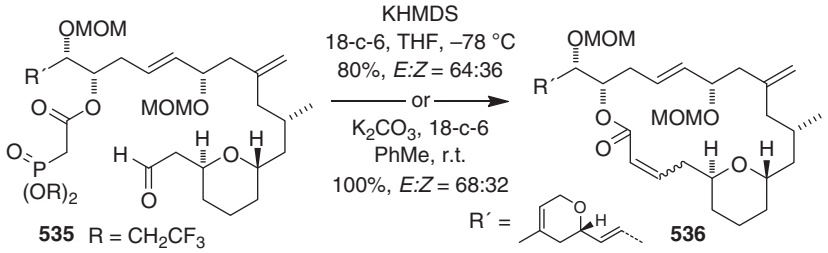
The first seven entries depict conventional HWE reactions involving carbonyl group-stabilized phosphonates and targeting complex (*E*)-configured alkenes (or '*trans*-like' alkenes) en route to dictyostatin (entry 1),[290] archazolid B (entry 2),[291] aplyronine A (entry 3),[292] concanamycin F (entry 4),[293] palmerolide A (entry 5),[294] 35-deoxyamphotericin B methyl ester (entry 6),[295] and terpestacin (entry 7).[296] These reactions are for the most part conducted at close to ambient temperature and employ simple dialkylphosphonates (e.g., $P(=O)(OEt)_2$). The choice of the deprotonating agent is dependent on the base sensitivity of the substrates. Thus, Fuchs and coworkers utilized the weakly basic lithium hexafluoroisopropoxide[277] to avoid epimerization at an α-methoxy ester moiety within the aldehyde component in their synthesis of a precursor to aplyronine A (entry 3).[292] For HWE cyclizations, very mild conditions are also required because of the presence of the aldehyde during the deprotonation stage; Masamune–Roush (LiCl, *i*-Pr_2NEt) or potassium carbonate-mediated protocols are popular as seen in entries 5–7. Problems with conventional HWE reactions are rare and stereoselectivity is usually close to perfection (at least for reactions involving aldehydes); however, failures do occur on occasion. For example, to obtain a precursor to the aldehyde needed for the reaction indicated by entry 2, Menche et al. attempted to exploit the HWE reaction between phosphonate **533** and aldehyde **534** under Masamune–Roush conditions (equation 112). None of the desired olefination product was obtained from this apparently straightforward transformation; rather, extensive decomposition occurred (presumably the result of various β-elimination possibilities) and the only salvageable remnant identified from the reaction mixture was the isomerized aldehyde **534′**.[291]



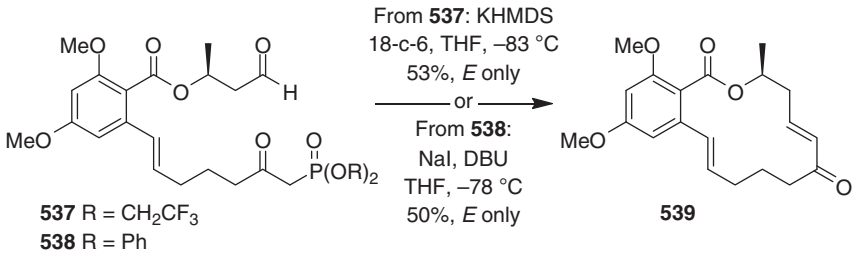
(112)

Entries 8–11 exemplify (*Z*)-selective HWE reactions en route to phoslactomycin A (entry 8),[297] discodermolide (entry 9),[298] 6-deoxyerythronolide B (entry 10),[299] and phorboxazole A (entry 11).[300] A majority of these examples employ the better known Still–Gennari protocol based on bis(trifluoromethyl)phoshonates,[289] but in most cases the Ando method involving comparable diphenylphosphonates[310] would undoubtedly perform equally well if evaluated. As illustrated, (*Z*)-selectivity is generally obtainable from either ester- or ketone-stabilized phosphonates for both intermolecular and intramolecular olefinations. *Cis* enone and enoates of great complexity can be readily assembled. Noteworthy in this regard is the elaboration of a late stage discodermolide fragment via intermolecular HWE reaction of a ketophosphonate under modified Still–Gennari conditions by Paterson and coworkers (entry 9).[298] The same group later employed a similarly complex coupling reaction to access the related microtubule-stabilizing agent dictyostatin.[340] In their first-generation total synthesis of phorboxazole A, Smith et al. utilized an

intramolecular Still–Gennari olefination to access the macrolidic core of this biologically active polyketide (entry 11).[300] Unusually, it was observed that the *Z*:*E* ratio improved with increasing temperature, thus at −78 °C an otherwise identical macrocyclization gave a 50:50 mixture of (*E*)- and (*Z*)-isomers. Of further note, the nature of the side-chain substituent R was found to signficantly influence stereochemical outcome. Thus, although the illustrated complex side-chain R led to a satisfactory level of (*Z*)-selectivity (*Z*:*E* = 80:20),[341] in a second-generation synthesis of the same natural product target molecule, setting R = (*E*)-MeC=CHI gave only *Z*:*E* = 71:29 (albeit in a higher yield, 96%).[342] Alternative (*Z*)-selective intramolecular HWE reactions to similar unsaturated lactone intermediates en route to phorboxazole A have been reported using dimethylphosphonates.[343] Other instances of intramolecular Still–Gennari or Ando reactions giving poor (*Z*)-selectivity, or even favoring the (*E*)-isomer, during the synthesis of macrocyclic alkenes have also been recorded. For example, Mulzer and coworkers observed that potassium base-mediated cyclization of an *ω*-formyl bis(trifluoroethylphosphono)acetate (**535**) en route to laulimalide led preferentially to the unwanted (*E*)-configured unsaturated lactone regardless of the conditions examined (equation 113).[344] Murphy and coworkers likewise failed to obtain desired *cis* enoate products when subjecting Still–Gennari (**537**) or Ando (**538**) type phosphonates to any of the usual protocols in their attempts to access **539**, including those illustrated in equation 114.[345]



(113)



(114)

Four examples of the HWE reactions of the less popular cyanophosphonate class of reagents follow en route to teubrevin G (entry 12),[301] the dietary carotenoid lutein (entry 13),[302] a polyene cyclization precursor (entry 14),[303] and the cembranoid diterpene cleomeolide (entry 15).[304] The HWE reactions of non-*α*-substituted phosphonoacetonitriles (e.g., entries 12 and 13) are characterized by slightly lower stereoselectivity than that expected from comparable carbonyl group-stabilized phosphonates; nonetheless, stereoselectivities in excess of 90:10 can usually be obtained by experimentation with reaction variables. Interestingly, *α*-substituted phosphonoacetonitriles typically give very high (*Z*)-selectivity in the formation of trisubstituted alkenes from aldehydes provided the HWE reaction is mediated by a potassium base and conducted at low temperature.[346] This well-known finding was applied to good effect by MacMillan and Rendler in the preparation of a substrate for a methodological development study (entry 14).[303] Paquette et al.'s synthesis of an unsaturated bicyclic precursor to cleomeolide demonstrates that good (*Z*)-stereoselectivity can also potentially be achieved in intramolecular reactions of a similar nature (entry 15).[304]

The final five entries of **Table 7** illustrate representative applications of the Horner–Wittig reaction in the synthesis of complex conjugated alkene targets en route to kalihinol A (entry 16),[305] tetronolide (entry 17),[306] bafilomycin A_1 (entry 18),[307] a trifluoroepothilone analog (entry 19),[308] and an ADDA derivative (entry 20).[309] As outlined above (Section 1.15.3.2.4.1), the one-step Horner–Wittig olefination is readily achieved provided the phosphine oxide carbanion species is equipped with a proximal stabilizing group. The kinds of phosphine oxide substrates used are typically allylic or benzylic and in these cases the Horner–Wittig olefination gives generally superior (*E*)-selectivity to that obtainable from comparable HWE reactions. It is noteworthy that high stereoselectivity can be realized from ketones, as seen in Danishefsky and coworkers' elaboration of a precursor to an epothilone analog (entry 19),[308] and in the widely employed Lythgoe–Roche vitamin D synthesis (e.g., equation 103).

1.15.4 Silicon- and Boron-Mediated Olefination Methods

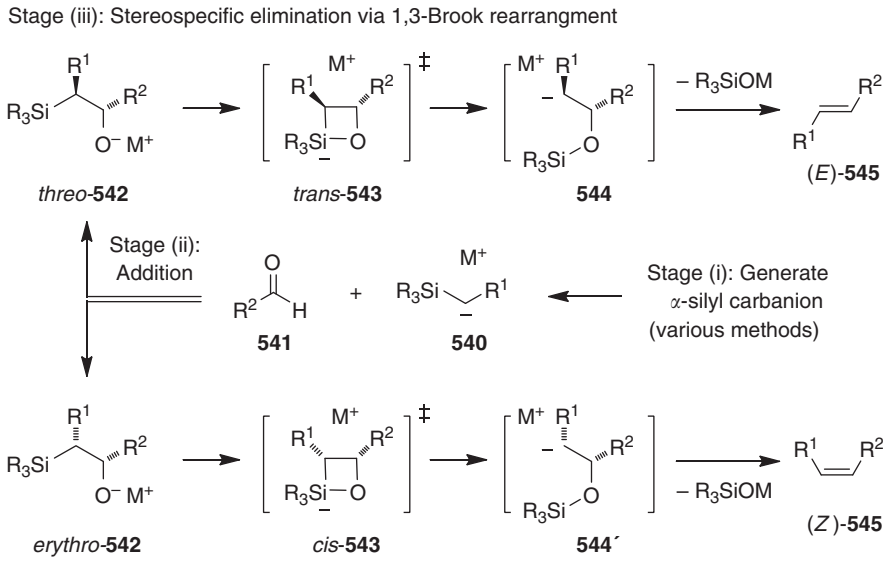
Silicon and boron are both highly oxophillic elements with organic derivatives that can be potentially employed in carbonyl olefination protocols. The generation of carbanions adjacent to silicon or boron is not as straightforward as analogous metallations of sulfones and organophosphorus compounds and as a consequence, the use of silicon- and boron-based olefination

methods is less prevalent than the various types of Julia and Wittig reactions. Nonetheless, in certain scenarios these alternative methods may prove optimal for the solution of a particular synthetic problem. The well-known silicon-based Peterson olefination is of greater significance than the nascent boron-Wittig reaction and it will be treated first and in greater detail. Both methods have been previously reviewed and readers wishing for a more comprehensive treatment should consult these accounts.[347,348]

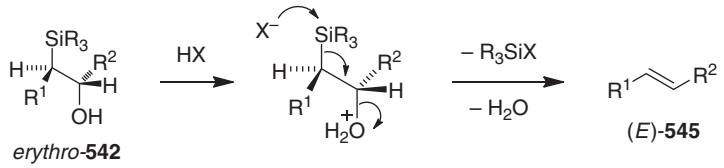
1.15.4.1 Alkene Formation With α-Silyl Carbanions: The Peterson Olefination

1.15.4.1.1 Overview and general considerations

Building on a suggestive earlier report from Gilman and Tomasi,[349] Peterson introduced the generic concept of carbonyl group olefination using α-silyl carbanions in 1968.[350] In its simplest guise the Peterson olefination involves the addition of an α-silyl carbanion (**540**) to a carbonyl compound followed by stereospecific *syn* elimination of a silanoxide anion from the resulting β-alkoxysilanes **542** to give an alkene. The mechanism is still very much a subject for debate[347c] and that illustrated (**Scheme 63**) is based on theoretical studies suggesting that elimination proceeds via a 1,3-Brook rearrangement with the commonly invoked oxasiletanide species **543** as a transition state rather than a reactive intermediate.[351] The veracity of this model is far from certain, however, and others argue in favor of an actual 1,2-oxasiletanide intermediate,[352] the genesis of which potentially lies in an initial interaction between the carbonyl group oxygen-atom and the silane silicon-atom.[353] Regardless of the true nature of the mechanism, it is a fact that in the absence of an anion-stabilizing group (e.g., $R^1 \neq CO_2R'$, Ph, etc.), the Peterson olefination does not progress spontaneously beyond the addition stage and typically yields β-hydroxysilanes upon initial work-up. As with the Horner–Wittig reaction (Section 1.15.3.2.4.1), the arrested olefination process can be pushed to completion by subsequent treatment of the isolated carbinol intermediates with a sodium or potassium base (i.e., conditions favoring a noncoordinated alkoxide anion). Adding greater flexibility to the method, *anti* rather than *syn* elimination can be triggered by exposing a β-hydroxysilane to acidic conditions instead of basic conditions (**Scheme 64**). Thus, it is possible to convert separate *erythro* and *threo* β-hydroxysilane isomers into the same geometrically pure alkene product by applying opposite elimination conditions to each compound or, alternatively, to convert a single type of β-hydroxysilane diastereoisomer into either an (*E*)- or a (*Z*)-alkene. A straightforward demonstration of this useful capability is illustrated below (**Scheme 66**), but the same principle can be applied more obliquely to control the regiochemistry of elimination from cyclic β-hydroxysilanes. In an instructive recent example, Roush

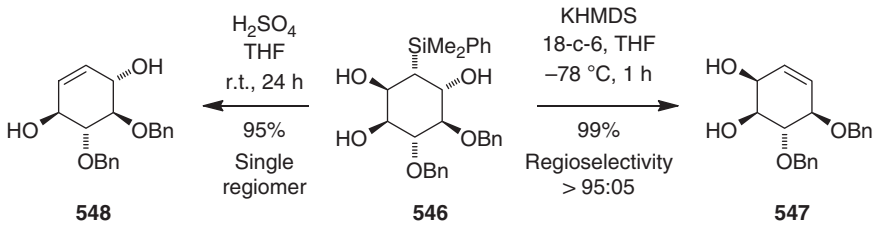


Scheme 63 An overview of the Peterson olefination (depicted toward a 1,2-disubstituted alkene product) with indication of one mechanistic possibility.



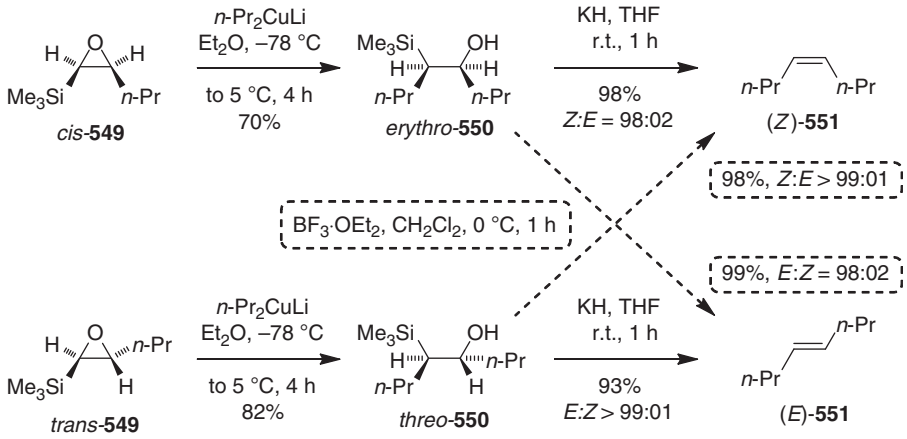
Scheme 64 *Anti* elimination of an *erythro* β-hydroxysilane (**542**) under acidic conditions giving rise to an (*E*)-alkene (*threo*-**542** would likewise give (*Z*)-**545**).

and coworkers transformed silainositol **546** regiodivergently into conduritol F precursor **547** via base-mediated *syn* elimination and into conduritol B precursor **548** via acid-induced *anti* elimination (Scheme 65).[354]



Scheme 65 Control of olefin regiochemistry by choice of *syn* or *anti* elimination conditions.

Attention herein will focus on alkene synthesis involving the addition of α-silyl carbanions to carbonyl compounds, although it should be noted that the pivotal β-hydroxysilane intermediates of the Peterson olefination can also be generated in many other ways and likewise converted to alkenes via acid- or base-mediated elimination. Indeed, the best evidence for the stereochemical outcome of 'Peterson elimination' comes from experiments involving nucleophilic opening of stereodefined epoxides. In a seminal study, Hudrlik et al. prepared *erythro* and *threo* β-hydroxysilanes **550** via the addition of $(n\text{-Pr})_2$CuLi to the corresponding *cis*- and *trans*-α,β-epoxysilanes **549** (Scheme 66).[355] Base-induced elimination resulted in stereospecific conversion of *erythro*-**550** to (*Z*)-4-octene (**551**) and *threo*-**550** to (*E*)-4-octene (**551**), while the opposite transformational relationships were encountered for acid-induced elimination. With this finding came the realization that epoxysilanes are effective stereodefined vinyl cation equivalents, a concept that has been subsequently well exploited in synthesis.[356] In other work establishing the stereochemical course of base-mediated elimination of β-hydroxysilanes, Dervan and Shippey noted that deoxygenation of epoxides to alkenes occurs with inversion of stereochemistry upon treatment with trimethylsilylpotassium.[357] Reetz and Plachky made closely related contemporaneous observations in a study of the conversion of stilbene oxides to stilbenes using dimethylphenylsilyllithium.[358]

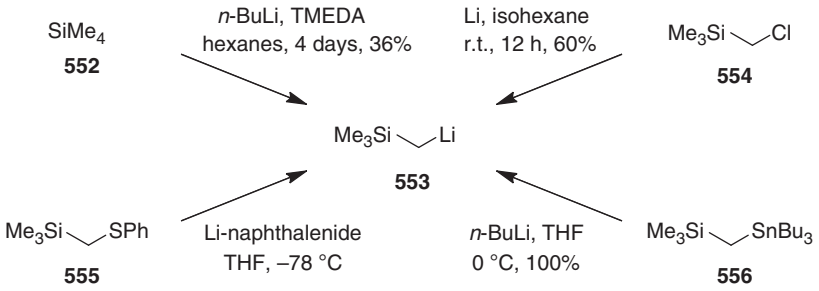


Scheme 66 Synthesis of stereodefined β-hydroxysilanes from epoxysilanes and subsequent base (solid lines) and acid (dashed lines)-mediated elimination processes.

1.15.4.1.2 Generation of α-silyl carbanions for Peterson olefination

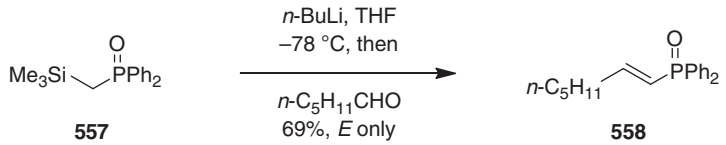
While silicon does offer modest stabilization to adjacent negative charge, the α-C-H bonds of simple silanes have low kinetic acidity. Accordingly, the generation of α-silyl carbanions is seldom a matter of merely adding a base to the obvious silane precursor although a combination of *n*-BuLi and *N,N,N′,N′*-tetramethylethylene diamine (TMEDA) will slowly lithiate (> 24 h) tetramethylsilane (TMS, **552**) and methylsilyl groups in other chemically robust nonfunctionalized silanes.[359] Alternate methods to prepare the archetypal α-silyl carbanion (trimethylsilyl)methyllithium (**553**) exemplify some of the more versatile approaches that are available to access reagents for the Peterson olefination (Scheme 67). For example, besides direct metallation of TMS, methylenation agent **553** has also been prepared by reduction of halomethyltrimethylsilanes (e.g., **554**)[360] or bis(trimethylsilylmethyl)mercury (not illustrated)[361] with lithium metal, reductive lithiation of phenylthiotrimethylsilane (**555**) with lithium naphthalenide,[362] and transmetallation of organostannane **556** with *n*-BuLi.[363] The Grignard reagent analogous to **553** is likewise prepared conventionally from chloromethyltrimethylsilane by treatment with magnesium metal in ether.[364]

As might be expected, silanes equipped with additional anion-stabilizing groups are comparatively easy to metallate by the action of a suitable base. Interesting in this regard are readily accessed species of the form R_3SiCHX^- where X equals one of the



Scheme 67 A selection of methods to generate (trimethylsilyl)methyllithium (**553**).

other common types of olefination activators such as $^{+}PPh_3$,[349,365] $P(=O)(OEt)_2$,[366] $P(=O)Ph_2$,[367] or $B(OR')_2$.[368] In all cases studied, when such intermediates are added to appropriate carbonyl electrophiles the Peterson olefination is found to compete against the alternate type of alkene-forming process. For example, Kawashima et al. demonstrated the generation of vinylphosphine oxide **558** by deprotonation of **557** followed by the addition of hexanal (equation 115),[367] while Matteson and Majumdar were able to produce vinyl boronates in a similar fashion via metallation of silylmethyl boronate **559** followed by Peterson olefination (equation 116).[368] Although somewhat sensitive to desilylation processes, α-silyl ketones and esters can be likewise directly metallated with nonnuclephilic bases to give the corresponding active species for Peterson olefination (see Section 1.15.4.1.3).[369]



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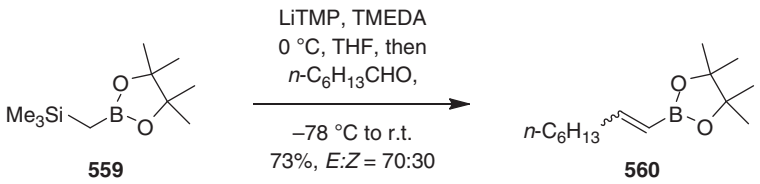

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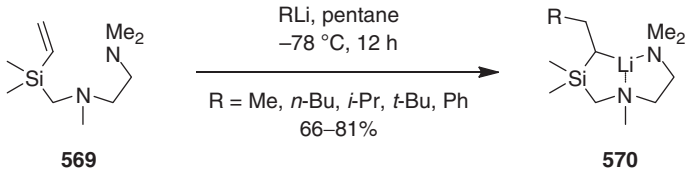
Halogen–metal exchange from α-halosilanes provides a versatile entry to functionalized metallated silanes.[370] Barrett et al. discovered that α-iodosilanes work best for this purpose and that suitable substrates are conveniently obtained from aldehydes via silylhydrin formation followed by iodination (**561** to **562**; Scheme 68).[371] As illustrated, α-lithiosilanes (**563**) generated by low temperature iodine–lithium interchange from **562** gave the expected olefin products **564** following the addition of aldehydes and subsequent acid-mediated elimination. To improve on the poor stereoselectivity encountered, an alternate sequence was developed whereby cuprate reagents derived from **563** were instead intercepted by acyl chlorides to give α-silyl ketones **565**. Addition of nucleophiles to the latter gave β-hydroxysilanes with high diastereoselectivity that were eliminated *in situ* to afford olefin products **566** in the usual stereospecific manner. Given that the final nucleophile (R^3M) can be a hydride source or a carbanion, stereoselective access to disubstituted or trisubstituted alkenes is possible with this methodology. Similar results were later obtained from cuprates derived from the analogous Grignard reagents generated from α-chlorosilanes by the action of magnesium metal.[372]

Finally, one of the most useful but less obvious approaches to substituted α-silyl carbanions involves the facile addition of organolithiums to vinylsilanes. This process was first encountered serendipitously by Cason and Brooks during their attempted preparation of triphenylvinylsilane from vinyltrichlorosilane and phenyllithium,[373] and it was later used to good effect by Hudrlik and Peterson to prepare a substituted α-lithiosilane (**567**) for stereochemical investigations of the Peterson olefination (Scheme 69).[374] More recently, vinylsilanes equipped with internal amino moieties capable of ligating lithium have been shown to efficiently capture organolithium reagents in the absence of coordinating solvents at low temperature (equation 117).[375] The conjugate addition of cuprates and other carbon nucleophiles to α-silyl α,β-unsaturated carbonyl compounds generates stabilized α-silyl carbanions that will engage in direct one-step Peterson olefination reactions.[376] Evans and coworkers successfully demonstrated this sequence from α-silylcyclopentenones (e.g., **571**) generated via Pauson-Khand reaction (e.g., equation 118).[377]



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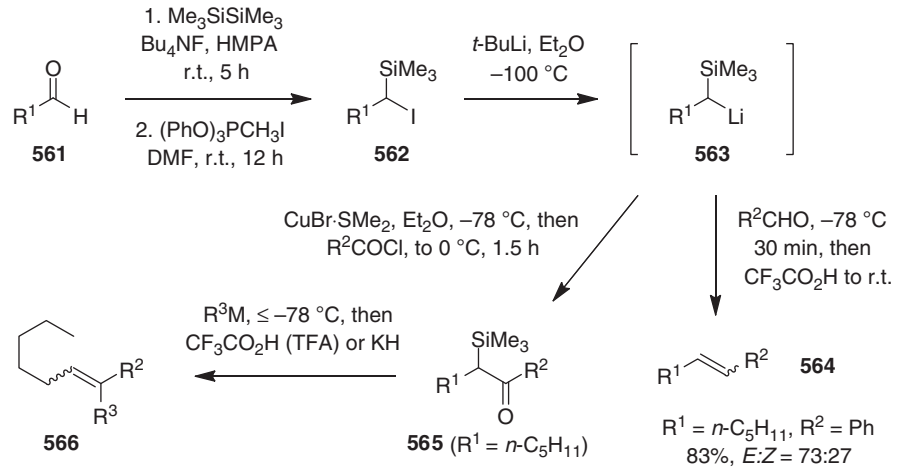


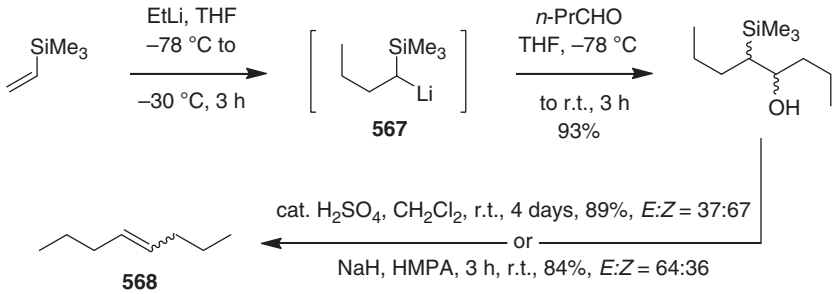
R^2	R^3–M	Elimination	Yield **566**	*E*:*Z* (**566**)
Me	H-Al(*i*-Bu)$_2$	TFA	64%	< 05:95
Me	H-Al(*i*-Bu)$_2$	KH	63%	> 95:05
Me	*n*-Bu–Li	TFA	59%	94:06
Me	*n*-Bu–Li	KH	57%	05:95
Ph(CH$_2$)$_2$	Me–Li	TFA	57%	09:91

R^1 = *n*-C_5H_{11}, R^2 = Ph
83%, *E*:*Z* = 73:27

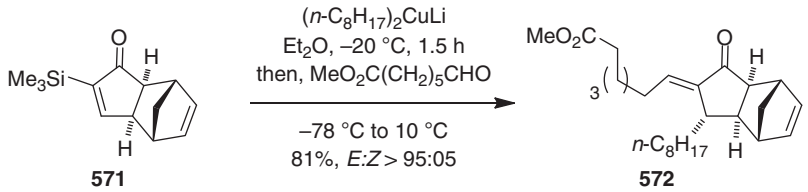
R^1 = Ph(CH$_2$)$_2$, R^2 = Ph
84%, *E*:*Z* = 79:21

R^1 = *n*-C_5H_{11},
R^2 = Ph(CH$_2$)$_2$, 71%, *E*:*Z* nd

Scheme 68 Generation of α-lithiosilanes by iodine–lithium exchange and ensuing Peterson olefination type processes.



Scheme 69 Generation of an α-lithiosilane by addition of an organolithium to a vinylsilane and subsequent Peterson olefination of butyraldehyde.



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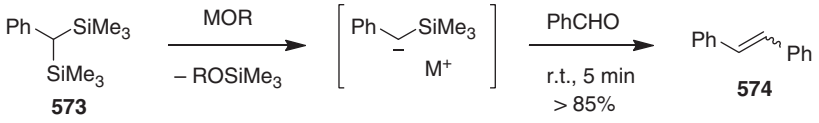
1.15.4.1.3 Factors affecting reaction efficacy and stereoselectivity

The addition of nonstabilized α-silyl carbanions to carbonyl compounds does not generally occur with any great diastereoselectivity and simple Peterson olefination reactions typically afford alkene products as a significant mixture of both (*E*)- and (*Z*)-isomers (e.g., **563** to **564**, Scheme 68, and **567** to **568**, Scheme 69). This fate can of course be avoided if the diastereomeric β-hydroxysilane intermediates are separated before the elimination stage, or if they are instead prepared in some indirect manner that is either more stereoselective (e.g., by nucleophilic addition to β-silyl ketones) or else entirely stereospecific (e.g., opening of α, β-epoxysilanes).[356] Restricting attention here to the direct one-pot Peterson olefination processes of stabilized α-silyl carbanions, it is generally found that the degree of stereoselectivity is dependent on substrate substituent effects but not necessarily strongly influenced by reaction conditions. For example, Bassindale et al. discovered that stereoselectivity in the synthesis of stilbene (**574**) from the reaction of benzaldehyde and PhCH$^{(-)}$SiMe$_3$ species is remarkably insensitive to the type of metal counter-cation, the

nature of the solvent medium, and the reaction temperature.[378] In this study, carbanions were generated by alkoxide-mediated disilylation of geminal disilane **573** (Scheme 70).

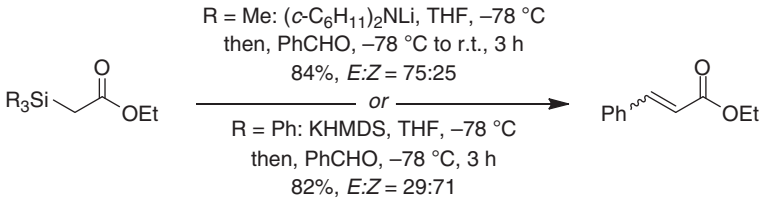


MOR	Solvent	*E*:*Z* **574**
LiO*t*-Bu	HMPA	59:41
NaOMe	HMPA	57:43
KO*t*-Bu	HMPA	57:43

MOR	Solvent	*E*:*Z* **574**
KO*t*-Bu	DMSO	57:43
KOMe + 18-Crown-6	THF	59:41

Scheme 70 Reaction conditions marginally influence stereoselectivity in the synthesis of stilbene (**574**) via the direct Peterson olefination.

α-Silyl esters can be deprotonated with base to give anions capable of the direct one-pot Peterson olefination of aldehydes and ketones.[369] The expected α,β-unsaturated ester products are obtained from these reactions; however, only rather modest stereoselectivity is encountered and superior results are realized with comparable Julia, HWE, or Wittig reactions. Interestingly, the sense of stereoselectivity shows a useful dependence on reaction conditions and the type of silyl group (equation 119).[369b,379] Larson and coworkers demonstrated that (*Z*)-enoates are obtained selectively from the reactions of α-substituted diphenylmethylsilyl acetate anions with aldehydes (Scheme 71).[380] In general, α-silylated carbonyl compounds are not trivial to prepare;[381] however, the substrates in this case are conveniently accessed via regioselective C-silylation of the corresponding lithium ester enolates with diphenylmethylsilyl chloride (**575** to **576**).[382] Stereoselectivity in the synthesis of **577** is thought to be a consequence of the conformation preference of the enolate produced (**578**) by a 1,3-Brook rearrangement from the initially generated addition adduct: minimization of steric interactions between R^1 and R^2 in **578** before β-elimination would proffer (*Z*)-**577**.[380] Such a scenario is consistent with the observation of heightened (*Z*)-selectivity for bulkier R^1 and R^2 and would disconnect any relationship between the final alkene *E*:*Z* ratio and the initial *threo*:*erythro* ratio of addition adducts **542**. More recently, phosphazene and proazaphosphatrane bases have been utilized to promote (*E*)-enoate formation from ethyl α-trimethylsilylacetate and aldehydes; however, these processes do not necessarily involve a traditional Peterson olefination mechanism.[383]



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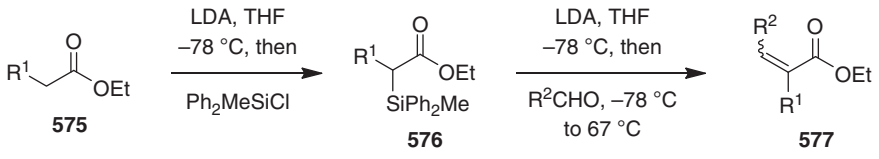
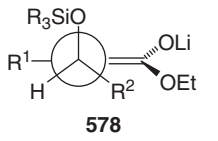
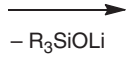






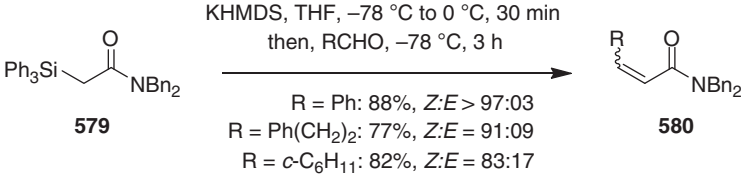
(*Z*)-**577**

R^1	R^2	Yield (%) **577**	*Z*:*E* **577**
Me	Ph	65	78:22
Me	*n*-Pr	57	75:25
Me	*i*-Pr	60	90:10
Et	*n*-C_6H_{13}	67	78:22
Et	*i*-Pr	55	82:18

Scheme 71 Synthesis of (*Z*)-enoates from α-substituted silyl acetates **576**.

By contrast to the fairly modest stereoselectivity of Peterson olefinations involving α-silyl esters, Kojima et al. discovered that synthetically useful levels of (*Z*)-selectivity are obtained in the synthesis of enamides from the potassium enolate of triphenylsilyl

acetamide **579** (equation 120).[379a,384] The trimethylsilyl congener of **579** gives the opposite stereochemical preference (*E*:*Z*~75:25), and *cis* selectivity is heightened progressively as the base counter-cation is varied from Li to Na to K (*Z*:*E*~54:46 to 80:20 to > 97:03, respectively). Building on seminal results from Yamamoto and coworkers,[385] the Kojima group were able to extend their earlier findings to a highly stereoselective synthesis of (*Z*)-acryonitrile derivatives **582** using the α-silylated acetonitrile agent **581** (equation 121).[386] In this case, stereochemical outcome was largely insensitive to the nature of the base counter-cation.



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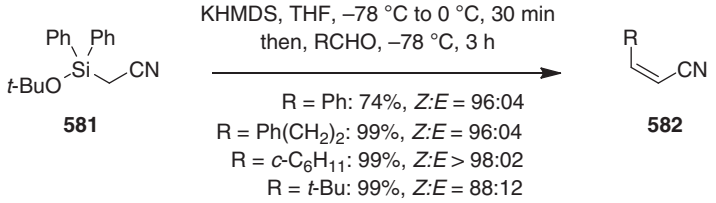

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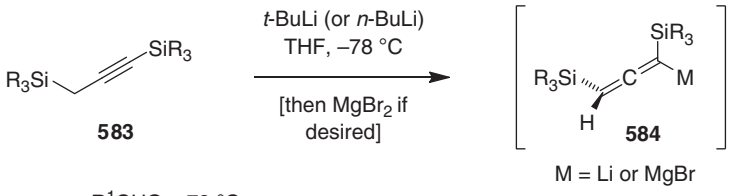
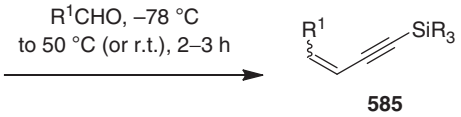
High stereoselectivity has likewise been obtained from Peterson olefination reactions involving propargylic α-silyl carbanions and leading to conjugated enyne products. Yamamoto and coworkers noted that metallated 1,3-bissilylated propynes yield (*Z*)-enyne products preferentially in THF solvent and that stereoselectivity increases with the steric bulk of the silyl groups and in transmetallation from lithium to magnesium (**Scheme 72**).[385] Corey and Rücker subsequently demonstrated that the closely related reactions of lithiated 1,3-bis(triisopropylsilyl)propyne also afford (*Z*)-enynes in THF solvent but that (*E*)-enynes can be obtained instead in the presence of an HMPA cosolvent.[387] A closed metal templated transition state (**586**) has been invoked to account for the observation of (*Z*)-selectivity in THF solvent, while the possibility of an open transition state in the presence of HMPA (**587**) (**Scheme 73**) was proffered as an explanation for (*E*)-selectivity.[385,387] In all cases, lower stereoselectivity is realized

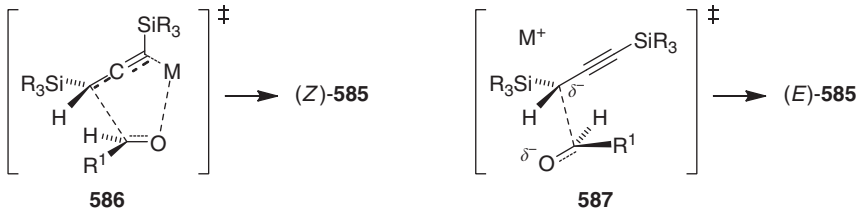




				enyne **585**	
R^1	'R_3Si'	M	Cosolvent	Yield	*Z*:*E*
n-C_5H_{11}	Me_3Si	Li	None	77%	75:25
n-C_5H_{11}	Me_3Si	MgBr	None	75%	88:12
n-C_5H_{11}	Et_3Si	MgBr	None	89%	97:03
n-C_5H_{11}	*t*-BuMe_2Si	MgBr	None	65%	>99:01
c-C_6H_{11}	*t*-BuMe_2Si	MgBr	None	75%	97:03
c-C_6H_{11}	*i*-Pr_3Si	Li	None	71%	>95:05
t-Bu	*i*-Pr_3Si	Li	None	79%	>95:05
Ph	Me_3Si	MgBr	None	76%	75:25
^{E}PhCH=CH	*t*-BuMe_2Si	MgBr	None	90%	88:12
n-C_6H_{13}	*i*-Pr_3Si	Li	HMPA	~ 65%	<09:91
c-C_6H_{11}	*i*-Pr_3Si	Li	HMPA	~ 65%	<09:91
t-Bu	*i*-Pr_3Si	Li	HMPA	~ 65%	<09:91

Scheme 72 Synthesis of enynes using metallated 1,3-bissilylated propyne reagents.

in the synthesis of enynes from aromatic aldehydes as compared to aliphatic aldehydes. A somewhat related Lewis acid-mediated synthesis of (*E*)-1,3-dienes from aldehydes and 1,3-bissilylpropenes was recently reported by Somfai and coworkers.[388]



586 587

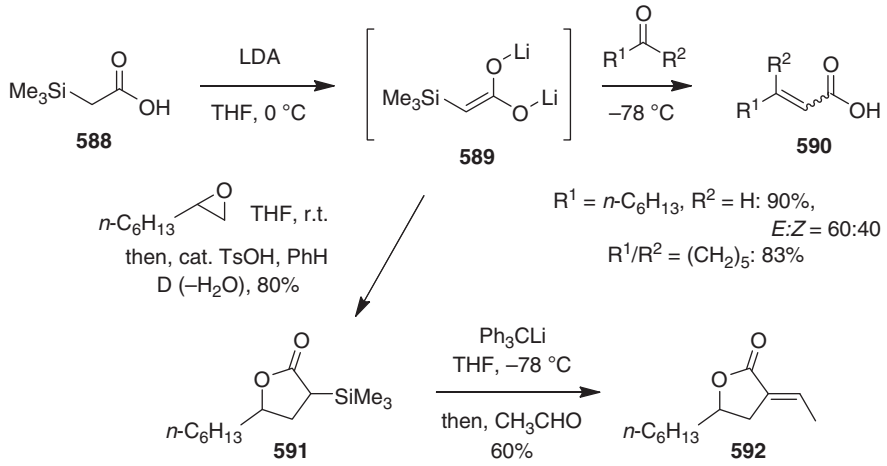
Scheme 73 Transition state models to account for stereoselectivity in the synthesis of enynes.

1.15.4.1.4 Notable reaction variants and specialized applications

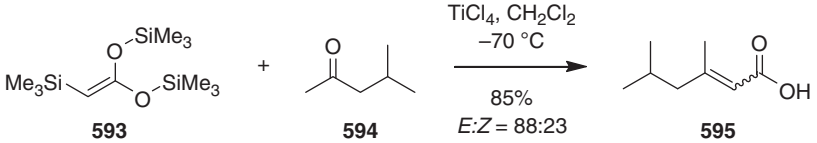
As mentioned in the outline, *β*-hydroxysilanes can be produced from a wide variety of reaction types and subsequently converted to alkenes via acid or base-mediated elimination. A complete survey of these many possibilities is beyond the scope of this account and instead only a small selection of Peterson olefination variants and specialized applications of the method will be highlighted herein. Readers wishing for further details are referred to more comprehensive treatments of the subject matter,[347] and discourse on the Brook rearrangment[389] and the chemistry of *α,β*-epoxysilanes[356] which are closely related to the Peterson olefination.

1.15.4.1.4.1 Specialized silicon reagents for the synthesis of useful structural motifs

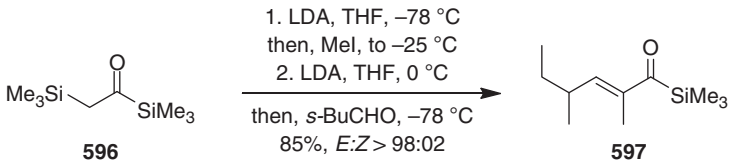
A number of ingenious nucleophilic silicon reagents have been introduced that facilitate the synthesis of commonly occurring structural motifs via the Peterson olefination. For example, Grieco and coworkers demonstrated that the dianion of trimethylsilylacetic acid (**589**) can be readily generated with LDA in THF solvent and that this species engages with aldehydes and ketones as expected to give *α,β*-unsaturated acids **590** (Scheme 74).[390] The dianion **589** is significantly more nucleophilic than the monoanions of alkyl trimethylsilylacetates and reacts smoothly with epoxides at room temperature to yield valuable *α*-silyl *γ*-butyrolactone products (e.g., **591**) in good yield following acid-mediated cyclization. These adducts will also participate in the Peterson olefination in the usual manner (e.g., **591** to **592**). A related synthesis of *α,β*-unsaturated acids is available via the Lewis acid-mediated reactions of *tris*(trimethylsilyl)ketene acetal **593** (e.g., equation 122).[391] Zweifel and Miller likewise demonstrated the synthetic utility of the enolate of [(trimethylsilyl)acetyl]trimethylsilane (**596**) which can be readily alkylated and then condensed with aldehydes to provide an entry to (*E*)-configured trisubstituted *α,β*-unsaturated acyl silanes with high stereoselectivity (e.g., equation 123).[392] The product acyl silanes have many uses and can for example be converted to the corresponding acids by treatment with basic hydrogen peroxide or transformed into aldehydes by protosilylation mediated by TBAF and formic acid.[393]



Scheme 74 Synthetic utility of the dianion of trimethylsilylacetic acid (**E20**).

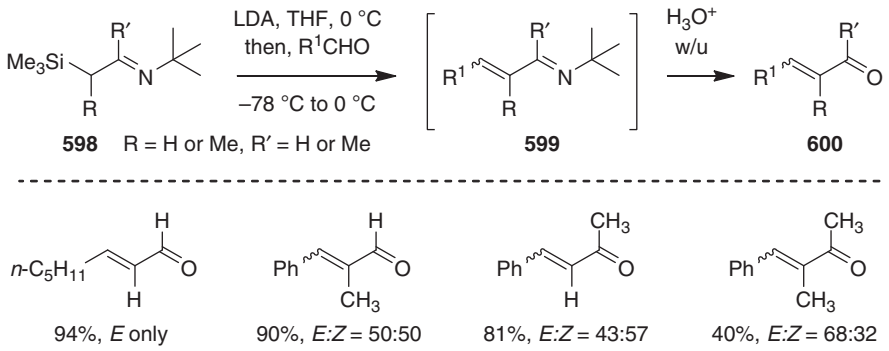


(122)

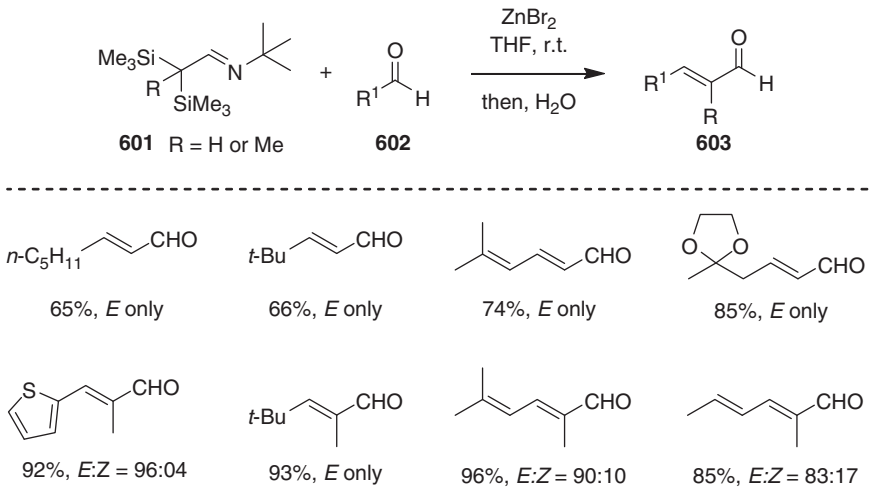


(123)

Corey and coworkers reported the use of metallated α-silyl *tert*-butylaldimines as an alternative to formylmethylenephosphorane reagents for the synthesis of α,β-unsaturated aldehydes (Scheme 75).[394] The approach, which was later extended to include analogous ketimine reagents by Croteau and Termini,[395] proceeds via Peterson olefination followed by acidic hydrolysis of the initial conjugated imine products **599**. It is high yielding but the bias and degree of stereoselectivity is variable. A superior method was subsequently introduced by Bellassoued et al. based on the Lewis acid-mediated reactions of α,α-bis(trimethylsilyl)-*tert*-butylaldimines **601** with carbonyl compounds (Scheme 76).[396] The Bellassoued protocol is particularly versatile and complements other approaches for the two-carbon-atom extension of aldehydes and ketones in that it does not rely on basic reaction conditions.



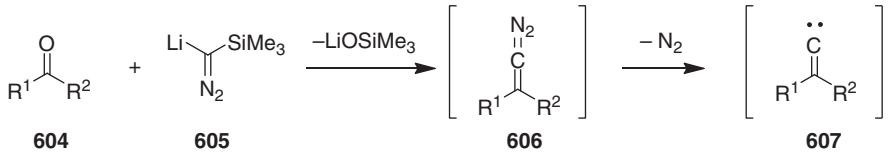
Scheme 75 Peterson olefination with lithiated α-silyl *tert*-butylaldimines.



Scheme 76 Lewis acid-mediated synthesis of α,β-unsaturated aldehydes from α,α-bis(trimethylsilyl)-*tert*-butylaldimines **601**.

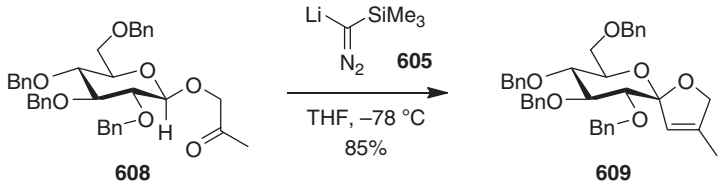
By analogy with the HWE reactions of metallated α-diazophosphonoacetates (e.g., the Seyferth–Gilbert reagent, Section 1.15.3.2.4.3), Ohira et al. reported that lithiated trimethylsilyldiazomethane (**605**) engages with carbonyl compounds via the Peterson olefination to give metastable diazoalkylidenes **606** that spontaneously afford alkylidene carbene species **607** capable of synthetically useful rearrangement and bond insertion chemistry (Scheme 77 and see Scheme 60 above).[397] As may be expected, treatment of aldehydes with **605** provides a synthesis of alkynes (e.g., decanal gives 1-undecyne in 61% yield); however, this reagent is more commonly used to affect stereospecific ring synthesis via intramolecular C-H insertion. For example, Wardrop et al. demonstrated an effective elaboration of spiroketal glycosides in this manner (equation 124),[398] while Hayes and coworkers similarly achieved the synthesis of a spirocyclic cyclopentene from Garner's aldehyde derivative **610** (equation 125).[399] More

recently, Li et al. have established that treatment of α-silyl ketones with **605** leads predominantly to silyl cyclopropenes via insertion of the transient alkylidene carbene into the adjacent C–Si bond; in most cases, this process is favored over 5-membered ring formation by C–H insertion (Scheme 78).[400] The α-silyl ketone substrates (**614**) are themselves available by a Lewis acid-mediated reaction between trimethylsilyldiazomethane (**613**) and aldehydes analogous to the Roskamp reaction.[271]



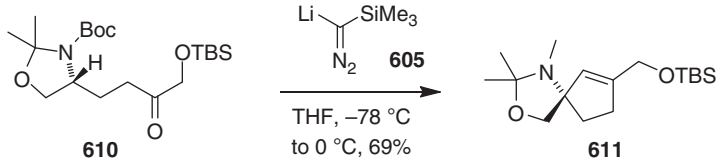
604 **605** **606** **607**

Scheme 77 Synthesis of alkylidene carbenes via Peterson olefination with trimethylsilyldiazomethyllithium (**605**).



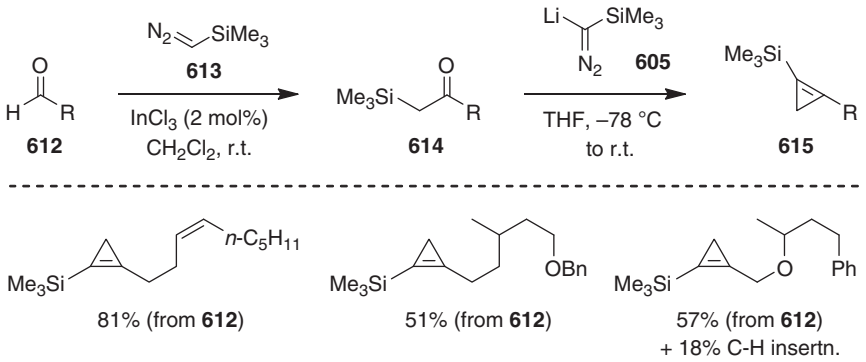
608 **609**

(124)



610 **611**

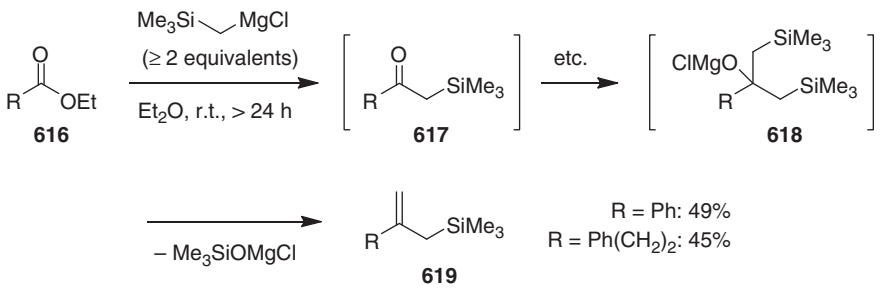
(125)



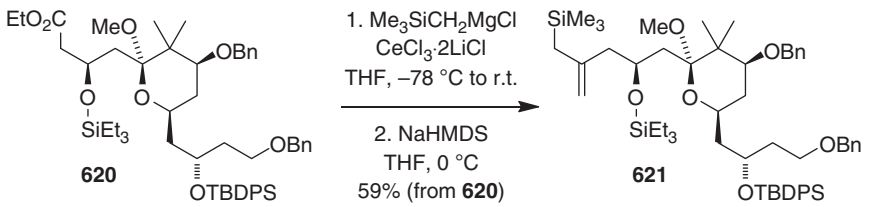
Scheme 78 Conversion of aldehydes to α-silyl ketones with trimethylsilyldiazomethane (**E10**) and further transformation to silyl cyclopropenes with trimethylsilyldiazomethyllithium (**E2**).

1.15.4.1.4.2 Reactions of α-silyl carbanions with carbonyl electrophiles other than aldehydes and ketones

α-Silyl carbanions are powerful nucleophiles and have suffcient reactivity to engage with carbonyl groups that are significantly less electrophilic than either aldehydes or ketones. For example, esters react with α-silyl carbanions in the expected manner to initially give α-silyl ketone products that react further *in situ* to give tertiary alkoxides that break down via the Peterson elimination to give synthetically useful allyl silanes. Building on a seminal report detailing the transformation as applied to formate esters,[401] Fleming and Pearce popularized this method by demonstrating the conversion of nontrivial ethyl esters to allyl silanes with excess (trimethylsilyl)methylmagnesium chloride (Scheme 79).[364] A combination of cerium chloride and (trimethylsilyl)methyllithium was later revealed to be optimal for the same kind of reaction.[402] A recent synthesis of a fragment of bryostatin 9 (**621**) by Wender and Schrier exemplifies a variation of this method (equation 126).[403]

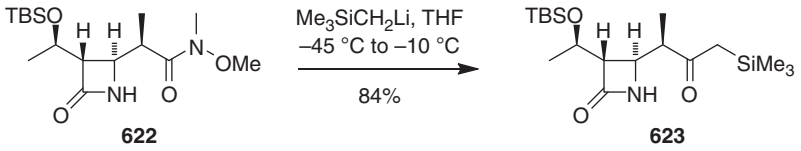


Scheme 79 Conversion of esters to allyl silanes by reaction with excess (trimethylsilyl)methylmagnesium chloride.

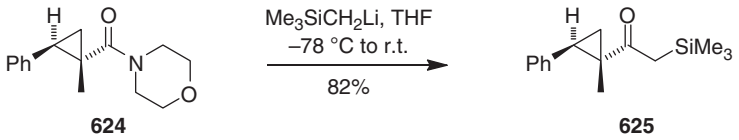


(126)

A high yielding synthesis of α-silyl ketones is achieved by adding trimethylsilylmethyllithium to Weinreb and morpholine amides (e.g., equations 127 and 128).[404,405] If desired, the products can be further converted to allyl silanes (as above) or deprotonated with LDA for subsequent Peterson olefination leading to α,β-unsaturated ketones.



(127)



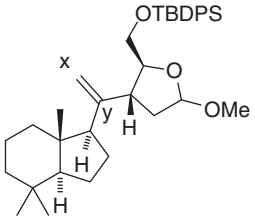
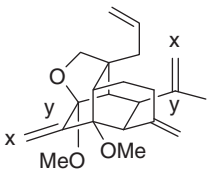
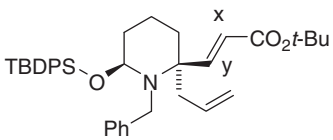
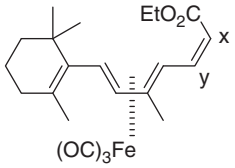
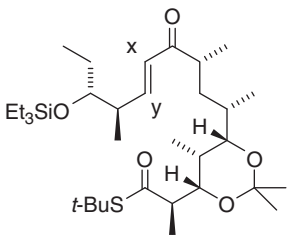
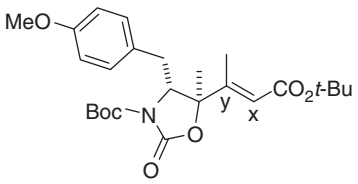
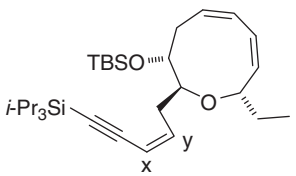
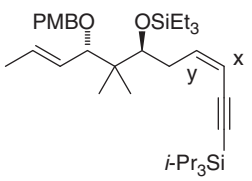
(128)

1.15.4.1.5 Illustrative examples in target-directed synthesis

Collected together in Table 8 is a selection of complex alkene targets that have been successfully prepared with the Peterson olefination. Except for certain well-recognized niche applications (e.g., methylenation, enyne synthesis), this silicon-based process is seldom the tactic of first choice for alkene synthesis but it is commonly evaluated if reactivity issues are encountered with alternate olefination methods. α-Silyl carbanions are considerably more nucleophilic than the reagents used in sulfur or phosphorus-based olefinations and the Peterson method is therefore advantageous for the olefination of hindered carbonyl groups that fail to react with phosphoranes or phosphoryl and sulfone anions.

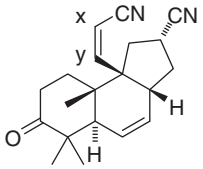
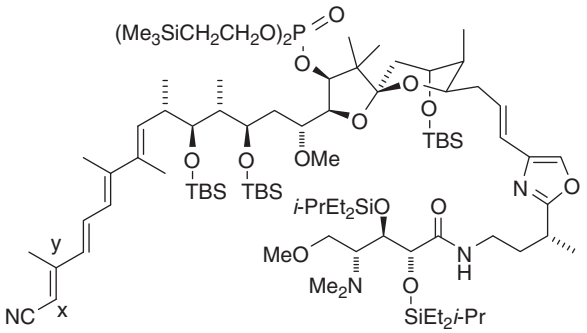
Given that Peterson olefination using nonstabilized α-silyl carbanions can exhibit poor intrinsic stereoselectivity, the method has enjoyed some of its greatest popularity as a tool for methylenation wherein issues of stereocontrol are inconsequential.[45] For example, Theodorakis et al. utilized a Peterson methylenation sequence to install a terminal olefin en route to the marine diterpene norrisolide (entry 1).[406] Wittig and Tebbe protocols failed to methylenate the same ketone due to its extremely hindered disposition. Snapper and coworkers more recently achieved the methylenation of a related and slightly more hindered ketone using Me_3SiCH_2MgCl, although in this case elimination did not occur unless the β-alkoxysilane intermediate was treated first with triflic anhydride.[416] En route to the vinigrol carbocyclic skeleton, Njardarson and coworkers prepared a crowded tetraene via double Peterson methylenation of a diketone substrate (entry 2).[407] Use of a cerium chloride additive here avoided competing enolization of carbonyl groups that can be caused by the basic (trimethylsilyl)methyllithium reagent. The elimination stage need not directly follow the addition step as seen in an inventive synthesis of a calcitriol A-ring synthon by Miles et al. (Scheme 80).[417] (Trimethylsilyl)methyllithium was added to hindered lactol **626** in the presence of cerium chloride and the desired exomethylene unit of the final target (**629**) later revealed after redox adjustments to the initial lactone product **627**. By contrast, Tebbe reagent-mediated methylenation of a ketoester akin to lactol **626** proceeded in only a 48% yield.[418]

Table 8 A selection of complex alkene targets prepared by the Peterson olefination

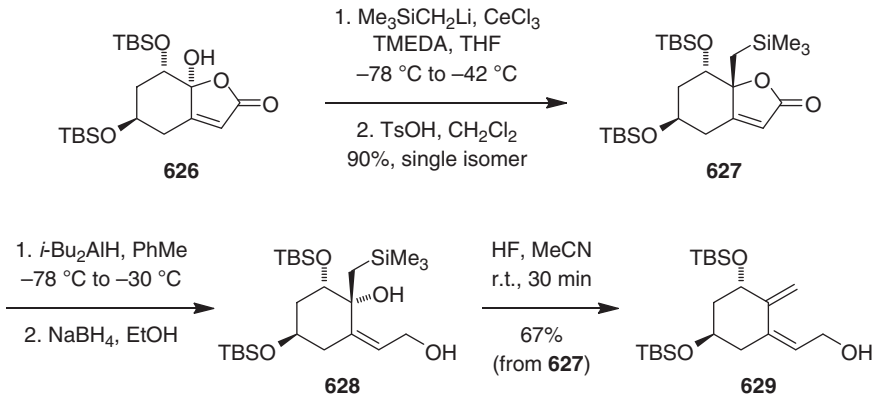
Entries	*Alkene target*[a]	*Reaction conditions and outcome*	*References*
1		1. Me_3SiCH_2Li, THF, 0 °C to r.t., 1 h 2. KH, THF, 67 °C, 2 h 72%	406
2		1. Me_3SiCH_2Li $CeCl_3$, THF, 0 °C, 1 h 2. KH, THF, 75 °C, 4 h 41%	407
3		$Me_3SiCH_2CO_2t$-Bu LDA, THF, −78 °C 70%, *E* only	408
4		$Me_3SiCH_2CO_2Et$ LDA, THF, −78 °C 92%, *Z*:*E* = 84:16	409
5		Silane: Me_3Si LiHMDS, THF, −78 °C 95%, *E* only	410
6		$Me_3SiCH_2CO_2t$-Bu LDA, THF, −78 °C, 4 h 53%, *E*:*Z*=60:40	411
7		*i*-$Pr_3SiCH_2C{\equiv}CSi$*i*-Pr_3 *n*-BuLi, THF, −74 °C to r.t., 8 h 83%, *Z*:*E*=86:14	412
8		*i*-$Pr_3SiCH_2C{\equiv}CSi$*i*-Pr_3 *n*-BuLi, THF, −78 °C, 30 min 62%, *Z*:*E*=89:11	413

(*Continued*)

Table 8 Continued

Entries	*Alkene target*[a]	*Reaction conditions and outcome*	*References*
9		Me_3SiCH_2CN, *n*-BuLi $(i\text{-PrO})_3B$, THF, −78 °C, 1 h 79%, *Z*:*E*=86:14	414
10		Me_3SiCH_2CN, *n*-BuLi, THF, −78 °C 94%, *E*:*Z*=63:37	415

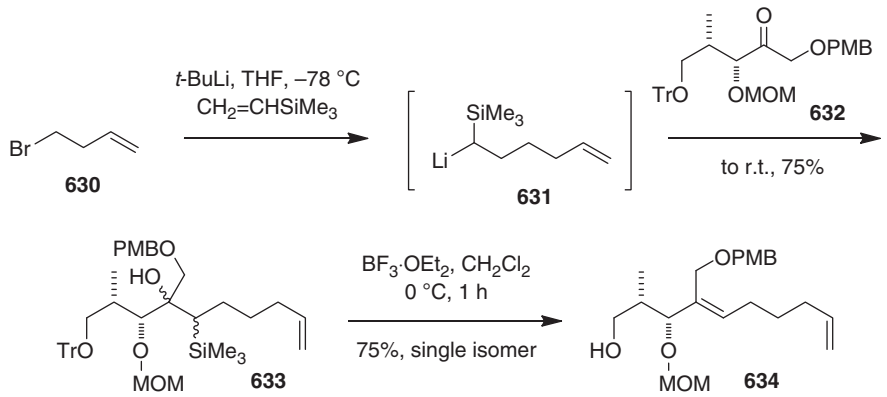
[a]Site of newly introduced alkene is located between x and y; x=original site of the silane and y=original site of the carbonyl group.



Scheme 80 A Peterson methylenation approach to a calcitriol A-ring synthon.

On occasion, the indirect Peterson olefination using nonstabilized α-silyl carbanions can give satisfactory levels of stereocontrol. For example, during their synthesis of the antitubercular agent tubelactomicin A, Tatsuta and coworkers prepared trisubstituted alkene **634** via a two-step Peterson olefination protocol involving lithiated silane **631** and ketone **632** (Scheme 81).[419] The nucleophile **631** was accessed *in situ* via addition of homoallyllithium to trimethylvinylsilane and subsequent treatment with ketone **632** led to a diastereomeric mixture of β-hydroxysilanes that collapsed fortuitously to a single olefin isomer upon their exposure to Lewis acid.

Direct one-pot Peterson olefination reactions involving α-silyl carbonyl compounds can offer good stereoselectivity and have been deployed in circumstances where the more prosaic HWE olefination has failed to give acceptable results (entries 3–6). Simpkins and Huxford utilized the Rathke silylacetate reagent[369a] to successfully olefinate a hindered aldehyde en route to halichlorine that would be difficult to convert to the same enoate with a phosphonate reagent (entry 3).[408] During their elaboration of 11*Z*-retinal, Wada and coworkers observed that reaction of an iron tricarbonyl complexed trienal with the lithium enolate of ethyl trimethylsilylacetate gave a (*Z*)-enoate product with good stereoselectivity (entry 4).[409] In the absence of the β-methyl group on the aldehyde substrate, the same conditions resulted in *Z*:*E*=53:47, while conventional Wittig and HWE reagents gave *trans*-enoate products exclusively. In a total synthesis of the macrolidic polyketide narbonolide, Masamune et al. applied the Peterson olefination to obtain a complex conjugated enone product in excellent yield after a comparable Wittig reaction gave lackluster results (entry 5).[410] The complex α-silyl ketone required for this transformation was prepared by addition of lithium *bis* [(trimethylsilyl)methyl]cuprate to the corresponding acid chloride. The synthesis of trisubstituted alkenes from ketones can never



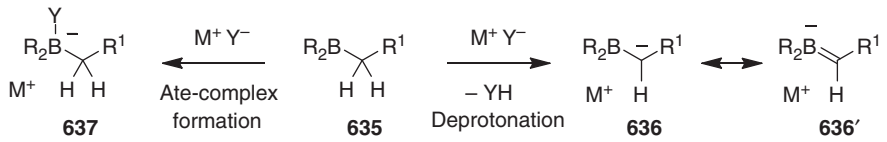
Scheme 81 Synthesis of a trisubstituted alkene via the Peterson olefination using a nonstabilized α-silyl carbanion.

be relied upon to proceed with wholly satisfactory stereocontrol via any type of carbonyl olefination method. As a case in point, Fujii and coworkers' preparation of an enoate precursor to a CXC chemokine type 4 receptor antagonist using the Rathke reagent gave a significant mixture of alkene isomers (entry 6); however, notable in this case is the fact that the reaction occurred at all from such a hindered ketone substrate (HWE and Wittig reactions failed completely).[411]

The final four entries of the table exemplify the utility of other types of stabilized α-silyl carbanions in the context of target-directed synthesis. Of note, the Yamamoto–Corey (*Z*)-enyne synthesis employing metallated 1,3-bissilylated propyne reagents has proved its worth in numerous total synthesis efforts. For example, Denmark and Yang prepared a late stage precursor to the nonterpenoid acetogenenin brasilenyne using this technology (entry 7),[412] while Wipf and Graham likewise accessed a required fragment of the macrolide disorazole C_1 in the same manner (entry 8).[413] Both of these examples are notable for the good yields obtained, despite the possibility of β-elimination from the substrate aldehydes. α-Silylacetonitrile reagents are also invaluable in certain scenarios, as seen in the generation of a β-substituted (*Z*)-configured acryonitrile from a remarkable hindered formyl group by Deslongchamps et al. en route to maritomol (entry 9).[414] In the final example, Smith and coworkers used the same reagent to olefinate a complex conjugated ketone to access calyculins A and B (entry 10);[415] here both configurations of the newly installed double bond were required to target the desired pair of isomeric natural products.

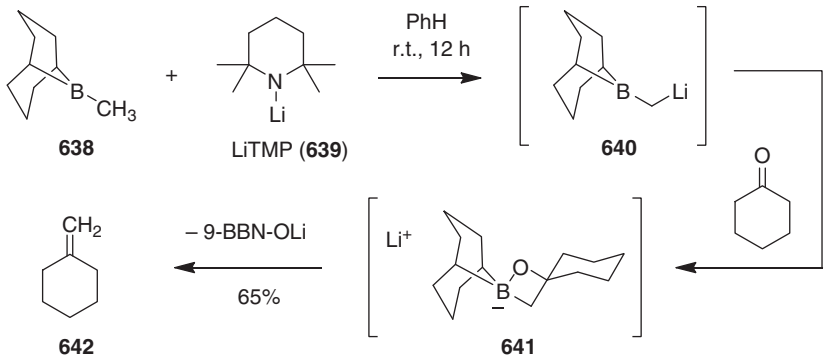
1.15.4.2 Alkene Formation With α-Boryl Carbanions: The Boron-Wittig Reaction

In some regards, the boron-Wittig reaction could be considered as a variant of the Peterson olefination for it is mechanistically closely related to the silicon-mediated process and Scheme 63 above would suffice to describe its broader aspects if viewed with R_2B in place of R_3Si. However, in practice, there are important differences between the two methods and the boron-Wittig reaction has yet to enjoy the prominence of sulfur, phosphorus, or silicon-mediated carbonyl olefinations. The purpose of this short subsection is to reaffirm the conceptual similarities between the various main-group element-mediated olefination processes met so far and to stimulate enthusiasm and reveal possibilities for the promising boron-mediated reaction (Scheme 82).



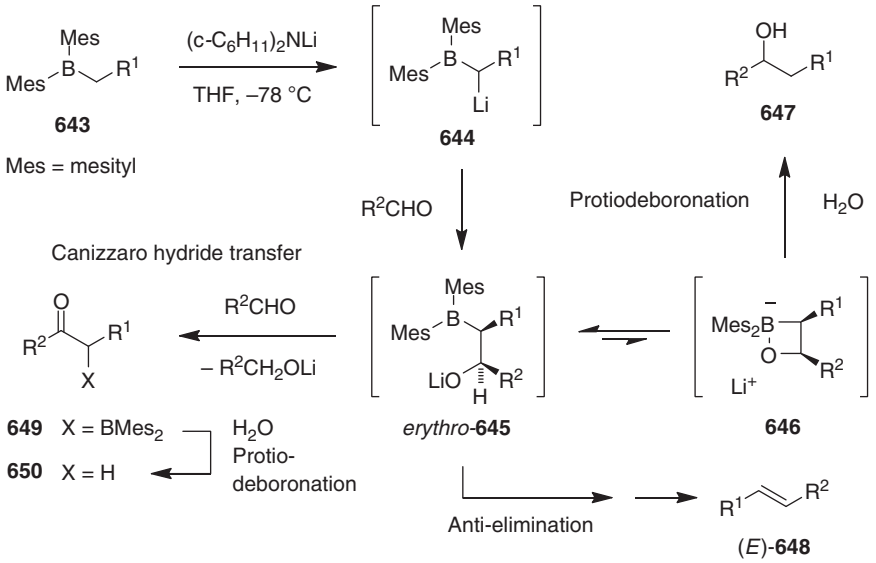
Scheme 82 Generation of α-boryl carbanions (**636**) via deprotonation from organoboron compounds (**635**) is complicated by ate-complex formation (**637**).

The vacant 2p orbital on boron in trivalent organoborons offers significant resonance stabilization to an α-carbanion (**636** ←→ **636′**); however, this defining electronic characteristic can also thwart attempts to generate α-boryl carbanions by deprotonation.[420] Thus, organoborons **635** can readily trap basic species (MY) via ate-complex formation (**637**) rather than experience the desired metallation process. Avoiding this problem by adopting an indirect metallation tactic, Cainelli and coworkers achieved the first successful generation of an α-boryl carbanion by deboronation of a geminal diboron compound by the action of *n*-butylithium.[421] Rathke and Kow later succeeded in the direct α-metallation of an organoboron compound by combining a hindered strong base (lithium 2,2,6,6-tetramethylpiperidide, LiTMP) with a hindered 9-borabicyclo[3.3.1]nonane (9-BBN) derivative (Scheme 83).[422] In the Rathke approach, steric crowding between base and substrate precludes ate-complex formation and allows for deprotonation to occur. The lithiated borane generated in this manner (**640**) was found to be a competent nucleophile and olefinated cyclohexanone in modest yield, presumably via the illustrated boraoxetane intermediate **641**. Unfortunately, this particular boron-Wittig process was not found to be extendable to more complex 9-BBN derivatives.[348b]



Scheme 83 The first successful boron-Wittig reaction by Rathke and Kow.

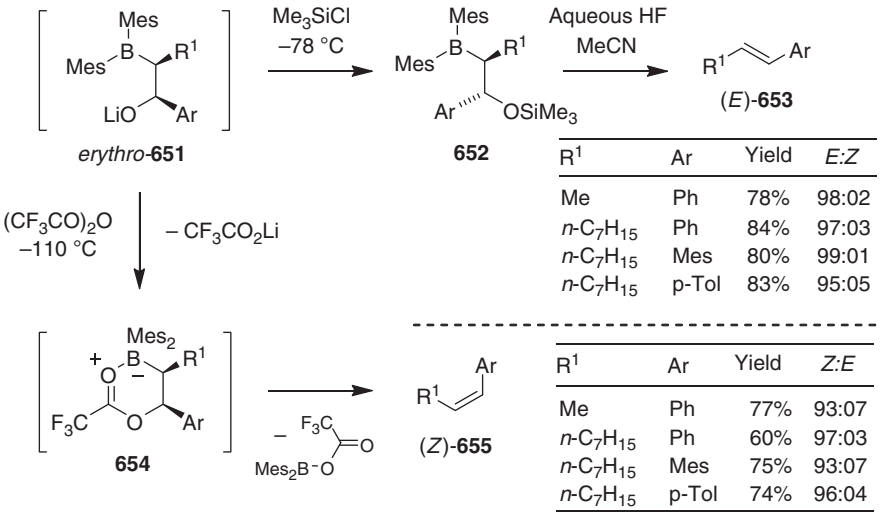
Pelter and coworkers later extensively developed the chemistry of alkyl dimesitylboranes (**643**) which are more hindered than 9-BBN derivatives and can be readily converted to α-boryl carbanions **644** by deprotonation with dicyclohexyllithium amide. In the absence of additives (*vide infra*), the boron-Wittig reactions of metallates **644** only proceed uneventfully for aromatic ketones (e.g., **644** R^1 = Me methylenated benzophenone in >75% yield) but attempts to olefinate other types of carbonyl compounds reveal more complex behavior (Scheme 84).[348b] The reaction between **644** and aldehydes leads to *erythro* β-alkoxyborane adducts (**645**) in high yield and with excellent diastereoselectivity; however, from this point forth a variety of contrary processes compete that lead to a mixture of alkene, ketone, and alcohol products. Given the extreme steric shielding afforded to the boron-atom center in adducts **645**, boraoxetane formation is problematic and alkene products are obtained from *erythro*-**645** via *anti*- rather than *syn*-elimination. Canizzaro-type hydride transfer from **645** to the aldehyde reduces the carbonyl substrate to an alcohol (R^1CH_2OH) and results in an α-borylketone **649** that suffers rearrangement to a boron enolate before protonolysis leading to ketone **650**. Another alcohol product (**647**) arises from protiodeboronation of the putative boraoxetane ate-complex **646**. Through careful mechanistic work, Pelter et al. were able to tame this complex reaction manifold and to control which pathway ultimately dominates from **645** by the use of additives.



Scheme 84 Multiple reaction pathways can stem from the addition of α-dimesitylboryl carbanions (**644**) to aldehydes.

Reactions of aryl aldehydes are steered toward (*E*)-alkenes by trapping of *erythro*-**651** at low temperature with trimethylsilyl chloride (Scheme 85).[348b] Treatment of the resulting silyl ethers (**652**) with aqueous HF in acetonitrile solvent triggers *anti*-elimination and affords (*E*)-alkene products **653** in high overall yield. By contrast, interception of *erythro*-**651** with trifluoroacetic anhydride at −110 °C results in a putative adduct (**654**) capable of *syn*-elimination and this approach provides (*Z*)-alkene products with equally high stereoselectivity. Curiously, neither of these two tactics is effective for comparable reactions involving aliphatic aldehydes which favor the production of ketone adducts **650** rather than alkenes under the same conditions (unless R^1 = Me).[423] Fortunately, it was discovered that high yielding (*E*)-selective boron-Wittig reactions of aliphatic aldehydes are realized by adding a *mixture* of a strong acid additive and the aldehyde substrate to metallates **656** at very low temperature

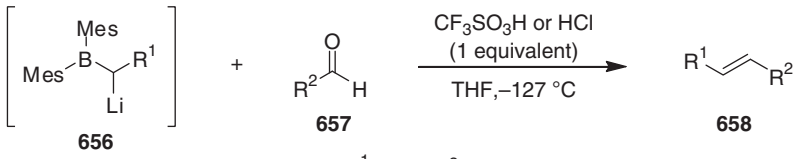
(equation 129).[424] This unusual process limits side-reactions by facilitating protonation of *erythro*-**645** upon its genesis and causes *anti*-elimination via the anticipated acid-mediated pathway (cf. Scheme 64).



R^1	Ar	Yield	*E:Z*
Me	Ph	78%	98:02
n-C_7H_{15}	Ph	84%	97:03
n-C_7H_{15}	Mes	80%	99:01
n-C_7H_{15}	p-Tol	83%	95:05

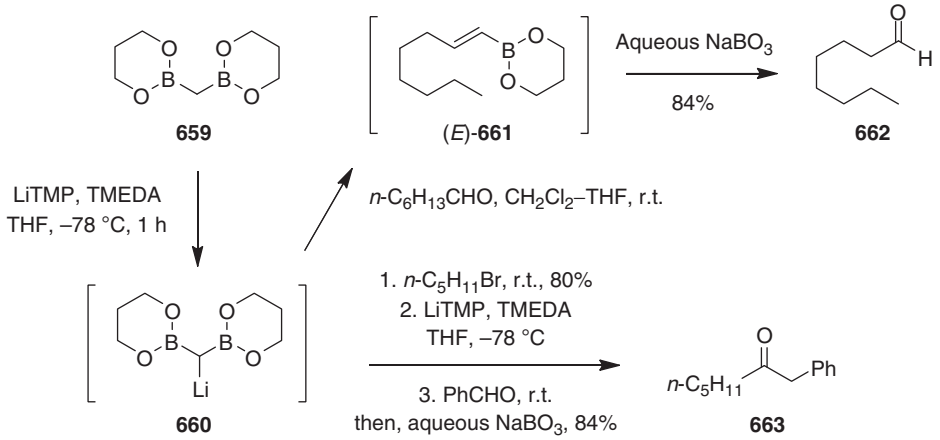
R^1	Ar	Yield	*Z:E*
Me	Ph	77%	93:07
n-C_7H_{15}	Ph	60%	97:03
n-C_7H_{15}	Mes	75%	93:07
n-C_7H_{15}	p-Tol	74%	96:04

Scheme 85 Synthesis of (*E*)- or (*Z*)-styrene derivatives via boron-Wittig reactions of metallated alkyl dimesitylboranes using electrophilic additives.



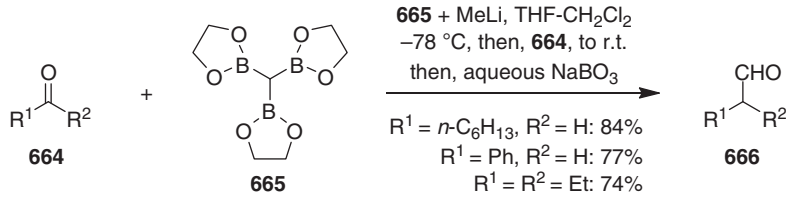
R^1 = Me, R^2 = Bn: 69%, *E:Z* = 93:07
R^1 = Me, R^2 = *c*-C_6H_{11}: 72%, *E:Z* = 97:03
R^1 = *n*-C_7H_{15}, R^2 = Et: 49%, *E:Z* = 91:09
R^1 = *n*-C_7H_{15}, R^2 = *t*-Bu: 72%, *E:Z* = 92:08 (129)

An alternative approach to succeed in the direct generation of α-boryl carbanions via deprotonation is to reduce the Lewis acidity of the boron-atom center (e.g., by moving away from boranes to boron species equipped with lone-pair donor atoms such as boronates) while lowering the pK_a of the α-CH bonds by adding an anion-stabilizing group at carbon. Matteson et al. pioneered this approach to α-boryl carbanions and initially demonstrated its application to geminal diboronic esters (e.g., **659** to **660**, Scheme 86),[425] before doing the same for α-thiophenyl boronates[426] and α-silyl boronates (e.g., equation 116).[368] Metallation of diboronic esters with LiTMP occurs in high yield and the resulting carbanions (e.g., **660**) participate in the boron-Wittig reaction to give vinylboronate products. The carbanion can also be alkylated before subsequent boron-Wittig reaction to yield higher



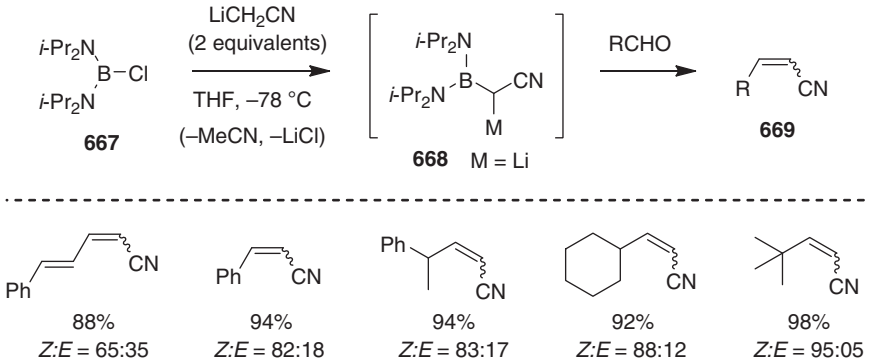
Scheme 86 Synthesis of vinylboronates via boron-Wittig reactions with lithiated bis(1,3,2-dioxaborin-2-yl)methane (**G14**).

substituted vinylboronates. In these particular experiments, primary reaction adducts were oxidatively worked up to afford aldehyde or ketone products; however, in principle, the vinylboronates could be subjected to further carbon–carbon bond-forming processes (e.g., Suzuki–Miyaura cross-coupling). Matteson et al. also established that the same kinds of diboryl carbanions can be conveniently accessed via deboronation of tris(ethylenedioxyboryl)methane (**665**) with methyllithium and in doing so realized a high yielding chain-extension of aldehydes and ketones (equation 130).[427]

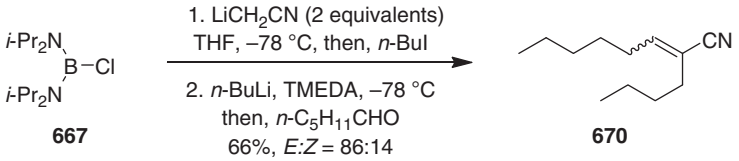


(130)

Tomioka et al. have built on the above principles and devised a readily metallated organoboron reagent (**668**, M=H) that deftly combines an electron withdrawing group on carbon (i.e., cyano) with bulky electron donating amino ligands on boron. The target α-boryl carbanion **668** (M=Li) is most easily assembled *in situ* via the addition of two equivalents of lithioacetonitrile (generated from acetonitrile and *n*-butyllithium) to *bis*(diisopropylamino)boron chloride (**667**). Subsequent addition of aldehydes results in high yielding boron-Wittig reactions that deliver (*Z*)-configured β-substituted acrylonitriles (**Scheme 87**).[428] *Cis* stereoselectivity is heightened as the steric bulk of the aldehyde substituent is increased. In an extension to this useful chemistry, the same group later demonstrated that anion **668** (M=Li) can be alkylated in high yield and then redeprotonated and used to olefinate aldehydes resulting in a one-pot connective synthesis of α,β-disubstituted acrylonitriles.[429] The synthesis of unsaturated cyanide **670**, a precursor to the alarm pheromone of the African weaver ant, is representative (equation 131). Interestingly, in this case, the boron-Wittig reaction favors the (*E*)-configured product but again synthetically useful levels of stereoselectivity are realized. More recently, the Tomioka reaction has been applied to the synthesis of 2-aminoquinolines from **668** (M=Li) and *ortho*-nitrobenzaldehydes.[430]



Scheme 87 Synthesis of (*Z*)-configured β-substituted acrylonitriles by α-boryl carbanions.



(131)

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1.16 Epoxidation and Related Processes

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Glossary

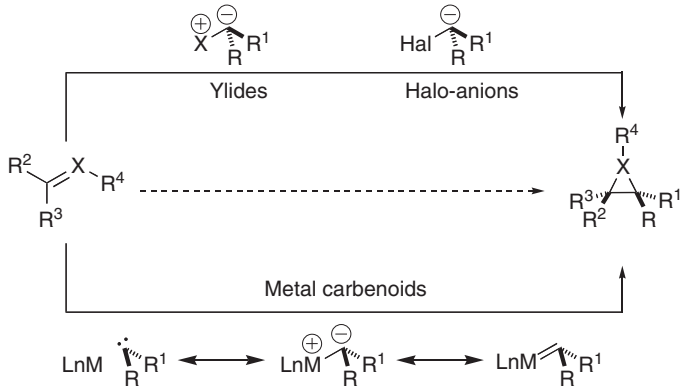
Betaine A type of zwitterion in which positive and negative charges are nonadjacent.
Density functional theory (DFT) A computational modeling method used to describe electronic structure.
Half-sandwich An organometallic complex containing one polyhapto lingand.
Montmorillonite A naturally occurring clay used as a heterogenous catalyst.
Ylide A nucleophilic molecule in which negative charge is located directly adjacent to a positive charge.

1.16.1 Introduction

This chapter concerns itself with the synthesis of epoxides and aziridines by addition of nucleophiles to C═O (aldehyde and ketone) and C═N (imine) bonds. The chapter is organized in an approximately chronological structure and describes advances in the area since 1991,[1] focusing on generally applicable processes and recent seminal advances; the reader is directed to pertinent chapters elsewhere[2] and throughout the text for the details of the research area.

1.16.2 General Considerations

The reactions of leaving group-containing nucleophilic species (Scheme 1) with aldehydes and (to a lesser extent) ketones represent a very satisfactory entry to epoxides, both from the perspective of efficiency (yields are often high) and practicality (e.g., reagents are nonoxidizing unlike those used in methods to prepare epoxides from alkenes). Similar reactions can be used to deliver aziridines from imines and although they are less extensively studied than the corresponding epoxidations, this area of chemical research has been the subject of intense interest of late. Both the target classes are particularly benefited in the recent development of catalytic reactions. Thus, a diverse range of efficient and highly stereoselective methods to deliver practical quantities of chiral epoxides and aziridines are available to a practicing synthetic chemist. For the nitrogenous heterocycles, there remains an additional issue of the precise structure of the *N*-substituent, which has a significant effect on downstream processing (usually ring opening) of aziridines. In particular, the removal of *N*-sulfonyl substituents (often need to ensure maximum yields in the aziridine-forming steps) is usually challenging and there has been a drive to deliver nonsulfonylated aziridines, considerably simplifying end-stage amine unmasking.



Scheme 1

1.16.3 Addition to C═O π-Bonds

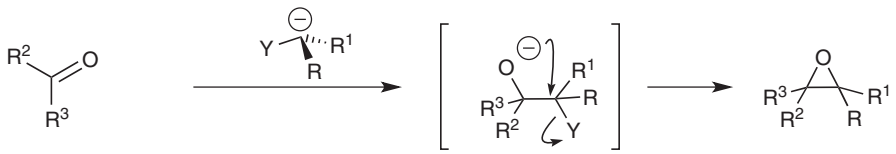
As mentioned in the Section 1.16.2, the addition of nucleophilic reagents to C═O bonds as a means of preparing three-membered heterocycles offers several advantages over other processes, such as there is no requirement to use (often high energy) oxidizing reagents and the reagents are usually stable. Furthermore, epoxidation by nucleophilic addition to C═O bonds creates one C–C and one C–O bond, rather than the two C–X bonds formed during alkene epoxidation, and thus the process is more elegant from a synthetic chemist's perspective.

1.16.3.1 Nonasymmetric Addition Reactions

1.16.3.1.1 Addition of anions of halides and pseudohalides: The Erlenmeyer–Darzens reaction[3]

The first report of epoxide synthesis by addition of anions of α-halocarbonyls to carbonyl compounds was reported by Erlenmeyer,[4] with subsequent reports following from Darzens.[5] Despite this chronology, the reaction is universally known by the latter

name, and the term 'Darzens reaction' is used here to describe the general process. An equivalent reaction is the addition of anions bearing adjacent nonhalogenic leaving groups; it is logical to consider these reactions as a single broad class, as generalized in equation 1.



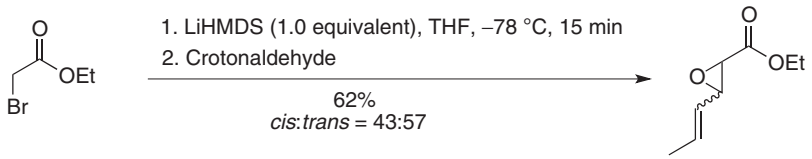
(1)

Y = Cl, Br, I, $\overset{\oplus}{S}R_2$, $\overset{\oplus}{S}(O)R_2$, $\overset{\oplus}{As}R_2$, $\overset{\oplus}{Te}R_2$, $\overset{\oplus}{N}_2$, $\overset{\oplus}{I}Ph$

R or R^1 = $C(O)_nR$, $P(O)_nR_2$, $S(O)_nR$, CN

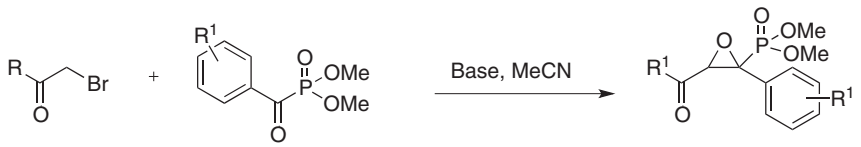
1.16.3.1.1.1 Addition of α-halogen anions

A wide, structurally diverse range of carbonyl compounds undergo Darzens reaction, and the reader is directed to earlier chapters for a detailed coverage.[1,3] Unsaturated carbonyls have infrequently been shown to participate in Darzens-like processes, seemingly due to the wide range of side reactions which occur using these ambient substrates. Notwithstanding this fact, reactions of lithio anions of bromoacetate have recently been shown to react with enals and enones in generally acceptable yields to give vinyl epoxides (equation 2). The reactions typically proceed with little or no stereocontrol.[6]



(2)

Benzoyl phosphonates undergo Darzens reaction with anions of 2-bromoacetophenones to give predominantly *trans*-epoxyphosphonates in acceptable yield (30–68%) (equation 3). The *trans*-products (but not the *cis*-epoxides) may be isomerized to give the opposite diastereomer[7] (**Table 1**).



(3)

Table 1 Epoxyphosphonates by Darzens reaction of acyl phosphonates

R	*R^1*	*Cs_2CO_3*			*DBU*		
		Time (h)	*Yield (%)*	trans:cis	*Time (h)*	*Yield (%)*	trans:cis
Ph	H	4	49	3:2	3	50	8:1
Ph	4-Me	5	54	3:2	5	56	7:1
Ph	3-Me	5	44	2:1	5	45	7:1
Ph	4-Cl	6	48	2:1	4	45	8:1
Ph	3-Cl	8	41	2:1	6	42	6:1
Ph	2-Cl	12	37	2:1	9	30	5:1
Ph	4-OMe	5	63	2:1	5	60	7:1
Ph	4-F	3	69	3:2	2	68	9:1
4-Br-C_6H_4	4-F	7	51	3:2	6	48	8:1
4-C_6H_4-C_6H_5	4-F	8	52	5:3	8	49	8:1
4-Br-C_6H_4	4-OMe	7	46	5:3	6	43	7:1
4-C_6H_4-C_6H_5	4-OMe	8	42	5:3	8	45	7:1

1.16.3.1.1.2 Addition of sulfonium ylides[8]

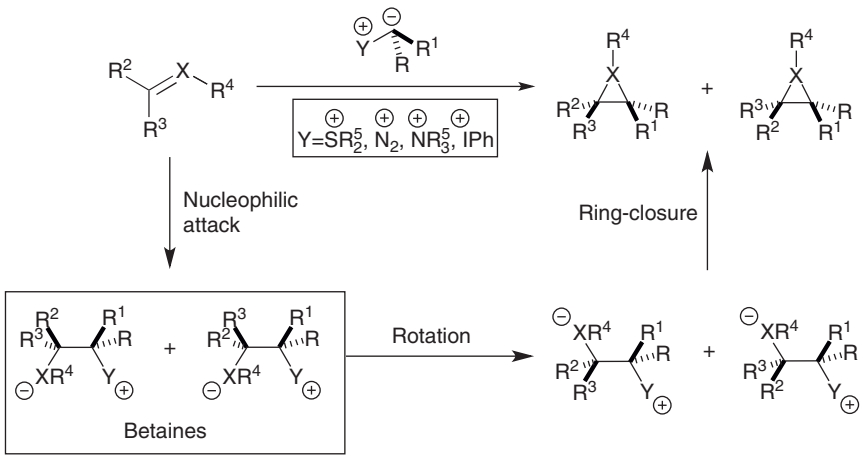
The first report of the use of sulfonium ylides (which may rationally be considered 'pseudohalides,' from the context of this chapter) in epoxide synthesis came in 1961,[9] describing the reactions of 9-(dimethylsulfonium)fluorenylide (a stable, isolable

ylide[10]) with aldehydes. Following this seminal report, the utility of simple sulfur ylides (i.e., where the anion is unstabilized) was quickly established.[11,12]

Although unstabilized and 'semistabilized' (where adjacent nonpolarized multiple bonds, such as benzyl or allyl groups, are adjacent to the anion) sulfonium ylides were shown to be very capable of delivering epoxides from carbonyl compounds, the general use of stable ylide (where the anion is directly stabilized by a resonance-delocalizing group, such as C═X bond) reagents in Darzens reactions was not originally considered feasible, as evidenced by the comment of Ratts and Yao, "stable sulfonium ylides, moreover, are of limited synthetic utility since nucleophilic reactivity is weak and reaction with carbonyl compounds sluggish or nonexistent." In this seminal paper,[13] the authors showed that the precise nature of the anion-stabilizing group was crucial, and they reported that dimethylacetamido sulfonium ylides reacted with benzaldehyde and 4-nitrobenzaldehyde to give *trans*-epoxides in 66% and 64% yield, respectively. This report provided the starting point for what has become one of the most intensely studied areas of epoxide synthesis.

1.16.3.1.1.2.1 General features of epoxide synthesis by addition of ylides to C═O bonds

As alluded in the Section 1.16.3.1.1.2, there are three broad classes of sulfur ylide: stabilized (where the anionic component is adjacent to a strongly resonance-delocalizing group), semistabilized (where the anionic component is adjacent to a moderately resonance-delocalizing group), and unstabilized (where the anion charge is not delocalized to any significant extent). The mechanistic features[14] of the reactions are, therefore, greatly influenced by the nature of the substituents; the general mechanism of the reaction (which apply to any chalcogenonium ylides, as shown) are outlined in **Scheme 2**.



Scheme 2

1.16.3.1.1.2.2 Stabilized ylides

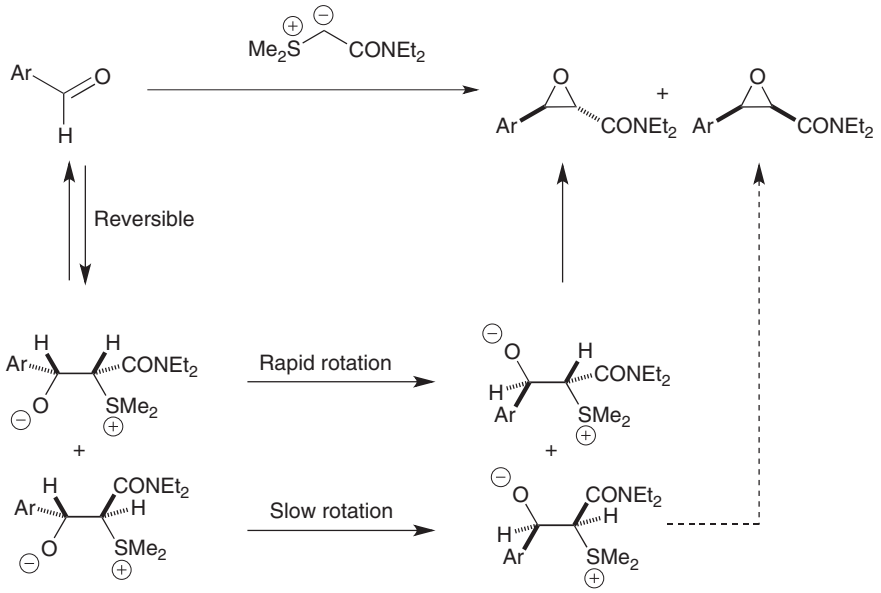
This class of ylides is populated by those having adjacent polarized C═X bonds. The high stability of the anions leads to a corresponding reduction in reactivity, so that ester-stabilized ylides, for instance, are stabilized to the extent that they do not usually[15] interact productively with aldehydes, reacting only with highly activated substrates (such as 1,2-dicarbonyl compounds[16]). Reduced capacity for resonance delocalization destabilizes ylides and increases reactivity, so that α-amido ylides react with aldehydes, giving exclusively disubstituted *trans*-epoxides.[17] The generally accepted mechanism involves three key steps: (1) addition of ylide to the C═O bond to form a betaine, (2) rotation of the betaine into the necessary conformation for cyclization, and (3) 3-*exo*-tet ring closure. In the case of stabilized ylides, the first step is reversible (as shown by crossover experiments) and the key step is rotation of the betaine into the conformation needed for ring closure; for the *anti*-betaines, there is a lower energy barrier to rotation and so the *trans*-epoxide is delivered (**Scheme 3**).

1.16.3.1.1.2.3 Semistabilized ylides

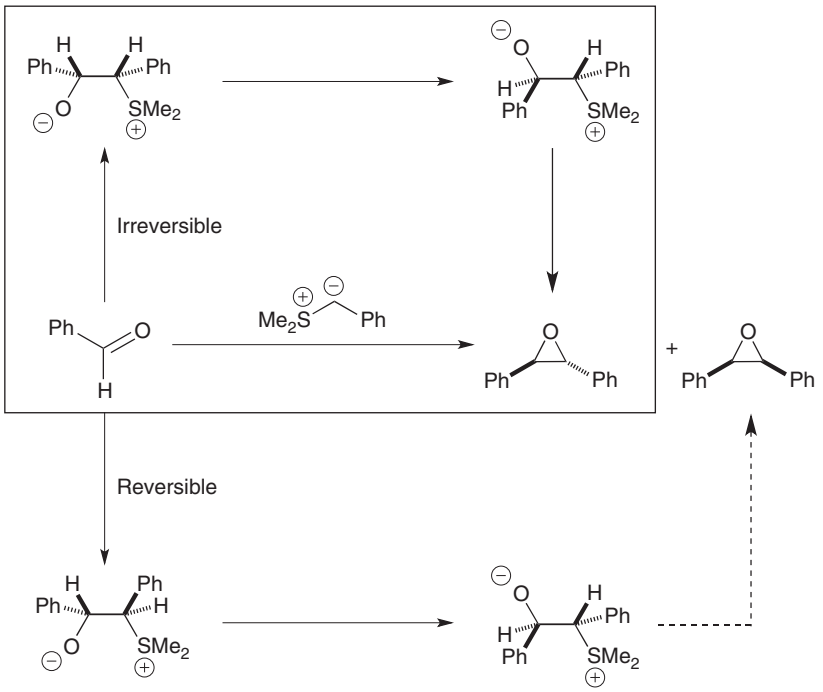
This class of ylides comprises reagents with adjacent nonpolarized C═X bonds, such as those of benzyl or allyl moieties. The anionic component of these ylide is only weakly delocalized and so the reagents are higher in reactivity. Semistabilized ylides react with aldehydes to give epoxides, but the stereocontrol of the reactions is under the control of a number of factors. Crossover experiments[18] confirm that in the reaction of benzaldehyde, the *anti*-betaine is formed irreversibly but the *syn*-betaine is formed reversibly, leading to preferential accrual of *trans*-epoxide (**Scheme 4**). The proposed mechanism was confirmed by Density functional theory (DFT) calculations.[19]

1.16.3.1.1.2.4 Unstabilized ylides

This class of ylides contains an anionic component which is unstabilized and highly reactive. The reaction of these species with aldehydes is irreversible and the stereochemistry of the intermediate betaines is dependent on the direction of attack on the C═O



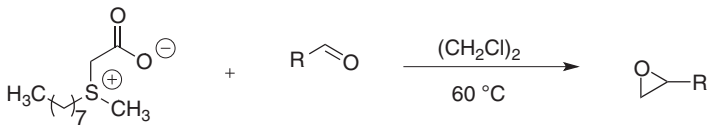
Scheme 3



Scheme 4

bond. These reactions often are unselective; testament to this fact is the observation that enantiocontrol in such process is a challenging goal, with unsubstituted chiral sulfur ylides inducing virtually no *ee* in reaction with aldehydes.[20]

The majority of reported achiral Darzens reactions using sulfonium ylides employ preformed sulfonium salts as precursors to the key ylides, which are formed by deprotonation. There is a base-free catalytic method to access sulfonium ylides from sulfoniums, involving decarboxylation of 2-sulfonium acetates (equation 4, Table 2).[21]



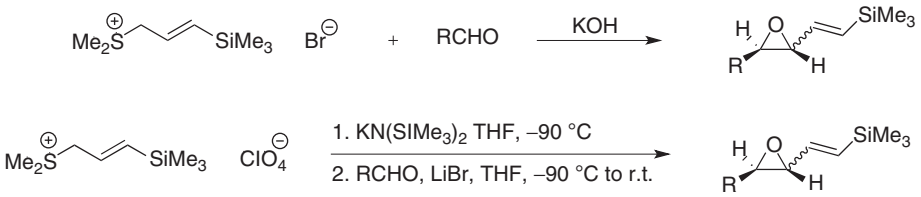
(4)

Table 2 Sulfur ylides by decarboxylation of 2-sulfonium acetates

R	*Yield (%)*
2,5-Cl-C_6H_3	85
4-NO_2-C_6H_4	84
4-Cl-C_6H_4	62
Ph	55
$PhCH_2CH_2$	45

Vinyl epoxides are versatile synthetic intermediates undergoing a range of useful ring-opening reactions, but access to these species using sulfonium ylides is complicated by competing [2,3]-sigmatropic rearrangement.[22] To circumvent this hindrance, arsonium[23] and telluronium ylides[24] have been used to prepare vinyl epoxides, but the reagents have numerous issues which limit their desirability to the practicing synthetic chemist, and recent studies have been confined predominantly to circumventing the possible rearrangement side reactions.

Hou et al. reacted (3-silyl)allyl sulfonium salts with aldehydes to give (2′-silyl)vinyl epoxides in good yields.[25] The diastereoselectivity of the reaction depended on the sulfur substituent: diphenylsulfoniums gave predominantly *cis*-epoxides (*cis*:*trans* = 80-95:20-5), whereas dimethylsulfoniums favored *trans*-products (*cis*:*trans* = 2-20:98:80) (equation 5, **Table 3**).

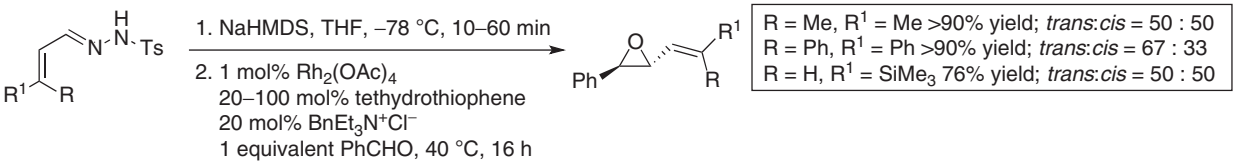


(5)

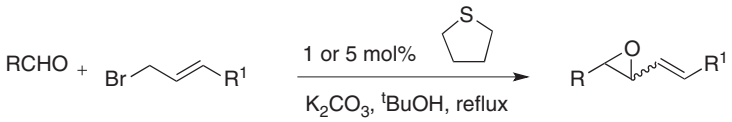
Table 3 Vinyl epoxide synthesis using preformed allylsulfonium ylides

Counter-ion	*R*	*Yield (%)*	trans:cis
Bromide	4-Cl-C_6H_4	95	98:2
Perchlorate	4-Cl-C_6H_4	96	6:94
Bromide	Ph	91	87:13
Perchlorate	Ph	96	15:85
Bromide	4-Br-C_6H_4	91	82:18
Perchlorate	4-Br-C_6H_4	95	14:86
Bromide	4-Biphenyl	84	80:20
Perchlorate	4-Biphenyl	93	7:93
Bromide	3-Pyridyl	91	87:13
Perchlorate	3-Pyridyl	81	5:95
Bromide	2-Naphthyl	84	80:20
Perchlorate	2-Naphthyl	92	8:92
Bromide	4-F-C_6H_4	88	98:2
Perchlorate	4-F-C_6H_4	88	12:88
Perchlorate	Cyclohexyl	85	20:80

Sulfide precursors to sulfonium salts which are used to access ylides are often unpleasant to handle; hence, contemporary methods often take advantage of the fact that the sulfide is regenerated at the end of ylide epoxidation to allow for *in situ* generation of the key sulfonium intermediates. This allows the use of substoichiometric sulfide, which reacts with an electrophile (halide or triflate) to generate the sulfonium species. Aggarwal used substochioimetric tetrahydrothiophene in his carbenoid capture process (*vide infra*) to prepare vinyl epoxides in moderate *de* (*trans*:*cis* = 50-67:50-33) (equation. 6),[26] whereas Tang et al. accessed these compounds using tetrahydrothiophene sulfonium ylides derived from allylic bromides.[27] The latter reactions also exhibited mediocre stereoselectivity (*trans*:*cis* = 50-76:50-24) (equation 7, **Table 4**).



(6)



(7)

Table 4 Vinyl epoxide synthesis by *in situ* sulfonium ylide formation

Loading (mol%)	*R*	*R¹*	*Yield (%)*	cis:trans
1	4-Cl-C_6H_4	H	94	36:64
1	4-NO_2–C_6H_4	H	85	33:67
1	Ph	H	96	38:62
5	4-OMe·C_6H_4	H	85	30:70
5	*n*-C_9H_{19}	H	75	55:45
1	4-Cl-C_6H_4	TMS	83	25:75
1	Ph	TMS	89	24:76
1	4-NO_2–C_6H_4	TMS	85	30:70
1	2-Cl-C_6H_4	TMS	85	27:73
5	*n*-C_9H_{19}	TMS	88	42:58
5	*cyclo*-C_6H_{11}	TMS	78	50:50

Abbreviation: TMS, trimethylsilyl.

Achiral 2-(trialkylammonium)acetamides react with aromatic aldehydes under phase-transfer conditions to give glycidamides in generally good yields.[28] Reactions with aliphatic aldehydes are less efficient (reported as proceeding in zero and 54% yield).[29]

1.16.3.2 Asymmetric Epoxidation by Addition to C=O Bonds

1.16.3.2.1 Asymmetric addition of α-halogen anions

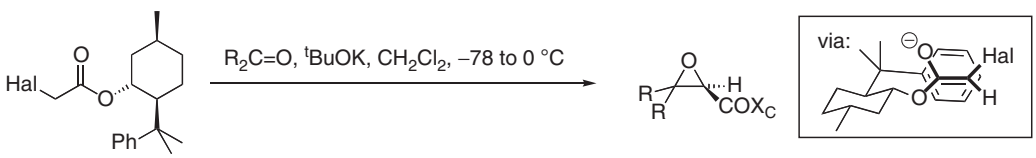
There has been a significant increase in the study of asymmetric reactions of aldehydes and (to a much smaller extent) ketones with 2-haloenolates and equivalents in the contemporary literature; the methods reported can be divided into two classes, those involving stoichiometric processes and those which are substoichiometric (often, misleadingly, termed 'catalytic').

1.16.3.2.1.1 Stoichiometric methods

1.16.3.2.1.1.1 Darzens reactions using chiral auxiliaries

The first reported Darzens reaction of a chiral ester came from Nozaki and coworkers.[30] Thus, (−)-menthyl and (+)-bornyl esters of chloroacetic acid were reacted with acetophenone to give a product which was not characterized but instead converted to known diols; the inferred *ee* of the reactions were 15% (for the menthyl ester) and 5% (for the bornyl ester).

(−)-8-Phenylmenthyl and (−)-menthyl esters of bromo and chloroacetic acid were subsequently reported to undergo Darzens reaction with benzaldehydes and ketones in variable yield (18–97%). The process generally delivers *cis*-epoxides but inconsistently, with *cis*:*trans* ratios being highly variable; face selectivities of the reaction were also variable, with ketones reacting with best selectivity (*dr* <10% to >95%). Benzaldehyde gave product of low *dr* (29–63%) (equation 8 and **Table 5**).[31] As often observed in reactions using menthyl auxiliaries, the face selectivity of the (*Z*)-enolate is controlled by the 8-phenyl substituent, with a π–π interaction stabilizing the enolate and shielding the *Re* face so that nucleophilic attack occurs preferentially from the enolate's *Si* face.



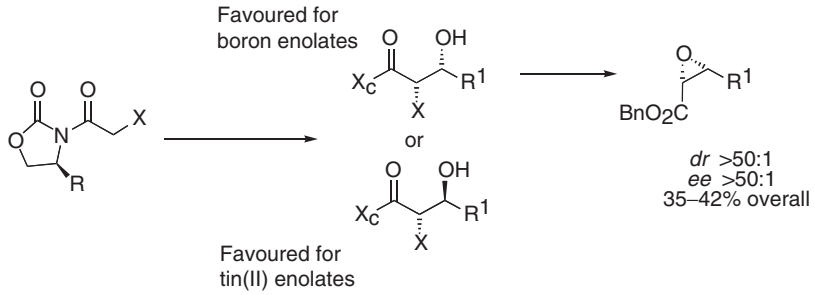
(8)

Asymmetric aldol methodology has been used to access chiral 2-carboxyepoxides. However, 2-halo-3-hydroxyesters, the aldol products derived from haloacetates, often exhibit reluctance to cyclize to the desired epoxide product.[32] Thus, Lantos et al. found

Table 5 Asymmetric Darzens reaction using menthyl bromoesters

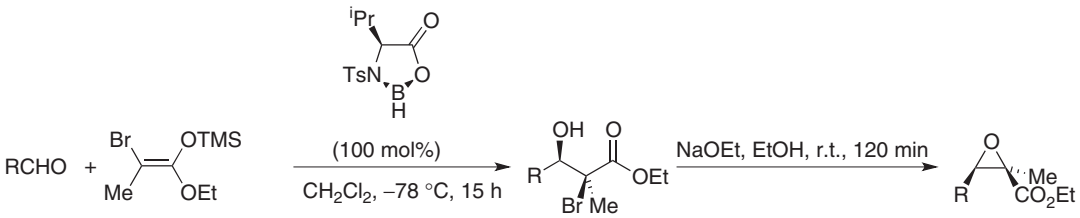
Hal	R^1	R^2	*Ketone*	*Yield (%)*	cis:trans	de *(%)*	
						cis	trans
Cl	H	Me	Acetophenone	66	1.0:1.3	–	–
Cl	H	(–)-Menthyl	Propiophenone	58	1.0:1.4	–	–
Cl	H	(–)-Menthyl	Acetophenone	83	8.3:1.0	38	<10
Cl	H	(–)-8-Phenylmenthyl	Acetophenone	79	7.6:10	93	52
Br	H	(–)-8-Phenylmenthyl	Acetophenone	56	5.6:1.0	>95	21
Cl	H	(–)-8-Phenylmenthyl	Propiophenone	47	4.5:1.0	87	78
Br	H	(–)-8-Phenylmenthyl	Propiophenone	43	4.2:1.0	>95	>95
Cl	H	(–)-Menthyl	Acetone	39	–	14	
Cl	H	(–)-8-Phenylmenthyl	Acetone	64	–	87	
Cl	H	(–)-8-Phenylmenthyl	Pentan-3-one	47	–	81	
Cl	H	(–)-8-Phenylmenthyl	Cyclopentanone	45	–	80	
Cl	H	(–)-8-Phenylmenthyl	Cyclohexanone	45	–	96	
Cl	H	(–)-8-Phenylmenthyl	Benzophenone	45	–	77	
Br	Me	(–)-8-Phenylmenthyl	Cyclohexanone	18	–	36	

that Evans' chiral oxazolidinone derivatives of chloroacetic acid gave the halohydrin, not the epoxide, on aldol reaction.[33] Only on treatment with benzyloxylithium was the Darzens product obtained (Scheme 5).



Scheme 5

cis-Epoxides are obtained in a two-step process featuring *S*-valine-derived oxazaborolidinone X (used in stoichiometric amounts and prepared *in situ*). This chiral controller mediates aldol reaction of 2-bromo silylketene acetals with aromatic and aliphatic aldehydes. *syn*-Aldols are the major products of the reactions, which give *cis*-epoxides on treatment with NaOEt (Scheme 6 and Table 6).[34]

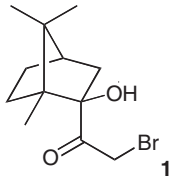


Scheme 6

Table 6 Asymmetric reagent-controlled Darzens reaction using oxazaboroldinones

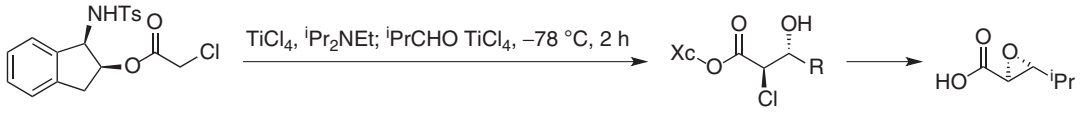
R	trans:cis	ee (trans) *(%)*	*Yield (%)*
Ph	7:1	95	87
$PhCH_2CH_2$	9:1	96	81
^{i}Pr	16:1	97	74
^{n}Pr	10:1	98	78
$TBSOCH_2CH_2$	15:1	95	93

Camphor-derived bromoketones **1** undergo highly selective Darzens reaction with aryl aldehydes to give *trans*-epoxides (*de* ≥97:3); reactions with aliphatic aldehydes are generally less stereoselective and favor *cis*-isomers. The auxiliary must be removed destructively using ceric ammonium nitrate (CAN).[35]



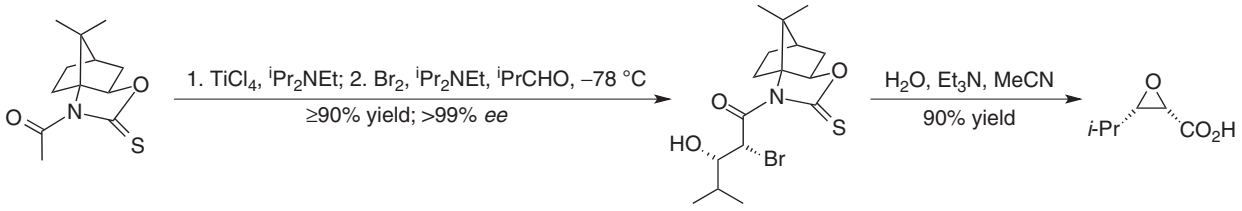
1

Chloroacetyl derivatives of 1R, 2S-indanol undergo stereoselective aldol reaction with aldehydes in good yield; the product halohydrins may be converted separately to chiral epoxides in good yield. Where the aldehyde does not have a substituent capable of chelation, *trans*-epoxides are obtained (via *anti*-aldol products); whereas bidentate substrates lead to *cis*-epoxides (via *syn*-halohydrins) (Scheme 7).[36]



Scheme 7

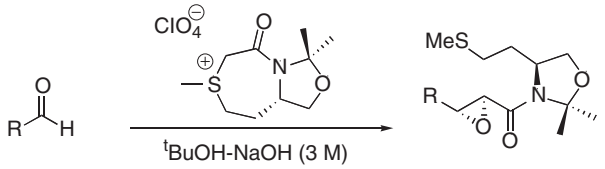
Thiocarbonyl camphor derivatives can be used in asymmetric Darzens reactions. The intermediate haloalcohols do not spontaneously cyclize until treated with aqueous base, whereupon corresponding *cis*-epoxy acids are obtained (Scheme 8).[37] The method offers complementary selectivity compared with sulfonium ylide epoxidation methods, where the *trans*-epoxide typically predominates.



Scheme 8

Pseudoephedrine-derived sulfonium amides react with aromatic and aliphatic aldehydes in good yield and with variable *ee* (33–94%).[38] Analogous *α*-phenylethylamine sulfonium ylides react with aldehydes to give chiral *cis*-glycinamides of poor *de* (≤73:27), but the method was used to prepare both enantiomers of Reboxetine®, a marketed treatment for depressive disorders.[39]

Chiral 3-thionium lactams[40] undergo efficient Darzens reaction with a diverse range of aromatic, hetaryl, and aliphatic aldehydes to give *trans*-glycinamides in good yield and with >98% *de* (equation 9 and Table 7).[41]



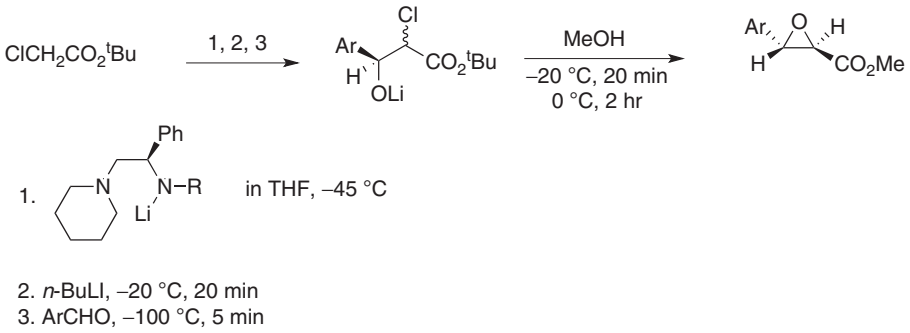
(9)

1.16.3.2.1.2 Chiral reagents

Koga et al. used their chiral lithium amide methodology to carry out diastereo- and enantioselective Darzens reactions of ^{t}butyl chloroacetate with a range of aryl aldehydes.[42] The reactions require very low temperature (−100 °C) and proceed in good yield to give *trans*-epoxides in 58–84% *ee*. In mechanistic terms, the process is complex; on quench with MeOH, the methyl ester is the product of the reaction, and asymmetric induction is dependent on addition of one equivalent of ^{n}BuLi to the reaction after the addition of the amide base (Scheme 9 and Table 8).

Table 7 Asymmetric sulfonium ylide epoxidation using sulfonium lactams

Aldehyde	*Yield (%)*	de *(%)*
4-$NO_2C_6H_4CHO$	84	>98
3-IC_6H_4CHO	82	>98
2,6-$(Me)_2CHO$	46	>98
1,3-OHC_6H_4CHO	58	>98
PhCH2CHO	74	>98
$CH_3(CH_2)_{10}$	56	>98
$CH_3(CH_2)_{14}CHO$	47	>98
2-Methylpropenal	70	>98

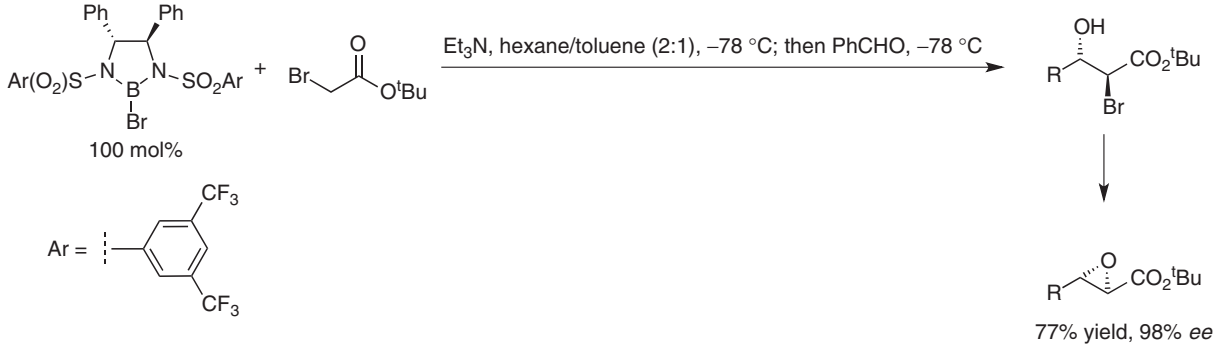


Scheme 9

Table 8 Asymmetric Darzens reaction using chiral base

R	*Ar*	*Yield (%)*	ee *(%)*
^iPr	Ph	74	79
Et	Ph	74	79
n-C_7H_{15}	Ph	78	77
$CH_2CH_2CHMe_2$	Ph	76	81
C_2H_4OMe	Ph	62	58
n-$C_5H_{10}OMe$	Ph	54	78
$CH_2CH_2CHMe_2$	4-OMe-C_6H_4	53	80
$CH_2CH_2CHMe_2$	4-Cl-C_6H_4	69	72

Corey and Kim reported bromodiazaborolanes as chiral mediator of aldol reactions of bromoesters with aldehydes, giving *anti*-bromohydrins in excellent yield;[43] on treatment with base, these products could efficiently be converted to *trans*-epoxides (Scheme 10).[44]



Scheme 10

Enantiomerically pure Cr(IV) complexes of 2-methylbenzaldehyde undergo asymmetric Darzens reaction with the enolate of (chloromethyl)phenyl ketone under phase-transfer conditions to give *trans*-epoxides in acceptable yield but with variable *ee*.[45]

1.16.3.2.1.3 Catalytic methods

1.16.3.2.1.3.1 Asymmetric Darzens reactions using chiral phase-transfer catalysis

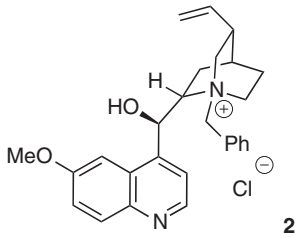
Phase-transfer catalysis[46] (PTC) has been widely used to good effect in asymmetric Darzens reactions. The processes generally involves reaction of 2-chloroanions with aldehydes in the presence of an ammonium salt and in a biphasic medium consisting of a nonprotic organic solvent and aqueous base (carbonate or hydroxide are most widely used). Even in achiral reactions, the nature of the ammonium salt is important, with changes in the catalyst structure leading to significant variations in yield and diastereoselectivity.[47]

1.16.3.2.1.3.2 Ephedrine-derived PTCs

One of the earliest reports of asymmetric catalytic Darzens reactions described the use of chiral ephedrine-derived ammonium salts as mediators of the addition of nonstabilized sulfonium ylides to benzaldehyde.[48] However, the processes exhibited questionable and generally low stereoselectivity.[49] Darzens reaction of anion of chloromethylsulfones with aliphatic and aryl aldehydes and ketones in the presence of ephedrine-derived ammonium salts gave 2-sulfonyl epoxides in good yield, but with low *ee* (≤23%).[50] Both soluble and polymer-bound (Biobeads, a polystyrene–vinylbenzene polymer) catalyst were used in the transformations.

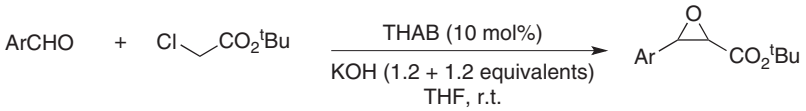
1.16.3.2.1.3.3 Cinchona-derived PTCs

Hummelen and Wynberg reported the use of quininium benzylchloride ('QUIBEC', **2**) as a chiral catalyst for Darzens reaction of phenacyl chloride with 4-chlorobenzaldehyde; the reaction again proceeded with little enantiocontrol (approximately 8% *ee* observed); the diastereomeric preference is not specified.[51]



2

Arai and coworkers have made extensive contributions in the area of PTC-catalyzed reactions. Darzens condensations of α-chloro ^{t}butyl acetate with aromatic aldehydes may be carried out in the presence of powdered potassium hydroxide and tetrahexylammonium bromide, giving *Z*-glycidates in modest yield (equation 10 and **Table 9**).[52] This reaction has been reported to involve the intermediacy of a mixture of *E*- and *Z*-products, the rapid hydrolyzes of the *E*-isomer leading to an apparently *Z*-selective process.[53]

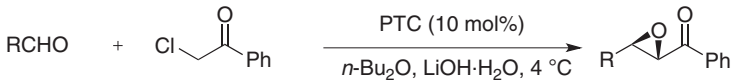


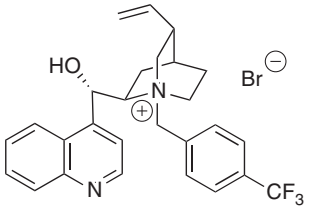
(10)

Table 9 Darzens condensation of α-chloro ^{t}butyl acetate with aromatic aldehydes

Aldehyde	*Time (h)*	*Yield (%)*
α-Naphthyl	25	54
2-Cl-C_6H_4	23	43
Ph	22	52
4-Me-C_6H_4	24	59
4-CF_3-C_6H_4	23	36
4-NO_2-C_6H_4	27	31

Arai and Shiori observed that commercially available quinidine-derived (4-trifluoromethyl)benzyl cinchonium salts catalyzed asymmetric Darzens reaction of phenacyl chloride with aldehydes to deliver *trans*-epoxy ketones with moderate enantioselectivity (42–79% *ee*) (equation 11 and **Table 10**).[54] Cyclic chloroketones give epoxides of higher enantiopurity (50–86% *ee*).[55]





PTC

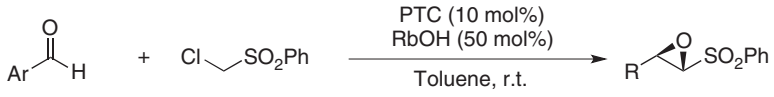
(11)

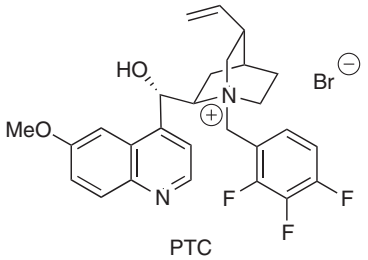
Table 10 Cinchonium salt-catalyzed asymmetric Darzens condensation

R	*Time (h)*	*Yield (%)*	ee *(%)*
^{i}Pr	60	80	53
Et	117	32	79
n-Pr	60	82	57
^{i}Bu	134	73	69
$^{i}BuCH_2$	91	50	62
Et_2CHCH_2	117	76	58
$Ph(CH_2)_2$	114	83	44
c-Hex	61	47	63
Ph	69	43	42

In the reaction of acyclic chloroketones, the authors suggest that the process is actually a kinetic resolution of the racemic aldol products, wherein only the 1R,2R-diastereomer cyclizes rapidly to give the observed products.[56]

In the presence of pseudoenantiomeric quinine-derived ammonium salts, the same group showed that chloromethyl sulfones undergo asymmetric Darzens reaction with aldehydes to give *cis*-sulfonyl epoxides in good yield and with 64–81% *ee* (equation 12 and **Table 11**).[57] These conditions could also be applied to reaction of ketones, but as yields were acceptable, stereoselectivities were low.[58]





PTC

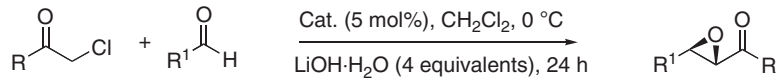
(12)

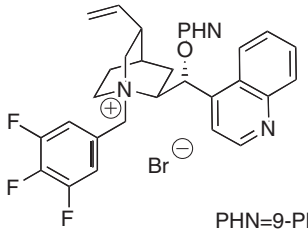
Chloromethyl sulfones react with aromatic aldehydes in the presence of 2,3,4-trifluorobenzyl-incorporated 9-hydroxy cinchona PTCs to give *trans*-α,β-epoxysulfones in good yields and with 71–97% *ee*.[59]

6′-Hydroxy cinchona salts mediate a highly enantioselective Darzens reaction of chloroacyl arenes and aromatic aldehydes. Thus, *trans*-epoxy ketones are isolated in excellent yield and with generally greater than 90% *ee* (equation 13 and **Table 12**). Cyclic chloroketones react with similar yields and enantioselectivities, although a higher (10 vs. 5 mol%) loading is required (equation 14 and **Table 13**).[60]

Table 11 Quninium-catalyzed Darzens reaction

Ar	*Time (h)*	*Yield (%)*	ee *(%)*
Ph	8	91	90
4-Me-C_6H_4	8	90	87
4-^{i}Pr-C_6H_4	10	93	93
4-^{i}Bu-C_6H_4	10	83	86
4-^{t}Pr-C_6H_4	8	81	97
4-Ph- C_6H_4	3	93	77
3-Me-C_6H_4	6	95	80
4-Cl-C_6H_4	8	91	71
4-Br-C_6H_4	4	91	72
3,5-(^{t}Bu)$_2$-C_6H_3	10	80	82
2-Naphthyl	3	92	74





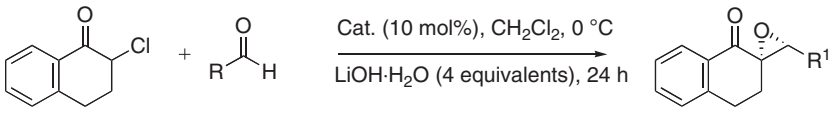
PHN=9-Phenthracenyl

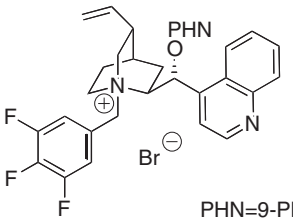
Cat

(13)

Table 12 6′-Hydroxy cinchonium-catalyzed Darzens reaction of chloroketones

R	*R*^{1}	*Yield (%)*	ee *(%)*
Ph	Ph	94	96
Ph	4-Cl-C_6H_4	96	96
Ph	3-Cl-C_6H_4	92	90
Ph	4-Br-C_6H_4	90	95
4-F-C_6H_4	2-Naphthyl	93	97





PHN=9-Phenthracenyl

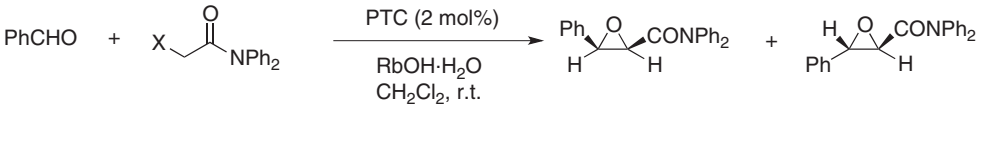
Cat

(14)

Table 13 6′-Hydroxy cinchonium-catalyzed Darzens reaction of cyclic chloroketones

R	*Yield (%)*	ee *(%)*
Ph	92	90
4-Cl-C_6H_4	91	93
3-Cl-C_6H_4	95	91
2-Cl-C_6H_4	96	94
2-Nap	96	97

Asymmetric Darzens reactions of haloacetamides are catalyzed by axially chiral binapthyl derived bisammonium salts; the enantioselectivities of the reactions are modest (equation 15).[61]



X = Cl : 81% (*cis*:*trans* = 3.5:1)
52% *ee* (*cis*; 51% *ee* (*trans*)
X = Br : 81% (*cis*:*trans* = 2.3:1)
58% *ee* (*cis*); 63% *ee* (*trans*) (15)

Chiral glucose-derived mono-aza crown ethers mediate asymmetric Darzens condensation of phenacyl chloride with aryl aldehydes (Table 14).[62] In most cases, the enantiomeric excess of the products is modest, but reaction of benzaldehyde with phenacyl chloride gives the epoxide product with 96% *ee*.[63]

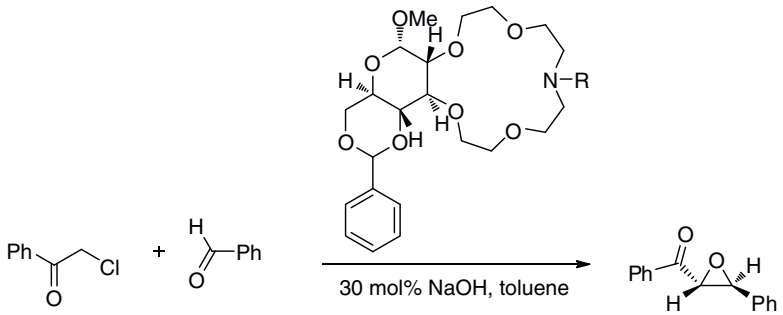


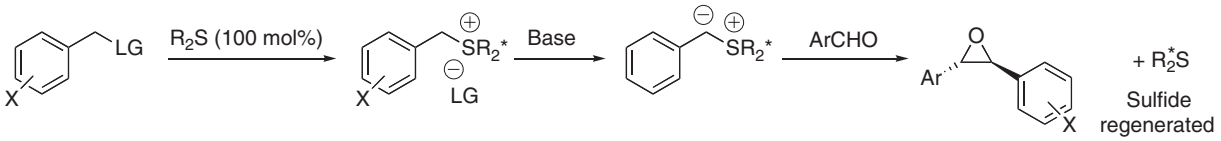
Table 14 Crown ether-catalyzed Darzens reaction

R	*Temperature (°C)*	*Time (h)*	*Yield (%)*	ee *(%)*
n-Butyl	22	4	74	21
Ph	22	1	43	4
Bn	22	1	67	13
$PhCH_2CH_2$	22	6	54	31
CH_2CH_2OH	22	1	90	42
CH_2CH_2OH	−5	2	88	59
CH_2CH_2OH	−20	4	76	64
$(CH_2)_3OH$	22	1	74	62
$(CH_2)_3OH$	−20	1	49	71
$(CH_2)_4OH$	22	1	65	26
$CH_2CH_2O\ CH_3$	22	1	59	19
CH_2CH_2OH	−20	3	44	39

1.16.3.3 Asymmetric Addition of Ylides

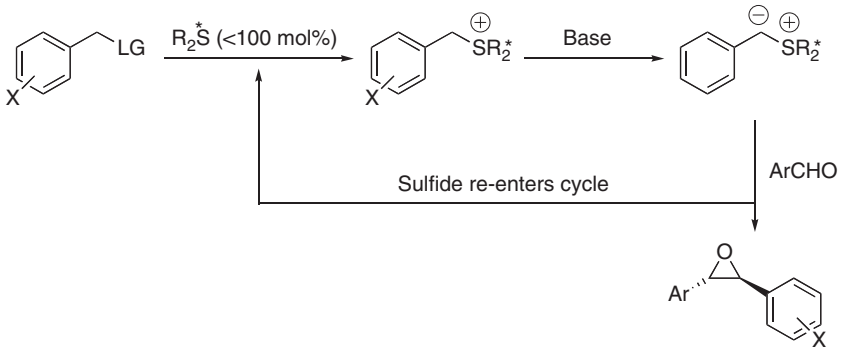
1.16.3.3.1 Chiral sulfonium ylides

The use of sulfonium ylides in asymmetric epoxidation of carbonyl compounds has been the subject of intense interest amongst contemporary researchers. The first reports described processes using stoichiometric amounts of chiral sulfoniums, which were either preformed or prepared *in situ* from chiral sulfides (Scheme 11).



Scheme 11

The sulfides could be considered to be acting as catalysts in these processes; thus, recent reports have focused on substoichiometric sulfide use (Scheme 12). This is of particular importance for asymmetric epoxide synthesis, where the chiral sulfoniums needed for the reactions are precious and substoichiometric methods are of correspondingly greater significance.



Scheme 12

1.16.3.3.1.1 Mechanistic features of epoxide synthesis using chiral sulfur ylides

Sulfonium ylide additions to C═O bonds all feature nucleophilic attack of the ylide on the C═O bond, followed by 3-*exo*-tet ring closure (*vide supra*), but the asymmetric methods often involve delicately balanced equilibria and there are often mechanistic subtleties which a cursory analysis will not detect. The reader is, therefore, urged to tread cautiously when considering the underlying reasons for stereoinduction in these processes. The generally accepted mechanism involves three key steps: (1) addition of ylide to the C═O bond to form a betaine, (2) rotation of the betaine into the necessary conformation for cyclization, and (3) 3-*exo*-tet ring closure. The desirable attributes of these reactions, high diastereo- and enantiocontrol, are controlled by the relative rates of the key steps[14]: high reversibility in the betaine-forming step leads to high diastereoselectivity but low enantioselectivity, whereas irreversible betaine formation leads to low diastereoselectivity and high enantioselectivity. The ideal reaction (exhibiting both high diastereoselectivity and enantioselectivity) demands irreversible formation of the *anti*-betaine and reversible formation of the *syn*-betaine.

The diverse and dense literature of asymmetric epoxide synthesis using chiral sulfonium ylides has been well reviewed;[64] Chart 1 summarizes some of the key reactions described in the recent literature.

As with many other areas of asymmetric synthesis, terpene-derived sulfonium ylides have been widely studied in stoichiometric asymmetric Darzens reactions. Furukawa et al. reported the use of camphor-derived sulfide in a catalytic Darzens reaction in 1989,[65] but the process was low yielding and poorly stereoselective.

Eliel's oxathiane **3** (available on scale from pulegone) is converted to the corresponding chiral benzyl sulfonium, which undergoes asymmetric Darzens reaction with aryl aldehydes to give *trans*-1,2-diarylepoxides generally in good yield and with excellent *ee* (Scheme 13).[66] The chiral sulfide **3** is recovered unchanged at the end of the process.

The method has been used to prepare the adrenergic compounds (*R*)-(−)-DCI and (*R*)-(−)-pronethalol[67] and can also be used to prepare 2-alkenyl-1-aryl epoxides[68] and hetaryl products.[69]

The majority of reports of Darzens-like asymmetric epoxidations describe the preparation of disubstituted epoxides. However, Aggarwal et al. reported the preparation of trisubstituted products (in generally >90% *dr* and >90% *ee*) using stochiometric chiral

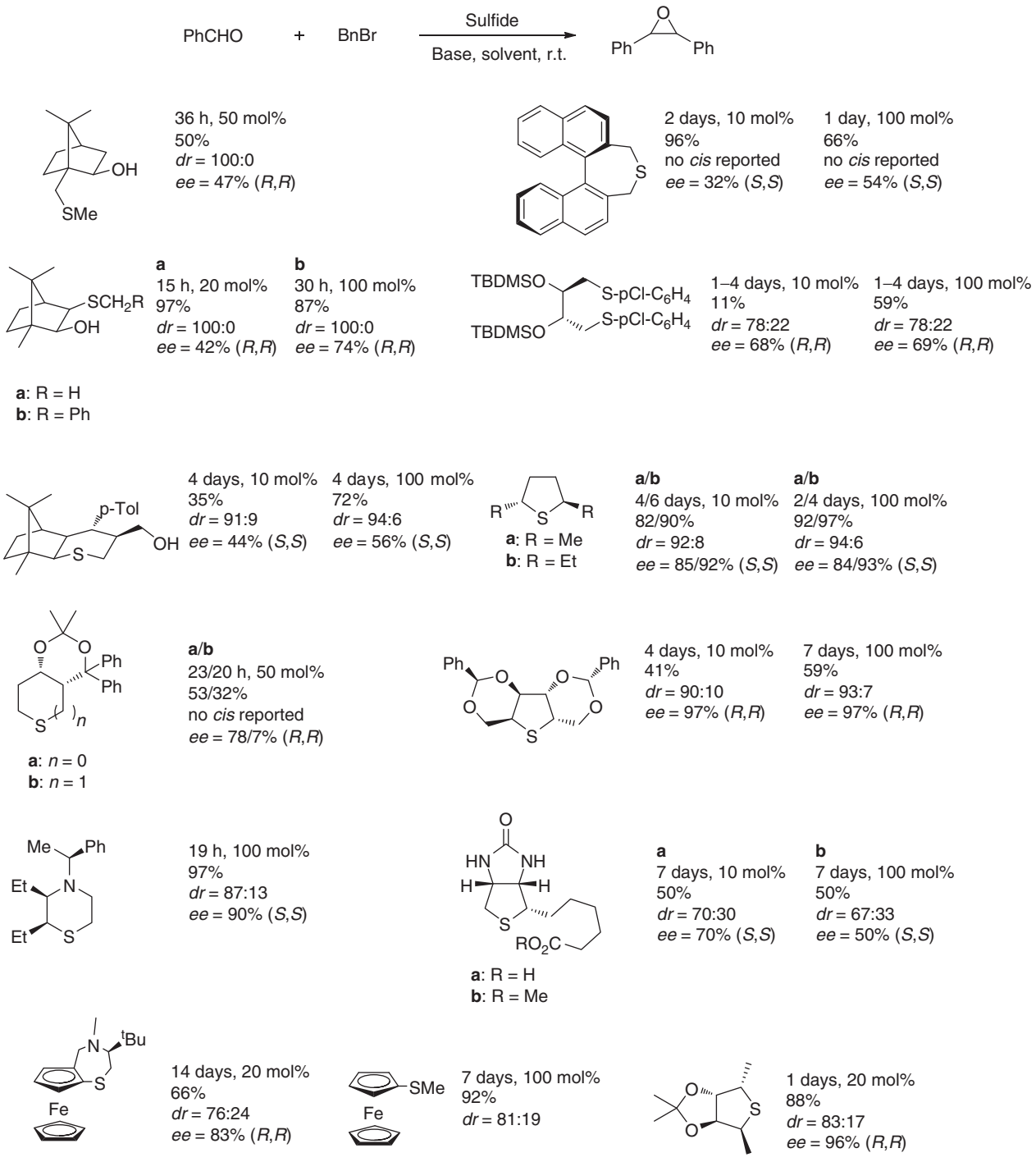
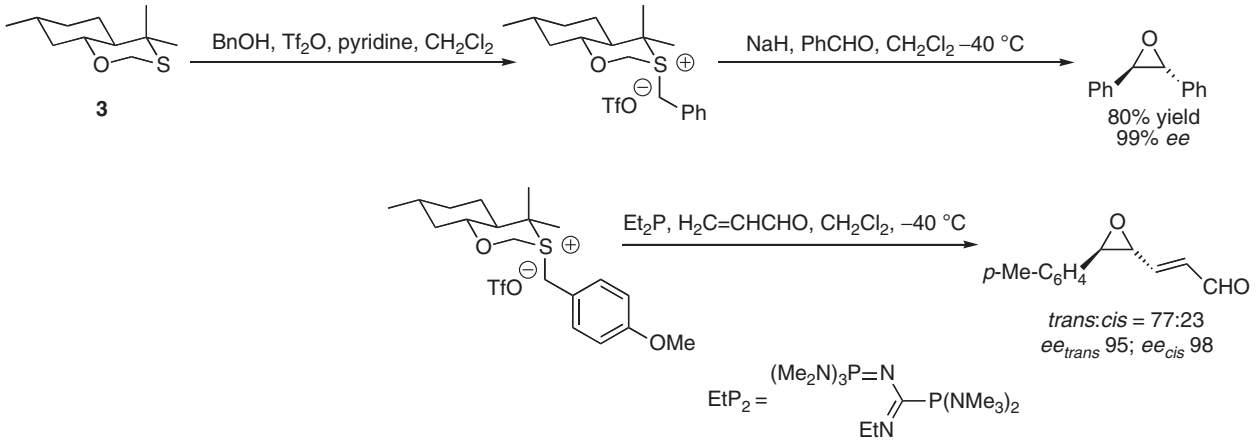


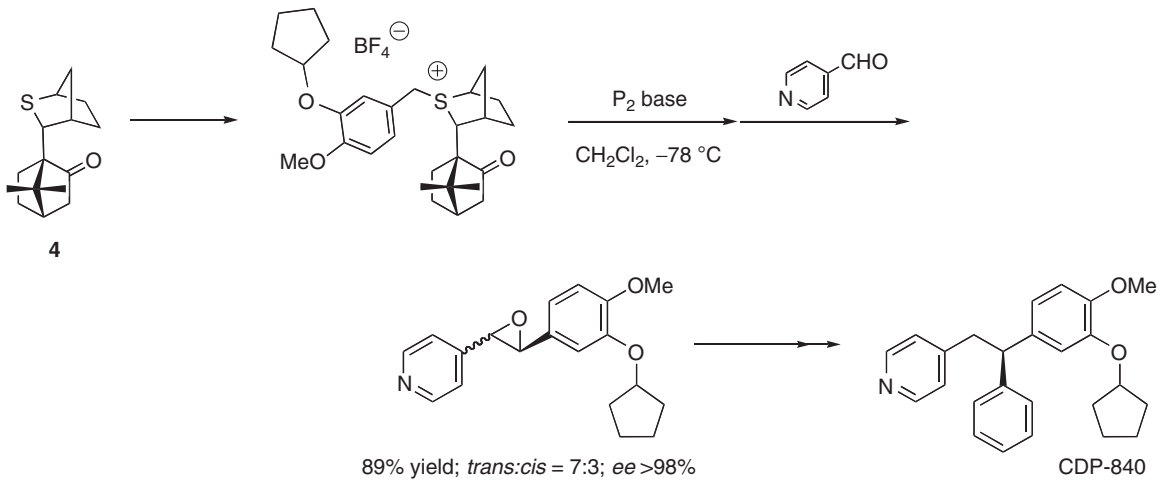
Chart 1 Adapted and reprinted from McGarrigle, E. M.; Myers, E. L.; Illa, O.; *et al. Chem. Rev.* **2007**, *107*, 5841–5883, with permission from American Chemical Society.

sulfoniums derived from chiral sulfide 4.[70] The method was used in a rapid synthesis of the antiinflammatory agent CDP-840 (Scheme 14).

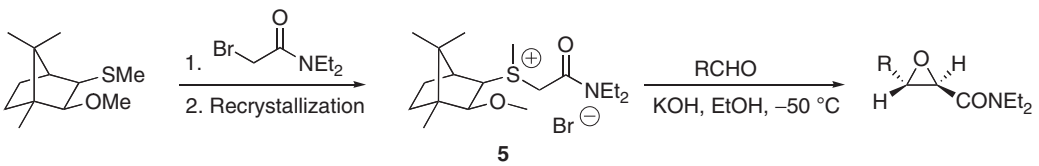
Camphor-derived chiral 2-sulfonium acetamide salts 5 undergo highly efficient and stereoselective Darzens reaction (Scheme 15 and Table 15).[71] Reactions of these ylides with a range of aromatic aldehydes yield glycidyl amides of ≥92% *ee*; aliphatic aldehydes react less selectively, with the exception of pivaldehyde, which is converted to the epoxide in excellent yield and in 93% *ee*.



Scheme 13



Scheme 14

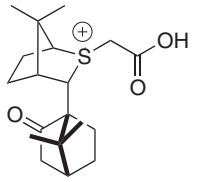


Scheme 15

Table 15 Asymmetric sulfonium ylide synthesis of glycidyl amides

R	*Yield (%)*	ee *(%)*	*Configuration*
4-$MeOC_6H_4$	90	97	(2*R*, 3*S*)
Ph	93	97	(2*R*, 3*S*)
4-ClC_6H_4	87	99	(2*R*, 3*S*)
4-MeC_6H_4	88	98	(2*R*, 3*S*)
4-FC_6H_4	85	96	(2*R*, 3*S*)
4-$CF_3C_6H_4$	89	96	(2*R*, 3*S*)
4-$NO_2C_6H_4$	85	92	(2*R*, 3*S*)
3-Pyridyl	87	95	(2*R*, 3*S*)
Dodecyl	84	63	(2*R*, 3*S*)
^{t}Bu	87	93	(2*R*, 3*S*)

Reactions using sulfonium carboxylates **6** rather than amides proceed with high diastereoselectivity but deliver products with low *ee* (23–59%). Mechanistic studies showed that the inferior enantiomeric excess observed in the carboxylate reaction is a consequence of the enantiodifferentiating step being the ring closure step rather than the betaine-forming step.[72]

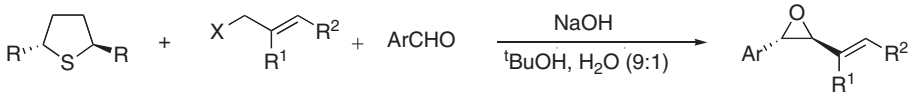


6

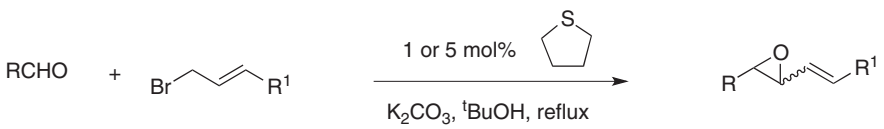
The use of C_2-symmetric 2,5-disubstituted tetrahydrothiophenes as catalysts is more efficient, delivering *trans*-epoxides in good yields, although with modest *ee* (≤89%);[73] the reactions are very slow, however, even when using stoichiometric amounts of the catalyst, and use of substoichiometric sulfide decreases the rate to the extent of 4 weeks being needed to complete the reaction. As with the Furukawa process, the key sulfonium intermediate was formed *in situ* by alkylation with benzyl bromide; the use of iodides (prepared in situ by addition of ammonium iodides to the reaction mixture) reduced the reaction times of the substoichiometric reaction, but certain substrates still demanded the use of 100 mol% catalyst for efficient preparation of *trans*-epoxides (**Table 16**).[74] The selanyl analog could be used in substoichiometric amounts but reacts with poor diastereoselectivity.[75]

Table 16 Stoichiometric C_2-symmetric sulfide epoxidation

R	*R*^{1}	*R*^{2}	*X*	*Ar*	*Yield (%)*	dr	ee	ee cis *(%)*
						trans:cis	trans *(S,S) (%)*	
Me	H	H	I	Ph	85	2.3:1	37	3
Me	H	Ph	Br	Ph	76	2.2:1	50	15
Et	H	Ph	Br	Ph	81	2.8:1	53	22
Me	Me	H	Br	Ph	55	24:1	85	40
Me	Me	H	I	Ph	60	≥50:1	84	n.a.
Me	$(CH_2)_4$		I		60	2.3:1	90	n.a.
Me	Ph	H	I	Ph	72	≥50:1	45	n.a.
Me	Me	H	I	2-Naphthyl	70	≥50:1	70	n.a.
Me	Me	H	I	4-Cl-C_6H_4	61	≥50:1	78	n.a.
Me	Me	H	I	2-Thienyl	–	≥50:1	77	n.a.
(*S,S*)	Me	H	I	Ph	65	≥50:1	77 (*R,R*)	n.a.

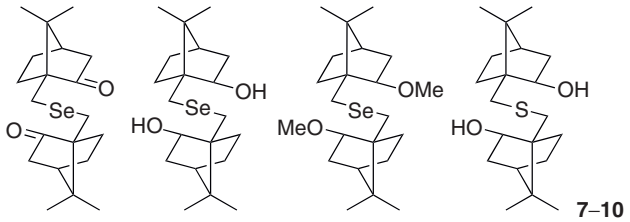


Vinyl epoxides have been prepared using chiral sulfide catalysis and carbonate base, but the yields were moderate and the stereocontrol mediocre even for nonasymmetric reactions (equation 16 and **Table 17**).[27]



(16)

Chiral camphor-derived selanides **7–10** catalyze Darzens reaction of phenacyl bromide and aldehydes in 3–95% yield; the reactions proceed via selanonium ylides and only *cis*-epoxides are obtained, but the stereoselectivity of the process is low (0–62% *ee*).[76]



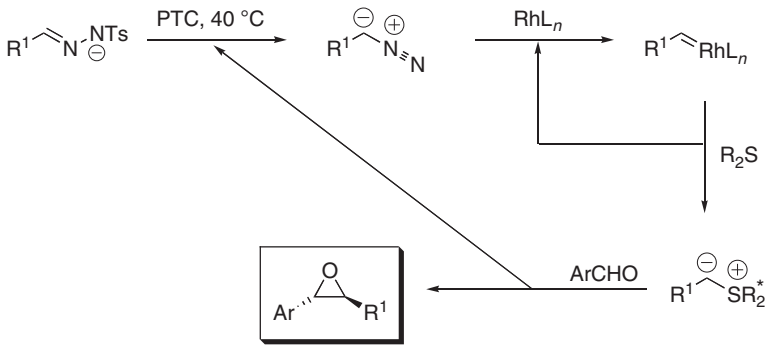
7–10

Table 17 Substoichiometric sulfonium ylides epoxidation of aldehydes

Loading (mol%)	*R*	*R*^{1}	*Yield (%)*	cis:trans
1	4-Cl-C_6H_4	H	94	36:64
1	4-NO_2–C_6H_4	H	85	33:67
1	Ph	H	96	38:62
5	4-OMe·C_6H_4	H	85	30:70
5	*n*-C_9H_{19}	H	75	55:45
1	4-Cl-C_6H_4	TMS	83	25:75
1	Ph	TMS	89	24:76
1	4-NO_2–C_6H_4	TMS	85	30:70
1	2-Cl-C_6H_4	TMS	85	27:73
5	*n*-C_9H_{19}	TMS	88	42:58
5	*cyclo*-C_6H_{11}	TMS	78	50:50

1.16.3.3.2 From metal carbenoids

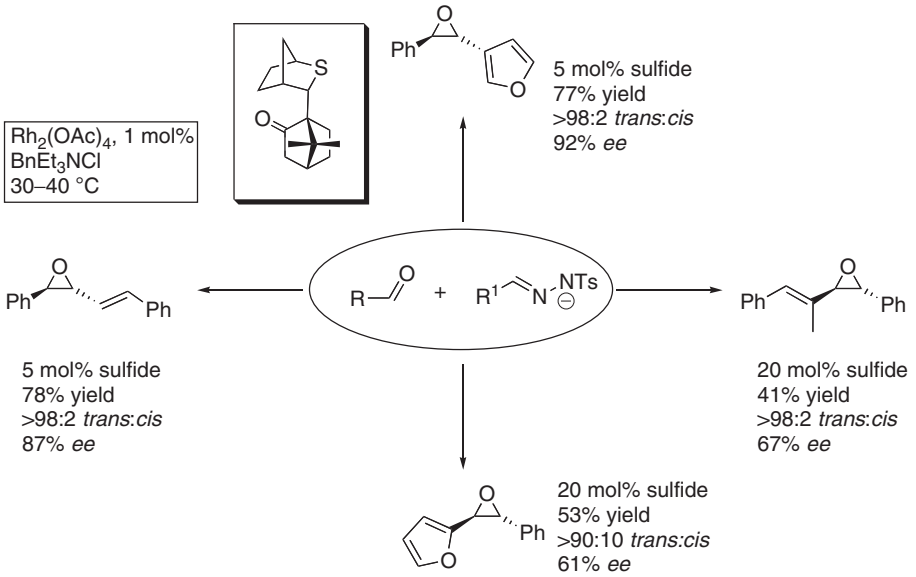
Aggarwal has developed a widely applicable methodology based on carbenoid capture, using a range of chiral sulfides, and this Darzens-like process is of great utility.[65] The reactions are three-compenent processes featuring the combination of a diazo species, a metal catalyst, chiral sulfide (usually present in substoichiometric amounts), and an aldehyde. The mechanism involves: (a) metal insertion into the C═N_2 bond, (b) carbenoid capture by chiral sulfide (generating the key chiral sulfonium ylide), (c) nucleophilic addition to the C═O bond, (d) rotation, and (e) 3-*exo*-tet closure to deliver the epoxide product. The original need for preformed alkyl diazo reagents[77] is no longer necessary, with these relatively inaccessible and highly reactive species being generated *in situ* from the corresponding tosylhydrazones. The overall reaction, therefore, is the combination of two aldehydes in the presence of metal and organic catalysts. As the diazo-forming reaction utilizes a phase-transfer catalyst, the Aggarwal epoxidation method is actually a diastereo- and enantioselective tricatalytic synthetic method (Schemes 16 and 17).



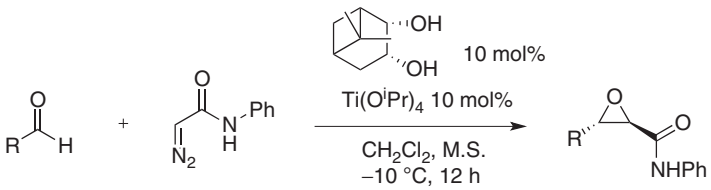
Scheme 16

1.16.3.3.2.1 Darzens-like synthesis using chiral lewis acid catalysis

(+)-Pinandiol–Ti(IV) catalysts mediate highly enantioselective reaction between diazobenzamides and aldehydes to give *cis*-glycidyl amides[78]; in contrast to many asymmetric synthetic methods, the reactions are generally more selective for aliphatic (>95% *ee*) than aromatic substrates (70–95% *ee*) (equation 17 and Table 18).



Scheme 17

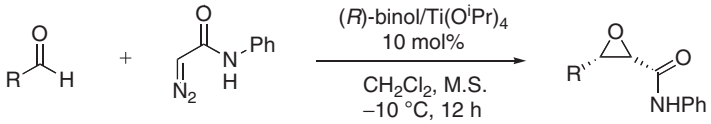


(17)

Table 18 Chiral pinanediol-titanate Darzens reaction of diazoamides

R	*Yield (%)*	ee *(%)*
Me	92	98.2
Et	90	99.1
n-Pr	91	97.1
Ph	83	95.4
^{i}Pr	83	98.1
Ph	81	85.1
4-NO_2-C_6H_4	88	95.2
3-MeO-C_6H_4	83	92.6
3-F-C_6H_4	78	89.2
1-Napthyl	67	70.4

Similar reactions using (*R*)-BINOL/Ti(IV) catalysts proceed with excellent stereoselectivity for both aromatic (giving *cis*-epoxides of ≥95% *ee*) and aliphatic aldehydes (87 to >99% *ee*) (equation 18 and Table 19).[79] The same authors subsequently reported that the same reagents react in the presence of a catalyst formed from *R*-3,3′-diiodobinaphthol and $Zr(O^{n}Bu)_4$ to give the opposite enantiomer of *cis*-glycinamides in good yield and with high *ee* (up to 99%).[80]



(18)

Both reactions are Darzens like, involving nucleophilic attack of the diazonium ylide followed by 3-*exo*-tet ring closure.

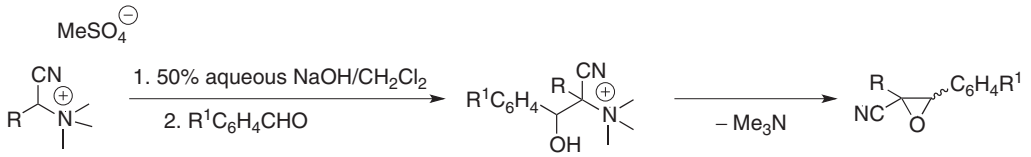
Chiral salen complexes catalyze reaction of *N*,*N*-diphenyl haloacetamides in good yield but with variable diasterocontrol and little enantioinduction.[81]

Table 19 Chiral BINOL-titanate Darzens reaction of diazoamides

R	*Yield (%)*	ee *(%)*
Ph	88	99
4-NO_2-C_6H_4	91	99
4-F-C_6H_4	82	98
3-MeO-C_6H_4	87	97
1-Napthyl	93	97
n-Bu	75	98
n-Pr	76	>99
Et	86	>99
^{i}Pr	80	98
Cyclohexyl	67	87

1.16.3.4 Addition of Other Ylides

In theory, ammonium ylides might be considered as potential reagents for Darzens-like C═O addition reactions. Such reactions occur much more slowly than the reactions of corresponding sulfur ylides, proceeding at room temperature rather than at −78 °C and are limited in scope and yield (Scheme 18 and Table 20).[82] Density functional calculations show that the barrier to ring closure of ammonium betaines is significantly higher than the same process for sulfonium betaines,[83] rationalizing the differing reactivity (and explaining why hydroxy ammonium salts are isolated from reactions of carbonyls and ammonium ylides at low temperature[84]).



Scheme 18

Table 20 Ammonium ylides in Darzens reaction

R	*R*^{1}	*Time (h)*	*Temperature (°C)*	*Isomer*	*Yield (%)*
Ph	H	8	40	*Z*	49
Ph	2-Cl	9	40	*Z*	48
Ph	4-Cl	9	40	*Z*	47
Ph	4-Me	8	40	*Z*	46
Ph	4-F	8	40	*Z*	45
4-OMeC_6H_4	H	15	40	*Z*	35
4-OMeC_6H_4	4-Cl	10	40	*Z*	32
Me_2C═CH	H	7	20–25	*Z*+*E*	52
Me_2C═CH	4-Cl	10	20–25	*Z*+*E*	32

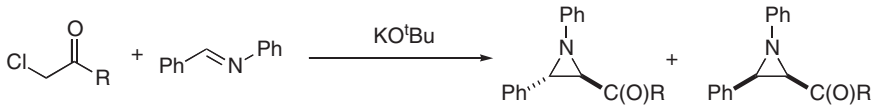
Preformed chiral, brucine-derived *N*-benzyl ammonium ylides react with aryl aldehydes in the presence of KO^{t}Bu to give *trans*-epoxides (*dr* 79:21 to >99:1) of low to moderate *ee* (28–84%).[85]

1.16.4 Addition to C═N π-Bonds

1.16.4.1 Aza-Darzens Reactions[1(b),(c)]

1.16.4.1.1 Using halogenated anions

Amido-stabilized sulfonium ylides were indicated first to react with imines to give aziridines in the mid-1960s, but the presumed aziridine products could not be isolated, instead they were found to react further *in situ* to give enaminocinnamides.[86] The first report of 'true' aza-Darzens reactions described the reactions of potassium enolates derived from chloroacetic acid with *N*-phenyl benzaldimine (equation 19).[87] Esters reacted with good stereoselectivity (favoring *trans*-products) but poor efficiency, whereas the corresponding diethylamide reacted in acceptable yields and inverted stereodifferentiation.



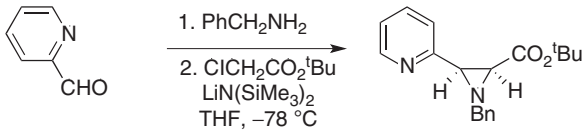
(19)

R = OEt; 29%, *trans*:*cis* >90:10
R = NEt_2; 65%, *trans*:*cis* = 10:90

The method was quickly developed into a general method, with a range of α-anions derived from 2-chloroesters, and nitriles were reported to react with similar imines to give *N*-phenyl aziridines in good yields.[88] Anions derived from dichloroacetates gave chloroaziridines as single diastereoisomers (of unspecified configuration).[89]

Bromomalonates have been infrequently reported in aza-Darzens reactions; these esters have recently been reported to be aziridinate *N*-tosylimines en route to highly functionalized donor–acceptor aziridines.[90]

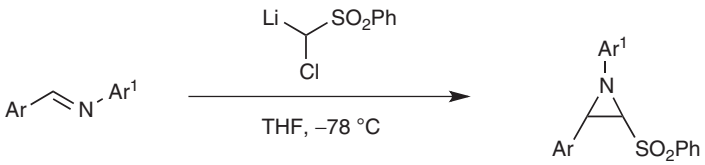
Using amide bases, α-halo anions have proved to be reliable reagents in accessing a diverse range of aziridine products; of particular note is the preparation of heteroaryl aziridines using the method (equation 20).[91]



(20)

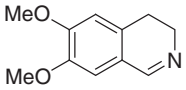
50%, *cis*- only

The stabilizing group present in halogenated anions is of clear importance; sulfone-derived anions react efficiently with *N*-phenyl and cyclic *N*-alkyl imines (equation 21 and **Table 21**).[92–95]



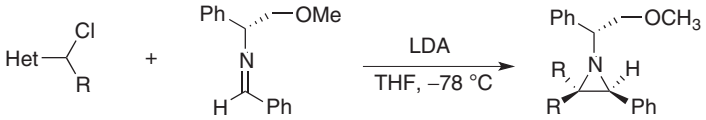
(21)

Table 21 aza-Darzens reaction of chlorosulfones and imines

Ar	*Ar*^{1}	*Yield (%)*
Ph	Ph	94
p-ClC$_6$H$_4$	Ph	97
m-ClC$_6$H$_4$	Ph	83
p-O$_2$NC$_6$H$_4$	Ph	73
p-MeOC$_6$H$_4$	Ph	72
		78

Imidate-stabilized chloroanions have been successfully employed in aza-Darzens reactions, with dihydrooxazoles delivering hetaryl aziridines in acceptable yields (although with variable stereoselectivity). These products could themselves take advantage of the anion-stabilizing group to be functionalized by deprotonation and reactions with a range of electrophiles.[96]

Hetarenes can also function as anion-stabilizing groups thereby facilitating aza-Darzens reactions. Thus, 2-(2′-thiazolyl)alkyl chlorides undergo sequential deprotonation and reaction with chiral imines to give nonracemic chiral hetaryl aziridines. The process proceeds with excellent yield and diastereoselectivity (equation 22 and **Table 22**).[97]

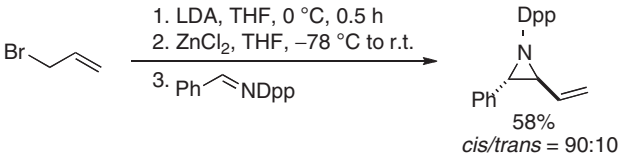


(22)

Aza-Darzens reactions were not widely reported in the older literature for preparation of 2-alkenylaziridines due to the ambident reactivity and instability of the imines required (*vide supra*, re. enal/enone epoxidation); however, alkenyl or benzylic α-substitution stabilizes haloanions to the extent that vinyl aziridines may now be accessed using such reagents. The first reported synthesis of *N*-alkyl vinylaziridines described the reaction of an α-chloroallyllithium with aldimines and ketimines.[98] These reactive anions were prepared by transmetallation,[99] but direct deprotonation is feasible and *N*-phosphinyl imines react with 1-bromo allyllithium to give *trans*-vinylaziridines (equation 23).[100]

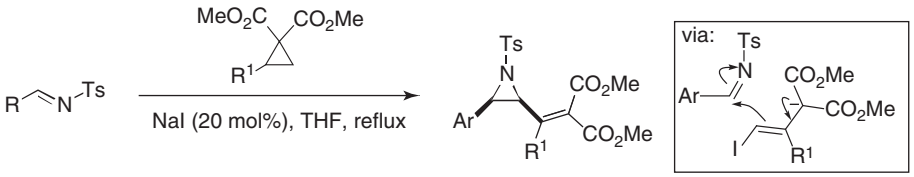
Table 22 aza-Darzens reaction of chloromethyl hetarenes

Het	*R*	*Yield (%)*	dr
4-Methylthiazol-2-yl	H	48	>98:2
4-Methylthiazol-2-yl	Me	90	>98:2
2-Benzothiazolyl	H	90	>98:2
Me	2-Benzothiazolyl	60	>98:2
4,4-Dimethyl-2-oxazolin-2-yl	H	45	>98:2
Me	4,4-Dimethyl-2-oxazolin-2-yl	35	>98:2
2-Pyridyl	H	60	>98:2
4-Pyridyl	H	30	>98:2



(23)

A less obvious entry to an α-halogenated allyl anion is gained through the reaction of 1,1-dicarboxycyclopropenes with iodide ion. The latter causes nucleophilic ring opening of the strained carbocycle, giving a (2-iodo)vinylenolate which reacts with *N*-Ts imines to gives *cis*-vinylaziridines (equation 24 and **Table 23**).[101] As iodide is regenerated by ring closure to give the aziridine, the reaction requires only a substoichiometric amount of NaI.

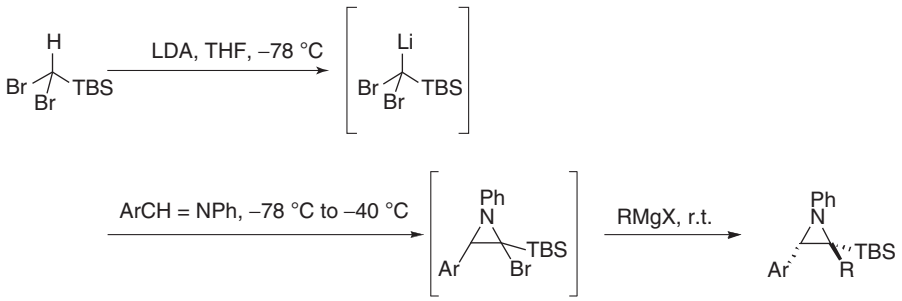


(24)

Table 23 aza-Darzens synthesis of vinylaziridines via 1,1-dicarboxycyclopropenes[101]

Ar	*R*^{1}	*Yield (%)*
4-NO_2-C_6H_4	$TBSOC_3H_6$	69
1-Naphthyl	C_5H_{11}	75
Ph	Bu	65
p-ClC_6H_4	C_5H_{11}	58
Ph	Bn	63

The ability of α-silyl substituents to stabilize anions means that silyldibromomethyllithium can be used to give 2-bromo-2-silylaziridines by reaction with *N*-arylimines.[102] These trisubstituted aziridines subsequently react with Grignard reagents to give trisubstituted *trans*-aziridines (**Scheme 19** and **Table 24**).



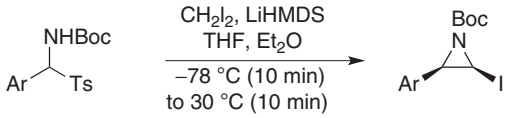
Scheme 19

Table 24 aza-Darzens synthesis of tetrasubstituted aziridines using (silyl)dibromomethyl lithium

Ar	*R*	*Yield (%)*	*dr*
Ph	Ph	71	>99:1
p-ClC_6H_4	Ph	74	>99:1
Ph	^nBu	82	>99:1
Ph	Allyl	82	>99:1
Ph	H	84	79:21

Simple halogen-stabilized alkyllithiums have recently been reported to deliver aziridines efficiently. Thus, *N*-alkyl[103] or *N*-sulfonyl[104] imines are aziridinated in good yield by reaction with chloro- and iodomethyl lithium.

Diiodomethyllithium reacts with *N*-Boc imines (generated *in situ* from the corresponding sulfinate addition compounds) to give *cis*-2-aryl iodoaziridines (equation 25 and Table 25).[105]



(25)

Table 25 aza-Darzens reaction of diiodomethyllithium

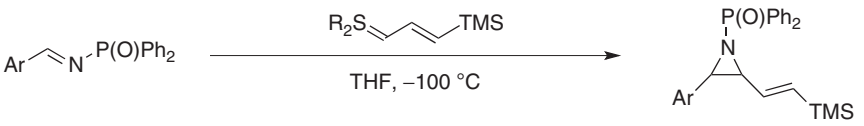
Ar	*Yield (%)*	*dr*
Ph	83	>95:5
Ph	88	>95:5
4-Tolyl	96	>95:5
2-Tolyl	89	90:10
2-Napthyl	92	>95:5
4-*t*-BuPh	67	>95:5
4-ClPh	51	>95:5
2-ClPh	52	97:13
4-BrPh	42	>95:5
4-FPh	76	>95:5
3-OMePh	77	>95:5
4-CF_3Ph	13	>95:5
3-Pyridyl	49	>95:5

1.16.4.1.2 Using ylides

1.16.4.1.2.1 Unsaturated sulfonium ylides

The first aziridination processes using reaction of ylides with imines were reported by Corey and Chaykovsky[106] and Frantzen and Driessen.[107] These reactions used sulfonium and sulfoxonium ylides, but the reactions received little attention until the 1990s, when the first of a plethora of reports appeared on the subject.

Other than the parent (unsubstituted) reagents, unstabilized sulfonium ylides often react inefficiently with imines due to the lesser reactivity of the C=N bond and the instability of the sulfur reagents. The presence of stabilizing groups such as allyl substituents[108] renders the ylides happier reagents and addition reactions proceed in considerably better yields with *N*-sulfonyl[109] and phosphinyl imines. These process frequently have reasonable breadth of scope, but there is often the limitation that (to obtain good stereocontrol) reactions need to be carried out at very low temperature (−100 °C) (equation 26 and Table 26).[110] The stereocontrol of the reaction is influenced by the nature of the nonreactive *S*-substitutents; diphenylsulfonium ylides tend to give *cis*-vinylaziridines and dimethylsulfoniums deliver *trans*-aziridines. *N*-Sulfamoylimines can also be used in these reactions, but the transformations exhibit mediocre diastereoselectivity.[111]

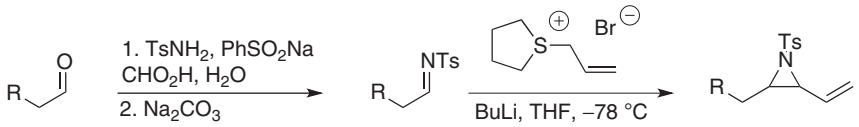


(26)

Stockman et al. showed that aliphatic vinyl aziridines could be prepared in acceptable yields by reaction of *S*-allyl tetrahydrothiophenium ylides with *N*-tosyl imines (Scheme 20, Table 27).[112]

Table 26 aza-Darzens synthesis of *N*-diphenylphosphinyl vinyl aziridines using sulfonium ylides

Ar	*Yield (%)*	cis:trans
Ph	93	91:9
p-$MeOC_6H_4$	90	>99:1
p-$F_3CC_6H_4$	72	85:15
p-ClC_6H_4	84	85:15
p-MeC_6H_4	94	>99:1
2-Furyl	90	>99:1



Scheme 20

Table 27 aza-Darzens synthesis of *N*-tosyl vinyl aziridines using sulfonium ylides

R	*Yield (%)*	cis:trans
^iPr	58	1:2
cyclo-C_6H_{11}	53	1:2
n-C_5H_{11}	51	1:2

1.16.4.1.2.2 Using iodonium ylides

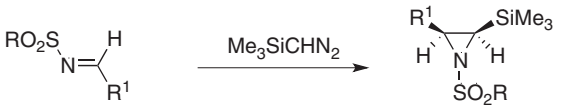
Iodonium ylides are readily available and these compounds react with imines to form aziridines via 2-iodonium amide anions; the method has been used to good effect for the synthesis of vinyl aziridines in particular. Monocarbonyl iodonium ylides give *cis*-2-acylaziridines from arylsulfonylimines and *trans*-aziridines from *N*-benzoylimines, often with good stereoselectivity.[113] Bismuthonium ylides can also be used in aziridination, giving 2,3-aziridino ketones.[114]

1.16.4.1.2.3 Using other ylides

As might be expected, telluronium ylides react after deprotonation with imines to give aziridines. When *N*-phenyl α,β-unsaturated imines are used, addition of a second equivalent of ylide occurs, giving 2-vinyl-3-(2′-vinyl)cyclopropyl aziridines.[115]

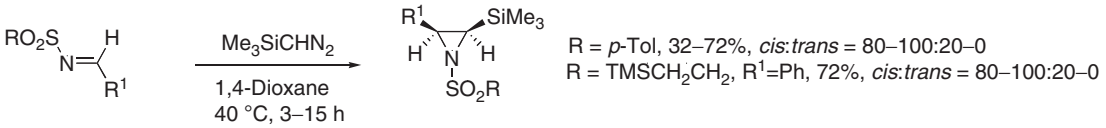
1.16.4.1.3 Using α-diazocarbonyl reagents

The reaction of simple diazoalkyl reagents with imines was traditionally a difficult reaction to control, but several elegant methods have demonstrated the use of these compounds in aza-Darzens-like processes. *N*-Sulfonylimines react with trimethylsilyldiazomethane to give predominantly *cis*-3-silylaziridines in good yield (equation 27 and **Table 28**).[116]



(27)

Aggarwal et al. have reported a highly diastereoselective aziridination of imines with trimethylsilyldiazomethane (TMSD) (equation 28).[117]



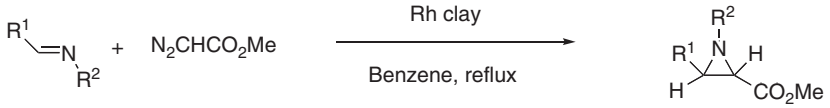
(28)

α-Diazocarbonyl compounds are so acidic (the pK_a of diazoacetate is approximately 10) that they are essentially ylidic in structure, and they can, therefore, react with imines to give aziridines, usually in the presence of Lewis acids. The ability of many metal salts and complexes to act as Lewis acids means that one must always take care when assigning an aziridination process as involving metal carbenoid species, because it is often possible that the reactions are simply acid-catalyzed processes.

Table 28 aza-Darzens synthesis using TMS diazomethane

R	R^1	*Yield (%)* (cis:trans)
4-MeC_6H_4	Ph	75 (100:0)
4-NO_2-C_6H_4	Ph	45 (91:6)
4-MeO-C_6H_4	Ph	80 (94:6)
2,4,6-Me_3-C_6H_2	Ph	85 (100:0)
Benzyl	Ph	65 (87:13)
2,4,6-Me_3-C_6H_2	4-Cl-C_6H_4	81 (100:0)
2,4,6-Me_3-C_6H_2	4-NO_2-C_6H_4	78 (100:0)
2,4,6-Me_3-C_6H_2	4-Me-OC_6H_4	76 (100:0)
2,4,6-Me_3-C_6H_2	2-Naphthyl	76 (100:0)
2,4,6-Me_3-C_6H_2	2-Furyl	82 (100:0)
2,4,6-Me_3-C_6H_2	3-Pyridyl	59 (100:0)
2,4,6-Me_3-C_6H_2	Styryl	12 (100:0)
2,4,6-Me_3-C_6H_2	Phenethyl	60 (100:0)
2,4,6-Me_3-C_6H_2	*n*-Pentyl	65 (100:0)
(1*R*)-10-Camphor	Ph	88 (100:0) (*de*=0%)

Lewis acid-catalyzed addition of diazoesters to imines was first reported in the 1980s,[118,142,143] but it was described as a general synthetic method only in 1996.[119] The key indicator of an acid-catalyzed mechanism is the absence of cycloadduct or dimerized by-products usually seen to a greater or lesser extent in carbenoid reactions; where these substances are absent from product mixtures, the mechanism likely involves diazo attack on the Lewis acid-activated imine followed by ring closure, and the overall process is thus an aza-Darzens reaction. Many metal salts and complexes catalyze imine aziridination by diazo species: Fe(II),[120] In (III),[121] lanthanide triflates, Rh(III), Sn(IV),[122] and W(II)[123] have all been reported as effective catalysts in this regard. Acidic surfaces such as Rh(III) montmorillonite K10 clays also act as acid catalysts for imine aziridination, mediating the preparation of *trans*-aziridines from aryl benzaldimines diazoacetate (equation 29, **Table 29**).[124]

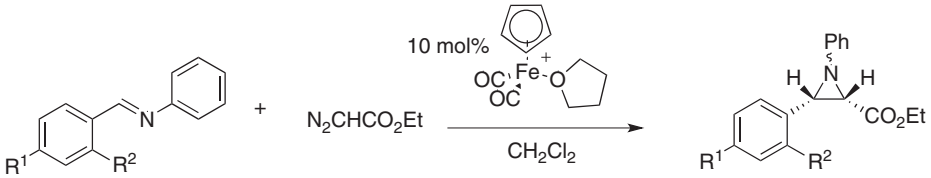


(29)

Table 29 Aziridination of imines catalyzed by clays

R^1	R^2	*Time (h)*	*Yield (%)*
4-Cl-C_6H_4	Ph	5	57
4-OMe-C_6H_4	Ph	3	32
3,4-$(OMe)_2C_6H_3$	Ph	7	42
3,4,5-$(OMe)_3C_6H_2$	Ph	10	75
4-ClC_6H_4	2,5-$Cl_2C_6H_3$	6	40
4-ClC_6H_4	3-NO_2-4-MeC_6H_3	9	50
2-Furyl	Ph	7	38
2-Furyl	Cyclohexyl	5.5	48
Bn	Ph	8	30
Pr^i	Ph	8	48

Iron half-sandwich Lewis acids mediate the reaction of *N*-aryl benzaldimines with diazoacetate to give the *cis*-aziridine (equation 30, **Table 30**).[125]



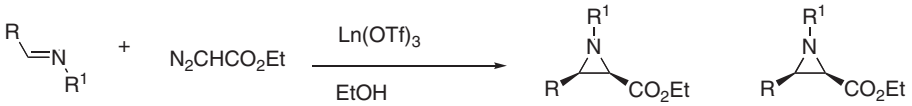
(30)

Table 30 Iron-catalyzed aza-Darzens reaction

R	R^1	*EDA*		*PDM*	
		cis:trans	*Yield(%)*	cis:trans	*Yield(%)*
H	H	100:0	40	100:0	95
Me	H	–	0	100:0	95
OMe	H	–	0	–	–
Cl	H	100:0	50	–	–
Cl	Cl	1:3	38	–	–
F	H	100:0	44	–	–
CF_3	H	100:0	53	–	–
NO_2	H	4:1	78	100:0	81

Abbreviations: EDA, ethyl diazoacetate; PDM, phenyldiazomethane.

Lanthanide Lewis acids have been widely used, with $Ln(OTf)_3$ effecting aziridination of aromatic and aliphatic imines (equation 31, **Table 31**).[126]



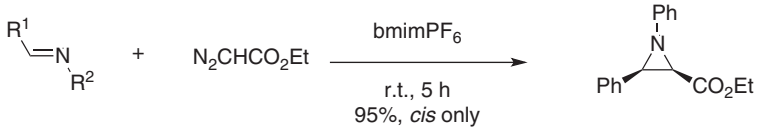
(31)

Table 31 Ln(III)-catalyzed aza-Darzens reaction

R	R^1	*Yield (%)* (cis:trans)
Ph	Ph	53 (100:0)
Ph	4-Cl-C_6H_4	54 (8:1)
4-Cl-C_6H_4	Ph	55 (100:0)
4-Cl-C_6H_4	4-Cl-C_6H_4	60 (100:0)
4-Cl-C_6H_4	4-Cl-C_6H_4	57 (100:0)
Ph	4-Cl-C_6H_4	62 (29:2)
Ph	2-OH-C_6H_4	49 (100:0)
4-Cl-C_6H_4	Ph	51 (100:0)
Ph	Bn	55 *cis* only
t-C_4H_9	Ph	52 (5:1)

Conveniently, the imine component of the reaction can be formed *in situ* by reaction of an aldehyde with amine in the presence of substoichiometric lanthanide Lewis acid, giving *cis*-aziridines directly in very good yield.[127]

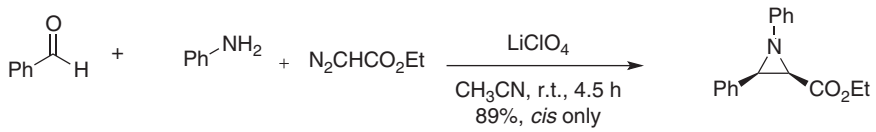
Diazoacetate imine aziridination can be carried out in ionic liquids (equation 32).[128]



(32)

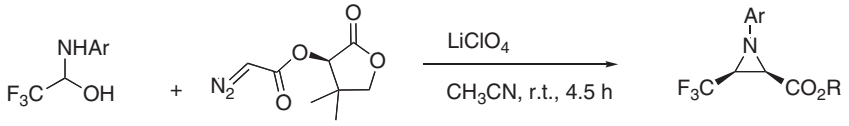
The structure of an intermediate in tin tetrachloride-catalyzed aziridination of *N*-(2-methoxy)phenyl imines has been characterized.[129]

Aryl aldimines react with diazoacetate in the presence of $LiClO_4$ to *cis*-aziridine (equation 33).[130] $InCl_3$ also catalyzes diazoacetate aziridination of imines[131]; $[Ir(COD)Cl_2]$ catalyzes a three-component coupling of aldehydes, amines, and diazoacetate to give trisubstituted products; the process can be used to prepare and react aliphatic imines, relatively unusual substrates for aziridination protocols.[132]



(33)

Chiral diazoesters derived from (*R*)-pantolactone react under Lewis-acid catalysis with *N*-aryl trifluoroacetaldimines 2-F_3C-aziridines (equation 34).[133]

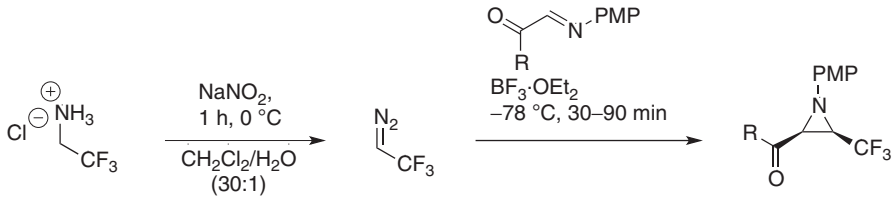


(34)

Ar = C_6H_4(*p*-OMe), 81%, *cis:trans* = >95:5, 94% *de*
Ar = C_6H_4(*p*-Br), 83%, *cis:trans* = >99:1, 94% *de*

Allyl Mo(II) complexes catalyze the reaction of *N*-phenyl benzaldimine and ethyl diazoacetate (EDA) to give racemic aziridines.[134]

Reaction of diazo(trifluoromethyl)methane (generated *in situ* from the corresponding ammonium chloride) with 2-acylimines in the presence of a stoichiometric amount of Lewis acid delivers *cis*-aziridines in good yield and with high stereoselectivity (≥11:1) (equation 35, Table 32).[135]

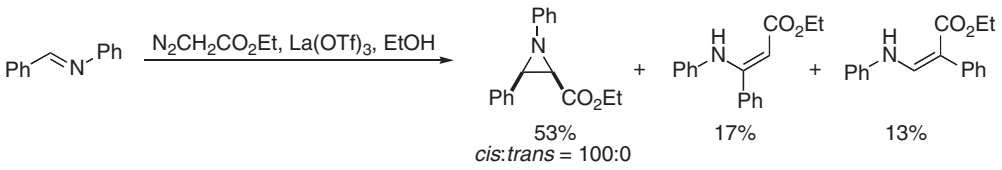


(35)

Table 32 Trifluoromethyl diazomethane in aza-Darzens reaction

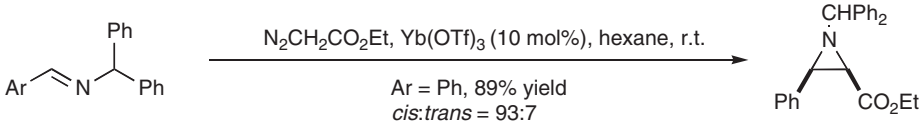
R	*Yield (%)*	cis:trans
Ph	64	17:1
4-F-C_6H_4	78	19:1
4-OMe-C_6H_4	50	12:1
OEt	60	11:1
3-Cl-C_6H_4	61	16:1
4-Me-C_6H_4	60	16:1
4-Br-C_6H_4	47	13:1
2-Napthyl	70	15:1
4-C_6H_5-C_6H_4	73	15:1

Lanthanide catalysis of imine aziridination can be carried out in protic solvent such as ethanol, although side products often accompany the aziridine products (equation 36).



(36)

$Yb(OTf)_3$ catalyzes highly *cis*-selective aziridination of *N*-benzhydrylimines with EDA; other lanthanide triflates induce lower stereoselectivity (equation 37, Table 33).[136]



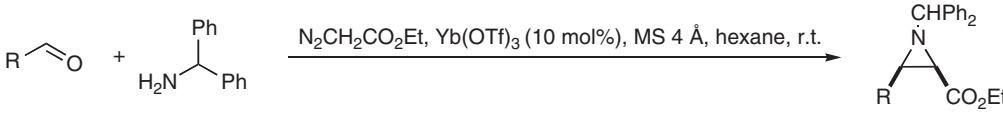
(37)

Aliphatic imines are frequently unusable in aziridination reactions due to problems with isomerization and side reactions; a Yb (III)-catalyzed telescoped process allows access to alkylaziridines by means of *in situ* imination of aldehydes. Thus, reaction of aryl and aliphatic aldehydes with benzhydrylamine in the presence of $Yb(OTf)_3$ gives aziridines with similar yields and

Table 33 Yb(III)-catalyzed aza-Darzens reaction

Ar	*Yield (%)*	cis:trans
p-Tolyl	75	95:5
p-$MeOC_6H_4$	90	94:6
p-ClC_6H_4	81	94:6
p-$NO_2C_6H_4$	83	93:7
2-Naphthyl	82	94:6

stereoselectivities to the process using preformed imines. As is often the case when aliphatic imines are substrates, the reactions are only moderately stereoselective (equation 38, **Table 34**).

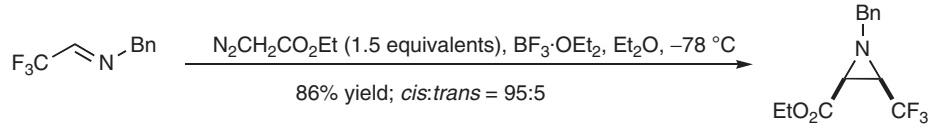


(38)

Table 34 Yb(III)-catalyzed three-component aza-Darzens reaction

R	*Yield (%)*	cis:trans
Ph	83	95:5
^{i}Pr	82	91:9
^{n}Bu	60	85:15
^{i}Bu	86	70:30
$^{c}C_6H_{11}$	82	93:7

Pharmacologically relevant trifluromethyl aziridines can be accessed by $BF_3{\cdot}OEt_2$-catalyzed reaction of 2-trifluromethyl aldimines with diazoacetate (*cis*:*trans* = 95:5) (equation 39).[137]

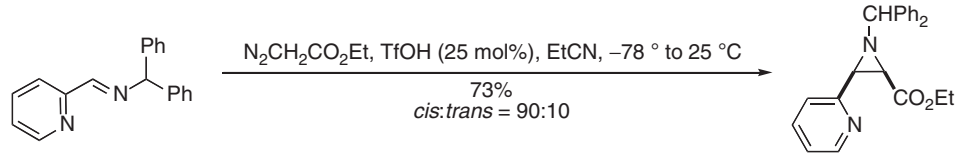


(39)

Although simple aziridines are easily polymerized by exposure to a proton source, imine aziridination by diazoesters can efficiently be catalyzed by Brønsted acids: *N*-benzhydryl aryl and aliphatic imines are *cis*-aziridinated on reaction with EDA in the presence of triflic acid, at low temperature. Not only is the aziridine unmolested during the course of the reaction but also other acid-sensitive functionality (alkenes and acetals) remains intact.[138]

The authors have shown that the reaction is a two-step process involving Mannich-like attack at an iminium to give a 2-diazonium-3-amino ester, followed by 3-*exo*-tet ring closure (equation 40).[139]

The method has been used in the preparation of a mitomycin C analog.[140]



(40)

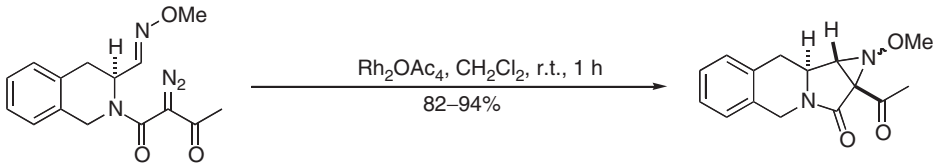
Fluoronium sources can be used as organocatalysts to produce aziridination of *N*-aryl and *N*-silyl imines by diazoacetate.[141]

1.16.4.1.4 Using metal carbenoids

One of the major focal points for researchers developing aziridine-preparing methods has been the use of metal catalysts to mediate addition of carbenes to C=N bonds. The reaction likely proceeds via metal carbenoids, which can undergo addition to imines to give either azomethine ylides (which undergo cyclization) or aziridines directly. The organic carbenoid precursor is most often a diazo reagent, with diazoacetates dominating the literature.

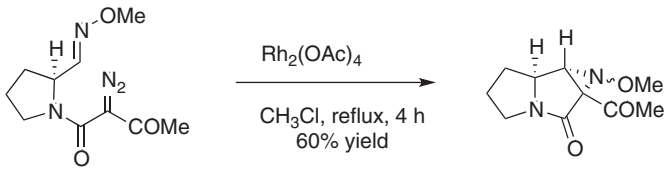
Schiff bases (i.e., imines) were first reported to yield aziridines on reaction in the presence of metal salts with carbene precursors with metal carbenoids in the 1970s. Thus, reaction of imines with Simmons–Smith reagents,[142] aryldiazomethanes and ZnI_2[143,144] and diazoacetates and metallic Cu,[145] were the first methods to be described. The original reports used stoichiometric (in fact, often superstoichiometric) metal loading, and research in this area was given new momentum in the mid-1990s, when the first reports of substoichiometric catalysis appeared. The modern processes routinely employ diazoesters with copper and rhodium catalysts most often used.

Reactions with oximes are sparsely reported in the literature. Tetrahydroisoquinoline-derived diazoacylcarbonyls undergo intramolecular aziridination onto a pendant oxime ether under mild conditions. The reaction is exceptionally facile to the extent that attempted trapping of the proposed intermediate azomethine ylide with methyl acrylate was not possible (equation 41).[146]



(41)

A similar intramolecular Rh(I)-catalyzed aziridination of proline-derived oxime X also proceeded in acceptable yield (equation 42).[147]



(42)

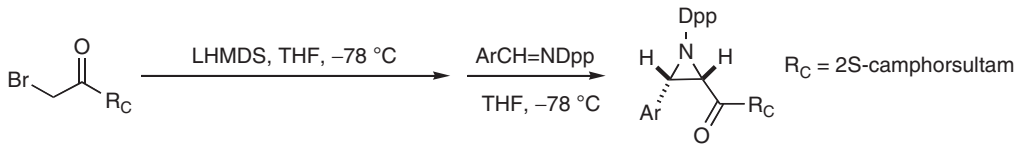
1.16.4.2 Asymmetric Aza-Darzens Reactions

1.16.4.2.1 Using substrate-control

Asymmetric aza-Darzens reactions were first reported using chiral acetals of 2-ketoimines, which reacts with haloenolates with good and tunable diastereocontrol.[148]

1.16.4.2.1.1 Chiral auxiliaries

Auxiliary control in the haloenolate has also been used to execute asymmetric aza-Darzens syntheses. Thus, reaction of a menthyl ester of bromoacetate gives aziridines inefficiently and with moderate stereoselection.[149] *N*-Phosphinyl aryl aldimines react with *N*-α-bromoacyl(camphorsultams) generally to give *cis*-aziridines in good yield;[150,151] however, *ortho*-substituted imines usually give *trans*-aziridines.[152] These aziridines are more easily processed than *N*-sulfonyl aziridines because of the relative ease of removal of the $Ph_2P(O)$ group (removed by reaction with $F_3B{\cdot}OEt_2$ in MeOH) (equation 43 and **Table 35**).

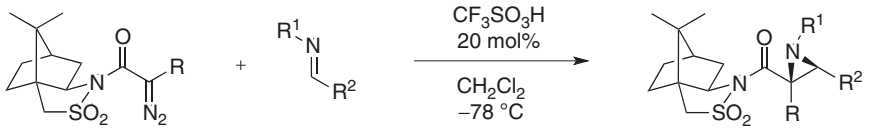


(43)

Table 35 Auxiliary-controlled aza-Darzens reaction of bromoacylsultams

Ar	*Yield (%)*	cis:trans	dr
Ph	71	100:0	>95:5
p-FC_6H_4	57	100:0	>95:5
m-BrC_6H_4	60	100:0	>95:5
p-$MeOC_6H_4$	60	100:0	>95:5
o-$NO_2C_6H_4$	72	100:0	>95:5
p-BrC_6H_4	65	100:0	>95:5

Chiral diazocarbonyl reagents have been prepared and used in aziridination reactions by Maruoka et al. (equation 44 and Table 36).[153] Thus, *N*-(2-diazo)acyl camphor sultams react with *N*-Boc aldimines to give aziridines in good yield and with <20:1 diastereoselectivity. As propionoyl and butanoyl reagents react well, the method offers a facile entry to trisubstituted aziridines, which are rarely delivered by other methods.



(44)

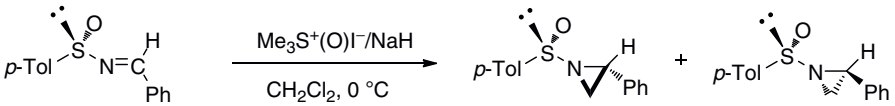
Table 36 Auxiliary controlled aza-Darzens reaction of diazosultams

R	R^1	R^2	*Yield (%)*	dr (trans)
Me	Boc	Ph	74	>20:1
Me	Boc	2-Tolyl	60	>20:1
Me	Boc	3-Tolyl	63	>20:1
Me	Boc	4-Tolyl	59	>20:1
Me	Boc	2-Np	54	>20:1
Me	Boc	4-Cl-C_6H_4	62	>20:1
Me	Boc	4-Piv-C_6H_4	56	>20:1
Me	Boc	3-OMe-C_6H_4	62	>20:1
Et	Boc	Ph	50	>20:1
Me	Cbz	Ph	61	>20:1
Me	Cbz	2-Tolyl	64	>20:1
Me	Cbz	3-Tolyl	66	>20:1
Me	Cbz	4-Br-C_6H_4	55	>20:1
Me	Cbz	3-OMe-C_6H_4	56	>20:1

Diazoacetate derivatives bearing chiral auxiliaries have also been used to prepare trisubstituted aziridines from aldehyde- and ketone-derived imines by an acid-catalyzed process.[154]

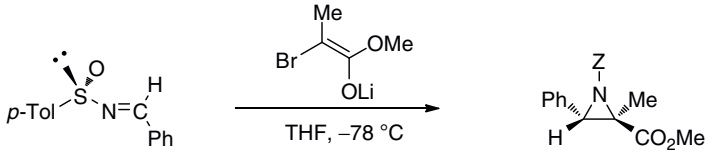
1.16.4.2.1.2 Chiral imines

Chiral imines react efficiently with sulfur ylides to give chiral aziridines, and the majority of reported processes of this type take advantage of the ready availability of chiral electrophilic sulfinyl reagents.[155] For instance, the parent sulfoxonium methylene ylide reacts with chiral tolylsulfinyl imines, albeit with moderate stereoselectivity to give 2-substituted products (equation 45).[156,157]



(45)

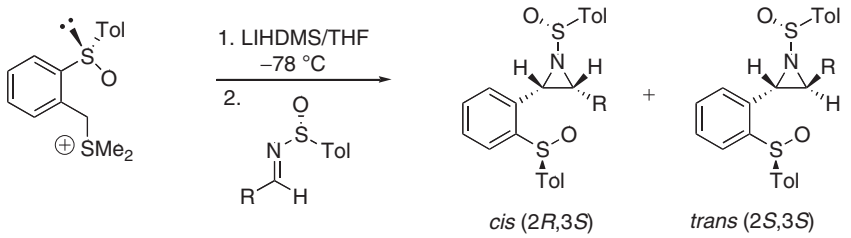
A widely used substrate-controlled process is the reaction of chiral nonracemic sulfinimines with α-bromo-[158,159] and α-chloroenolates, which delivers *cis*-*N*-sulfinylaziridine carboxylates and -phosphonates in good yield (equation 46).[160,161] The metal counterion of the enolate controls the face selectivity of the asymmetric aza-Darzens reaction and deters isomerization of the imine (equation 46).[162–164]



(46)

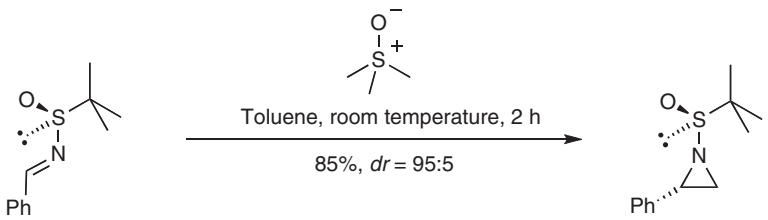
Planar chiral (2′-sulfinyl)benzyl sulfonium salts react with chiral tolyl sulfimines to give aziridines in a sterodivergent manner under double asymmetric control.[165] Thus, *S*-ylides react with *S*-sulfimine with high diastereoselectivity (>98% *trans*-selective)

but poor face selectivity, whereas the same ylides react with the antipodal imine with good *trans*-selectivity (≥81:19) and excellent enantiocontrol (equation 47).



(47)

If a bulkier *S*-substituent is present, as in *tert*-butylsulfinimines (Ellman imines), the reactions are more selective, and aliphatic imines (often not successfully used in a range of aziridination reactions) undergo efficient and stereoselective reactions (equation 48 and **Table 37**).[166,167]

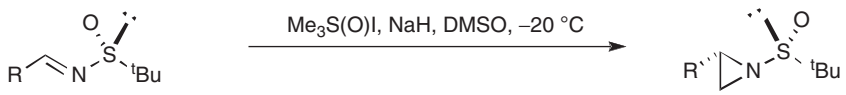


(48)

Table 37 Asymmetric aza-Darzens aziridination of chiral ^{t}butylsulfinimines[167]

R	*Yield (%)*	dr
PhCH=CH	75	95:5
$^{c}C_6H_{11}$	63	>97:3
$^{c}C_5H_{11}$	65	90:10
2-Pyridyl	77	95:5
2-Furyl	72	95:5
3-Pyridyl	77	88:12

If allylsulfonium ylides are used, vinyl aziridines can also be prepared in this way giving predominantly *trans*-isomers (equation 49 and **Table 38**).[168]

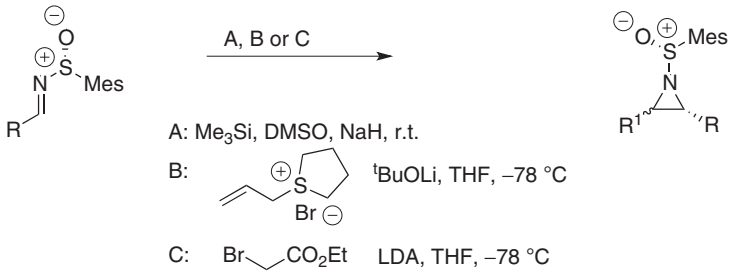


(49)

Table 38 Asymmetric aza-Darzens vinyl aziridination of chiral ^{t}butylsulfinimines

R	*Yield (%)*	cis:trans	dr (trans)
(*E*)-PhCH=CH	82	17:83	>97:3
2-Pyridyl	54	12:88	94:6
Ph	68	29:71	95:5
2-Furyl	55	33:67	>97:3
$^{c}C_6H_{11}$	78	17:83	>97:3
$^{n}C_5H_{11}$	67	18:82	>97:3

Chiral *S*-mesityl sulfinimines have been prepared[169] and shown to react with sulfonium ylides via an open transition state to give predominantly *cis*-aziridines in good yield.[170] Asymmetric induction is moderate to excellent (*dr* 75:25 to 99:1) (equation 50 and **Table 39**).

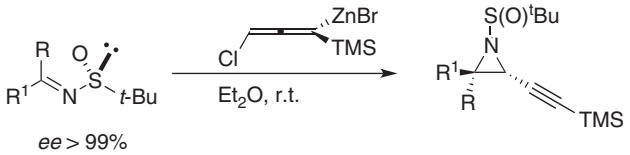


(50)

Table 39 Asymmetric aza-Darzens reactions of chiral S-mesityl sulfinimines

R	R^1	*Method*	*Yield (%)*	dr (cis:trans)
Pentyl	H	A	93	75:25
Cy	H	A	66	80:20
Ph	H	A	95	89:11
2-Napthyl	H	A	50	91:9
Cy	Vinyl	B	73	95:5 (1:4)
Cy	CO_2Et	C	74	96:4 (2:1)
Ph	CO_2Et	C	87	99:1 (49:1)
2-Furyl	CO_2Et	C	52	93:7 (12:1)

Asymmetric aza-Darzens reaction of (racemic) haloallenylzincs with enantiomerically pure Ellman imines[171] is highly di astereoselective, giving chiral *trans-N*-sulfinyl aziridines with high levels of enantiopurity (equation 51).[172] By adding hexamethylphosphoric triamide to the reactions, the diastereoselectivity of the process is inverted and *cis*-aziridines were favored (*cis:trans* >70:30) (Table 40).[173]



(51)

Table 40 aza-Darzens synthesis of 2-ethenylaziridines via chiral sulfoximines[172]

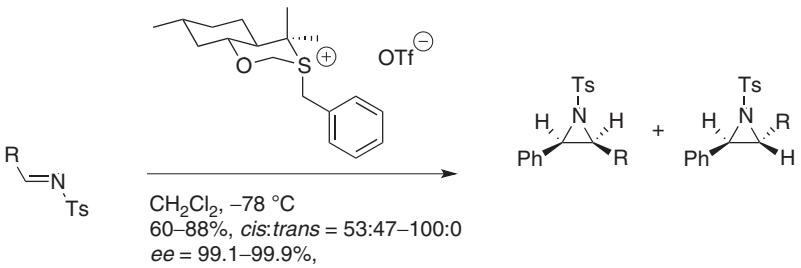
R	R^1	*Yield (%)*	cis:trans	dr
H	*n*-Pr	61	11:89	>98:2
Me	Ph	69	10:90	>98:2
H	^{i}Pr	69	6:94	>98:2
H	Ph	50	14:86	>98:2

1.16.4.2.1.3 Chiral sulfonium ylides

1.16.4.2.1.3.1 Stoichiometric processes

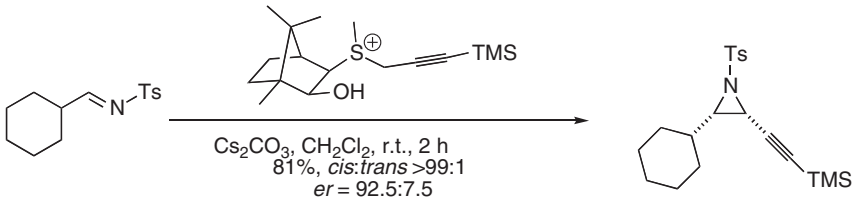
The use of chiral auxiliaries at sulfur has been elegantly exploited by a number of groups.[108] The mechanistic features[174] of the reaction are similar to the epoxidation processes described in the Section 1.16.3.1.1.2.1.

Solladié-Cavallo has described the use of ylides derived from the Eliel's oxathiane for highly diastereo- and enantioselective aziridinations.[175] The reactions are mediated by phosphazene base and proceed in good yields and with very high enantioselectivity (>99% *ee*) (equation 52).



(52)

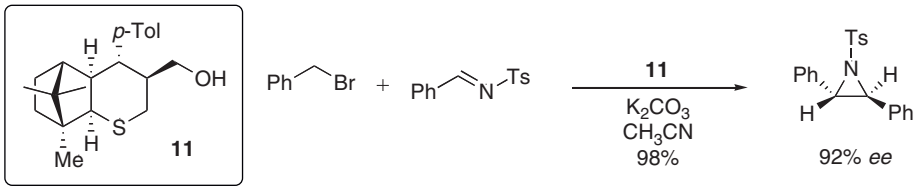
Camphor-derived (3-silyl)propargyl sulfonium ylides react with *N*-tosyl imines to give aziridines in high yield and with excellent diastereoselectivity. The crystallinity of the products enables simple enantiomeric enrichment of the products (equation 53).[176,177]



(53)

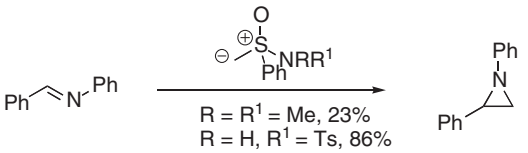
In analogy with the epoxidation reactions described in the Section 1.16.3.1.1.2.1, these reactions proceed via a three-step mechanism, featuring: (a) nucleophilic addition to the C=N bond to give a betaine, (b) rotation of the betaine, and (c) ring closure to give aziridine. A DFT study of these reactions showed that the first step is reversible and that the stereoselectivity is determined at the rotation step, an unusual fact for semistabilized ylide aziridination. This report also showed that the steric demands of the imine substituent are important and can reverse the diastereoselectivity (but not the enantioselectivity) of the reaction.[178]

Terpene-derived sulfide **11** reacts with benzyl bromide in the presence of *N*-tosyl imines to give mainly *trans*-aziridines (*trans*:*cis* = 63-78:37-22) in very high yield and with 89–92% *ee* (*trans*-isomer) (equation 54).[179]



(54)

Higher oxidation state sulfur chirality can also be used to facilitate synthesis of enantioenriched aziridines: *N*-(*p*-tolylsulfinyl) sulfoximines reacts with *N*-aryl imines to give aziridines, and the *N*-substituent is important. So although (dimethylamino) phenyloxosulfonium methylide reacts poorly with imines,[180] *N*-sulfonyl sulfoximines react in excellent yield, (equation 55),[181] and chiral analogs are able to execute stereoselective aziridination. However, the processes normally proceed with poor stereocontrol,[182] as do similar reactions of chiral sulfimides **12**[183]; the analogous chiral allylic ylides react with better (though still modest) enantioselectivity (equation 56).[184]



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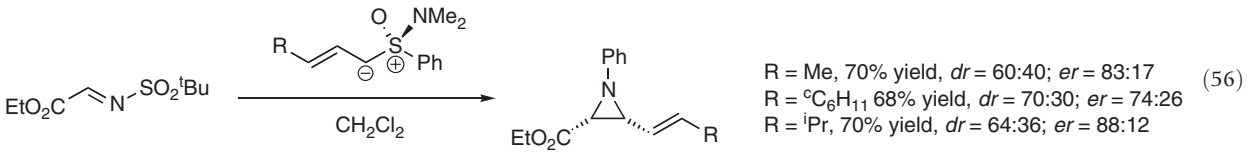

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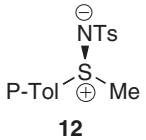
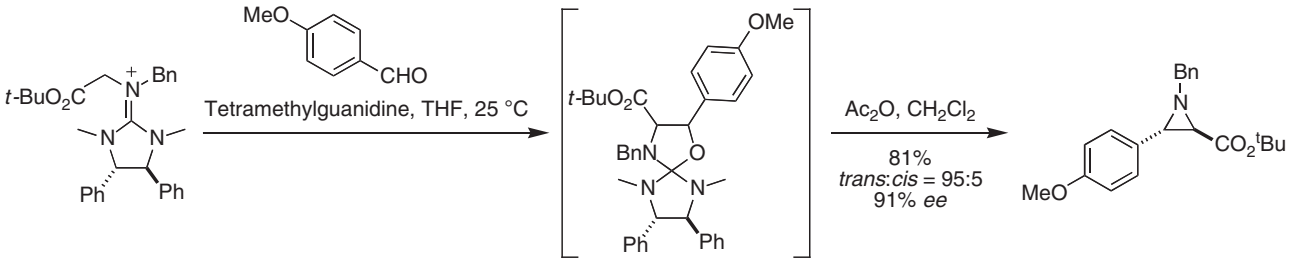


12

1.16.4.2.1.4 Using other ylides

Chiral iminoimidazolinium salts react with aryl aldehydes to give *N*-benzyl 2-carboxyaziridines via guanidinium ylides (equation 57);[185] the area has been reviewed.[186] The mechanism of the process depends on the electron nature of the aromatic substituent, but the key intermediate is presumed to be a spiro aminal.[187]



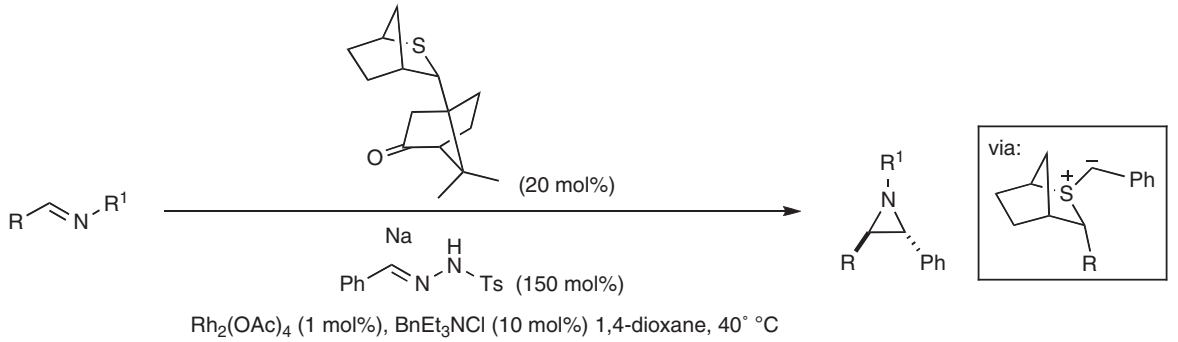
(57)

The same guanidines react with epoxides in the presence of acid to also give aziridines.[188] Chiral epoxides undergo inversion to aziridines of opposite configuration, reinforcing the supposition that an S_N2 mechanism is in operation.

1.16.4.2.2 Catalytic processes

1.16.4.2.2.1 Using carbenoid capture

The use of metal catalysts to generate chiral sulfonium ylides *in situ* from diazo compounds has invigorated asymmetric aziridination, and several elegant and powerful methods have been reported by Aggarwal and coworkers. Optimized processes use sulfonyl hydrazones as stabler precursors to the necessary diazo intermediates, which when generated react with the catalyst (often Rh(I)) to give a metal carbenoid, which is trapped by the nucleophilic chiral sulfide to give a chiral sulfonium ylide (which reacts with imine present in the reaction medium), thereby concomitantly regenerating the metal catalyst. These chiral sulfonium ylides react with a range of imines (including *N*-sulfonyl, phosphinyl, and carbamoyl substrates) to give aziridines with acceptable diastereo- and enantiocontrol (equation 58 and **Table 41**).[189] Because the imines can bear tractable substituents (such as 2-(trimethylsilyl)ethylsulfonyl (SES) and Dpp groups), the method offers significant advantages over other process.[190]



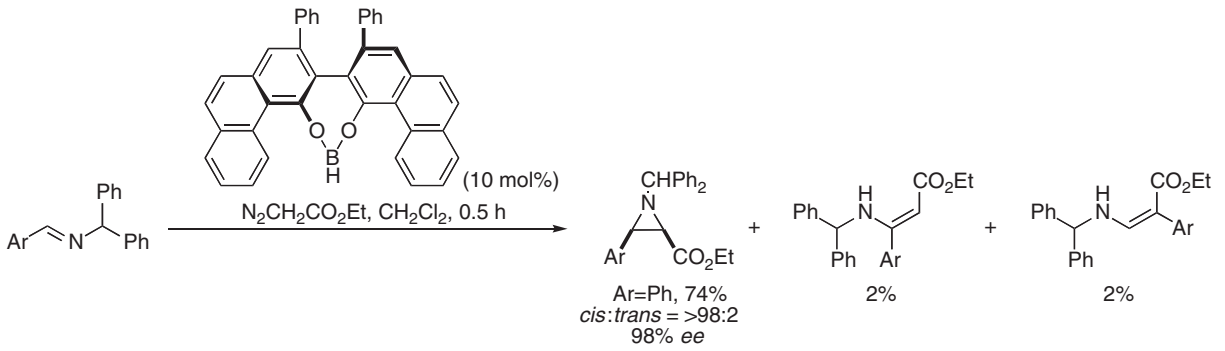
(58)

Table 41 Sulfonium ylide aza-Darzens reaction using carbene capture[191]

R	*R*^{1}	*Yield (%)*	cis:trans	ee_{cis}	ee_{trans}
4-ClC_6H_4	SES	82	33:67	81	98
4-ClC_6H_4	TcBOC	56	14:86	90	94
E-PhCH=CH	SES	59	11:89	–	94

1.16.4.2.2.2 Using chiral Lewis acids

Asymmetric Lewis acid-catalyzed imine aziridination was first reported in the late 1990s and was only moderately stereoselective.[192] Axially chiral vaulted Lewis acids are more effective mediators, with the bisnaphthol boronates 3,3′-diphenyl-2,2′-bi-1-naphthalol, (*R*)-3,3′-diphenyl-2,2′-bi-1-naphthol and 2,2′-diphenyl-(4-biphenanthrol)[193] reported by Wulff et al., mediating highly diastereo- and enantioselective aziridination processes. High-yielding and stereoselective reactions occur between EDA and *N*-benzhydryl[194,195] and *N*-dianisyl[196] imines to give *cis*-aziridines (equation 59 and **Table 42**). The reactions are operationally simple, with catalysts typically prepared *in situ* from the commercially available diols and BH_3. The *N*-substituents do not activate aziridines to ring opening, which may necessitate *N*-unmasking and activation, but the processes are of utility and have been used to deliver efficient syntheses of chloroamphenicol[197] and the LFA – 1 antagonist BIRT-377.[198] The protocol has been refined to allow the preparation of *trans*-aziridines.[199] The active catalytic species in the reaction has been shown to be a boroxinate (BOROX) Brønsted acid.[200]



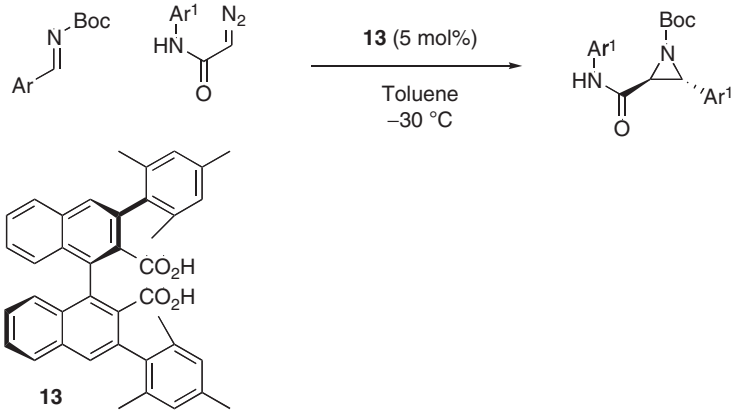
(59)

Table 42 Vaulted Lewis acid-catalyzed aza-Darzens reaction

Ar	*Yield (%)*	cis:trans	ee *(%)*
p-BrC_6H_4	64	16:1	97
2-Furyl	55	16:1	95
o-MeC_6H_4	51	3:1	98
2-Naphthyl	70	30:1	97
p-$AcOC_6H_4$	67	40:1	96
p-$NO_2C_6H_4$	68	11:1	91
^{n}Pr	54	>98:2	91
Cyclohexyl	72	35:1	96

The scope of the Wulff procedure was limited by the necessity to use preformed imines, particularly a problem when less-stable aliphatic imines are demanded. This limitation was removed by the development of a three-component method in which the imine is formed *in situ*.[201] The methodology has been shown to involve rapid amine-directed self-assembly of the BOROX catalyst.[202]

Organocatalysis has recently been shown to be applicable to asymmetric aza-Darzens-like reactions of diazocarbonyls and carbonyl compounds; the catalysts are Brønsted acids. For instance, *trans*-aziridines are obtained in high *ee* on reaction of diazoacetamides with aryl imines in the presence of axially chiral dicarboxylic acid **13** (equation 60 and **Table 43**).[203]

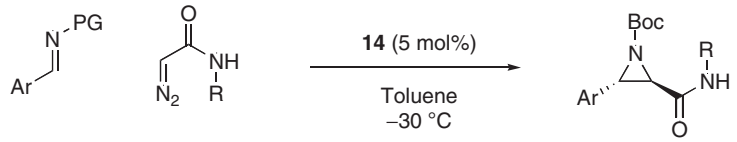


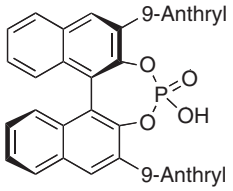
(60)

Table 43 Axially chiral biscarboxylate catalysis of asymmetric aza-Darzens reaction

Ar	*Ar*^{1}	*Yield (%)*	dr	ee *(%)*
Ph	Ph	61	90:10	97
p-Tol	Ph	51	73:27	99
Ph	4-$OMeC_6H_4$	61	87:13	97

Planar asymmetric phosphorus-based acids have also been used to effect asymmetric aza-Darzens reactions; anthryl-substituted binapthyl phosphoric derivative **14** has been reported to mediate the preparation of chiral *trans*-aziridine 2-craboxamides from imines and diazoacetamides (equation 61 and Table 44),[204] whereas silyl-substituted phosphoric acid **15** is an effective catalyst for preparation of *cis*-aziridine 2-carboxylates from diazoacetate and *in situ*-generated glyoxyl imines (equation 62 and Table 45).[205]

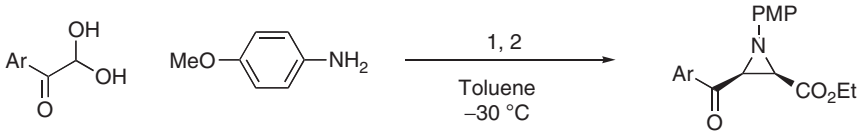


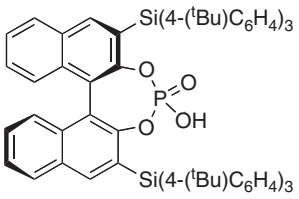


14 (61)

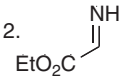
Table 44 Bi(anthryl)napthylphosphonic acid catalysis of asymmetric aza-Darzens reaction

Ar	*Ar*[1]	*Yield (%)*	dr	ee *(%)*
Ph	Ph	95	>95:5	92
Ph	4-OMeC$_6$H$_4$	97	>95:5	93
p-Tol	4-OMeC$_6$H$_4$	90	>95:5	88
4-Br-C$_6$H$_4$	4-OMeC$_6$H$_4$	95	>95:5	90





15

1. **15** (2.5 mol%), $MgSO_4$, r.t.
2. 

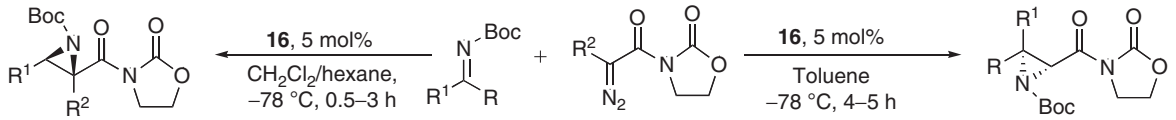
, toluene, –30 °C

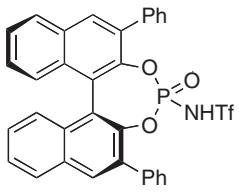
(62)

Table 45 Bi(silyl)napthylphosphonic acid catalysis of asymmetric aza-Darzens reaction

Ar	*Yield (%)*	ee *(%)*
Ph	95	97
2-Thienyl	100	92
4-F-C$_6$H$_4$	100	94

A stereodivergent aziridination using a chiral Brønsted acid has been reported by Maruoka et al.[206] Aziridination of *N*-Boc imines by *N*-(diazo) acyl oxazolidinones in the presence of 5 mol% **16** gives trisubstitued aziridines in good yields and with 74–98% *ee*. The absolute stereochemical course of the reaction depends on the substrate's structure. 2-Alkyl (diazo)acyl oxazolidinone reacts with aldimines to give *cis*-2S-aziridines, whereas ketimines give *trans*-2R-products (equation 63 and Table 46).





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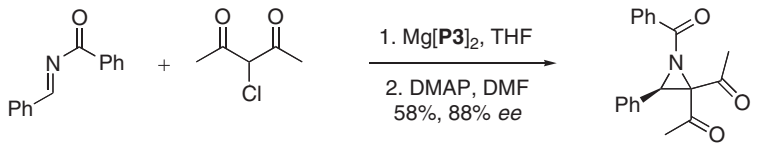
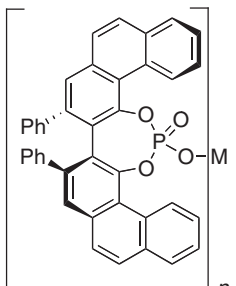
(63)

Table 46 Enantiodivergent binaphthylphosphoramidate-catalyzed aza-Darzens reaction

R	R^1	R^2	*Yield (%)*	ee *(%)*
H	Ph	Me	86	83
H	3-Tolyl	Me	77	80
H	4-Cl-C_6H_4	Me	80	92
H	3-NO_2-C_6H_4	Me	80	89
H	3-OMe-C_6H_4	Me	80	74
H	4-Cl-C_6H_4	Et	83	91
$CO_2{}^tBu$	Ph	H	89	95
$CO_2{}^tEt$	Ph	H	88	92
$CO_2{}^tBu$	4-Tolyl	H	89	98
$CO_2{}^tBu$	3-OMe-C_6H_4	H	80	91

Asymmetric synthesis of trisubstituted *N*-benzoyl aziridines can also be accomplished by use of chiral 'vaulted' biphenanthrenol phosphates, which catalyze the aziridination of benzoyl aldimines by chloromalonates.[207] The reactions proceed in 79–92% *ee* (equation 64).



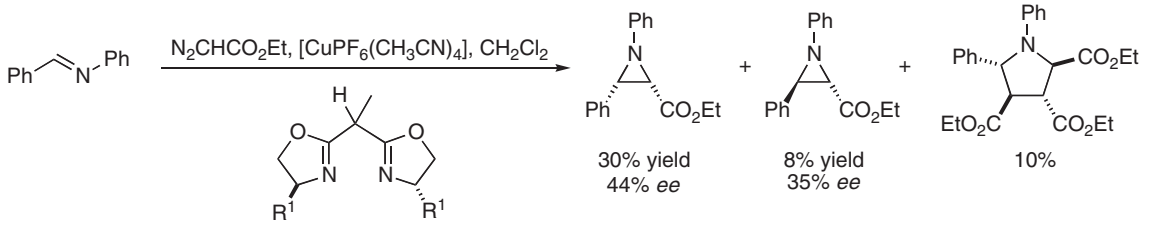


P3 (*R*)

(64)

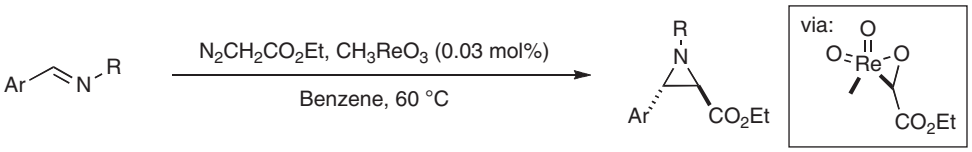
1.16.4.2.2.3 Using chiral metal carbenoids

Racemic copper-catalyzed imine aziridination using diazoacetate was first reported in the mid-1990s using *N*-aryl aldimines as substrates.[208] The intermediacy of azomethine ylides in these reactions is indicated by the frequent observation of pyrrolidine cycloadducts as side products, as in Jacobsen's report of the use of chiral bis-oxazoline–Cu(I) complexes to effect imine aziridination (equation 65).[209] By modern catalysis standards, the reactions are inefficient, any enantioselectivity observed is often mediocre, and successful reaction often demands synthetically intractable *N*-substituents.



(65)

As mentioned in the Section 1.16.4.1.4, copper and rhodium catalysts dominate the methods reported for carbenoid aziridination of imines, but there are notable reports of the use of other catalytic metals. For instance, substoichiometric MTO (methylrhenium trioxide, CH_3ReO_3) catalyzes reaction of imines (both *N*-alkyl and *N*-aryl) with EDA to give *trans*-aziridines.[210] In addition to being very stereoselective, the process is also chemoselective, with few by-products observed. As there is no evidence of pyrrolidine formation, this implies that azomethine ylides are not involved, and an oxarhenacycle was instead suggested as the key intermediate (equation 66 and Table 47).

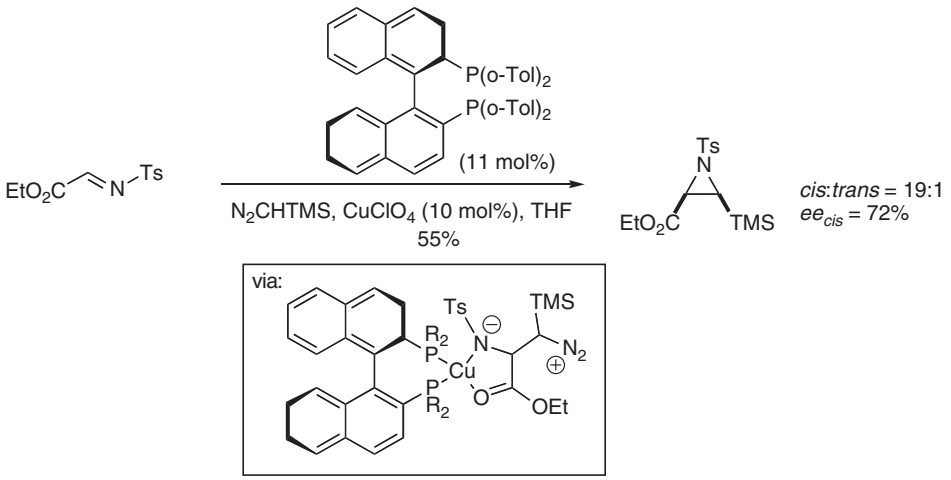


(66)

Table 47 Methylrhenium trioxide-catalyzed aza-Darzens reaction

Ar	*R*	*Yield (%)*
Ph	Ph	87
Ph	^{n}Bu	92
p-$MeOC_6H_4$	^{n}Bu	94
p-$MeOC_6H_4$	Ph	92
p-$O_2NC_6H_4$	^{n}Bu	91
Ph	^{n}Hex	93
p-MeC_6H_4	^{n}Hex	93
2-Naphthyl	^{n}Hex	96
p-$O_2NC_6H_4$	^{n}Bu	91

Reaction of copper catalysts with diazo compounds cannot always be assumed to lead inevitably to a metal carbenoid. Reactions of *N*-sulfonylimines with TMSD with $CuClO_4$ in the presence of (*R*)-Tol-BINAP are more enantioselective than the Jacobsen chemistry, but the process seems to proceed via an aza-Darzens-like mechanism (equation 67).[211] However, the same reaction using diazoacetate does involve the copper carbenoid.

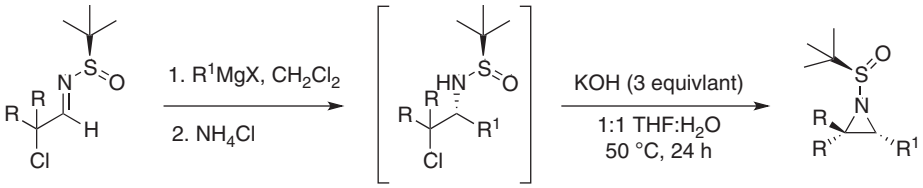


(67)

1.16.4.3 Aziridines by Nucleophilic Addition to 2-Haloimines

Reduction or alkylation of 2-haloimines is a productive method for aziridine synthesis via the corresponding amide anion intermediate.

Chiral *N*-sulfinyl aziridines may be prepared by nucleophilic addition of Grignard reagents to 2-chloro aldimines[212] and 2-chloro-ketimines.[213] The reactions proceed via the amide anion which cyclizes either on warming the reaction mixture or treatment with KOH (equation 68 and Table 48).



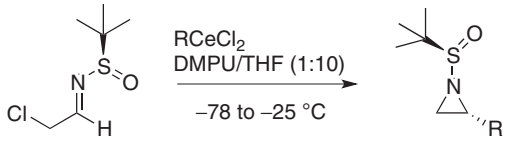
(68)

Table 48 Chiral aziridine synthesis by nucleophilic addition of Grignard reagents to chiral imines

R	*R*^{1}	*Yield (%)*	dr
Me	Et	76	96:4
Et	Et	66	92:8
cyclo-C_5H_{10}	Et	63	92:8
Me	Ph	73	99:1
Et	Ph	57	96:4
cyclo-C_5H_{10}	Ph	20	70:30
Me	$CH{=}CH_2$	65	94:6
Et	$CH{=}CH_2$	62	93:7
cyclo-C_5H_{10}	$CH{=}CH_2$	56	86:14
Me	$CH_2CH{=}CH_2$	57	62:38
Et	$CH_2CH{=}CH_2$	45	62:38
cyclo-C_5H_{10}	$CH_2CH{=}CH_2$	41	70:30

Reduction of 2-chloroimines can also be used to prepare chiral *N*-sulfinyl imines, and the process can be controlled to deliver either diastereomer by the choice of reducing agent.[214]

Organocerium reagents also react efficiently with the Ellman imines derived from chloroacetaldehyde, and the aziridine is the only product isolated (equation 69 and Table 49).[215]

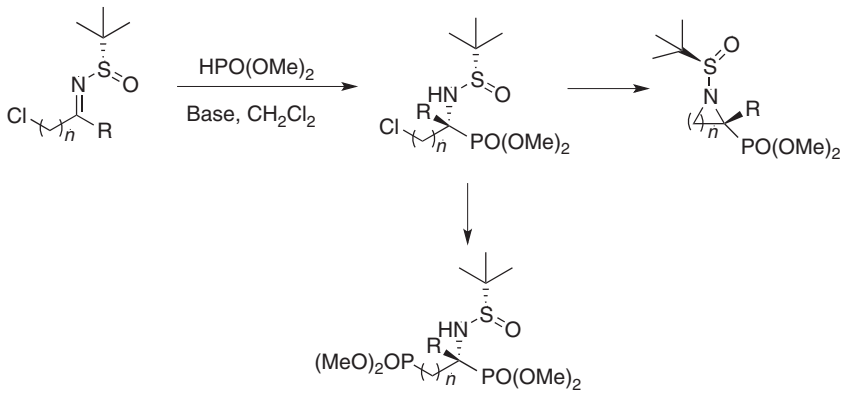


(69)

Table 49 Chiral aziridine synthesis by nucleophilic addition of organocerium reagents to chiral imines

R	*Yield (%)*	dr
n-Bu	86	99:1
^{t}Bu	76	99:1
$CH_2CH{=}CH_2$	83	99:1
Ph	92	92:8
4-Cl-C_6H_4	84	85:15

Dimethyl phosphite adds to chiral *t*-butylsulfinyl 2-chloroimines to give aziridine products (equation 70).[216]



(70)

Acknowledgment

Dedicated in the memory of Sarah Hicks, a talented young chemist, who died at Hillsborough on 15 April 1989, JFT96.

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1.17 Addition of Heteroatom Nucleophiles to C=O and C=N pi Bonds

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Glossary

Acetal Acetal means a functional group that contains two alkoxy or aryloxy groups connected to the same saturated carbon. The two alkoxy or aryloxy groups can be the same or different. The center-saturated carbon has a tetrahedral geometry. In organic synthesis, acetals are a comment protecting groups for ketones and aldehydes.

Aminal Aminal represents a type of compounds that contains two-amine group attached to the same saturated carbon. Aminals have similar structures like that of acetals.

Asymmetric catalysis Asymmetric catalysis describes one type of catalysis that can catalyze the transformation of racemic and prochiral substrates into enantioenriched products.

Hydrophosphonylation Hydrophosphonylation is a chemical reaction that involves the addition of phosphite or phosphite oxide to alkene, aldehyde, imine or other unsaturated organic compounds. The reaction usually needs catalyst to promote.

Organocatalysis Organocatalysis refers to one kind of catalysis that uses small-molecule organic compounds as activators to catalyze chemical reactions. The term normally represents chiral organocatalysis.

1.17.1 Introduction

The addition of heteroatom nucleophiles to C═O and C═N pi bonds has been developing rapidly in the past decade, for the purpose of natural products synthesis and preparation of biologically active molecules. This chapter deals with methodology development in this area; particular focus has been on the asymmetric studies, as well as the use of these reactions in the context of natural products synthesis. The chapter has been organized by different heteroatoms (nitrogen, oxygen, phosphorus, sulfur, and selenium) in their nucleophilic additions to C═O and C═N pi bonds.

1.17.2 Additions to C═N pi Bonds

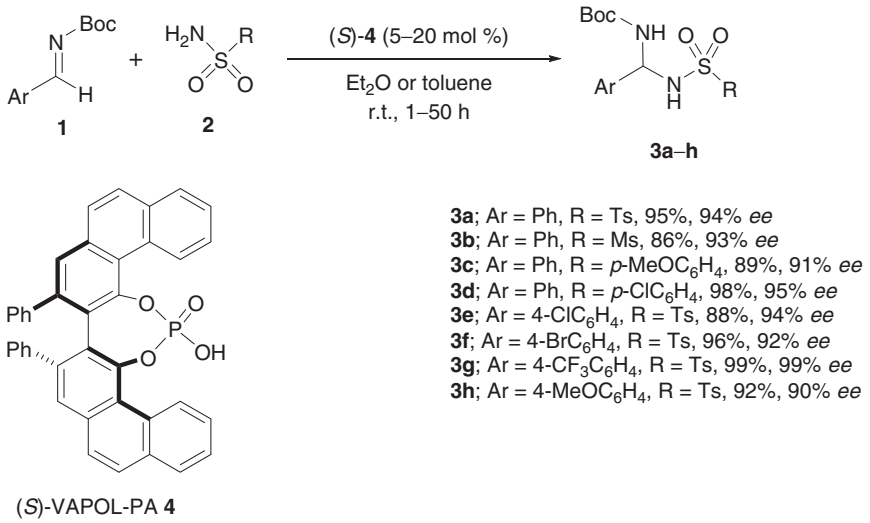
1.17.2.1 Addition of Nitrogen

1.17.2.1.1 Scope

Protected *N,N′*-aminals, obtained from the addition of nitrogen nucleophiles to imines, are an important class of biologically active compounds, which are present within retro-inverso peptide mimics.[1] With the pioneering work by Goodman, the retro-inverso peptide mimics have found wide application in medicinal chemistry.[2] The protected *N,N′*-aminals were also found as a common structure in an array of natural products that have drawn great attention from organic chemists due to both their fascinating structures and their impressive bioactivities.[3] Depending on the differences in nitrogen and C═N sources, the preparation of aminals can be broken down into three different types: (1) the addition of amides to performed imines, (2) the addition of imides to performed imines, and (3) the addition of nitrogen to imines generated *in situ*. Both chiral and achiral examples and synthetic utility associated with recent developments are shown in each section.

1.17.2.1.2 Addition of amides to preformed imines

The amidation of imines provides a straightforward way for the preparation of aminals. However, due to the poor nucleophilicity and the higher pKa values (17–25)[4] of amide derivatives, this method is more challenging than the well-developed addition of carbon nucleophiles to imines. In 2005, the Antilla group reported a seminal study in this area, which described an efficient method for the catalytic asymmetric formation of aminals.[5] As shown in Scheme 1, with a chiral phosphoric acid, addition of sulfonamides **2** to Boc-protected imines **1** afforded the chiral aminals **3a–h** with excellent yields (up to 99%) and excellent enantioselectivities (up to 99%). VAPOL phosphoric acid (*S*)-**4** provided relatively higher enantioselectivities than BINOL-based phosphoric acids.



3a; Ar = Ph, R = Ts, 95%, 94% *ee*
3b; Ar = Ph, R = Ms, 86%, 93% *ee*
3c; Ar = Ph, R = *p*-MeOC$_6$H$_4$, 89%, 91% *ee*
3d; Ar = Ph, R = *p*-ClC$_6$H$_4$, 98%, 95% *ee*
3e; Ar = 4-ClC$_6$H$_4$, R = Ts, 88%, 94% *ee*
3f; Ar = 4-BrC$_6$H$_4$, R = Ts, 96%, 92% *ee*
3g; Ar = 4-CF$_3$C$_6$H$_4$, R = Ts, 99%, 99% *ee*
3h; Ar = 4-MeOC$_6$H$_4$, R = Ts, 92%, 90% *ee*

Scheme 1

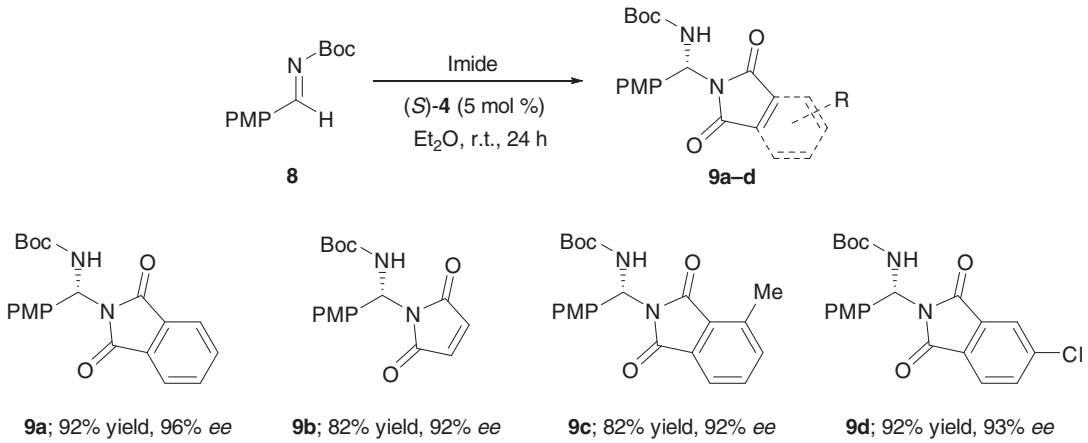
A Cu(II)-catalyzed amidation of imines was developed recently by Zeng et al. (Scheme 2).[6] The reaction of *C*-acylimines **5** with amides **6**, catalyzed by Cu(OTf)$_2$ with PPh$_3$ as ligand, afforded the corresponding aminals **7** in moderate-to-excellent yields. The coordination of copper with both carbonyl and the imine nitrogen was proposed to account for the enhanced reactivity.

1.17.2.1.3 Addition of imides to performed imines

Followed by the initial results of imine amidation (Section: 1.17.2.1.2), the Antilla group further extended the concept to an asymmetric addition of imides to imines (Scheme 3).[7] Chiral VAPOL phosphoric acid (*S*)-**4** is the best catalyst, with the resulting aminals **9** being produced with high enantiopurities by addition of imides to Boc-imine **8**.

EtO
O
N
R1
5
+
R2
NH2
6
Cu(OTf)2 (20 mol%)
PPh3 (20 mol%)
Toluene, r.t., 6–36 h
H
N
NH
7
20 examples
40–95%
Cu2+

Scheme 2

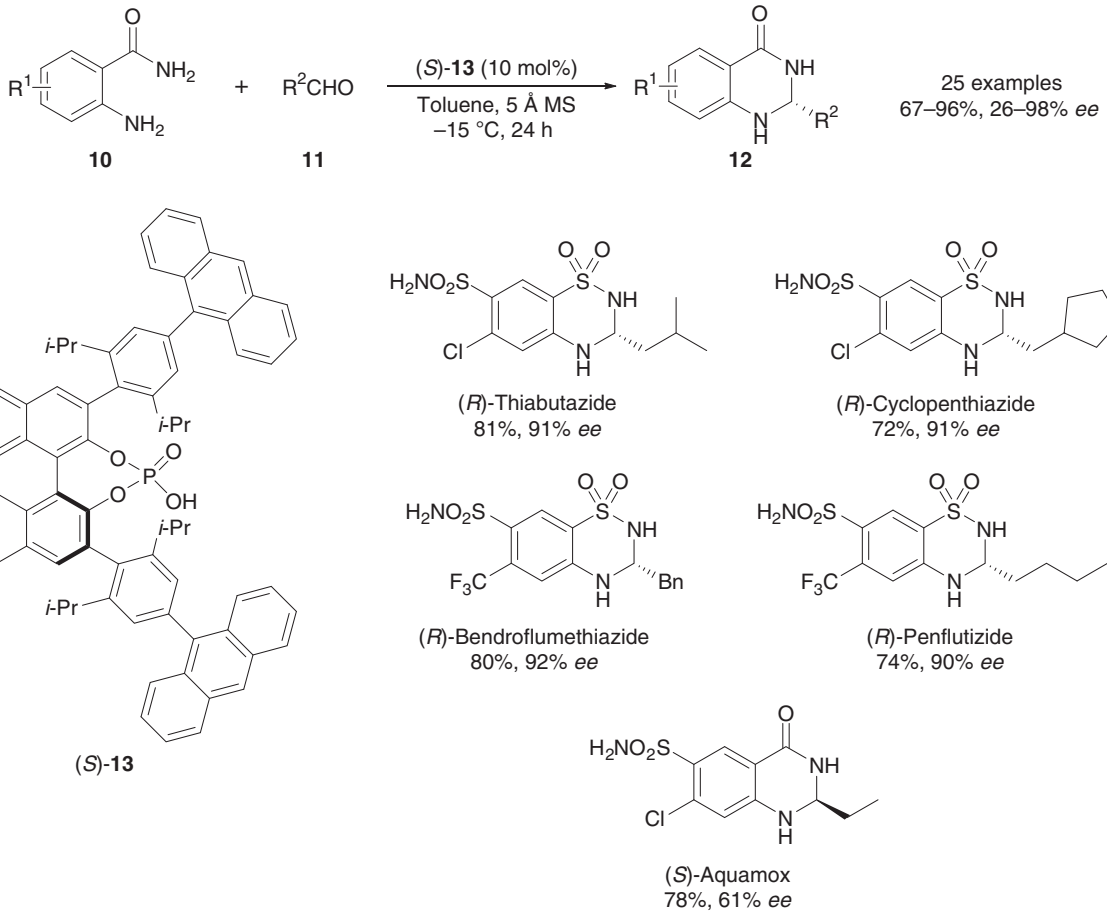


Scheme 3

1.17.2.1.4 Addition of nitrogen to imines generated in situ

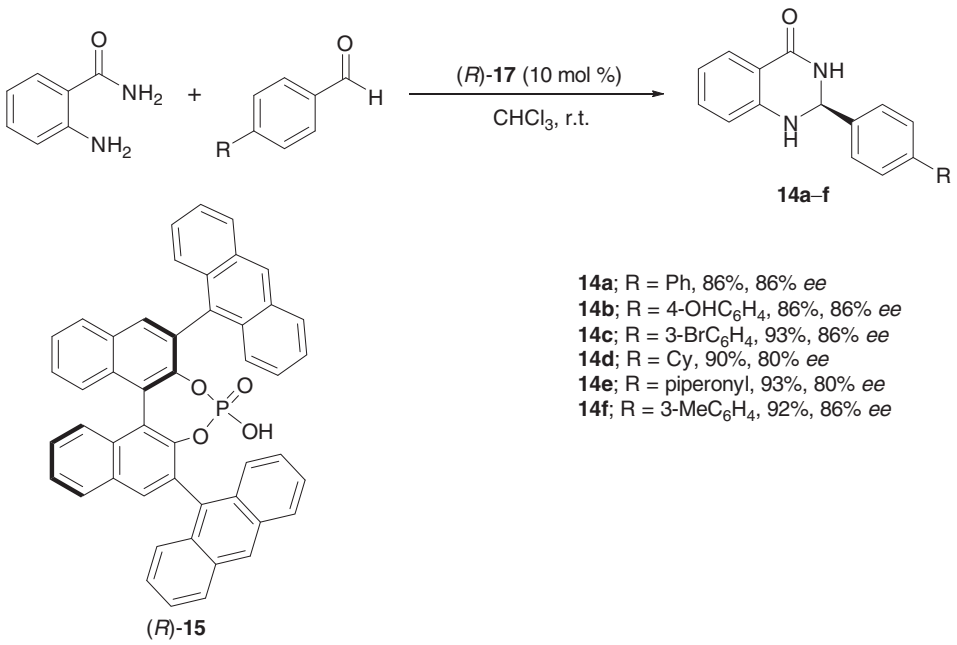
1.17.2.1.4.1 Chiral phosphoric acid-catalyzed addition of nitrogen to imines generated in situ

List and coworkers reported a synthesis of cyclic aminals **12** catalyzed by chiral phosphoric acid (*S*)-**13**, involving the condensation of 2-aminobenzamides **10** with aldehydes **11**, where the *in situ* formed imines were trapped by amides intramolecularly (Scheme 4).[8] Excellent selectivities were observed using aliphatic aldehydes, whereas somewhat low selectivities were obtained for aromatic aldehydes. In addition, the synthetic application of this methodology was highlighted by the one-pot preparation of several bioactive molecules with moderate-to-excellent selectivities.



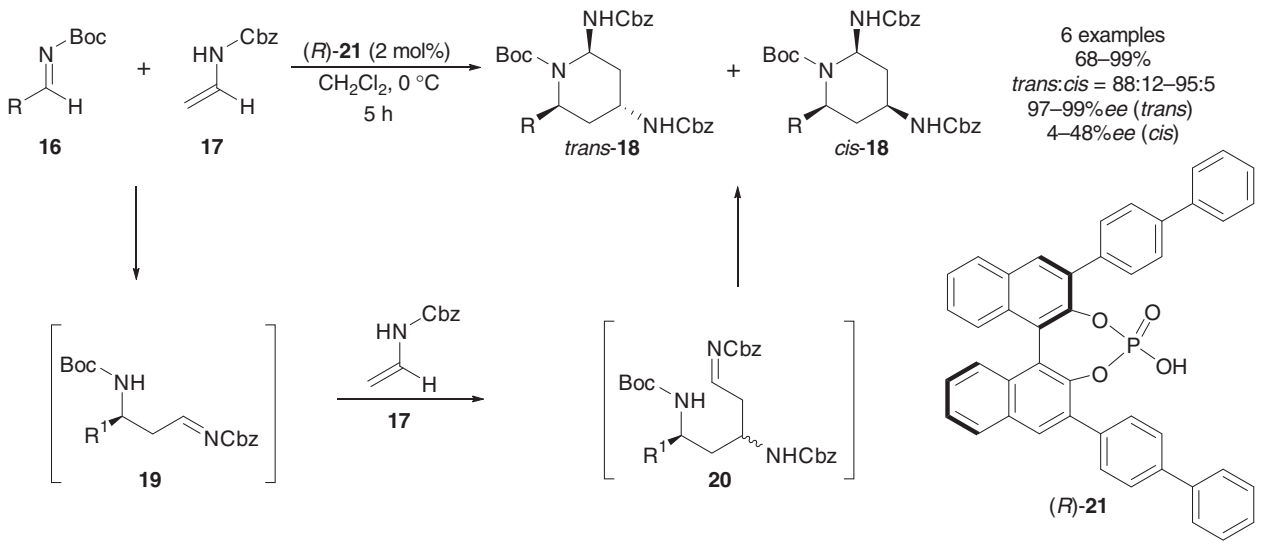
Scheme 4

In the meantime, the Rueping group reported the same type of intramolecular amidation reaction,[9] catalyzed by a 9-anthracenyl BINOL phosphoric acid (*R*)-**15**, allowing for the formation of 2-aromatic cyclic aminals **14** with good enantioselectivities. This reaction (Scheme 5) provided a complementary approach to the synthesis of cyclic aminals **12** derived from aliphatic aldehydes (Scheme 4).



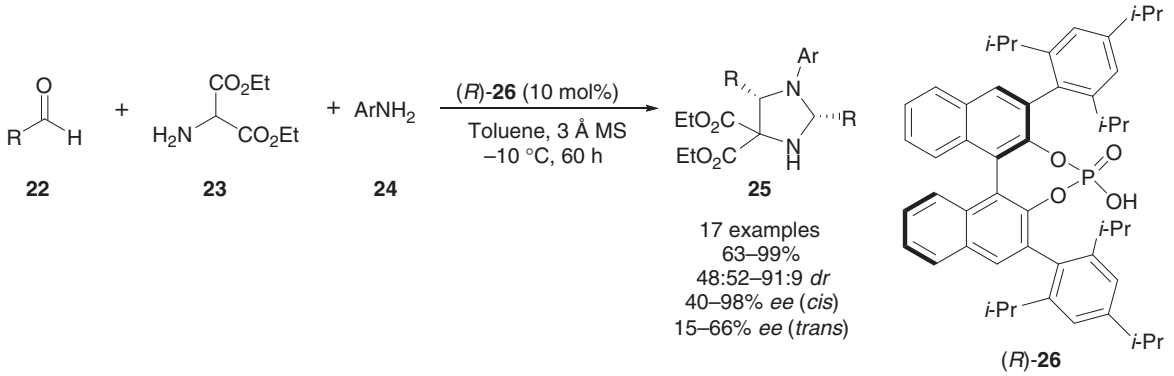
Scheme 5

In 2007, the Terada group[10] developed a chiral phosphoric acid-catalyzed asymmetric cascade process involving the following steps: (1) *N*-acyl aldimines **16** undergo aza-ene-type reaction with mono-substituted enecarbanates **17**, (2) the formed imines **19** undergo a second aza-ene reaction, and (3) the intramolecular amidation of the *in situ* generated imines **20** leads to the biologically important piperidine derivatives **18** (Scheme 6). With *para*-biphenyl-substituted BINOL phosphoric acid (*R*)-**21** in CH_2Cl_2 at 0 °C, good diastereoselectivities and excellent enantioselectivities for the major *trans*-isomer were obtained. It is noteworthy that with an achiral phosphoric acid, only two out of four possible diastereomers were formed with 2:1 selectivity (*trans:cis*), which is the identical preference with chiral catalysts. It was proposed that the chiral phosphoric acids induced the double asymmetric processes in the first two steps. The stereoselectivity of the final amidation step was proposed to proceed via substrate control.



Scheme 6

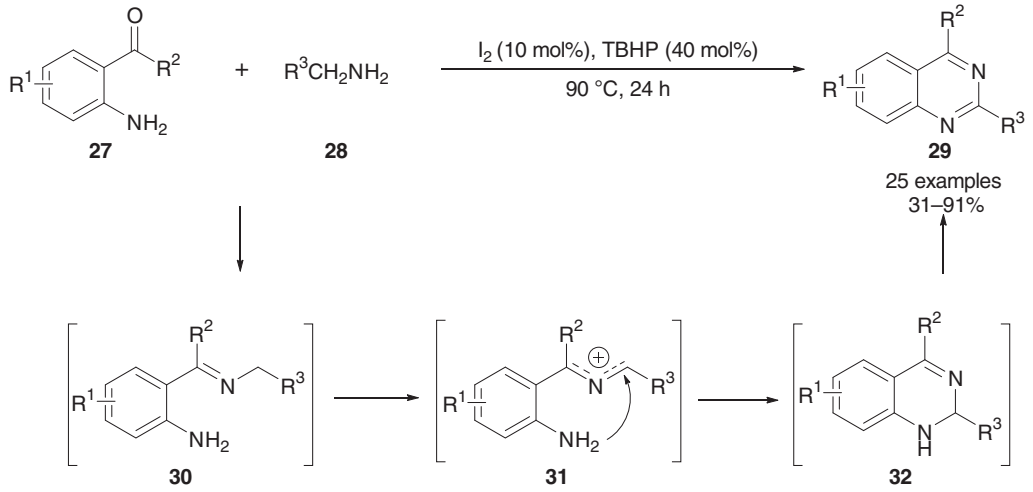
Gong et al. described a chiral phosphoric acid (*R*)-**26**-catalyzed three-component reaction, which incorporates aldehydes **22**, aminomalonate **23**, and anilines **24**, via the 1,3-dipolar cycloadditions of *in situ* formed azomethine ylides and imines, allowing for the formation of imidazolidines **25** with good yields and moderate-to-good diastereo- and enantioselectivities (Scheme 7).[11]



Scheme 7

1.17.2.1.4.2 *Novel catalytic systems involving the addition of nitrogen to imines generated* in situ

Starting from easily available 2-aminobenzophenones **27** and benzylic amines **28**, the Wang group reported an efficient approach for the synthesis of quinazolines **29**, catalyzed by I_2 and *tert*-butyl hydroperoxide (TBHP) (Scheme 8).[12] Moderate-to-high yields of the medicinally valuable quinazolines were obtained in one pot, which involved four cascade steps: (1) formation of imine **30**, (2) oxidation to form the cationic imine intermediate **31**, (3) amidation to generate the aminal **32**, and (4) further oxidation to furnish the final quinazoline products **29**.



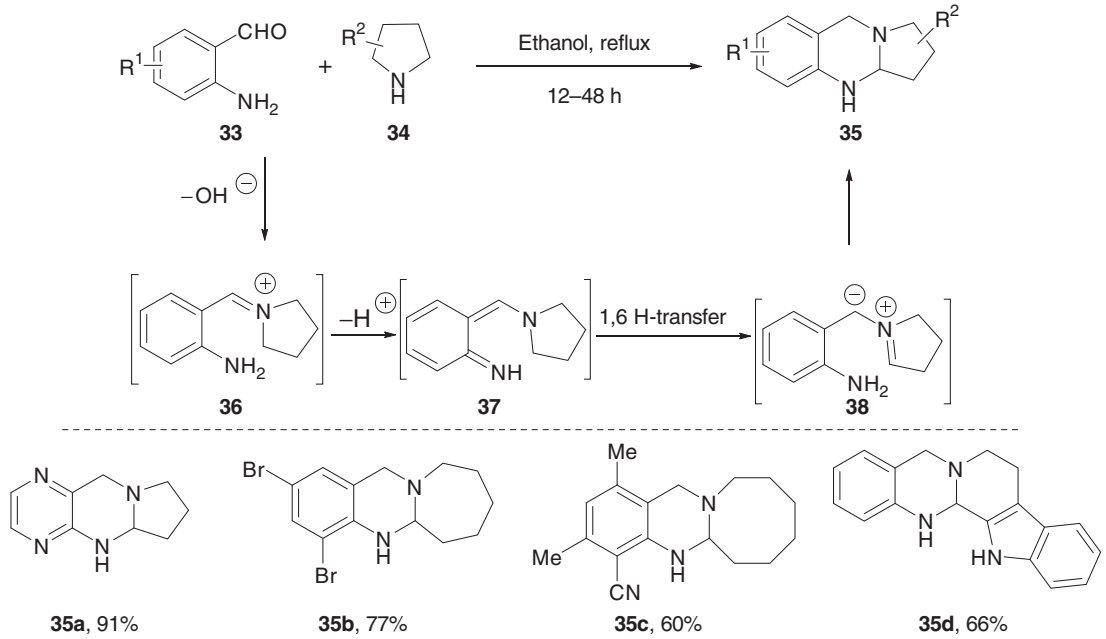
Scheme 8

In 2007, Seidel and coworkers developed a novel system for the synthesis of ring-fused aminals (Scheme 9).[13] Without any catalysts or additives, the reaction between aminobenzaldehydes **33** and cyclic amines **34** in refluxing ethanol provided the formation of ring-fused aminals **35** with different ring sizes and substitutions in good yields. It was proposed that the formation of iminium ion **36** undergoes rearrangement to generate the azoquinone methide **37**. Subsequently, 1,6-hydrogen transfers to form the dipolar azamethine ylides **38**, which undergo intramolecular amidation to furnish the final product **35**.

Various combinations of amines and aldehydes, either catalyzed by Lewis/Bronsted acid or without catalyst, were also presented to generate structurally different cyclic aminals.[14]

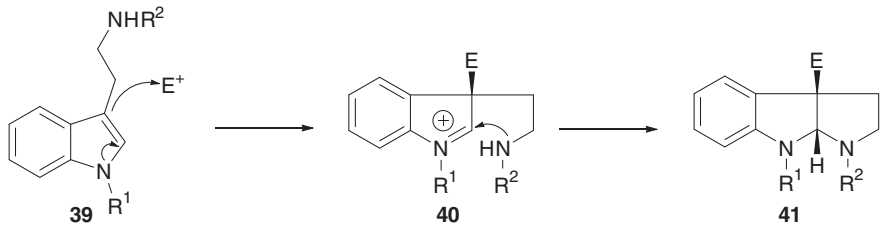
1.17.2.1.4.3 *Construction of pyrroloindolines via addition of nitrogen to imines generated* in situ

Pyrroloindolines represent an important class of alkaloid natural products,[3] which have shown several promising biological activities.[15] Biogenetically, pyrroloindolines **41** can arise from electrophilic attack on a tryptophan or tryptamine **39** unit at the indole C-3 position, followed by capture of the resulting C-2 iminium ion **40** by the side-chain nitrogen (equation 1). Herein,



Scheme 9

several examples developed recently using this strategy are presented. Based on the difference in electrophiles, this section is separated into three sub-sections: carbon electrophiles, nitrogen electrophiles, and halogen electrophiles.



(1)

1.17.2.1.4.3.1 Carbon electrophiles

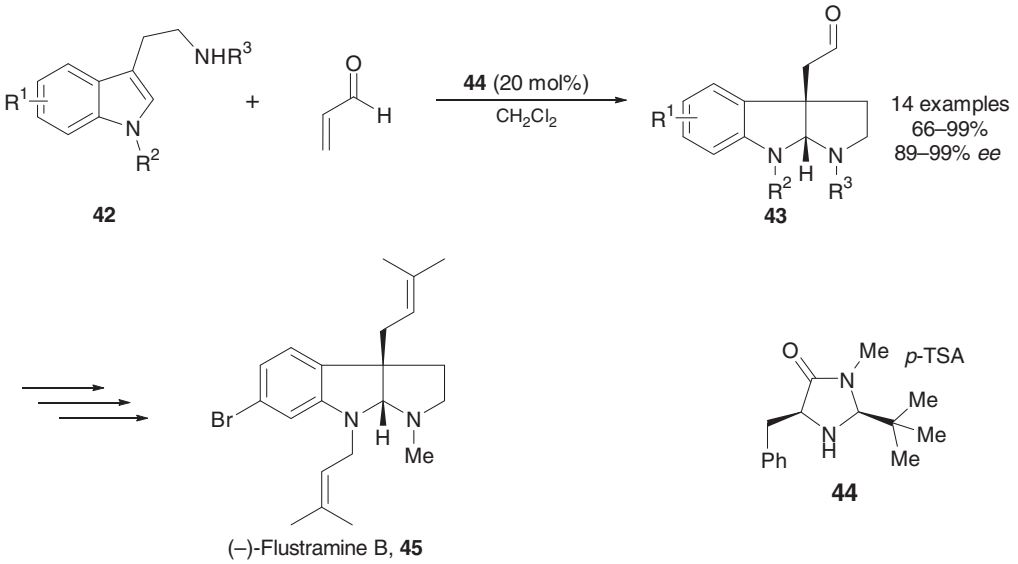
In 2004, the MacMillan group reported a seminal study on the catalytic asymmetric approach for the formation of pyrroloindolines **43** in good yields and with excellent enantioselectivities, where tryptamines **42** were added to acrolein in the presence of chiral imidazolidinone catalysts **44** (Scheme 10).[16] Enantioselectivity was strongly solvent-dependent: a high-dielectric-constant solvent (MeOH) gave one enantiomer (+77% *ee*) whereas the low-dielectric-constant solvent (toluene) provided the opposite selectivity (−84% *ee*). Application of the protocol to the synthesis of natural products was demonstrated by the first asymmetric synthesis of (−)-flustramine B **45**.

The same group further developed a concise total synthesis of (−)-minfiensine with a key feature of a cascade organocatalysis sequence to build the tetracyclic pyrroloindoline framework.[17]

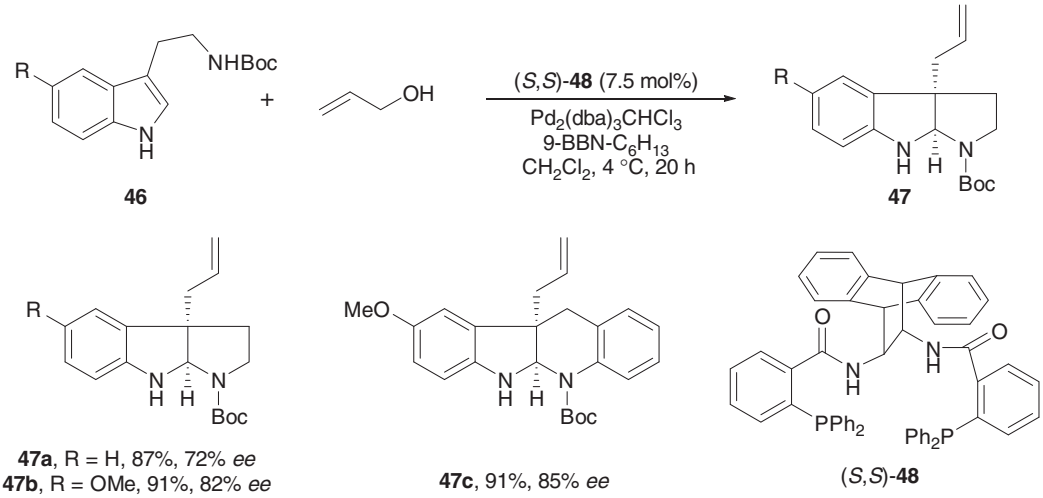
In 2006, inspired by Tamaru's work on the C3-selective indole allylation,[18] the Trost group described an asymmetric allylation reaction starting from tryptamines **46** and allylic alcohols, catalyzed by palladium complex with its chiral ligand (*S*,*S*)-**48** (Scheme 11).[19] The trialkyl borane is critical for its reactivity via activation of allylic alcohol and can influence the enantioselectivities.

By application of a cyclopropanation strategy, the Qin group[20] developed an interesting protocol for the synthesis of pyrroloindoline derivatives. Starting from a diazotryptamine **49**, a three-step sequence occurred, including copper-catalyzed intramolecular cyclopropanation to form **50**, ring opening to generate **51**, and iminium amidation to furnish **52**. As shown in Scheme 12, (±)-vincorine **53** was obtained efficiently from the well-designed diazo tryptamine **49** by this protocol.

Garg and coworkers reported a different approach for the synthesis of pyrroloindoline, which comprised an interrupted Fisher indoline synthesis (Scheme 13).[21] Acetic acid was used to catalyze the reaction of phenylhydrazines **54** with α-disubstituted aldehydes **55** to form the enamine species **57**, which undergo 3,3′-signatropic rearrangement and rearomatization to generate the anilines **58**. Subsequent cyclization with loss of NH_3 afforded the iminium intermediate **59**, which reacted with the proximal sulfonamide and formed the final products **56**. Corresponding pyrroloindolines **56** were obtained in good yields by this efficient cascade process with diverse substrates. Very recently, List reported asymmetric Fischer indole synthesis also involve the addition of nitrogen to *in-situ* formed iminium process.[22]



Scheme 10



Scheme 11

1.17.2.1.4.3.2 Nitrogen electrophiles

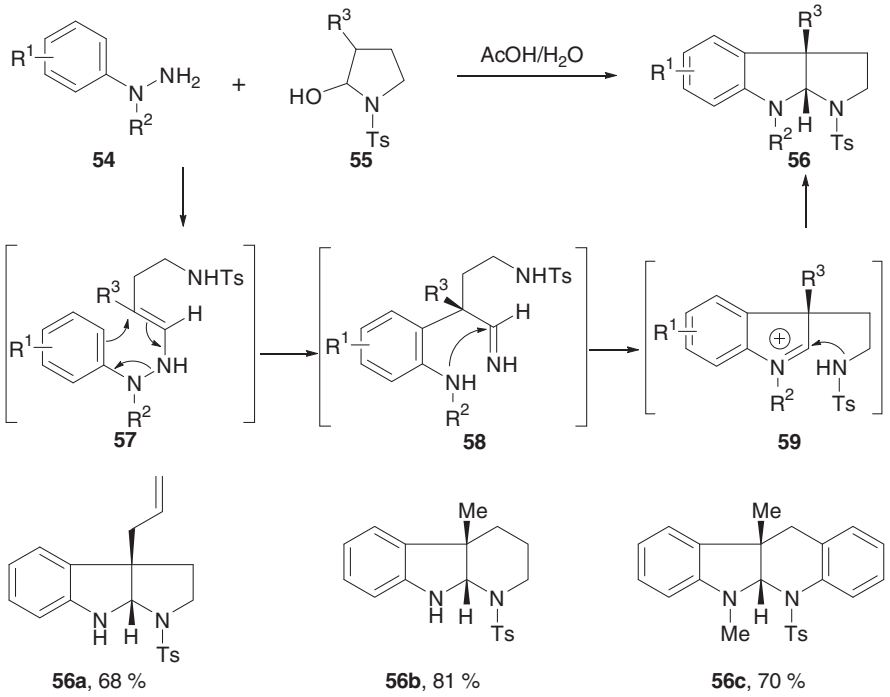
Compared to carbon electrophiles, nitrogen as electrophile is less developed due to its high electronegativity. Recently, the Baran group reported an elegant strategy of such a method involving a novel indole–aniline coupling reaction (Scheme 14).[23] The reaction of tryptamine **60** with aniline **61** provides the amination product **62** promoted by *N*-iodosuccinimide (NIS). A mechanistic study indicates that a reactive phenylnitremiun iodide pair **63** was formed from the reaction of *N*-iodoaniline with NIS, which reacts with tryptamine to generate the reactive iminium intermediate **64**. The utility of this study was demonstrated for the concise synthesis of psychotrimine **65** and several related natural products.

1.17.2.3.4.3.3 Halogen electrophiles

Gouverneur and coworkers reported an organocatalyzed enantioselective fluorocyclization of tryptamines **66**, which comprised the first asymmetric fluoro-promoted cyclization (Scheme 15).[24] Both selectfluor and *N*-fluorobenzenesulfonimide (NFSI) can undergo the fluorination smoothly, and the corresponding fluoro-pyrroloindolines **67** were obtained with moderate-to-good enantioselectivities in the presence of chiral cinchona alkaloid, $(DHQ)_2PHAL$ **68**. For most substrates, using a slight excess of promoter provided somewhat higher selectivities than a catalytic amount.

MeO
NHTs
N
Boc
MeO2C
N2
O
49
CuOTf (5 mol%)
CH2Cl2, r.t., 12 h
82%
NHBoc
CO2Me
MeO
N
Boc
O
50
51
52
53, (±)-Vincorine
Me
Ts

Scheme 12



Scheme 13

1.17.2.2 Addition of Oxygen

1.17.2.2.1 Scope

N,O-aminal motifs, obtained from the addition of oxygen to imines, are found in an array of natural products and biologically active compounds.[25] For example, Figure 1 illustrates several important natural products, with an *N,O*-aminal substructure; these have been shown to exhibit several impressive biological responses, such as antibacterial, antimalarial, and anticancer activities.[26] Moreover, these biological activities are inseparable from the *N,O*-aminal motifs.[27] Depending on the differences in catalyst and C═N sources, the preparation of *N,O*-aminals can be broken down into three different types: (1) chiral phosphoric acid catalyzation of the addition of oxygen to performed imines, (2) addition of peroxide to imines to synthesize oxaziridines, and (3) addition of oxygen to imines generated *in situ*. The synthetic utilities of recent developments are shown in each section.

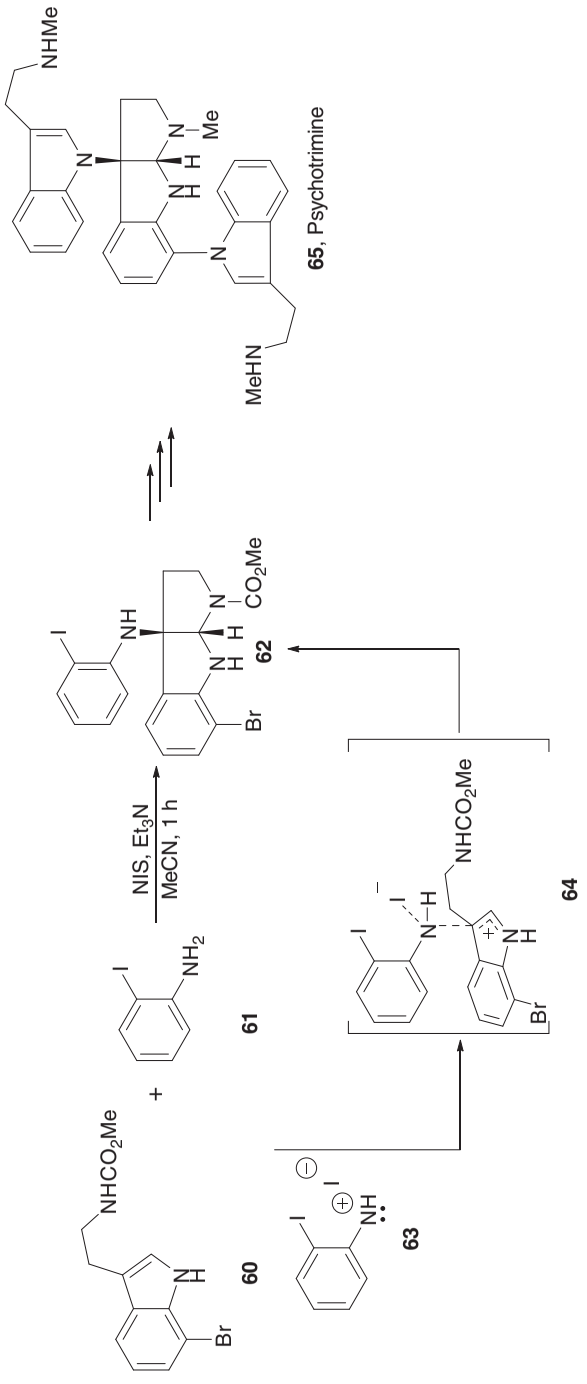
1.17.2.2.2 Chiral phosphoric acids catalyzed the addition of oxygen to performed imines

It has been shown that the biological activities of *N,O*-aminal-containing natural products are closely related to the stereochemistry of the *N,O*-aminal motifs.[28] For this reason, the development of enantioselective methods for the formation of *N,O*-aminal motifs has become important. At the same time, it has proven to be a very challenging topic, with the first report in this area coming from Antilla and coworkers in 2008.[29] As shown in Scheme 16, chiral phosphoric acid (*S*)-**15** is the best catalyst, giving aminals with high enantiopurities by addition of alcohols to *N*-acyl imines. The substrates scope is quite general, with primary alcohols, secondary alcohols, and tertiary alcohols delivering excellent selectivities with respective aminals **69a–j**. In addition, *N*-acyl imines with different substituted groups all furnished the aminals **69k–w** with high enantioselectivities, whereas aliphatic imine provided relatively lower selectivity.

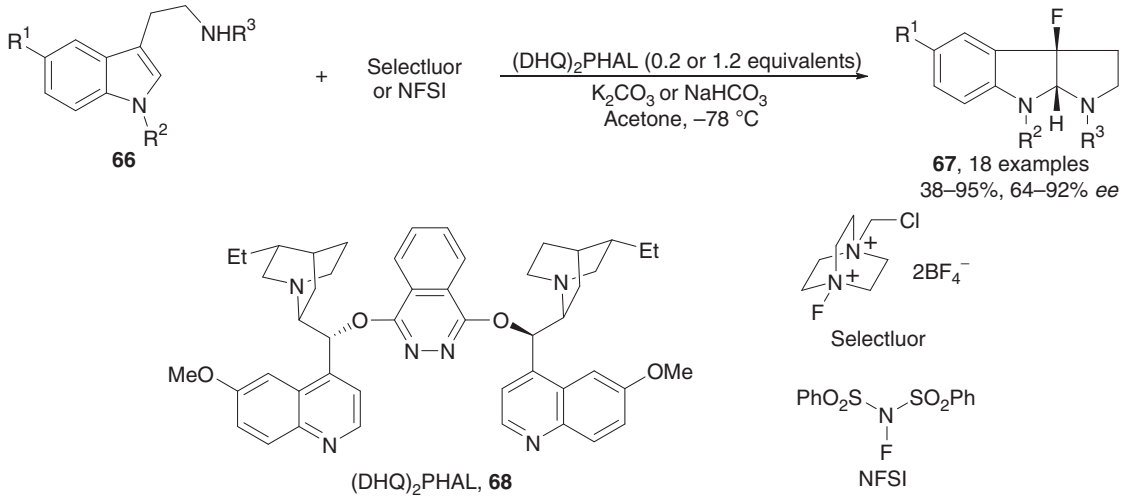
Considering the importance of peroxide-containing compounds for both biological purposes and chemical activities for versatile transformations,[25a] in 2010, the Antilla group developed an efficient method for the direct formation of α-amino peroxide by addition of peroxides to imines catalyzed by chiral phosphoric acid (Scheme 17).[30] With the chiral phosphoric acid (*R*)-**15**, addition of peroxides to imines afforded the chiral aminals **70** with excellent yields (75–92%) and excellent asymmetric induction (up to 89–98%). The selectivity remained at the same level upon prolonging the reaction time, which indicated that the product was stable and the reaction was irreversible under the reaction conditions.

The proposed transition states, as shown in Figure 2, highlight the bifunctional nature of the phosphoric acid. The concurrent activation of both the electrophile and nucleophile through hydrogen bonds presumably accounts for the observed high enantioselectivities for the imine peroxidation reactions.

In 2010, the List group designed a new Bronsted acid, *N*-phosphinyl phpsphoramide **71**, for the direct asymmetric *N,O*-acetalization of aldehydes (Scheme 18).[31] From substituted salicylamides and aldehydes, chiral benzoxazinones **72**, an important class of pharmaceutical compounds,[32] were obtained directly. Higher selectivities were obtained with newly designed Bronsted acid than with regular phosphoric acids. High enantioselectivities were obtained with aliphatic aldehydes **72a–g** whereas moderate selectivities were seen for aromatic aldehyde **72h**.


NHMe
Me
MeHN
65, Psychotrimine
CO2Me
62
Br
NIS, Et3N
MeCN, 1 h
NH2
61
NHCO2Me
60
63
64

Scheme 14



Scheme 15

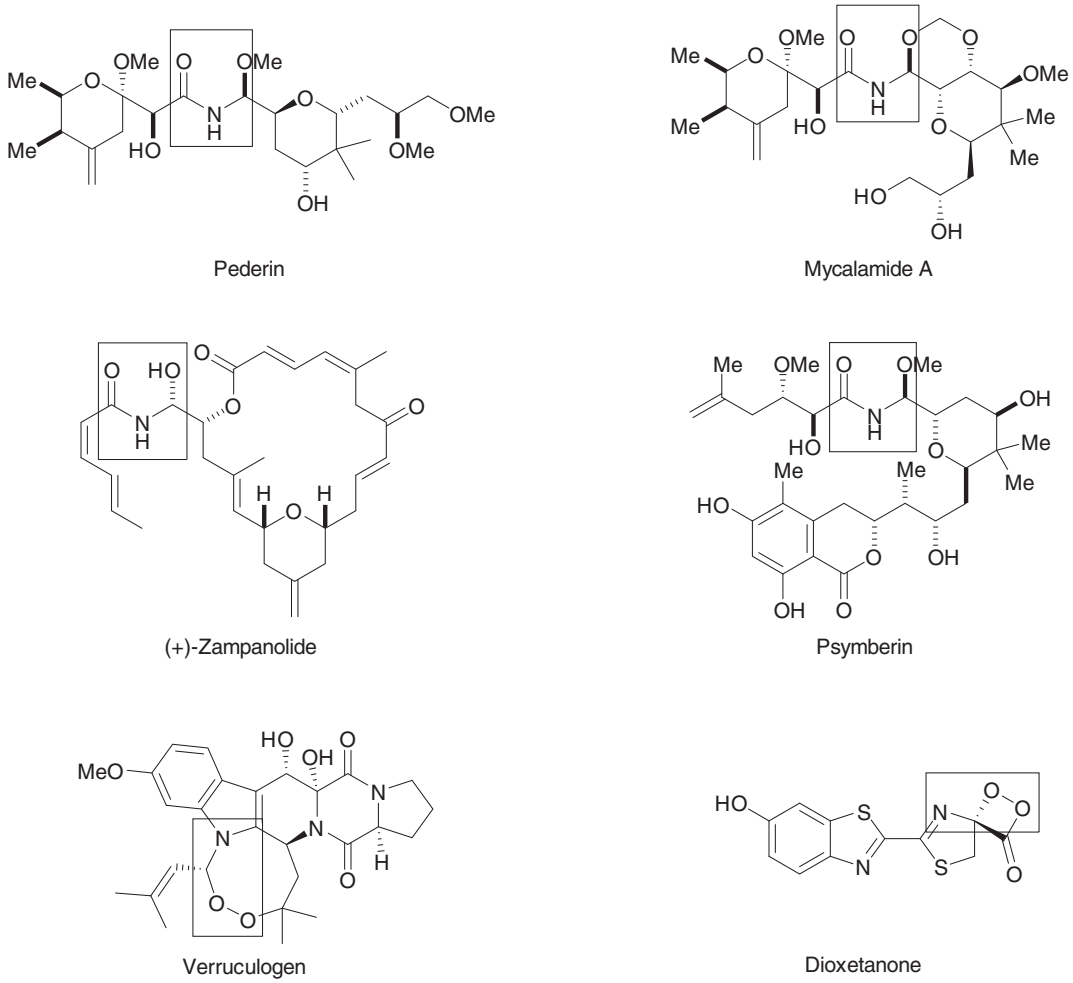
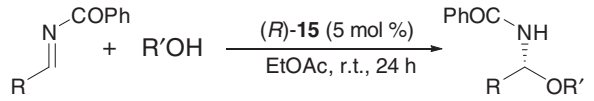
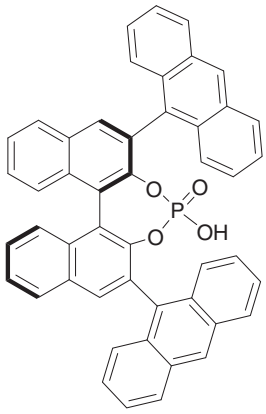


Figure 1 Natural products with *N*-acyl aminal subunits.

The transition state was proposed as shown in Figure 3. The *N*-benzoylimine, generated from the salicylamide and aldehyde, was protonated by catalyst and formed a tight ion pair, which combined with the hydrogen bond between the Bronsted basic phosphinyl oxygen (P═O) and the phenol.



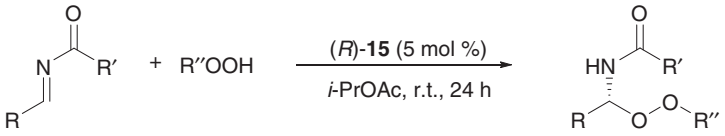
69a–t



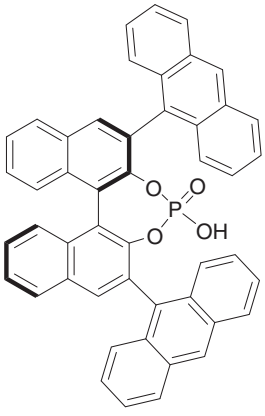
(*R*)-**15**

69a; R = Ph, R′ = Me, 93%, 94% *ee*
69b; R = Ph, R′ = Et, 95%, 90% *ee*
69c; R = Ph, R′ = *i*-Pr, 81%, 88% *ee*
69d; R = Ph, R′ = *t*-Bu, 81%, 92% *ee*
69e; R = Ph, R′ = $ClCH_2CH_2$, 87%, 92% *ee*
69f; R = Ph, R′ = Cy, 84%, 81% *ee*
69g; R = Ph, R′ = Bn, 92%, 93% *ee*
69h; R = Ph, R′ = $CH_2{=}CH(CH_2)_4$, 92%, 91% *ee*
69i; R = Ph, R′ = $CH{\equiv}C(CH)CH_2$, 94%, 95% *ee*
69j; R = Ph, R′ = 3,4-$(MeO)_2C_6H_3$, 85%, 93% *ee*
69k; R = 4-BrC_6H_4, R′ = Me, 99%, 92% *ee*
69l; R = 4-FC_6H_4, R′ = Me, 76%, 88% *ee*
69m; R = 4-ClC_6H_4, R′ = Me, 96%, 93% *ee*
69n; R = 4-$CF_3C_6H_4$, R′ = Me, 93%, 89% *ee*
69o; R = 4-MeC_6H_4, R′ = Me, 95%, 91% *ee*
69p; R = 4-$MeOC_6H_4$, R′ = Me, 91%, 83% *ee*
69q; R = 3-MeC_6H_4, R′ = Me, 91%, 84% *ee*
69u; R = 2-MeC_6H_4, R′ = Me, 96%, 91% *ee*
69v; R = 4-ClC_6H_4, R′ = $BrCH_2CH_2CH_2$, 82%, 90% *ee*
69w; R = CH_3CH_2, R′ = Me, 62%, 65% *ee*

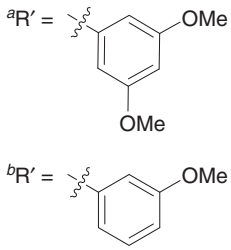
Scheme 16



70a–l



(*R*)-**15**



70a;[a] R = 4-FC_6H_4, R″ = *t*-Bu, 88%, 95% *ee*
70b;[a] R = 4-ClC_6H_4, R″ = *t*-Bu, 87%, 98% *ee*
70c;[a] R = 4-BrC_6H_4, R″ = *t*-Bu, 82%, 98% *ee*
70d;[a] R = 4-$MeOC_6H_4$, R″ = *t*-Bu, 77%, 95% *ee*
70e;[a] R = 2-$MeOFC_6H_4$, R″ = *t*-Bu, 75%, 91% *ee*
70f;[b] R = 3-MeC_6H_4, R″ = *t*-Bu, 91%, 91% *ee*
70g;[b] R = 4-$MeOC_6H_4$, R″ = *t*-Bu, 86%, 90% *ee*
70h;[b] R = 4-ClC_6H_4, R″ = *t*-Bu, 86%, 89% *ee*
70i;[b] R = 4-MeC_6H_4, R″ = *t*-Bu, 92%, 98% *ee*
70j;[a] R = 4-ClC_6H_4, R″ = $C(CH_3)_2Ph$, 91%, 96% *ee*
70k;[a] R = 4-FC_6H_4, R″ = $C(CH_3)_2Ph$, 90%, 93% *ee*
70l;[b] R = 4-MeC_6H_4, R″ = $C(CH_3)_2Ph$, 89%, 98% *ee*

Scheme 17

1.17.2.2.3 Addition of peroxide to imines: synthesis of oxaziridines

The synthesis of oxaziridines by oxidizing imines with *m*-chloroperoxybenzoic acid (*m*-CPBA) or Oxone® under biphasic conditions was pioneered by the Davis group,[33] and has garnered significant attention due to the utility of the products in hydroxylations[34] and [3+2] reactions.[35] Chiral oxaziridines have been prepared from chiral imines by Davis et al.[36] Very recently, the

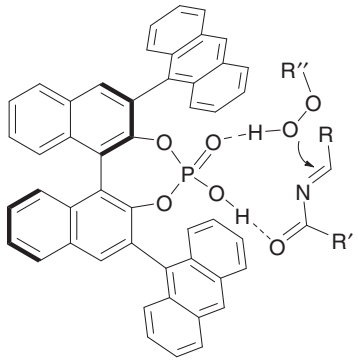
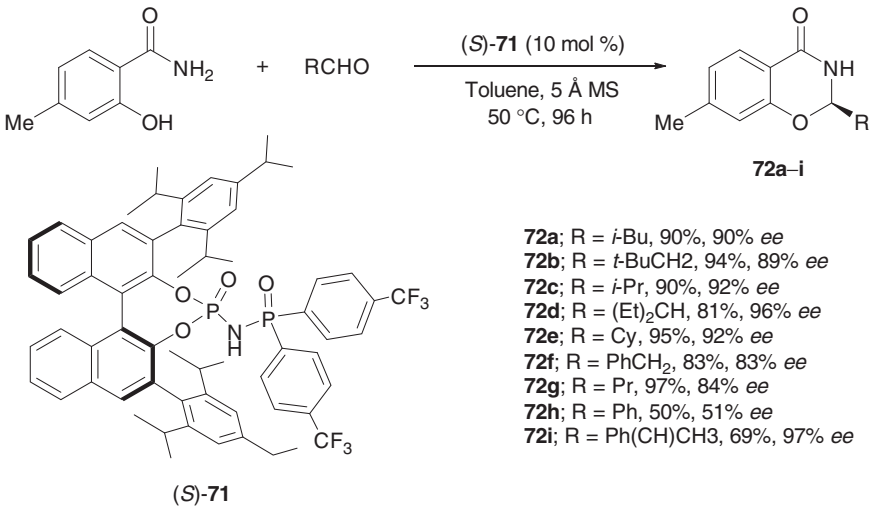


Figure 2 Proposed transition state for the addition of peroxides to imines.



Scheme 18

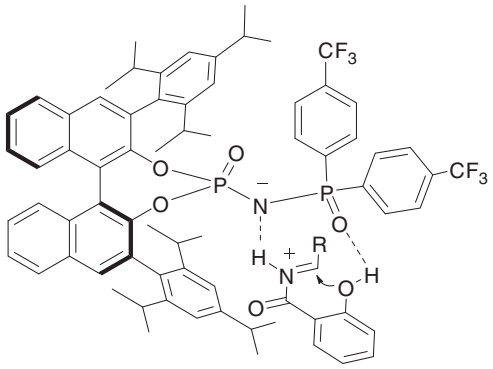
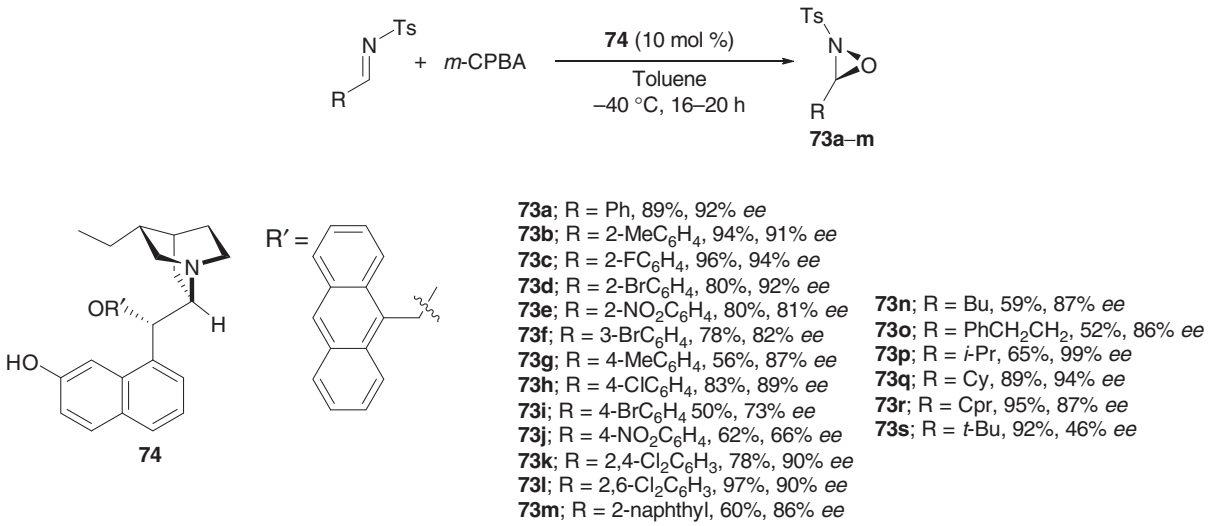


Figure 3 Proposed transition state for the cyclic *N,O*-aminals formation.

Jorgensen group developed a catalytic asymmetric approach for the synthesis of chiral oxaziridines **73** (Scheme 19).[37] Compared with Antilla's system,[30] it is clear that the use of cinchona alkaloid **74** as catalyst and tosyl imines as starting material is crucial for both reactivities and selectivities. Good selectivities were observed using aromatic imines, which have slightly electron-donating substituents or weak electron-withdrawing substituents (**73a–m**). Strong electron-withdrawing groups (such as $-NO_2$, **73j**) decreased the enantioselectivities. Electron-rich imines did not provide the desired products, which is in accord with Davis's earlier results.[33] Investigation of aliphatic N-tosyl imines shows that linear imines and α-branched imines gave rise to the corresponding oxaziridines **73n–r** with moderate-to-good yields and high selectivities. The imine with a tertiary substituent also undergoes the oxidation reaction smoothly with moderate enantioselectivity (**73s**).



Scheme 19

Based on experimental studies, a stepwise mechanism was proposed. Protonation of the catalyst with peroxide results in a tight ion pair that, combined with the hydrogen bond between the catalyst and *N*-tosyl imine, presumably serves to create the chiral environment (Figure 4).

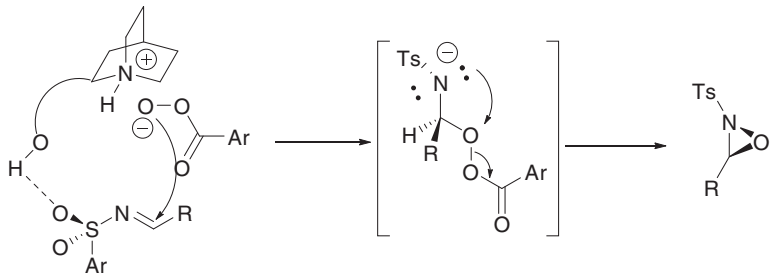


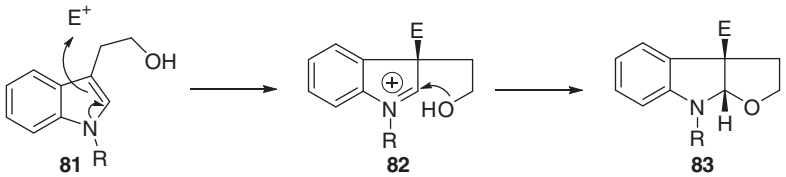
Figure 4 Proposed mechanism for oxaziridines formation.

1.17.2.2.4 The addition of oxygen to in situ generated imines

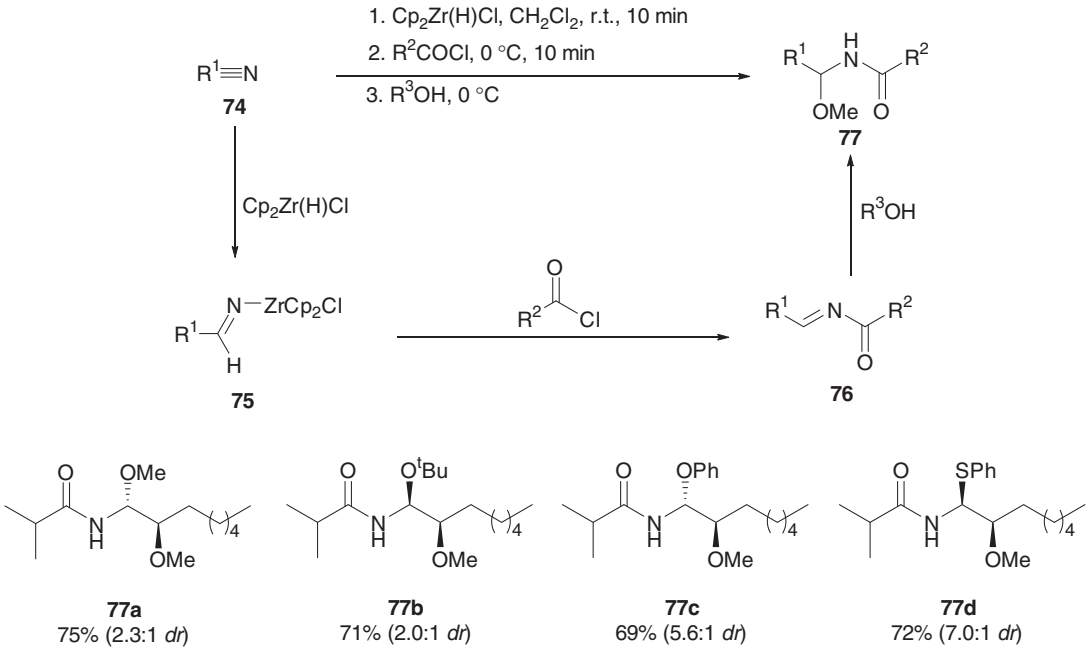
In 2007, the Floreancig group reported an efficient protocol for the synthesis of *N*,*O*-aminals from simple nitriles (Scheme 20).[38] Treating the nitriles **74** with Schwartz's reagent (Cp_2ZrHCl), the reduced intermediates **75** were formed, which would give rise to acylimines **76** after adding acid chlorides. The *N*,*O*-aminals were obtained in good yields by adding alcohols to the *in situ* formed acylimines **76**. As shown in Scheme 20, diverse nucheophiles, including MeOH, ^{t}BuOH, phenol, and thiophenol, provided the corresponding products **76a–d** with good yields and moderate-to-good diastereoselectivities.

In 2011, the same group extended the new method for the formation of *N*,*O*-aminals to the total synthesis of a series of natural products.[39] As shown in Scheme 21, the total synthesis of pederin, a potent cytotoxin, was achieved using a late-stage multi-component reaction to form the *N*,*O*-aminal linkage. Hydrozirconation of well-designed nitrile **77** with Cp_2ZrHCl, followed by the addition of acid chloride **78**, resulted in the formation of acylimine **79**, which was quenched by the addition of MeOH. The desired *N*,*O*-aminal **80** was obtained in moderate yield. $Mg(ClO_4)_2$ was supposed to coordinate with both the nitrogen of imine and the oxygen of tetrahydropyran, allowing for the formation of stable acylimine conformation, and MeOH can attach through the desired less hindered *si*-face. Deprotection of two hydroxyl groups under mild conditions gives rise to the final natural product in good yield. In addition, this approach was also used for the synthesis of psymberin and related analogs, as well as other *N*,*O*-aminals containing natural products.[40]

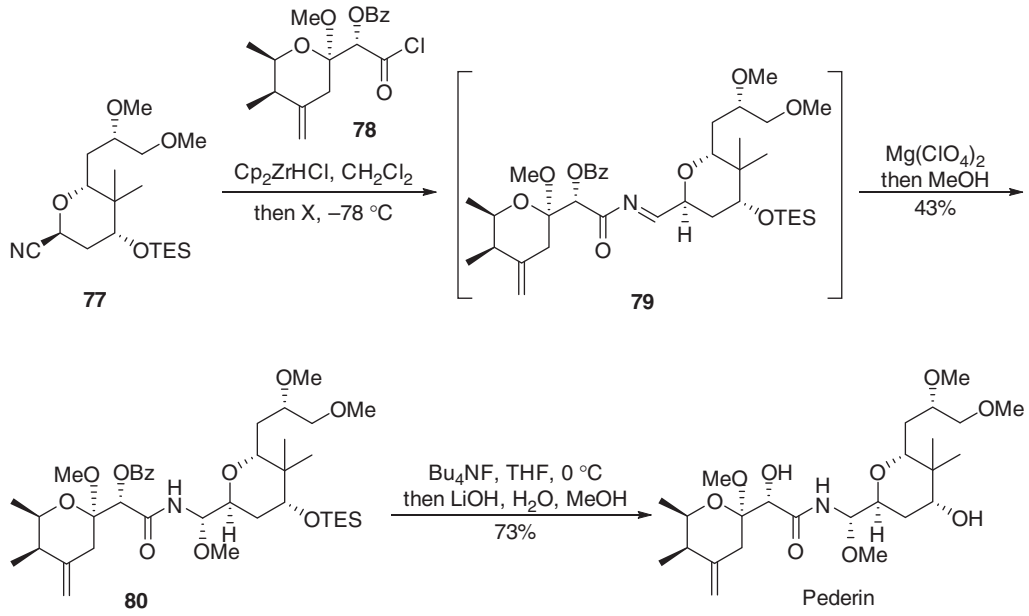
Indole derivatives such as **81** undergo electrophilic trapping at the indole C-3 position, followed by capture of the resulting C-2 iminium ion **82** by the side-chain oxygen.



(2)

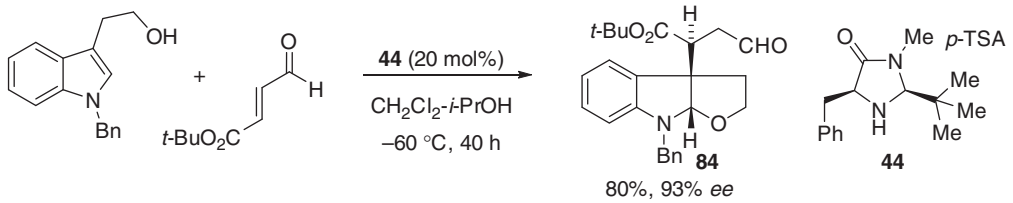


Scheme 20

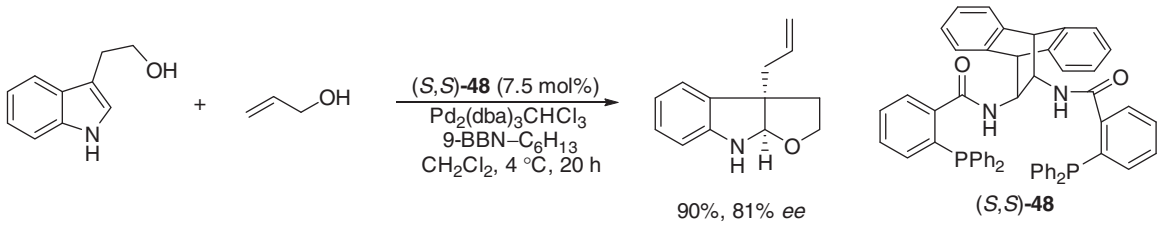


Scheme 21

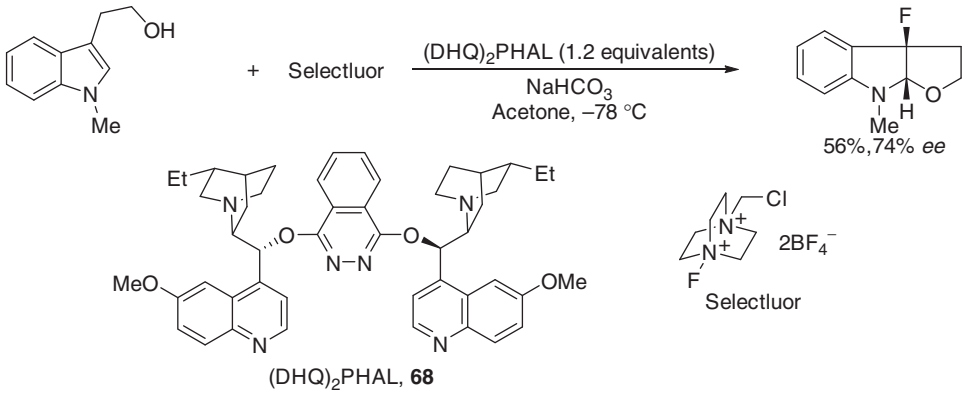
Similar to the protocols described in Section 1.17.2.1.4, the MacMillan group reported a catalytic asymmetric approach for the formation of cyclic aminal **84** in good yields and with excellent enantioselectivities from tryptophol catalyzed by chiral secondary amine (Scheme 22).[16] The Trost group described an asymmetric allylation reaction starting from tryptophol and allylic alcohols, catalyzed by palladium complex with their chiral ligand (*S*,*S*)-**48** (Scheme 23).[19] Gouverneur and coworkers reported that a chiral cinchona alkaloid, $(DHQ)_2PHAL$ **68**, catalyzed enantioselective fluorocyclization of tryptophols (Scheme 24) with moderate yield and enantioselectivity.[24] Garg and coworkers reported an acetic acid-catalyzed interrupted Fisher indoline synthesis, involving the oxygen addition to the *in situ* formed imine (Scheme 25).[21]



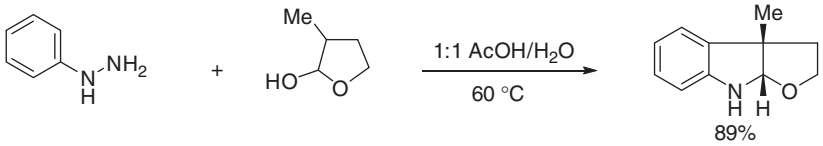
Scheme 22



Scheme 23



Scheme 24



Scheme 25

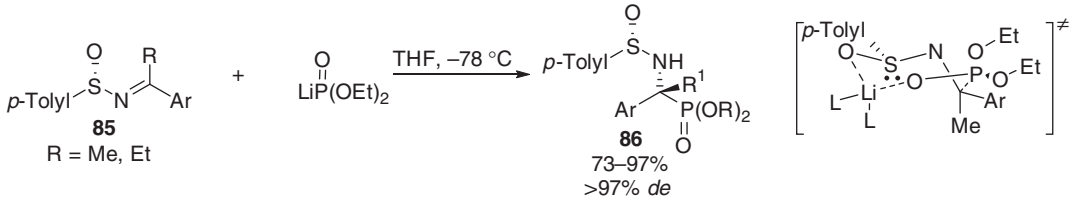
1.17.2.3 Addition of Phosphorus

1.17.2.3.1 Scope

α-Aminophosphonic acids are biologically important molecules, which display broad-range activity as antibiotics,[41] herbicides,[42] insecticides,[43] fungicides,[44] and antiviral agents.[45] They have also been shown to affect enzyme inhibition, with HIV protease being an important target.[46] The nucleophilic addition of alkyl or aryl phosphites to imines, known as the Pudovik reaction,[47] is a crucial method for the synthesis of α-aminophosphonates. These key intermediates are readily converted into the corresponding α-aminophosphonic acids,[48] generally, without loss of optical purity. Along these lines, the stereoselective synthesis of α-aminophosphonates can be broken down into two categories: (1) the addition of phosphites to chiral imines and (2) the addition of phosphites to nonchiral imines, in the presence of a chiral catalyst.

1.17.2.3.2 The addition of phosphites to chiral imines

Considering the well-established methods developed for the preparation of chiral amines and the ready availability of corresponding chiral imines, the addition of phosphite to chiral imines provided an appealing method for the chiral α-aminophosphonates preparation. After the first report in 1972 by Gilmore and McBride,[49] much progress has been achieved.[50] One of the state-of-art developments in this area was reported in 2001 by the Davis group (Scheme 26).[51] They developed the first synthesis of quaternary α-aminophosphonates **86** by the addition of lithium diethylphosphites to enantiopure ketosulfinimines **85** in high diastereoselectivities and good yields. A transition state was proposed to rationalize the observed results, where the lithium cation is chelated to both the sulfinyl and phosphite oxygens through a seven-membered twisted chairlike transition state.

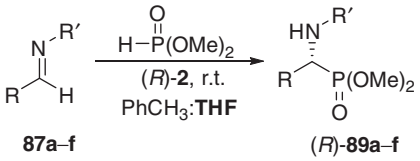


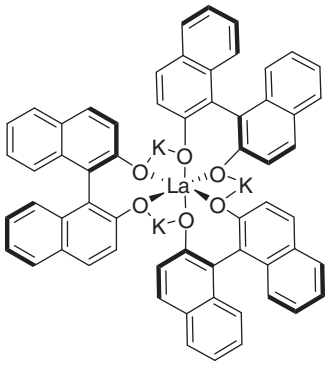
Scheme 26

1.17.2.3.3 Catalytic enantioselective hydrophosphonylation of imines

1.17.2.3.3.1 Metal-catalyzed imine hydrophosphonylation

Catalytic enantioselective synthesis serves as the most efficient method to produce optically active α-aminophosphonic acids and their derivatives. Shibasaki and coworkers reported the first catalytic enantioselective hydrophosphinylation of imines.[48] Addition of dimethyl phosphite to imines **87a–f**, catalyzed by a lanthanum–potassium–BINOL complex (*R*)-LPB **88**, afforded (*R*)-α-aminophosphonates **89a–f** in modest-to-high enantiomeric excesses (Scheme 27). This methodology allows for the synthesis of α-amino phosphonic acids at industrial level.[48]



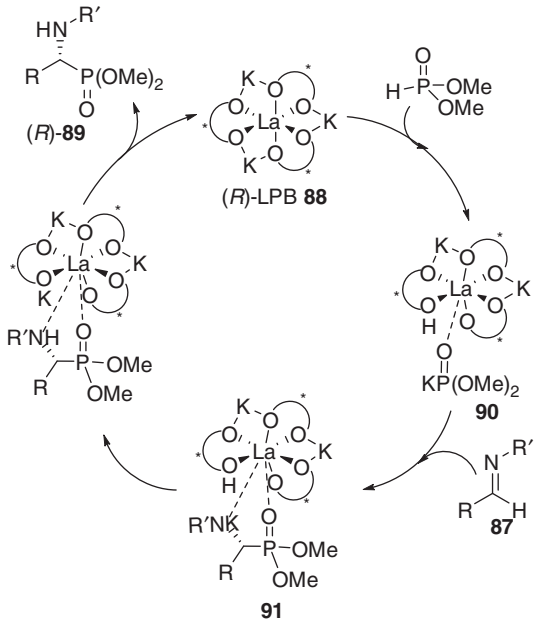


89a; R = *i*-Pr, R′ = DAM, 70%, 96% *ee*
89b; R = *i*-Pr, R′ = $CHPh_2$, 82%, 92% *ee*
89c; R = Me, R′ = $CHPh_2$, 73%, 75% *ee*
89d; R = Et, R′ = $CHPh_2$, 80%, 91% *ee*
89e; R = *c*-Hexyl, R′ = $CHPh_2$, 87%, 85% *ee*
89f; R = *c*-Hexyl, R′ = 4-$MeOC_6H_4$, 71%, 49% *ee*

Scheme 27

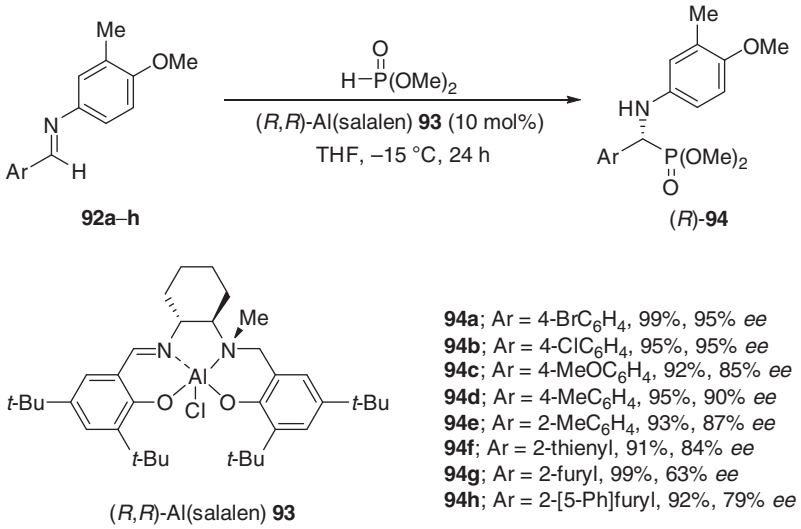
The mechanism of the catalytic enantioselective hydrophosphonylation reaction of imines **87a–f** is shown in Scheme 28. Dimethyl phosphite must first be deprotonated by (*R*)-LPB **88** to generate the corresponding potassium dimethyl phosphonate anion **90**, which reacts with the imine, forming the optically active potassium salt of the α-aminophosphonate **91**. Proton exchange releases the optically active α-aminophosphonate **89** and catalyst (*R*)-LPB **88**, completing the catalytic cycle.

Katsuki et al. reported the use of an Al(salalen) catalyst **93** for the asymmetric hydrophosphonylation of aromatic aldimines **92a–h** with dimethyl phosphite to afford the corresponding (*R*)-α-aminophosphonates **94a–h** in excellent yields (up to 99%) and excellent enantioselectivities (up to 95% *ee*), as shown in Scheme 29.[52] The *N*-protecting group (4-methoxy-3-methylphenyl) was crucial to the high yield and *ee*. The enantioselectivity was at its highest when the imine carried an electron-withdrawing



Scheme 28

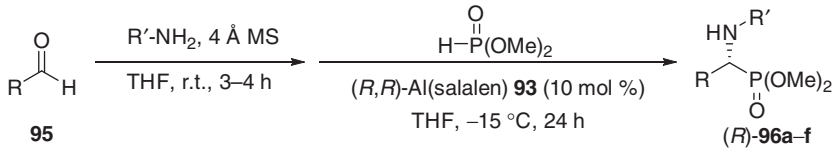
p-substituent. The *ee* decreased to 85% when the strongly electron-donating 4-methoxy-phenyl substituent was present (Scheme 29, **94c**).

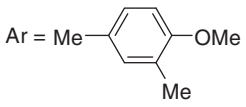


Scheme 29

The same group showed that the methodology could be extended to the one-pot hydrophosphonylation of aldehydes **95**, electron-donating amines, and dimethyl phosphite, with Al(salalen) **93**.[53] (*R*)-*α*-aminophosphonates **96a–f** were obtained in low-to-high yield (28% and 92% (Scheme 30), **96a** and **96e**, respectively). The enantioselectivity could be optimized to 94% (Scheme 30, **96b**).

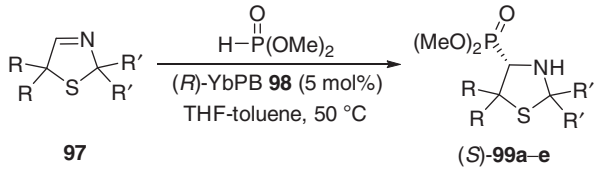
Shibasaki and coworkers reported the first catalytic enantioselective hydrophosphonylation of cyclic imines.[54a] Cyclic imine **97** undergoes hydrophosphonylation with dimethyl phosphite, in the presence of ytterbium–potassium–BINOL complex (*R*)-YbPB **98**, yielding biologically interesting (*S*)-4-thiazolidinylphosphonates **99** in moderate-to-high yields and high enantioselectivity, up to 95% (Scheme 31). Thiazolidinylphosphonates **99** are the *N*,*S*-acetal-protected derivative of the cyclic phosphonic acid. Shibasaki and coworkers hoped to optimize the yields and enantioselectivities of the aforementioned methodology.[54b] The yields and enantioselectivities were maximized through the use of constrained cyclic phosphites, which introduced an element of rigidity. Variation of the catalyst loading, alkyl phosphite, and cyclic imine **97** allowed for the formation of various thiazolidinylphosphonates **100** in excellent yields and enantioselectivities, of up to 99% (Table 1).

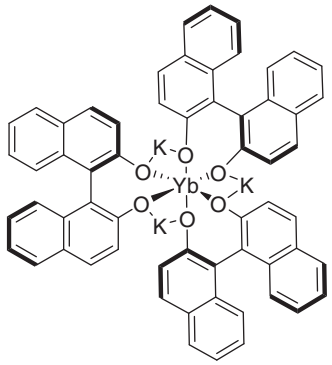




96a; R = *t*-Bu, R′ = Ar, 28%, 88% *ee*
96b; R = *c*-Hexyl, R′ = Ar, 84%, 94% *ee*
96c; R = *i*-Bu, R′ = $CHPh_2$, 80%, 91% *ee*
96d; R = Octyl, R′ = $CHPh_2$, 83%, 84% *ee*
96e; R = PhC≡C, R′ = $CHPh_2$, 92%, 86% *ee*
96f; R = (*E*)-PhC=CH, R′ = $CHPh_2$, 51%, 15% *ee*

Scheme 30





(*R*)-YbPB-**98**

99a; R = H, R′ = Me, 85%, 87% *ee*
99b; R = R′ = Me, 88%, 95% *ee*
99c; R = Me, R′ = $–(CH_2)_5–$, 81%, 93% *ee*
99d; R = Et, R′ = Me, 53%, 96% *ee*
99e; R = Et, R′ = Me, 79%, 92% *ee*

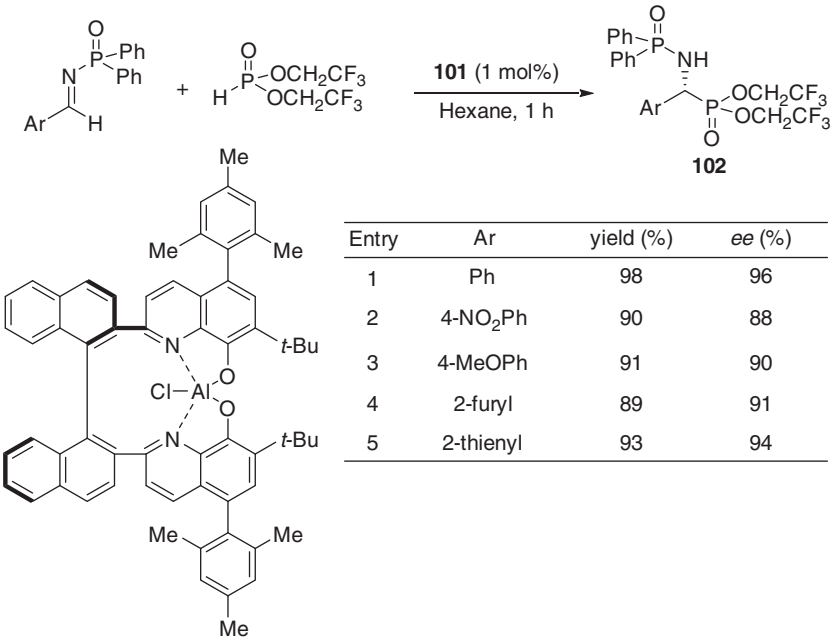
Scheme 31

Table 1 Catalytic enantioselective hydrophosphonylation of **97**

Product	*R/R*	*R′/R′*	*R″/R″*	*Yield (%)*	ee *(%)*
100a	Me/Me	Me/Me	$–(CH_2)_3–$	99	97
100b	Me/Me	Me/Me	$–CH_2C(Me)_2CH_2–$	90	92
100c	Me/Me	Me/Me	$–CH_2CH=CHCH_2–$	87	93
100d	Me/Me	$–(CH_2)_5–$	$–(CH_2)_3–$	61	97
100e	Me/Me	$–(CH_2)_5–$	$–CH_2C(Me)_2CH_2–$	82	98
100f	$–(CH_2)_5–$	Me/Me	$–(CH_2)_3–$	85	97
100g	$–(CH_2)_5–$	Me/Me	$–CH_2C(Me)_2CH_2–$	69	96

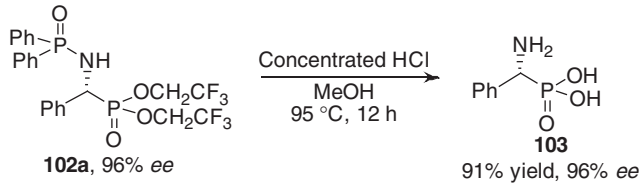
In 2008, the Yamamoto group reported a catalytic asymmetric addition of phosphites to imines catalyzed by their (*R*)-TBOxAlCl complex **101** (Scheme 32).[55] The introduction of electron-withdrawing trifluoroethyl groups is important for the reactivity. The protection group of imine has also been shown to be important for the enantioselectivities and yields. With 1 mol% of catalyst, the reaction furnished α-aminophosphonates **102** in 1 h with excellent yields and enantioselectivities. The protecting groups can be removed in refluxing methanolic HCl and the chiral amino phosphonic acid **103a** was obtained without loss of enantiopurity (Scheme 33).

In 2011, the Antilla group developed a new method for the synthesis of chiral α-amino phosphine oxides **104** by addition of diphenylphosphine oxide to imines catalyzed by magnesium phosphate **105** (Scheme 34).[56] Catalyst screening shows that the phosphoric acid purified on silica gel can promote the reaction and afford the desired product with almost the same level of



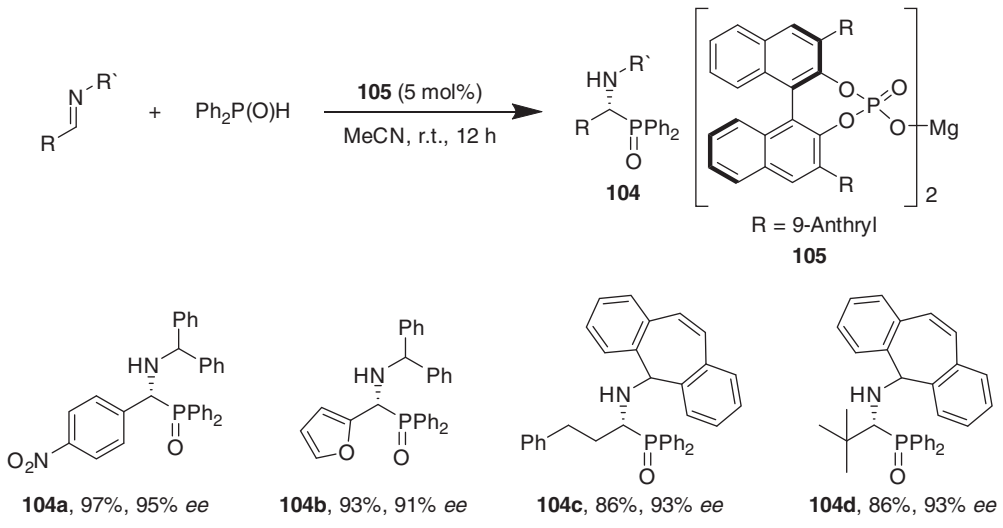
Entry	Ar	yield (%)	*ee* (%)
1	Ph	98	96
2	4-NO_2Ph	90	88
3	4-MeOPh	91	90
4	2-furyl	89	91
5	2-thienyl	93	94

Scheme 32



Scheme 33

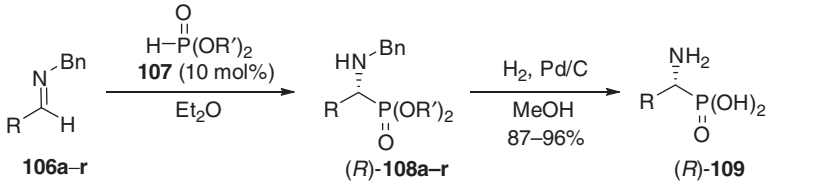
enantioselectivity, whereas lower *ee* obtained from the catalyst washed with HCl, which indicated that the phosphoric acid purified on silica gel was contaminated with phosphate. Both calcium and magnesium phosphates generated the products with high enantioselectivities. Electron-neutral benzhydryl or dibenzocycloheptene provided suitable protecting groups for the imines, which were allowed to undergo the phosphination with high enantioselectivities for both aromatic and aliphatic imines.



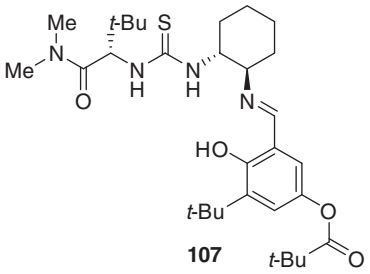
Scheme 34

1.17.2.3.3.2 Organocatalytic imine hydrophosphonylation

In 2004, Jacobsen and coworkers reported the first organocatalytic hydrophosphonylation of imines. The addition of di-(*o*-nitrophenyl)phosphite to *N*-benzoyl imines **106** was carried out in the presence of chiral urea **107**.[57] (*R*)-*α*-aminophosphonates **108a–r** were produced in excellent yields and enantioselectivities (Scheme 35). Aromatic, heteroaromatic, and branched aliphatic aldimines were successful under the reaction conditions. The utility of hydrophosphonylation products **108** was demonstrated through deprotection, by means of mild hydrogenation, giving *α*-aminophosphonic acids **109** in high yields and without loss of optical purity.



108a; R = Ph, 87%, 98% *ee*
108b; R = 3-Pentyl, 90%, 96% *ee*
108c; R = *i*-Pr, 93%, 90% *ee*
108d; R = *c*-Hexyl, 91%, 90% *ee*
108e; R = *t*-Bu, 83%, 93% *ee*
108f; R = Me_2C=CH, 91%, 82% *ee*
108g; R = 4-ClC_6H_4CH=CH, 89%, 98% *ee*
108h; R = 4-$MeOC_6H_4$, 90%, 96% *ee*
108i; R = 4-$MeoC_6H_4$, 78%, 96% *ee*
108j; R = 2-MeC_6H_4, 81%, 92% *ee*
108k; R = 2-ClC_6H_4, 52%, 96% *ee*
108l; R = 3-ClC_6H_4, 83%, 98% *ee*
108m; R = 4-ClC_6H_4, 87%, 99% *ee*
108n; R = 2-Naphthyl, 86%, 98% *ee*
108o; R = 3-Pyridyl, 77%, 96% *ee*
108p; R = 2-Furyl, 89%, 92% *ee*
108q; R = 2-Thienyl, 89%, 94% *ee*
108r; R = 2-Pyrrolyl, 86%, 81% *ee*



107

Scheme 35

Akiyama et al. reported the first chiral phosphoric acid-catalyzed imine hydrophosphonylation employing chiral phosphoric acid **111**.[58] Addition of diisopropyl phosphite to imines **110** afforded (*R*)-*α*-aminophosphonates **112a–k** in moderate-to-high enantioselectivities (Scheme 36). The methodology is applicable to a wide variety of aryl- and cinnamyl- derived aldimines.

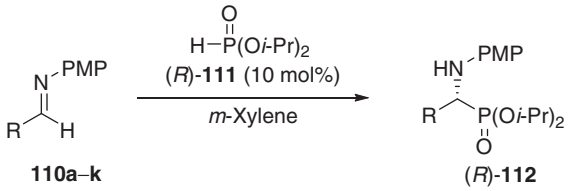
A nine-membered transition state was proposed (Figure 5), wherein the chiral phosphoric acid has two functions: (1) the phosphoric acid aids in activation of the imine, by acting as a Brønsted acid and forming a hydrogen-bond interaction with the imine and (2) the phosphoryl oxygen activates the nucleophilic phosphite by acting as a Brønsted base. The unique Brønsted acidic and basic properties of the chiral phosphoric acid allow for the observed facial selectivity. This mechanism shows the versatility of chiral phosphoric acids as competent bifunctional organocatalysts.

In 2008, the List group reported the three-component reaction of *α*-branched aldehydes, *p*-anisidines, and phosphites, catalyzed by a chiral phosphoric acid (*S*)-**13** (Scheme 37).[59] Moderate-to-excellent diastereoselectivities and enantioselectivities of *α*-aminophosphonates **113** were obtained by a dynamic kinetic resolution. It was found that degassing the reaction mixture to prevent the oxidation of phosphites to the corresponding phosphoric acid is important for the stereoselectivities, since the latter can catalyze the racemic reaction. In general, bulky alkyl groups on the *α*-position of aldehydes were essential for high *dr* and *ee*; branched methyl and ethyl groups gave only moderate optical purity of products (**113b** and **113c** (Scheme 37)).

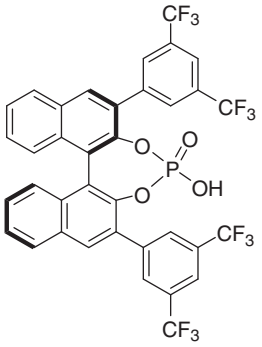
In 2009, the Nakamura group reported the first catalytic asymmetric hydrophosphonylation of ketimine **114** catalyzed by cinchona alkaloids **115** and a base.[60] The 2,4,6-trimethylphenyl group on the nitrogen in the sulfonylimine **114** proved to be the best substituent to obtain the high yields and enantioselectivities. Dialkyl phosphites did not afford the good yields of the products due to the slower deprotonation. Aromatic ketimines work better than aliphatic ones in terms of the enantioselectivities of corresponding quaternary *α*-aminophosphonates (**115c** and **115d** vs. **115a**, **115b**, **115e** and **115f**).

The sodium phosphite was proposed as the active nucleophile, which was activated by the catalyst through the coordination of nitrogen on cinchona alkaloid with sodium ion. This coordination, combined with imine activation through hydrogen bonding with the catalyst's hydroxyl group, contributes to the observed high enantioselectivities (Scheme 38; Figure 6).

Pettersen et al. reported an organocatalytic approach to imine hydrophosphonylation employing commercially available and inexpensive quinine **117** as the catalyst.[61] The straightforward protocol allowed for the addition of diethyl phosphite to *N*-Boc



110a–k (*R*)-**112**



(*R*)-**111**

112a; R = Ph, 84%, 52% *ee*
112b; R = 3-MeC$_6$H$_4$, 76%, 69% *ee*
112c; R = 3-NO$_2$C$_6$H$_4$, 72%, 77% *ee*
112d; R = PhCH=CH, 92%, 84% *ee*
112e; R = 4-MeC$_6$H$_4$CH=CH, 86%, 86% *ee*
112f; R = 4-ClC$_6$H$_4$CH=CH, 97%, 83% *ee*
112g; R = 3-MeC$_6$H$_4$CH=CH, 80%, 82% *ee*
112h; R = 3-ClC$_6$H$_4$CH=CH, 82%, 87% *ee*
112i; R = 3-NO$_2$C$_6$H$_4$CH=CH, 92%, 88% *ee*
112j; R = 3-CF$_3$C$_6$H$_4$CH=CH, 86%, 90% *ee*
112k; R = 1-Naphthyl-CH=CH, 76%, 81% *ee*

Scheme 36

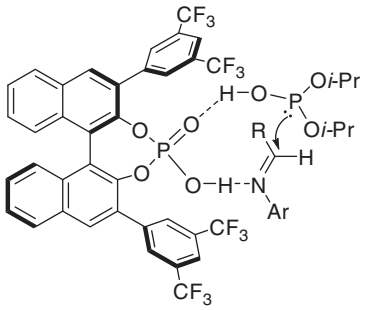
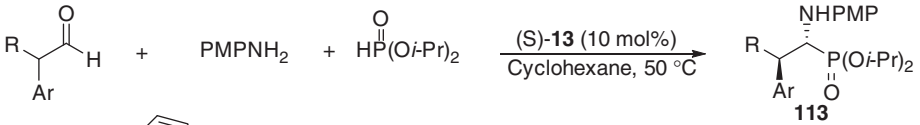
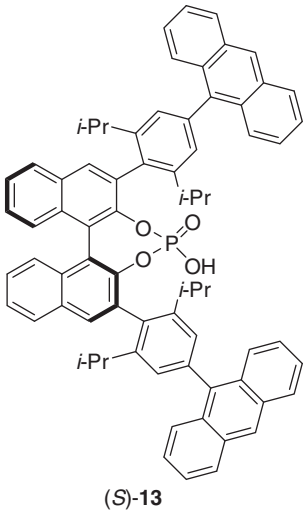
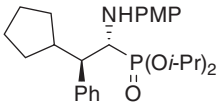


Figure 5 Reaction mechanism of chiral phosphoric acid-catalyzed imine hydrophosphonylation.

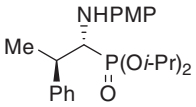




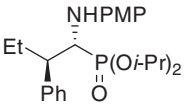
(*S*)-**13**



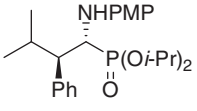
113a, 86%
16:1 *dr*
92% *ee*



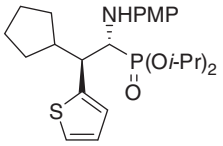
113b, 63%
3:2 *dr*
2% *ee*, 58% *ee*



113c, 84%
3:1 *dr*
72% *ee*, 84% *ee*

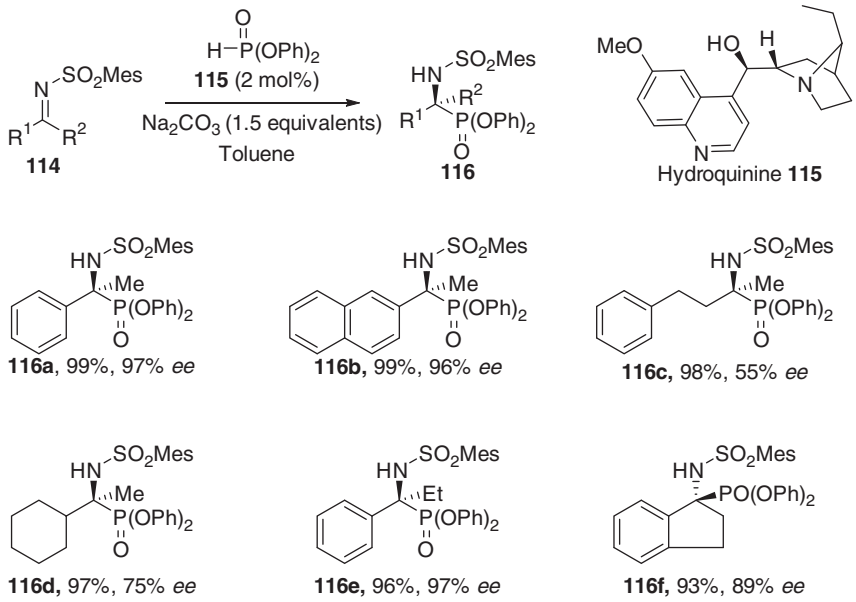


113d, 85%
17:1 *dr*
90% *ee*



113e, 61%
20:1 *dr*
94% *ee*

Scheme 37



Scheme 38

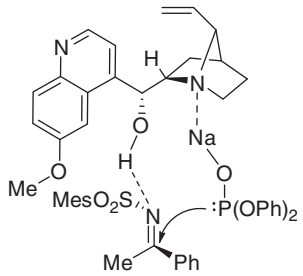


Figure 6 Proposed transition state for asymmetric hydrophosphonylation of ketimine.

imines **116**, leading to (*R*)-*α*-aminophosphonates **118** in moderate-to-acceptable yields of 83% and high enantioselectivity up to 94% (Scheme 39). The reaction gave higher enantioselectivities, with slightly lower yields when run at −20 °C.

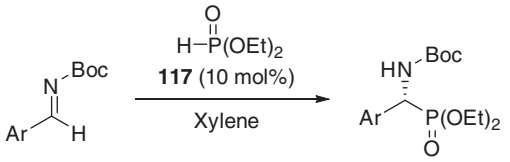
The authors used experimental evidence to propose a reaction mechanism where quinine acts as a bifunctional organocatalyst, activating both the imine and the phosphite as shown in Figure 7.

Tan and coworkers reported that chiral guanidinium salt **119** catalyzed enantioselective phospha-Mannich reaction (Scheme 40).[62] The catalyst can be prepared in one single step from the commercially available diamine. Phosphine oxides and H-phosphinates provided suitable phosphine nucleophile, affording the amino phosphine oxides (**120a** and **120b** (Scheme 40)) and amino phosphinates (**120c** and **120d** (Scheme 40)) with high enantioselectivities and diastereoselectivities.

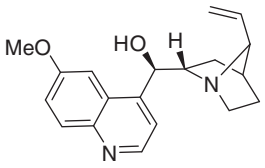
1.17.2.4 Addition of Sulfur and Selenium

The addition of sulfur or selenium to C═N bonds will generate *N*,*S*-acetals or *N*,*Se*-acetals, which are biologically important molecules.[63] They have also been shown to be useful ligands and intermediates.[64] Moreover, *N*,*S*-acetals-containing molecules were found in natural products such as penicillin G, fusaperazine A, and (+)-11,11′-dideoxyverticillin A (Figure 8).[65] However, the addition of sulfur or selenium nucleophiles to C═N bonds has been less developed compared with oxygen, nitrogen, or phosphorus nucleophiles.

In 2009, the Movassaghi group achieved the total synthesis of (+)-11,11′-dideoxyverticillin A, which has impressive biological activities and is endowed with complex architecture (Scheme 41).[66] The dimeric **121** was obtained in six steps from commercially available amino acid derivatives. After efficient tetrahydroxylation and selective protection of two hydroxyl groups out of four, the key intermediate **122** was treated with potassium trithiocarbonate under acidic conditions, forming the desired bisdithiepanethione **124** as a single isomer in moderate yield. The reactive iminium ion **123** was proposed to form *in situ* in acidic



116a–i (*R*)-**118a–i**



Quinine **117**

Reaction temperature [a]20 °C, [b]–20 °C

118a;[a] Ar = Ph, 83%, 80% *ee*
118b;[a] Ar = 1-Naphthyl, 76%, 72% *ee*
118c;[a] Ar = 2-Naphthyl, 82%, 85% *ee*
118d;[a] Ar = 3-MeC_6H_4, 71%, 78% *ee*
118e;[a] Ar = 4-MeC_6H_4, 65%, 86% *ee*
118z;[a] Ar = 3,5-di-MeC_6H_3, 50%, 86% *ee*
118g;[a] Ar = 4-MeOC_6H_4, 50%, 88% *ee*
118h;[a] Ar = 3-Pyridyl, 72%, 48% *ee*
118i;[a] Ar = 4-ClC_6H_4, 57%, 77% *ee*
118a;[b] Ar = Ph, 52%, 88% *ee*
118c;[b] Ar = 2-Naphthyl, 69%, 92% *ee*
118d;[b] Ar = 3-MeC_6H_4, 61%, 94% *ee*
118e; Ar = 4-MeC_6H_4, 62%, 93% *ee*
118g;[b] Ar = 4-MeOC_6H_4, 57%, 94% *ee*
118i;[b] Ar = 4-ClC_6H_4, 62%, 89% *ee*

Scheme 39

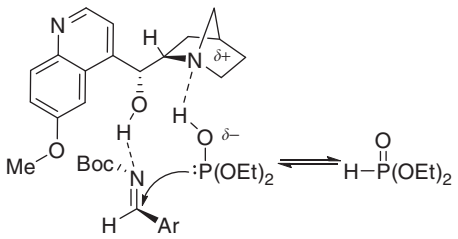
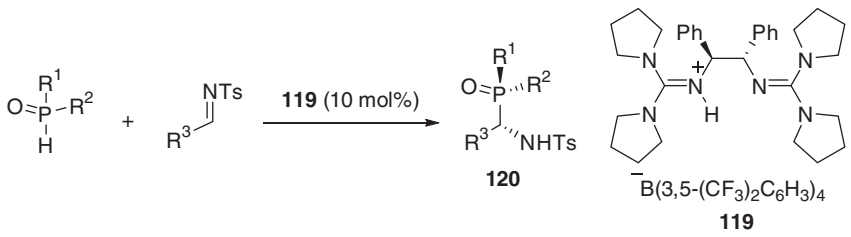
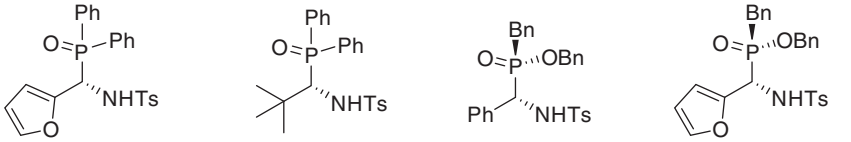


Figure 7 Mechanism for quinine-catalyzed hydrophosphonylation of **117**.





Scheme 40

conditions and was trapped by the sulfur nucleophile. In this single-step reaction, four carbon–oxygen bonds were replaced by four carbon–sulfur bonds. Interestingly, the reverse stereochemistry was obtained in the newly formed carbon–sulfur bonds likely via a kinetic trapping process. After rapid further transformations, the natural product (+)-11,11′-dideoxyverticillin A was obtained efficiently.

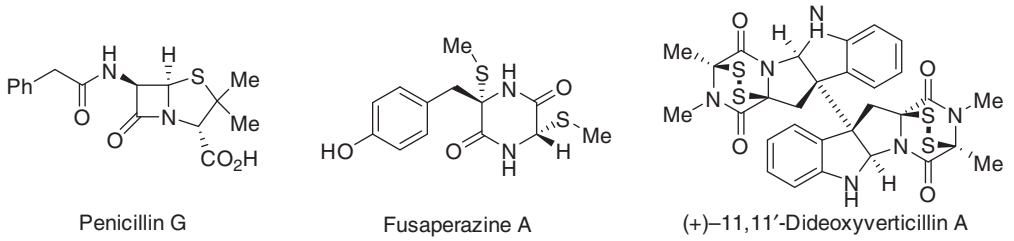
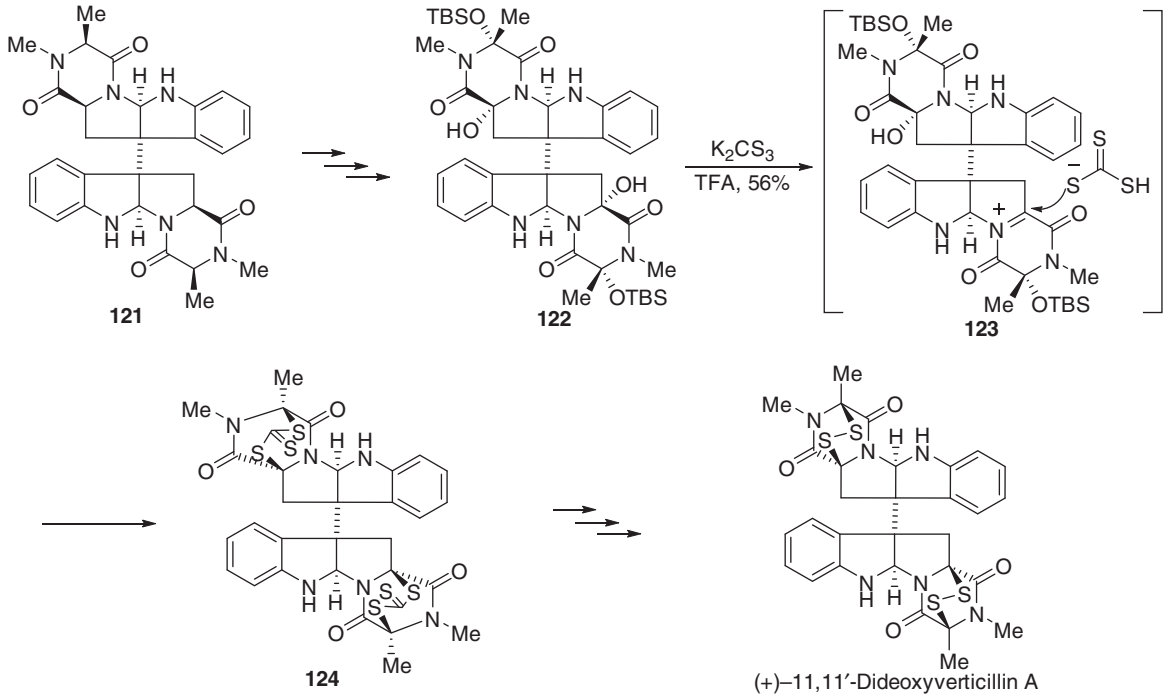


Figure 8 Represent examples of *N,S*-acetals-containing natural products.



Scheme 41

The sulfenylation strategy via *in situ* formed iminiums has been proven to be a powerful protocol in the total synthesis of natural products. For example, Reisman and coworkers used this key step in the total synthesis of (−)-acetylaranotin,[67] and the Overman group reported the total synthsis of epidithiodioxopiperazines involving the addition of sulfur to iminiums.[68] The addition of sulfur to *in situ* formed imines has also been applied in the preparation of several sulfur-containing heterocycles.[69]

Recently, the Antilla group reported the first example of a catalytic asymmetric method for the addition of sulfur to C═N bonds, affording *N,S*-acetals with excellent yields and enantioselectivities, catalyzed by chiral phosphoric acids (Scheme 42).[70] The chiral phosphoric acid **26** proved to be an extremely efficient catalyst: only 2 mol% is needed to catalyze the reaction selectively in 5 min at room temperature. Broad substrates, including the aromatic thiols, aliphatic thiols, and L-cysteine ester, were tested under the reaction conditions; excellent selectivities of **125** were obtained in all cases. Interestingly, the addition of simple liquefied H_2S to imine was successfully developed with 99% *ee* for **125d**. With thiophenol, catalyst-loading screening shows that even with 0.01 mol% of catalyst, the desired product was obtained with 91% *ee*, which represents the lowest catalyst loading reported to date for organocatalysis.

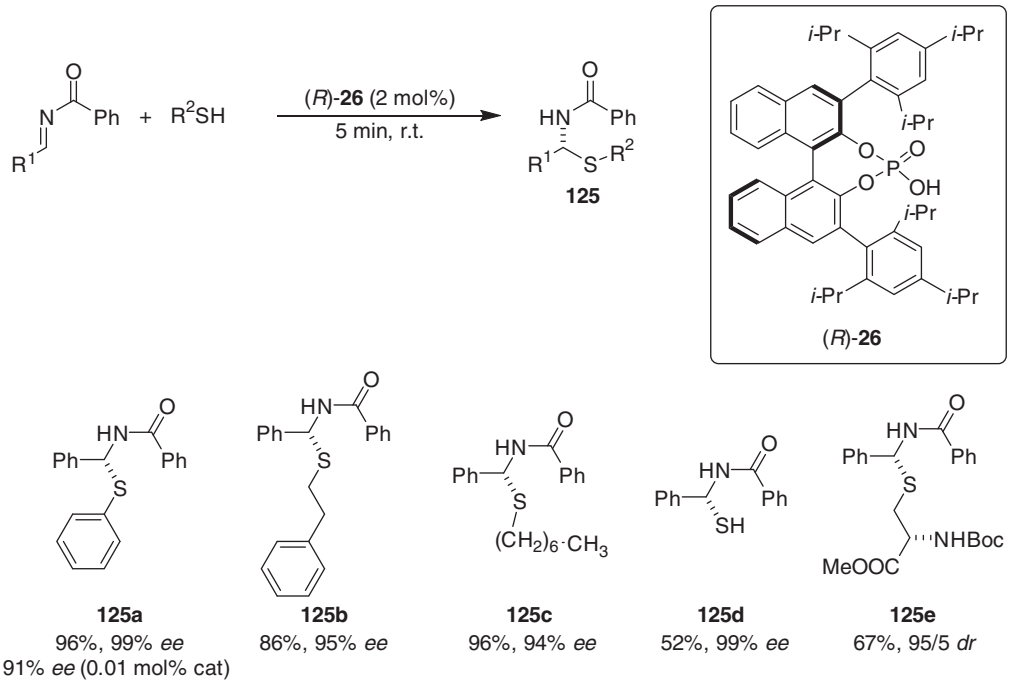
In the same report, the authors show that the same catalytic system can be applied to the addition of selenophenol to imine with excellent *ee*, which represents the only case of the catalytic asymmetric formation of *N,Se*-acetals (Scheme 43).

1.17.3 Additions to C═O pi Bonds

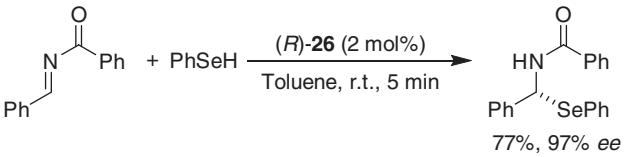
1.17.3.1 Addition of Nitrogen

1.17.3.1.1 Scope

Compared with the addition of oxygen to C═N bonds (Section 1.17.2.2), the addition of nitrogen across C═O bonds provides a complementary approach to afford *N,O*-aminals. *N,O*-aminals are not stable under certain conditions, which allowed them to



Scheme 42



Scheme 43

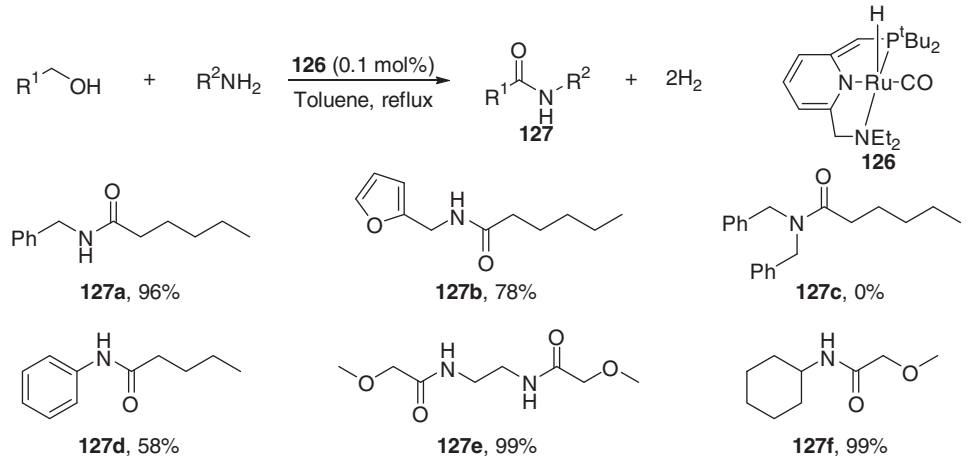
undergo further transformations, such as oxidation to form amide, and dehydration to form imines. The formation of imines from amines and carbonyl groups represents one of the most useful organic transformations, involving the addition of nitrogen to C═O and subsequent dehydration of the *N,O*-aminals. Herein, recent examples of adding the nitrogen to C═O are presented in two sections: (1) the addition of nitrogen to C═O and subsequent transformations and (2) the addition of nitrogen to C═O to form aminals.

1.17.3.1.2 The addition of nitrogen to C═O and subsequent transformatnions

In 2007, the Milstein group reported an efficient and simple method for the formation of amides from readily available alcohols and amines, catalyzed by a ruthenium complex (Scheme 44).[71] In this new transformation, no acid or base is required and hydrogen gas is the single byproduct. With 0.1 mol% of catalyst **126**, in refluxing toluene without any additives, the desired amides **127** were obtained in excellent yields for primary amines, whereas the secondary amines and aromatic amines displayed moderate activities. Primary diamines were also examined under the conditions, and the desired bis-amide product **127e** was produced in excellent yield. This method provided a completely different approach for the preparation of fundamental amide motifs, which was further optimized by many groups.[72]

Mechanically, as shown in Figure 9, the oxidation of alcohols catalyzed by the catalyst **126** led to the corresponding aldehydes **128**, which undergo amination reactions to form the *N,O*-aminals **129**. Aromatic intermediate **130** was generated on the reaction of catalyst with the *in situ* formed aminal. *β*-H elimination of **130** delivered the product amides **127** and generated the *trans* Ru dihydride complex **131**, which would regenerate the catalyst **126** on releasing H_2.

In 2008, the Gong group reported a chiral phosphoric acid-catalyzed asymmetric catalytic three-component cyclization reaction of a cinnamaldehyde, an aromatic amine, and a 1,3-dicarbonyl compound, allowing the formation of 4-aryl-1,4-dihydropyridines with high enantioselectivities (Scheme 45).[73] The reaction was proposed to undergo a stepwise process including: (1) the condensation of *α,β*-unsaturated aldehydes with amines to form *α,β*-unsaturated imines, which react with 1,3-dicarbonyl compounds in the presence of chiral phosphoric acid **131** via the transition state as **133**, forming the enamine intermediate **134**; (2)



Scheme 44

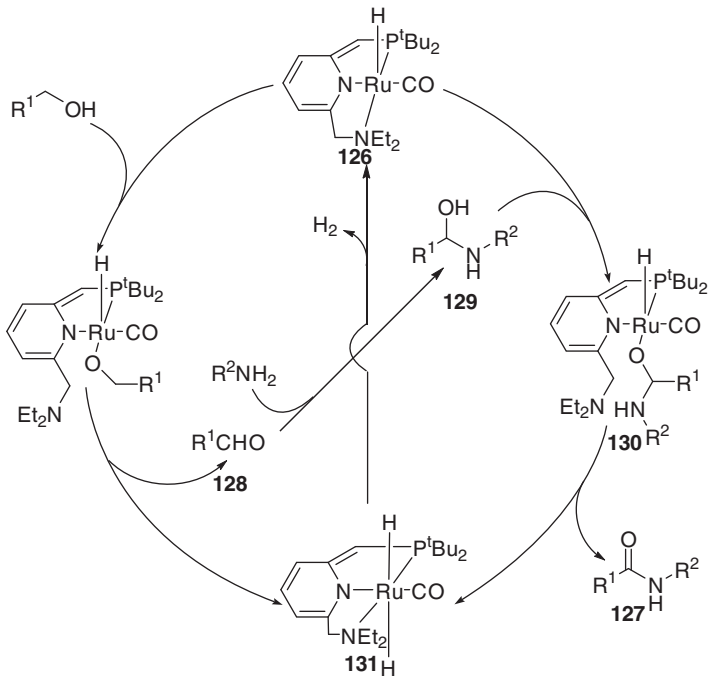


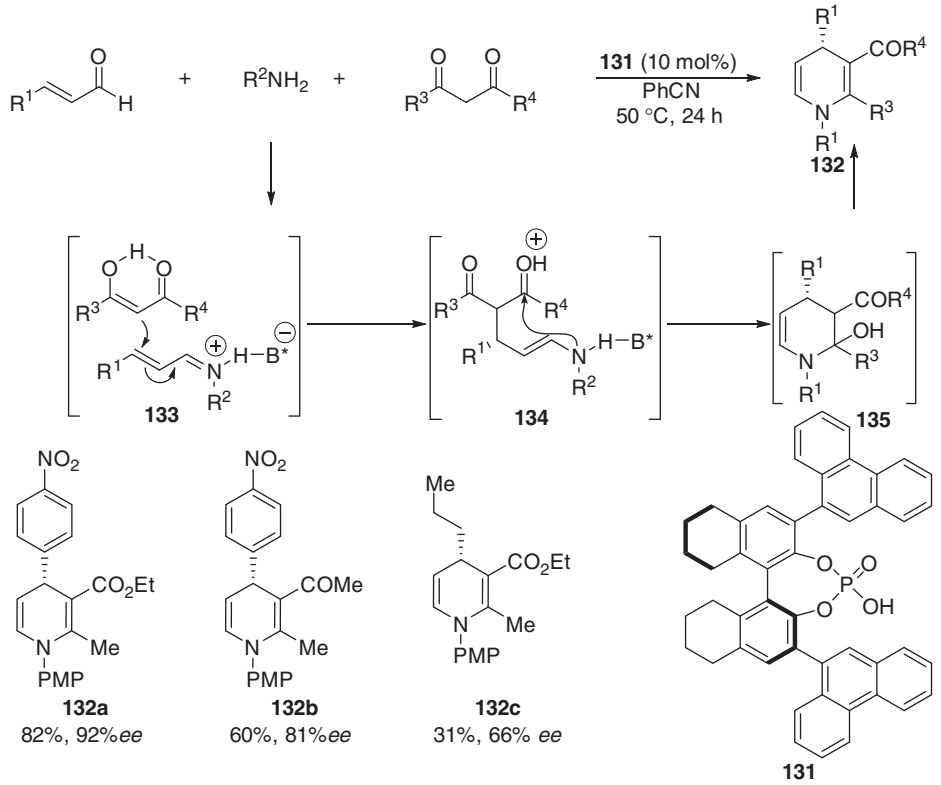
Figure 9 Mechanism of ruthenium-catalyzed amides formation.

the nucleophilic addition to activated carbonyl intramolecularly to form the *N,O*-aminal **135** undergone by the nitrogen of enamine; and (3) the spontaneous dehydration to yield the final 4-aryl-1,4-dihydropyridines **132**.

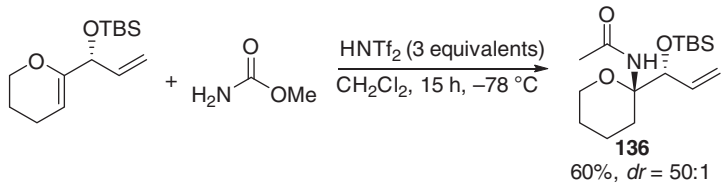
1.17.3.1.3 The addition of nitrogen to C═O to form aminals

In 2007, Hsing and coworkers reported an $HNTf_2$-catalyzed diastereoselective addition of carbamates to *in situ* formed oxo-carbenium ion to form *N,O*-aminals **136** (Scheme 46).[74] Interestingly, it was found that the diastereoselectivity was closely related to the amount of $HNTf_2$ used. The diastereoselective was increased from 2.3:1 to 50:1 as the $HNTf_2$ increased from 0.10 equivalents to 3.0 equivalents. Nuclear magnetic resonance (NMR) studies and calculations suggested that the diastereoselectivity is a result of thermodynamic equilibration of the protonated *N,O*-aminals.

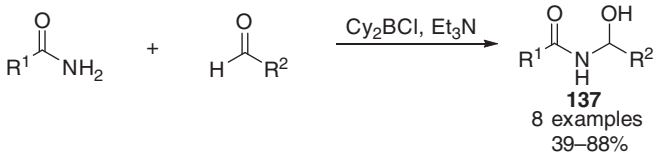
Williams and coworkers reported that a system of Cy_2BCl and triethylamine catalyzed the direct addition of carboxamines to aldehydes, affording *N,O*-aminals **137** with moderate-to-good yields (Scheme 47).[75] The boron imidate was presumably formed under the reaction conditions. With chiral carboxamines, no significant diastereoselectivity was observed.



Scheme 45



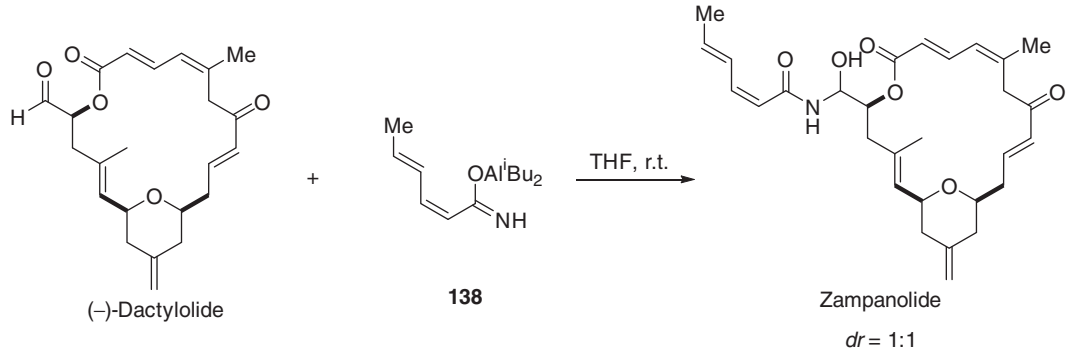
Scheme 46



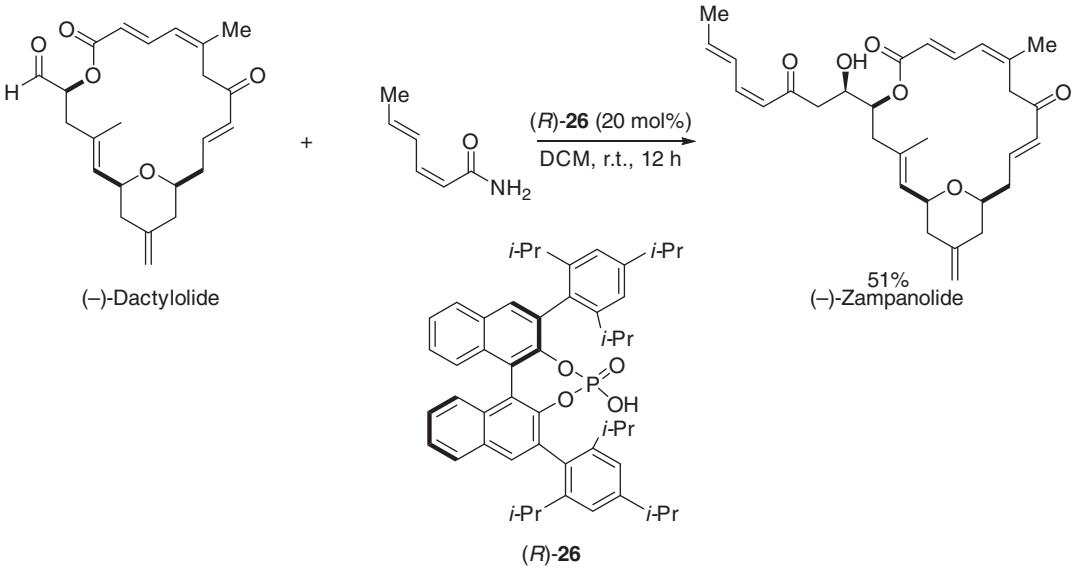
Scheme 47

In 2003, the Hoye group used a key step of late-stage *N,O*-aminal formation for the total synthesis of zampanolide (Scheme 48),[76] which was isolated by Tanaka and Higa in 1996,[77] and possessed potent microtubule-stabilizing properties and cytotoxic activity against SKM-1 and U937 cell lines.[78] Hoye and coworkers reported that the *in situ* formed aluminum imidate **138** derived from titration of (*Z*, *E*)-sorbamide with DIBAL-H could undergo the nucleophilic addition to the (−)-dactylolide aldehyde, albeit affording zampanolide with 1:1 diastereoselectivity.

Recently, Ghosh et al. optimized Hoye's protocol and reported that the chiral phosphoric acids can catalyze the desired aminal formation via direct addition of amide to (−)-dactylolide aldehyde (Scheme 48).[79] Fifty-one percent of desired enantiopure (−)-zampanolide and 18% of *epi*-zampanolide were obtained with (*S*)-**26**, while the (*R*)-**26** afforded a 1:1 mixture of diastereoisomers (Scheme 49).



Scheme 48



Scheme 49

1.17.3.2 Addition of Oxygen

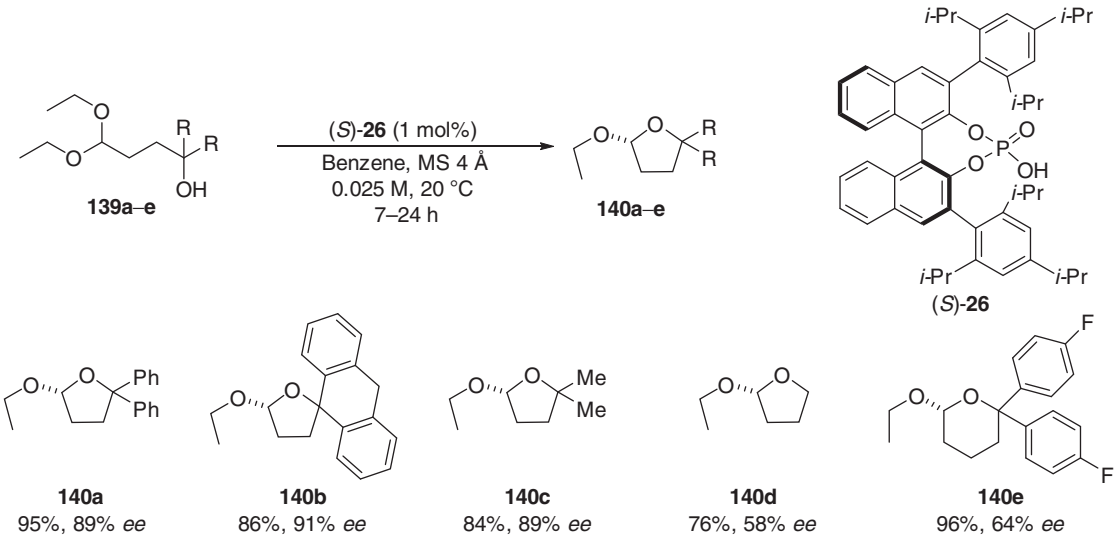
1.17.3.2.1 Scope

Acetals, obtained from the addition of oxygen to carbonyls, are an important class of biologically active compounds and natural products, which are used in cells to construct carbohydrates and are found in spiroketal polyketides.[80,81] The chiral acetals are extremely important for the purpose of medicinal chemistry.[82] Depending on the catalyst used for this transformation, the preparation of aminals can be broken down into two different types: (1) organocatalyzed acetal formation and (2) metal complex-catalyzed addition of oxygen to C═O.

1.17.3.2.2 Organocatalysis-catalyzed addition of oxygen to C═O

In 2010, the List group reported the first example of organocatalytic addition of oxygen to the carbonyl group to form stereogenic acetals, catalyzed by a chiral phosphoric acid **26** (Scheme 50).[83] Molecular sieves and low concentration are important factors to enhance the enantioselectivity. No decrease in optical purity was observed by prolonging the reaction time, which indicates that the phosphoric acid-catalyzed reverse reaction is not competitive. Substrate scope studies show that both aromatic and aliphatic substituents on tertiary alcohols **139a–e** work equally well, affording the desired acetals **140a–e** with high enantioselectivities. However, primary alcohol **139d** undergoes the transacetalization and delivers the cyclic acetal **140d** with lower enantioselectivity. Extension to six-membered acetal **140e** provides a lower level of asymmetric induction compared to its five-membered counterpart.

The bifunctional activation of phosphoric acid, via two hydrogen bonds with the hydroxyl acetal, was proposed to account for the high enantioselectivity (Figure 10(a)). The cyclization might proceed through two different ways: (1) the formation of



Scheme 50

oxocarbenium intermediate with the chiral phosphate anion environment (Figure 10(b) and (2) a more SN2-like pathway (Figure 10(c)).

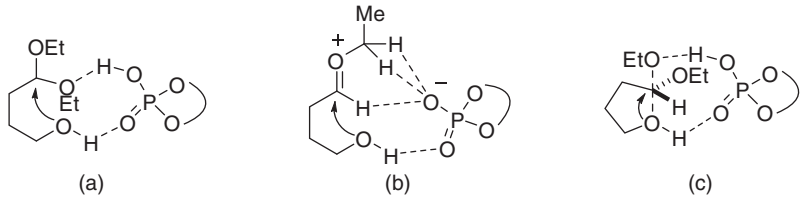
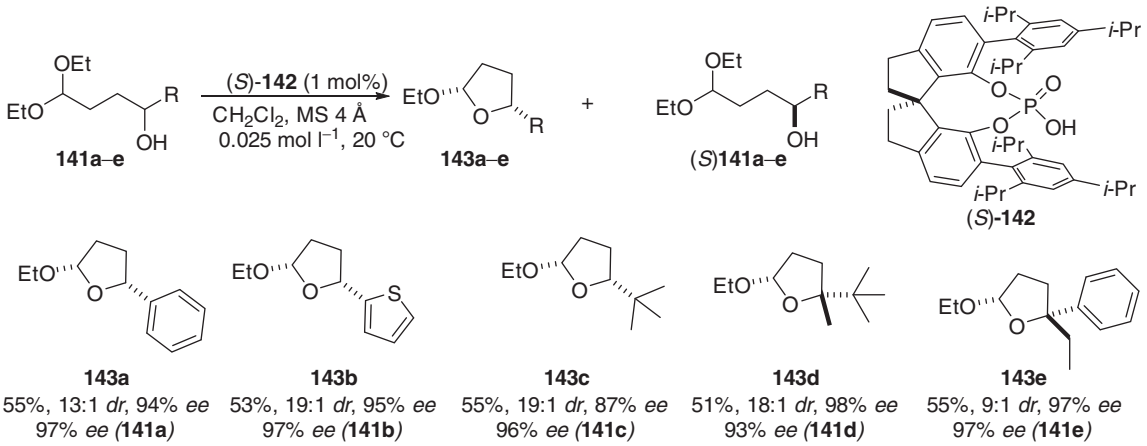


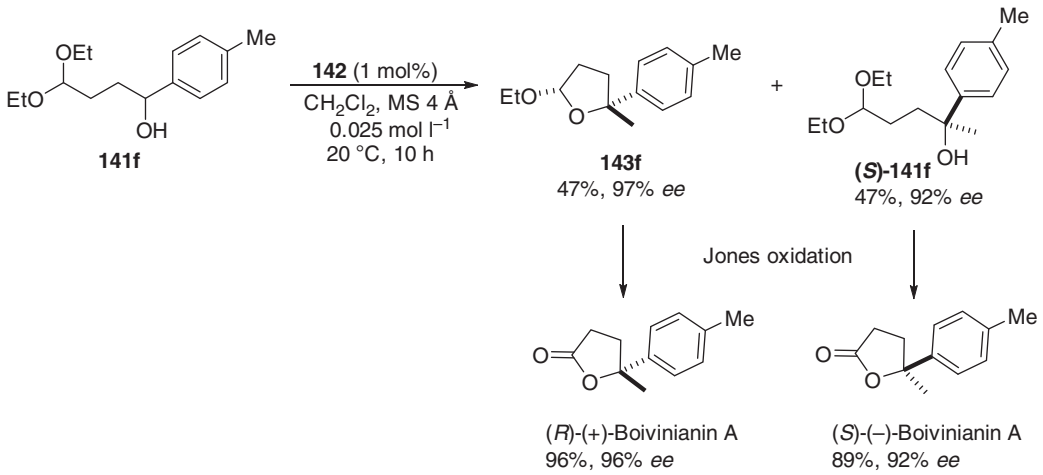
Figure 10 Proposed transition state for acetals formation.

As an extension of the above report, the same group introduced the kinetic resolution of hydroxyacetals via a chiral phosphoric acid-catalyzed transacetalization reaction (Scheme 51).[84] With the newly developed spiro-phosphoric acid **142**, secondary alcohols **141a–e**, with either aromatic or aliphatic substituent, underwent the kinetic resolution, resulting in both the cyclic acetals **143a–e** and chiral secondary alcohols **141a–e** with excellent enantioselectivities and approximately 50% of yield for each. Tertiary alcohols **141d–e** also performed remarkably well.



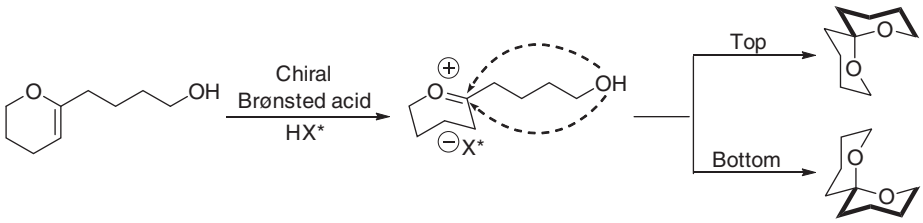
Scheme 51

To demonstrate the utility of the products, with a single step of Jones oxidation, both enantiomers of natural products biovinianin A were obtained with excellent yields and high optical purities as shown in Scheme 52.



Scheme 52

With the success of the above transacetalization, List and coworkers proposed that the acetal formation can be extended to the synthesis of spiroacetals,[85] which are found in a range of natural products.[81] As shown in Scheme 53, in the presence of chiral Brønsted acid, hydroxyenol ether would undergo transacetalization, leading to the spiroacetal via the oxocarbenium intermediate. The chiral phosphate presumably forms the ion pair with the oxocarbenium intermediate to control the enantiofacial selectivity. Unfortunately, only low enantioselectivity was obtained with BINOL-derived chiral phosphoric acids, which was presumably attributed to the large active sites of the catalyst (Figure 11(a)). With this in mind, the authors designed a new catalyst **145** with confined active space (Figure 11(b)) to limit the freedom of the transition state. Due to the steric impulsion of the substitutes on the 3,3′-positions, the P-N bonds' rotation was inhibited and induced the deep active site. This elegant design was inspired by the enzymes endowed with folded proteins and the artificial catalytic cavities.[86] With the newly designed Brønsted acid **145**, spiroacetals **146a–f** with different ring sizes were obtained in excellent enantioselectivities (Scheme 54). Even a large substrate **144f** can undergo the cyclization to afford the desired product **146f** with good diastereoselectivity, albeit higher temperature is required.



Scheme 53

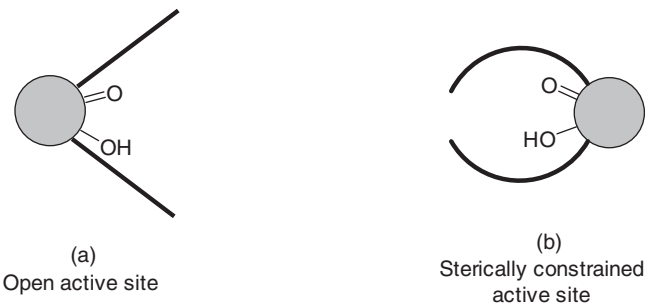
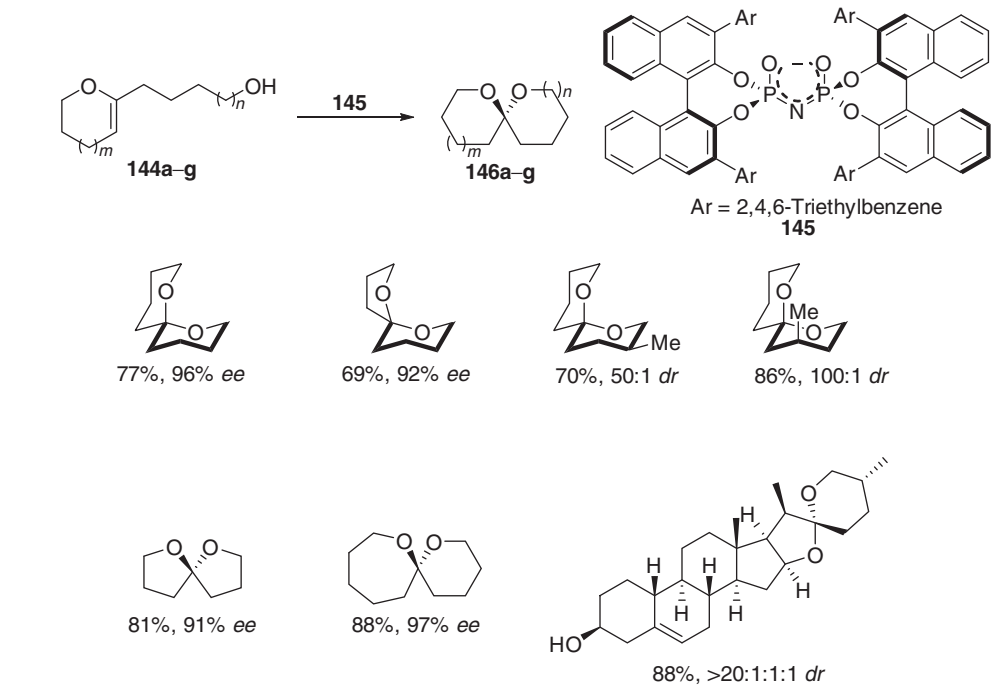
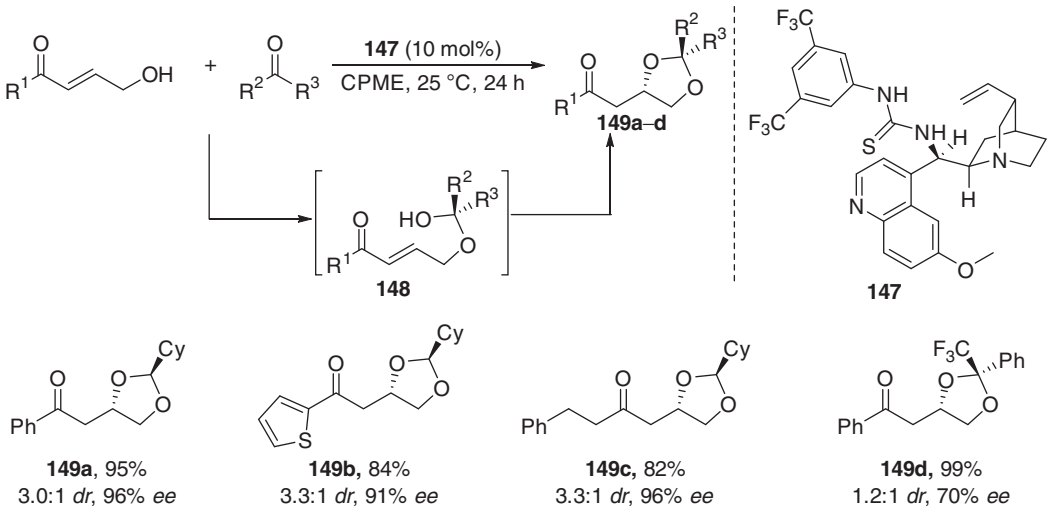


Figure 11 Geometrical models of phosphoric acids.

Rencently, Asano and Matsubara reported an asymmetric [3+2] cycloaddition reaction catalyzed by cinchona-alkaloid-thiourea-based bifunctional organocatalyst **147**, to generate optical aminals **149** (Scheme 55).[87] The reaction was proposed to proceed through a stepwise process via a hemiacetal intermediate **148**. In general, moderate diastereoselectivities and excellent enantioselectivities of acetals **149** were obtained under the reaction conditions.



Scheme 54

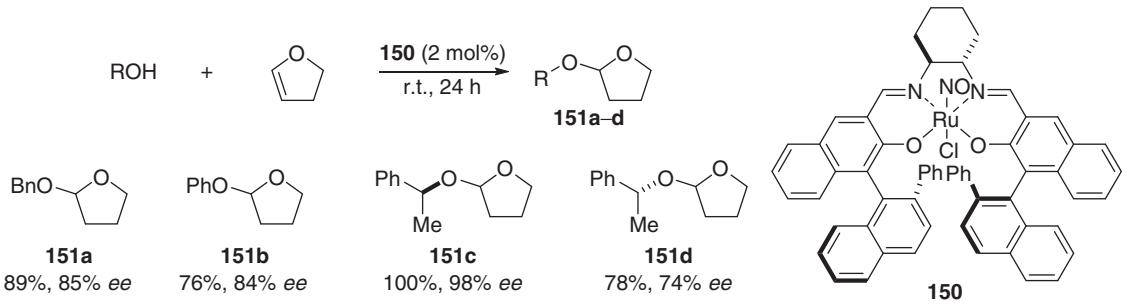


Scheme 55

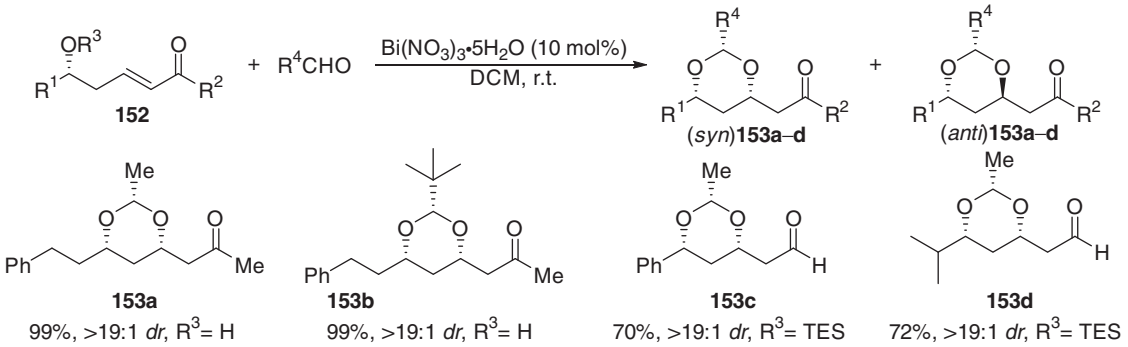
1.17.3.2.3 Metal complex catalyzed the addition of oxygen to C═O

In 2002, the Katsuki group reported the first catalytic acetal formation via the addition of alcohols to dihydrofuran, catalyzed by a ruthenium (II) complex **150** (Scheme 56).[88] A control experiment of enantiomerical-enriched acetal under the reaction conditions showed no change of *ee* value, which indicates that the enantioselectivity of the acetal was achieved through kinetical control. Both alcohols and phenols delivered the corresponding acetals **151a–d** in good enantioselectivities. Starting from the chiral alcohols, different enantioselectivities were observed depending on the match or mismatch of the catalyst with the substrates (**151c** vs. **151d**).

In 2012, Evans and coworkers demonstrated a simple protocol for the *syn*-1,3-dioxanes formation by the addition of *δ*-triorganosilyloxy, *δ*-hydroxy-*α*,*β*-unsaturated aldehydes, or ketones **152** with alkyl aldehydes catalyzed by $Bi(NO_3)_3{\cdot}5H_2O$ (Scheme 57).[89] The acetals **153a–d** were formed through a stepwise process involving the intermolecular addition of oxygen to the carbonyl group to generate hemiacetal and subsequent intramolecular oxy-Michael addition. Good yields and excellent diastereoselectivities of the *syn*-1,3-dioxanes **153a–d** were obtained under the mild reaction conditions.

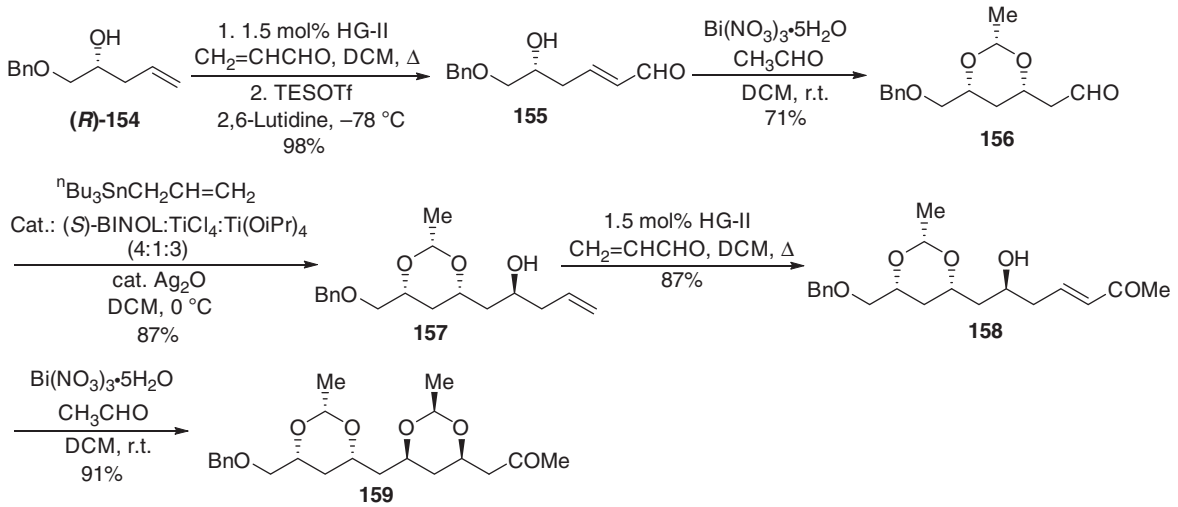


Scheme 56



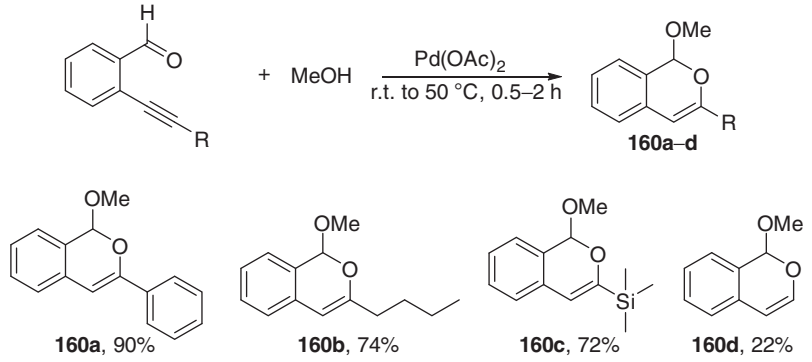
Scheme 57

To show the synthetic utility of this process, the authors displayed a concise preparation of the critical fragment of the polyene macrolide RK-397, utilizing the iterative sequence as shown in Scheme 58. Treatment of the optically pure homoallylic alcohol **(*R*)-154** with acrolein in the presence of Hoveyda–Grubbs second-generation catalyst and subsequent protection generated the *δ*-triorganosilyloxy-*α,β*-unsaturated aldehyde **155**, which was converted into the syn-1,3-dioxane **156** catalyzed by bismuth nitrate with excellent diastereocontrol. Asymmetric allylation of the resulting aldehyde provided the homoallylic alcohol **157**, which undergoes cross-metathesis with methyl vinyl ketone, providing *δ*-hydroxy-*α,β*-unsaturated ketone **158**. The key fragment of the polyene macrolide RK-397 **159** was obtained with excellent diastereocontrol and high yield by treating **158** under the reaction conditions shown in Scheme 58.



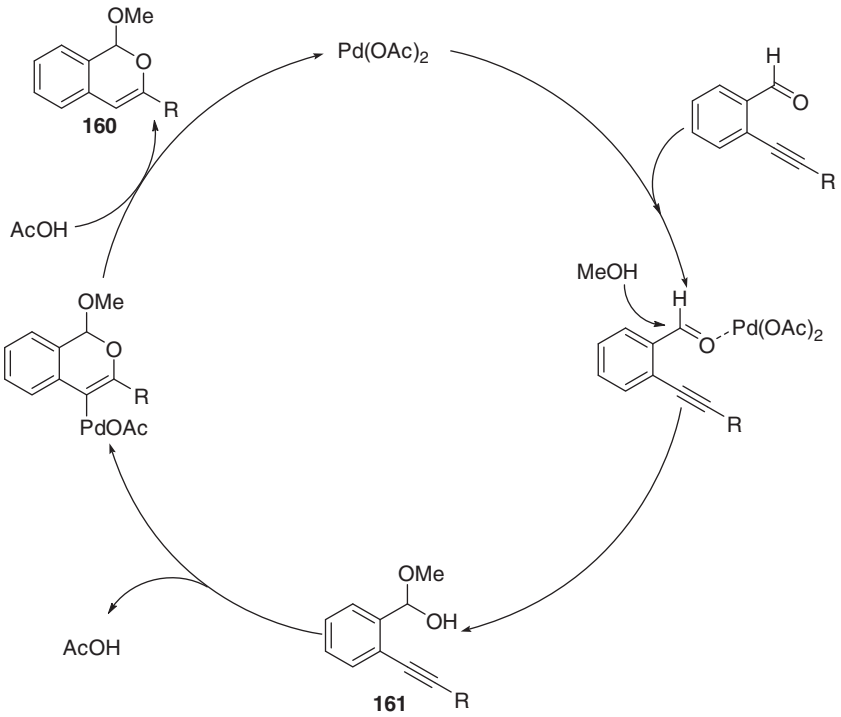
Scheme 58

In 2002, Yamamoto and coworkers developed a palladium(II)-catalyzed synthesis of cyclic acetals from readily available acetylenic aldehydes (Scheme 59).[90] Good yields of cyclic acetals **160a–c** were obtained under mild reaction conditions for the internal alkyne, whereas there was a low yield of desired product **160d** from the terminal alkyne.



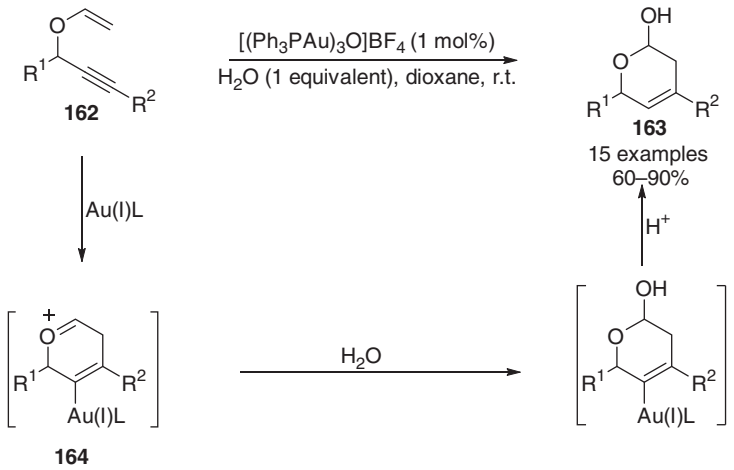
Scheme 59

As shown in Scheme 60, palladium acetate was proposed to act as both a Lewis acid and a transition-metal catalyst. Specifically, nucleophilic addition of methanol to the carbonyl, which was activated by Lewis acidic $Pd(OAc)_2$, formed the hemiacetal intermediate **161**. The intramolecular addition of hemiacetal to Pd(II)-alkyne provided the alkenyl ester **160** after proto-demetallation. The double role of $Pd(OAc)_2$ was confirmed by NMR analysis of the mixture of substrate and catalyst. In addition, the synthetic utilities of the products were presented.



Scheme 60

Toste and coworkers reported a gold(I)-catalyzed synthesis of dihydropyran **163** from propargyl vinyl ethers **162**. It was proposed that reactive oxocarbenium intermediate **164** formed in the presence of Au(I) catalyst. Good yields were obtained with an array of substrates under mild reaction conditions (Scheme 61).[91]



Scheme 61

1.17.3.3 Addition of Phosphorus

1.17.3.3.1 Scope

Similar to the α-aminophosphonic acids, α-hydroxyphosphonic acids also present multiple potent biological activities, such as antibiotics, and antiviral agents, represented by a renin inhibitor (Figure 12).[92] The nucleophilic addition of alkyl or aryl phosphites to aldehydes or ketones (Pudovik reaction)[47] is one of most widely applied methods for the stereoselective synthesis of α-hydroxyphosphonates. Depending on the chiral catalyst employed, this section can be broken down into four categories: (1) chiral titanium(IV)-catalyzed asymmetric Pudovik reaction, (2) chiral aluminum(III)-catalyzed asymmetric Pudovik reaction, (3) chiral lanthanum(III)-catalyzed asymmetric Pudovik reaction, and (4) organocatalytic asymmetric Pudovik reaction.

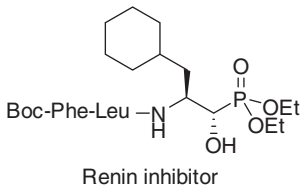
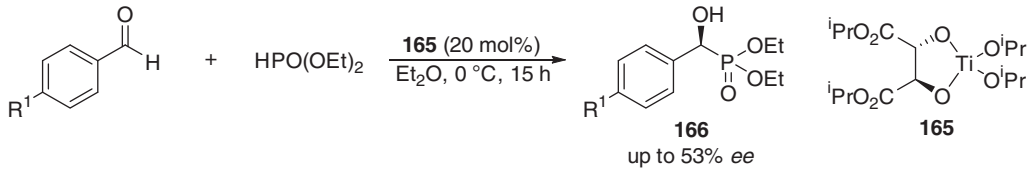


Figure 12 Represent example of α-hydroxyphosphonic acid.

1.17.3.3.2 Chiral titanium(IV)-catalyzed asymmetric hydrophosphonylation

In 1993, Shibuya et al. reported the first asymmetric addition of phosphites to aldehydes, catalyzed by titanium(IV) tartrate complex **165** (Sharpless catalyst).[93] Only moderate enantioselectivities of α-hydroxyphosphonates were obtained from this seminal report. The proposed mechanism indicates that one isopropanol was released from the reaction of catalyst with diethyl phosphite and generated the chiral diethyl phosphite titanium complex **167**, which then reacted with aldehyde via a transition state **168** to form the product and regenerate the catalyst (Scheme 62; Figure 13).



Scheme 62

In 1998, a similar catalytic system was reported by Spilling et al., whereby the cyclohexanediol was employed as the chiral ligand.[94] However, only moderate stereoselectivities were observed.

In 2008, You et al. reported a robust catalytic system, including the combination of substituted BINOLs, cinchona alkaloids, and Ti(O*i*Pr)$_4$, for the highly efficient asymmetric hydrophosphonylation of aldehydes.[95] Excellent enantioselectivities were

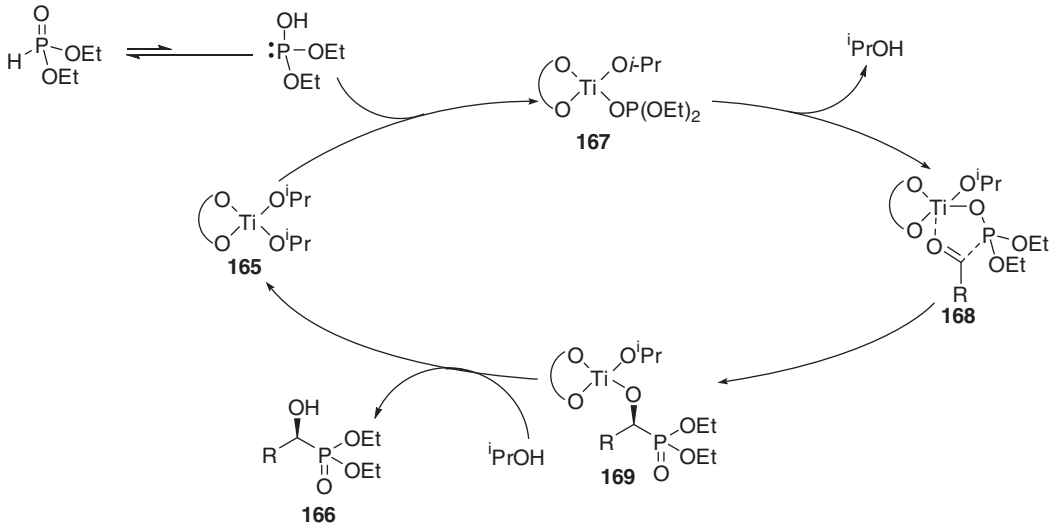
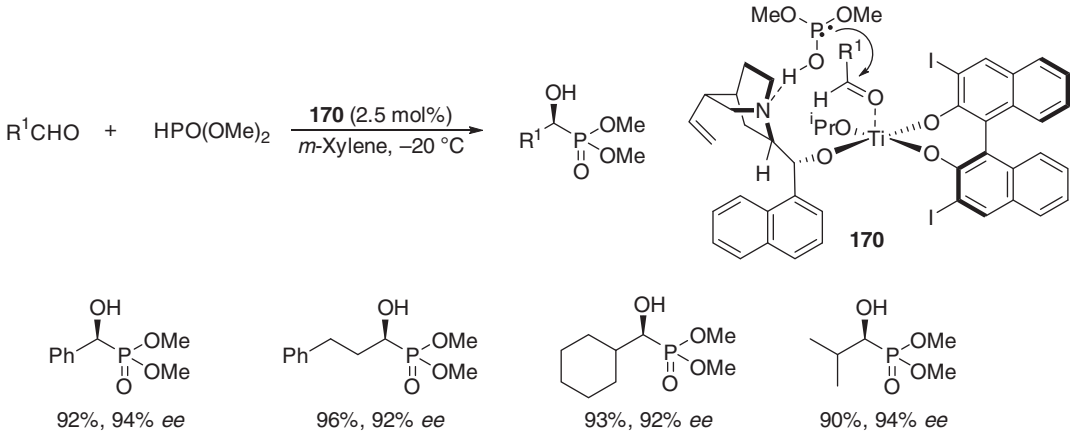


Figure 13 Proposed mechanism for titanium(IV)-catalyzed the addition of phosphites to aldehydes.

obtained from both aromatic and aliphatic aldehydes. A transition state **170** was proposed, in which the Ti(IV) metal center acts as Lewis acid to activate the aldehydes, while the nitrogen atom of cinchona alkaloids activates the phosphites through a hydrogen bond (Scheme 63).



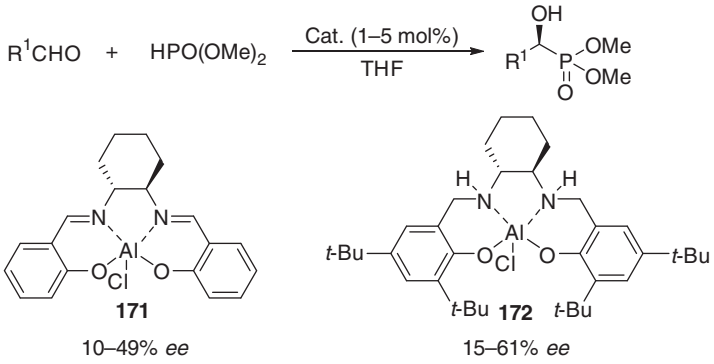
Scheme 63

1.17.3.3.3 Chiral aluminum(III)-catalyzed asymmetric hydrophosphonylation

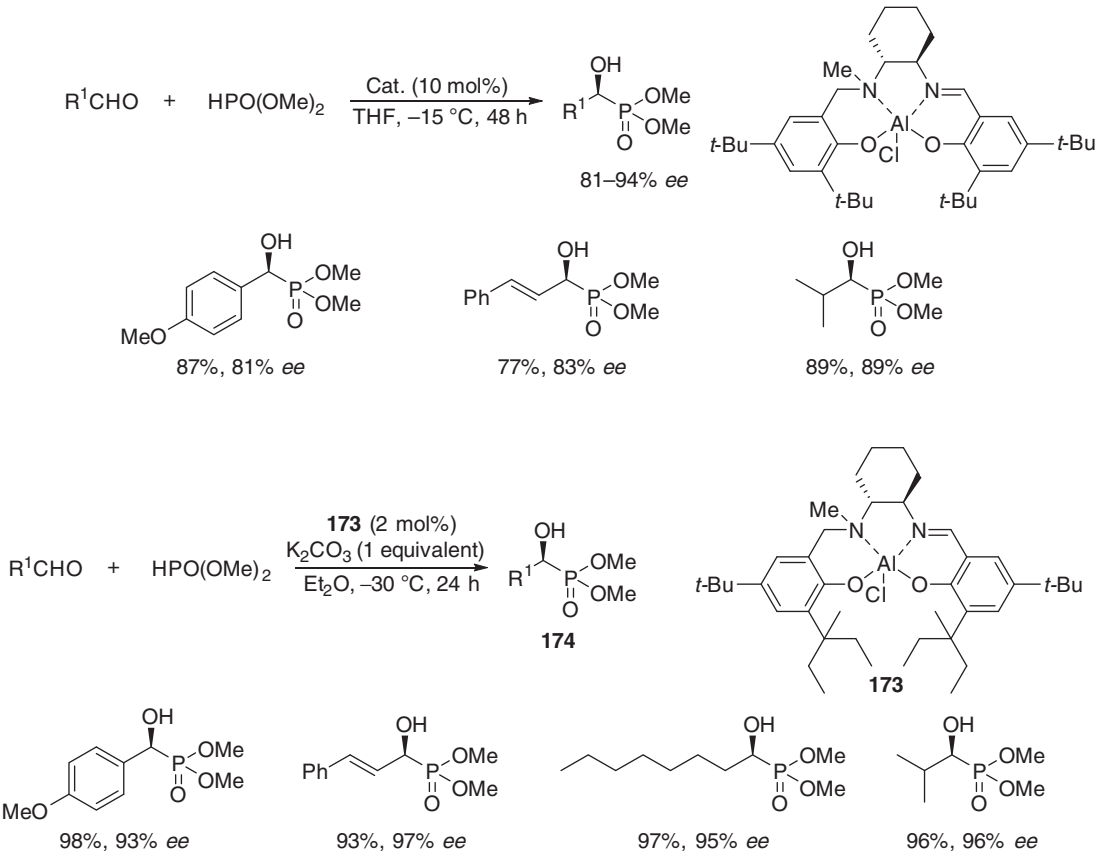
Kee et al. reported the first aluminum(III)-catalyzed enantioselective hydrophosphonylation of aldehydes.[96] Both SALEN-Al(III) complex **171** and SALAN-Al(III) **172** were found to be efficient for the hydrophosphonylation, but only afforded the products with low-to-moderate enantioselectivities (Scheme 64).

In 2005, Katsuki and coworkers reported the use of an Al(salalen) catalyst **173** for the asymmetric hydrophosphonylation of aldehydes with dimethyl phosphite to afford the corresponding α-hydroxy phosphonates **174** in high enantioselectivities (81–94%) (Scheme 65).[52] Although the Al(salalen) catalyst **173** provided much higher enantioselectivities for the hydrophosphonylation than the Al(salen) catalyst developed by Kee, the reaction proceeded slowly, taking 48 h to complete in the presence of 10 mol% of catalyst. To overcome this limitation, the authors developed a simple and efficient method, wherein by adding 1 equivalent of potassium carbonate, the reaction finished in 24 h with only 2 mol% of catalyst (Scheme 66).[97] In addition, higher yields and higher enantioselectivities were obtained in the presence of K_2CO_3 than without base additives. The base was presumably to deprotonate the phosphite and generate the active phosphite anion.

Feng and coworkers developed a chiral Schiff base Al(III) complex-catalyzed, highly efficient asymmetric hydrophosphonylation of aldehydes (Scheme 67).[98] The complex was obtained *in situ* from the reaction of Schiff base **176** with diethyl aluminum(III) chloride. Both aromatic and aliphatic aldehydes undergo hydrophosphonylation with diethyl phosphite, in the



Scheme 64

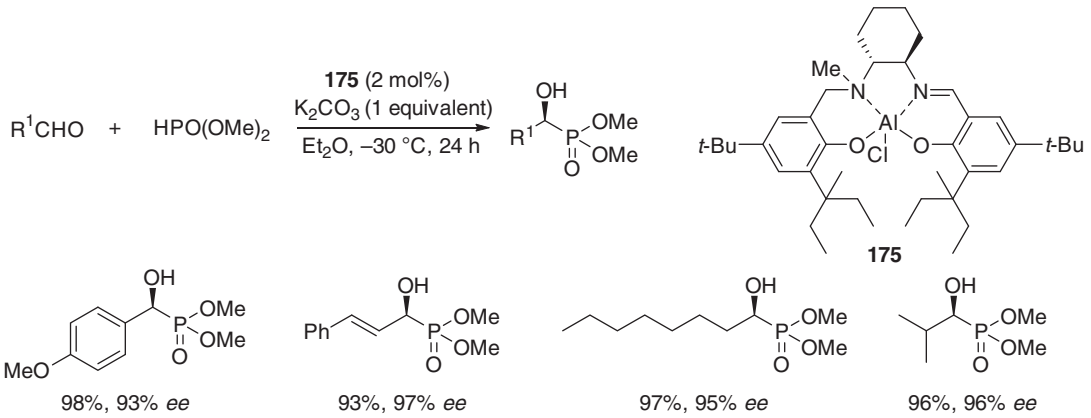


Scheme 65

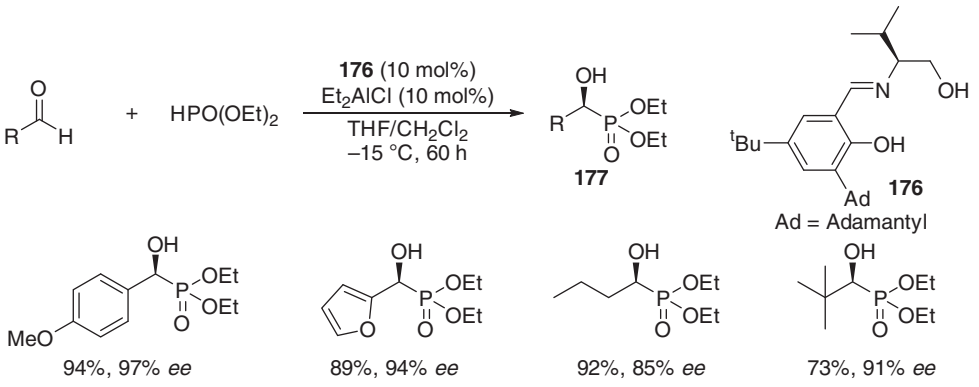
presence of Schiff base Al(III) complexes, yielding α-hydroxy phosphonates **177** in high yields and high enantioselectivity, up to 97%. Strong positive nonlinear effort was observed for the hydrophosphonylation. Moreover, HRMS analyses of the complex showed a dimeric species of the catalyst.

The same group further applied hydrogenated tridentate Schiff base Al(III) complex to the catalytic asymmetric hydrophosphonylation of trifluoromethyl ketones, affording the corresponding α-hydroxy trifluoromethyl phosphonates **178** in good yields (82–95%) and enantioselectivities (74–90%) (Scheme 68).[99]

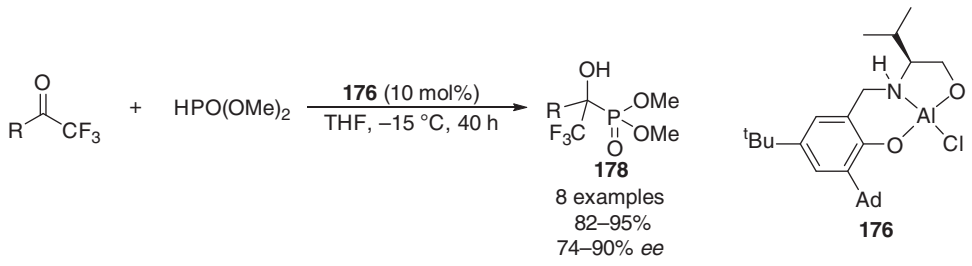
The Yamamoto group reported a catalytic asymmetric addition of phosphites to aldehydes catalyzed by (*R*)-TBOxAlCl complex **179** (Scheme 69).[100] With 1 mol% of catalyst, the reaction only takes 5–20 min to complete by virtue of the electron-withdrawing trifluoroethyl group on phosphite, which influences the equilibrium distribution of the two tautomers. Aliphatic aldehydes provide lower stereoselectivities than aromatic aldehydes (entries 1–3 vs. entries 4–5).



Scheme 66



Scheme 67

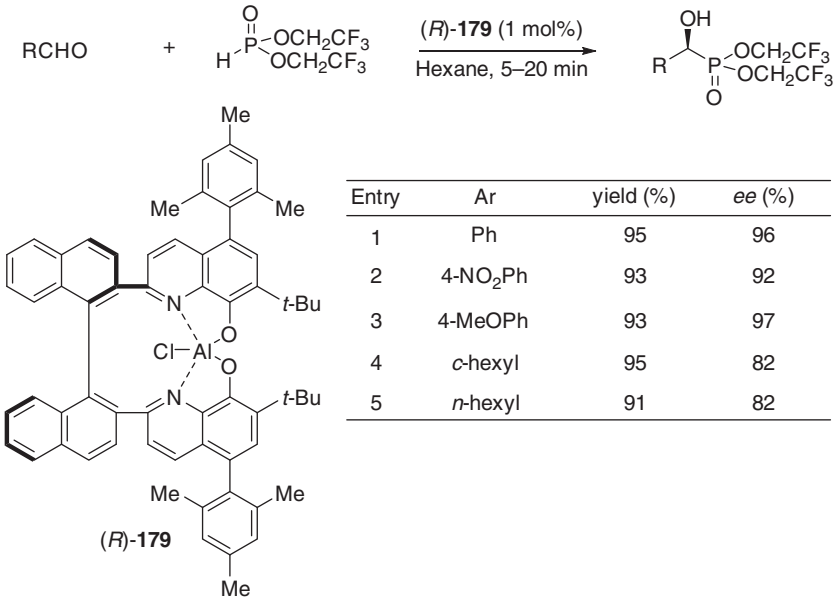


Scheme 68

1.17.3.3.4 Chiral lanthanum(III)-catalyzed asymmetric hydrophosphonylation

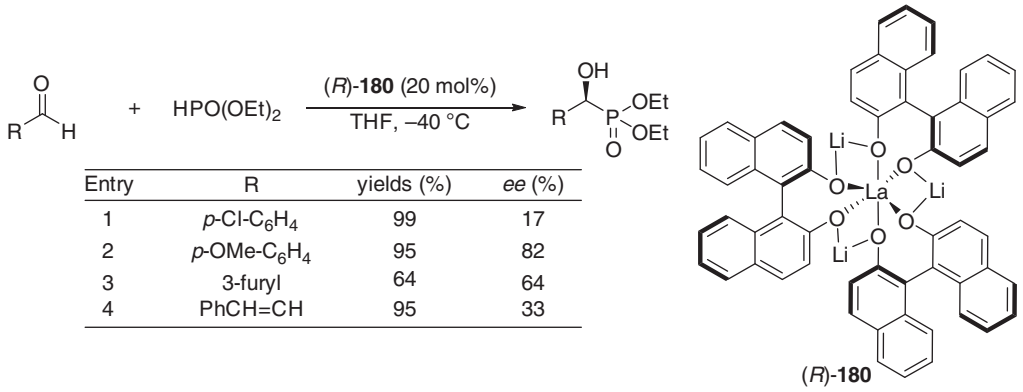
Bifunctional Lewis acid/Lewis base lanthanum–alkali metal complexes have been employed in a number of important asymmetric organic transformations by activation of both nucleophiles and electrophiles.[101] In 1993, Shibuya et al. reported the first examples of lithium–lanthanum–BINOL complex-catalyzed asymmetric hydrophosphonylation of aldehydes (Scheme 70).[102] Spilling reported similar results independently in 1994.[103] However, only moderate enantioselectivities were obtained and the substrates are limited. For example, Shibuya's system only works well for aromatic aldehydes with electron-donation substituents, wherein up to 82% *ee* in the presence of 20 mol% of catalyst was obtained (entries 1–3), whereas Spilling reported the hydrophosphonylation of cinnamaldehyde with 33% *ee* (entry 4).

The Shibasaki group reinvestigated the catalytic system and found that the enantioselectivities can be enhanced up to 95% by improving the catalyst preparation procedure and by slowing addition of aldehydes (Scheme 71).[104] In addition, aliphatic aldehydes were tested and moderate enantioselectivities were obtained. The authors explained that the observed improved selectivities upon slow addition of aldehydes resulted from inhibition of background reaction.



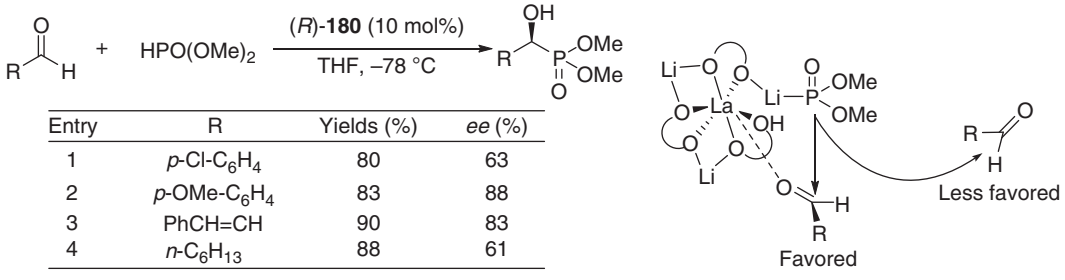
Entry	Ar	yield (%)	*ee* (%)
1	Ph	95	96
2	4-NO_2Ph	93	92
3	4-MeOPh	93	97
4	*c*-hexyl	95	82
5	*n*-hexyl	91	82

Scheme 69



Entry	R	yields (%)	*ee* (%)
1	*p*-Cl-C_6H_4	99	17
2	*p*-OMe-C_6H_4	95	82
3	3-furyl	64	64
4	PhCH=CH	95	33

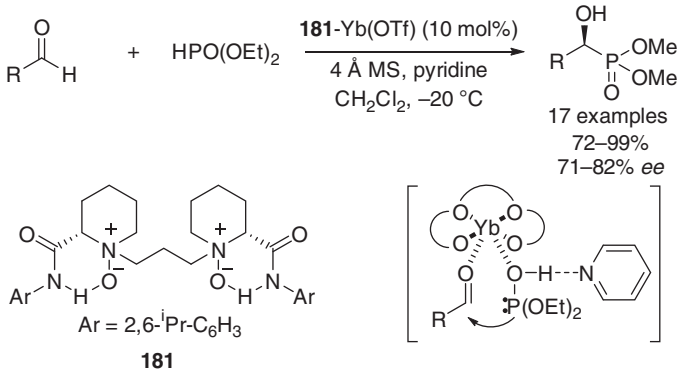
Scheme 70



Entry	R	Yields (%)	*ee* (%)
1	*p*-Cl-C_6H_4	80	63
2	*p*-OMe-C_6H_4	83	88
3	PhCH=CH	90	83
4	*n*-C_6H_{13}	88	61

Scheme 71

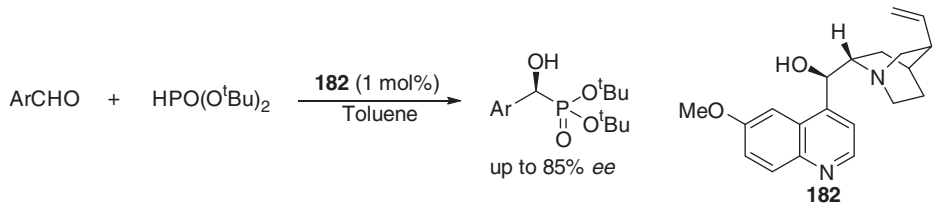
Feng et al. reported an asymmetric hydrophosphonylation of aromatic aldehydes using *N,N′*-dioxide ytterbium(III) complex as a catalyst with pyridine as an additive, affording the corresponding adducts in good-to-excellent yields (up to 99%) with moderate enantioselectivities (71–82% *ee*) (Scheme 72).[105] The proposed transition state indicates the ytterbium(III) as Lewis acid activating both aldehydes and phosphites, whereas pyridine acts as Brønsted base to deprotonate the phosphite tautomer.



Scheme 72

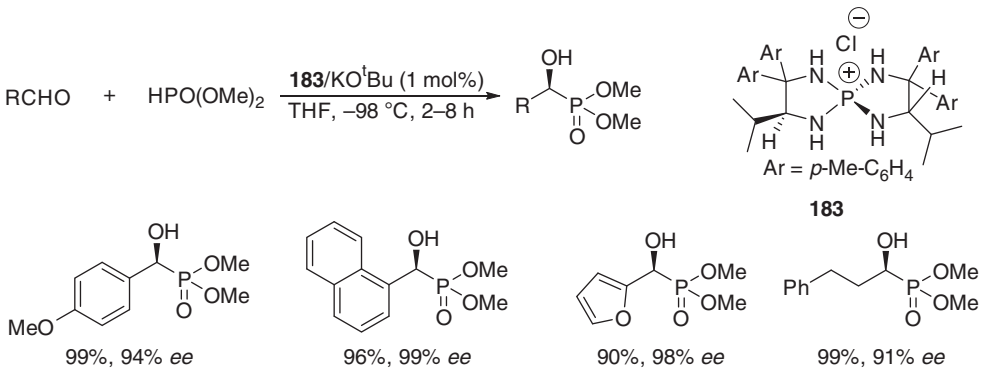
1.17.3.3.5 Chiral organocatalytic asymmetric hydrophosphonylation

In 1983, Wynberg et al. reported the first organocatalytic hydrophosphonylation of aldehydes catalyzed by quinine **182** (Scheme 73).[106] The addition of di-*tert*-butyl phosphite to aldehydes was carried out in the presence of quinine and up to 85% *ee* was produced. Only a few aromatic aldehydes were tested under the reaction conditions. The authors also show that the use of bukyl phosphite is essential for the high selectivities, whereas the trimethyl phosphite only delivered 28% *ee*.



Scheme 73

No progress was made in this area until Ooi and coworkers reported a chiral tetraaminophosphonium salt **183**-catalyzed asymmetric hydrophosphonylation of aldehydes in the presence of inorganic base potassium *tert*-butyloxide in 2009 (Scheme 74).[107] The straightforward protocol allowed for the addition of dimethyl phosphite to aromatic and aliphatic aldehydes with excellent yields and enantioselectivity.



Scheme 74

As shown in Figure 14, triaminoiminophospharane **184** was proposed to be formed *in situ* from aminophosphonium salt **183** and KO^{t}Bu, which is supposed to be a strong base capable of deprotonation of phosphite and formation of double hydrogen bonds as shown in the reactive intermediate **185**. Moreover, the phosphite anion was detected by low-temperature NMR analysis. Subsequent nucleophilic addition to aldehydes in the chiral environment, as shown in **186**, delivered the desired products with excellent enantioselectivities.

The same group further developed the catalytic asymmetric hydrophosphonylation of ynones using the same kind of catalyst (Scheme 75).[108] Under similar reaction conditions, high enantioselectivities of α-tetrasubstituted a-hydroxy phosphonates were obtained for the first time.

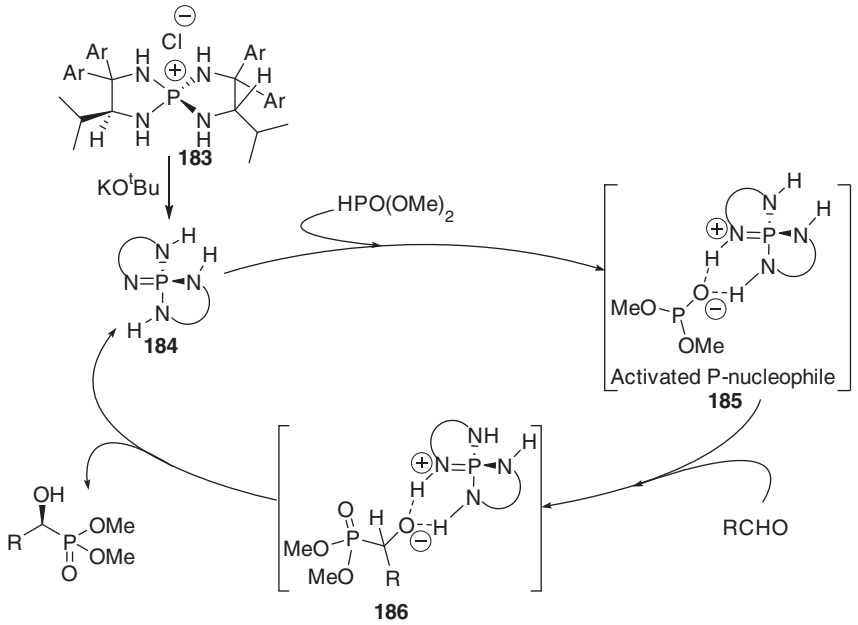
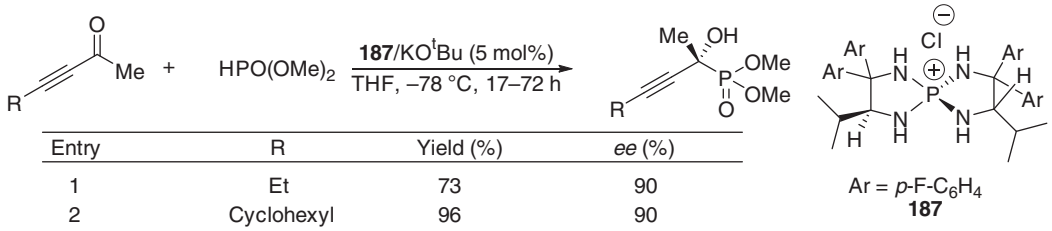


Figure 14 Proposed mechanism for aminophosphonium salt-catalyzed the addition of phosphites to aldehydes.



Entry	R	Yield (%)	*ee* (%)
1	Et	73	90
2	Cyclohexyl	96	90
3	Me_3Si	96	91

Scheme 75

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1.18 CN Addition to C=O and C=N Bonds

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Glossary

Bifunctional Applied to catalysts having two different functionalities, usually a Lewis acid and Lewis base capable of activating at least two reagents involved in the reaction.

Heterobimetallic complex A metal complex containing two different metal atoms in its structure.

Homochiral Applied to enantiomerically pure molecules.

Hydrocyanation The process whereby hydrogen cyanide is added to a substrate like carbonyl compounds, imines or related compounds.

Mesoporous A material containing pores with diameters between 2 and 50 nm.

Salen Chelating ligand used in asymmetric catalysis. The name arises from the contraction for salicylaldehyde and ethylenediamine.

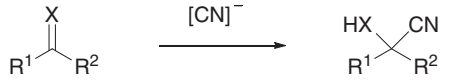
Trimethylsilylcyanation The process whereby trimethylsilylcyanide is added to a substrate like carbonyl compounds, imines or related compounds with transference of both cyanide and trimethylsilyl groups.

1.18.1 Important Safety Notice – Hazardous Materials

Any cyanating agent mentioned in this chapter must be considered extremely toxic. Hydrogen cyanide (a colorless gas or bluish-white liquid with a bitter almond odor) and its solutions may be fatal following exposure via all routes including inhalation, ingestion, or skin contact. It must only be used in a properly vented fume hood, with the adequate equipment (gloves and gas mask) and in the presence of a coworker previously informed that cyanide will be handled in the area and capable of using a Cyanokit (cyanide antidote kit), which must be present in the laboratory. Other cyanide compounds are also highly toxic because they can decompose to form hydrogen cyanide on boiling, drying, or in the presence of humidity. Sodium and potassium cyanide are converted into HCN on contact with acid. Trimethylsilyl cyanide is highly flammable and extremely toxic. It also forms hydrogen cyanide on contact with water and alcohols. Ammonium cyanide decomposes at 36 °C to ammonia and HCN. Organic cyanides (e.g., acyl cyanides, tributyltin cyanide, and dialkylcyanophosphonates) are also toxic, highly flammable, irritating to eyes and skin, and can form HCN on contact with acid or water. Any material employed during the laboratory operation must be cleaned. Cyanide residues should be conveniently stored in plastic bottles containing aqueous sodium hydroxide or, preferably, destroyed by oxidation or complexation. Solid waste related with cyanide manipulation must be stored in a container for chemical waste labeled adequately. As a general rule all manipulations involving cyanide reagents should be carried out in full compliance with the national safety regulations concerning the use of cyanides.

1.18.2 Introduction

The cyanation of carbon–oxygen and carbon–nitrogen double bonds has become a strategically important methodology widely employed in the organic synthesis of complex molecules, including asymmetric approaches.[1] A range of carbonyl compounds **1**, from aldehydes to ketones, can be cyanated providing synthetically useful α-hydroxy nitriles (also termed cyanohydrins). The asymmetric version of the reaction provides enantiomerically pure compounds that have been widely investigated.[2] Compared to carbonyl compounds, imines and related compounds are less electrophilic, but under appropriate conditions including the presence of Lewis acids, their cyanation produces synthetically useful α-amino nitriles.[3] Furthermore, the three-component Strecker reaction is a fundamental carbon–carbon forming bond process that represents a simple method for accessing α-amino acids (equation 1).[4]



1 **2** (1)

X = O, NR^3, $N^+(O^-)R^3$, $NNHR^3$, NOR^3

R^1, R^2, R^3 = Alkyl, aryl

The synthetic utility of cyanated compounds **2** is because of the presence of two functional groups (a nitrile and either an alcohol in α-hydroxy nitriles, or an amino group, in α-amino nitriles) that can be easily transformed to provide a variety of 1,2-difunctionalized synthetic intermediates.[5] Moreover, in the case of enantiomerically pure compounds such transformations can be carried out without loss of optical purity. Those intermediates have been widely used in the preparation of a diverse range of bioactive natural products.

In general, the cyanation of carbonyl and imino groups **1** is carried out by using reagents that transfer the cyanide to the unsaturated C═X bond in an indirect way. The reagents most often used for indirect cyanation are (1) acetone cyanohydrin, (2) trimethylsilyl cyanide, (3) diethylaluminum cyanide, (4) tetrabutylammonium cyanide, (5) dialkyl cyanophosphonates, and (6) acyl cyanides. These cyanations are more convenient and much more commonly used than direct cyanation methods such as those that involve the use of hydrogen cyanide or alkali metal cyanide salts.

The addition of cyanide to aldehydes and ketones as well as to imines and related compounds is a typical nucleophilic addition in which the two partners are clearly identified, i.e., the electrophile (C═X unsaturated system) and the nucleophile (the cyanide reagent). Owing to their inherent nature, the reaction can be promoted by either increasing the electrophilicity of the former or the nucleophilicity of the latter. Also, these two activations can be carried out in a simultaneous way through the so-called dual activation mode. Activation of the electrophile is achieved by conventional methods involving coordination to Lewis acids, which offers a vast number of possibilities because a great variety of metals can be used. Moreover, chiral complexes could be used as catalysts thus providing an entry to enantioenriched compounds. An alternative to the use of Lewis acids is to employ H-bond activation, mainly by using enantiomerically pure organocatalysts that lead to enantioselective reactions (**Figure 1**).

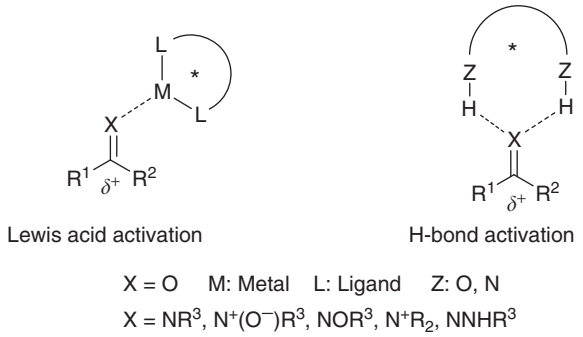


Figure 1 Activation of electrophiles.

The activation of nucleophiles like trimethylsilyl cyanide (TMSCN), a typical cyanating reagent, is mainly achieved by Lewis bases. Typically, a tertiary amine or other Lewis base like an *N*-oxide activates the cyanide reagent through an interaction that enhances the nucleophilicity of the cyanide anion. In the case of hydrogen cyanide and a tertiary amine such an interaction is a typical H-bond. In some particular cases, other models, based on the same type of interactions, are possible as proposed by Corey (Figure 2).

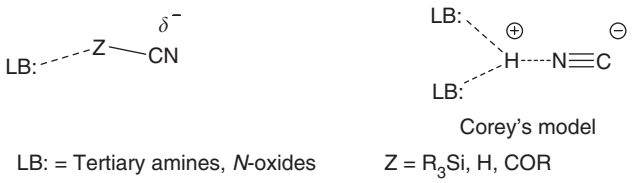


Figure 2 Activation of nucleophiles.

The dual activation of both electrophile and nucleophile in a synergistic way can proceed through two different paths. The first one is referred to as 'double activation' and it is produced when two different reagents, acting as Lewis acid and Lewis base, are used to activate separately the electrophile and the nucleophile, respectively; combination of an *N*-oxide with a compatible metal complex is an example of this type of activation. The other approach called 'bifunctional activation' consist of an only compound bearing two different functionalities playing the roles of Lewis acid (or H-bond donor) and Lewis base (or H-bond acceptor). Both double and bifunctional activation can be conducted in a catalytic way but in terms of versatility, the first one presents more alternatives to choose activators thus giving more opportunities to find adequate conditions to achieve good enantioselectivity (Figure 3).

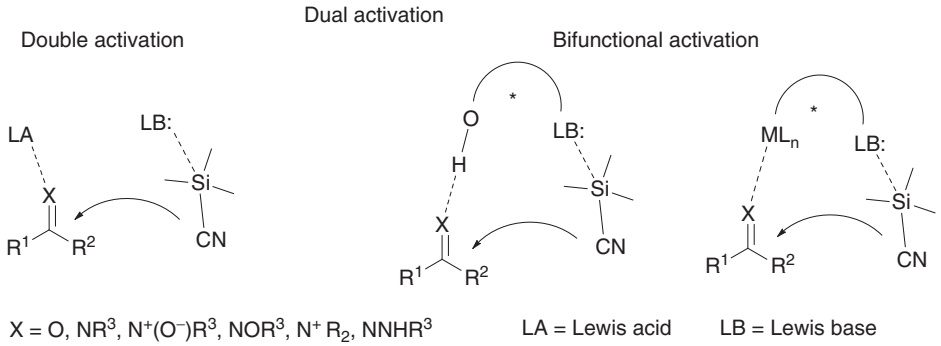


Figure 3 Dual activation of nucleophile and electrophile.

The cyanation reaction of aldehydes and ketones, and in particular the asymmetric synthesis of cyanohydrins, has been reviewed on numerous occasions.[6] Also, the addition of cyanide reagents to imines and related compounds have received considerable attention[7] and the catalytic asymmetric variant of the Strecker reaction has emerged as a reliable method for enantioselective carbon–carbon bond formation.[8]

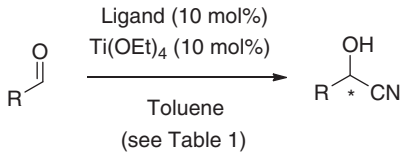
The main concern in this chapter is to illustrate the range of cyanation approaches available for the laboratory preparation of α-hydroxy and α-amino nitriles with a special focus on catalytic asymmetric processes.

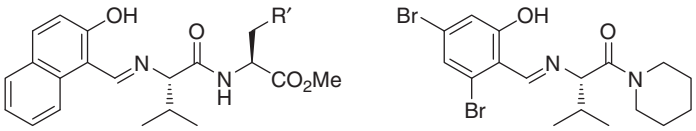
1.18.3 Addition of Cyanide to Aldehydes and Ketones

1.18.3.1 Addition of Hydrogen Cyanide

1.18.3.1.1 Metal-based catalysis

The asymmetric addition of hydrogen cyanide to aldehydes takes place with high enantioselectivities when catalyzed by a mixture of $Ti(OEt)_4$ and a dipeptide ester bearing a salicylal-type Schiff base. Enantiomeric compounds are obtained by modification of the salicylic moiety and *C*-terminal amino acid unit thus enabling the obtention of both enantiomers by employing easily available natural (*S*)-amino acids as the only source of chirality (Scheme 1). For example, ligands **3** and **4** promotes the obtention of (*R*)- and (*S*)-isomers, respectively (equation 2, Table 1).



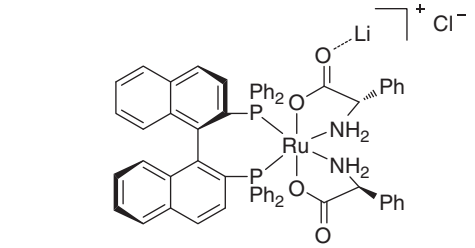


3a R′ = Ph
3b R′ = 3-Indolyl

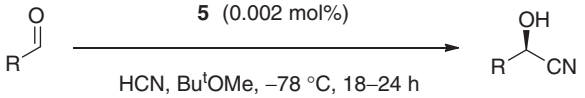
4

(2)

Theoretical calculations have been carried out with these types of catalysts to determine the origin of the selectivity. According to these calculations the precise mechanism of the formation of optically active cyanohydrins appears to be highly dependent not only by the attack directions of cyanide to the aldehyde, but also by different coordination modes of the aldehyde to the *in situ* formed chiral Lewis acid. A highly efficient approach leading to optically active cyanohydrins consists of the addition of hydrogen cyanide to aldehydes in the presence of only 0.002 mol% of bimetallic complex **5** (equation 3).[9]



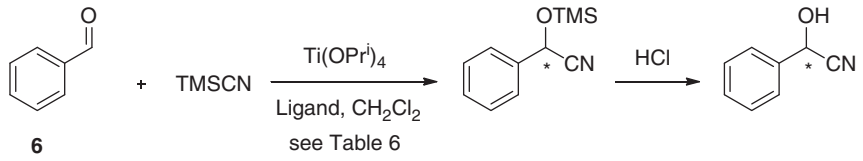
5 (0.002 mol%)



(3)

R	Yield (%)	*ee* (%)
Ph	96	96
2-MeC_6H_4	89	89
2-FC_6H_4	97	97
2-ClC_6H_4	98	98
4-MeC_6H_4	82	95
4-$MeOC_6H_4$	82	93
4-$CF_3C_6H_4$	96	96
1-Naphthyl	99	94

R	Yield (%)	*ee* (%)
3-MeC_6H_4	90	96
3-$MeOC_6H_4$	96	94
3-ClC_6H_4	98	98
3-BrC_6H_4	98	99
2-Furyl	89	92
Bu^t	91	94
n-C_6H_{13}	42	57
(*E*)-PhCH=CH	95	92



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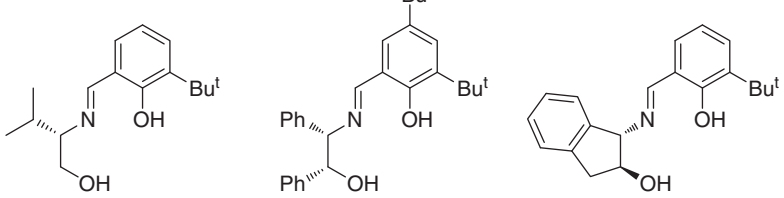
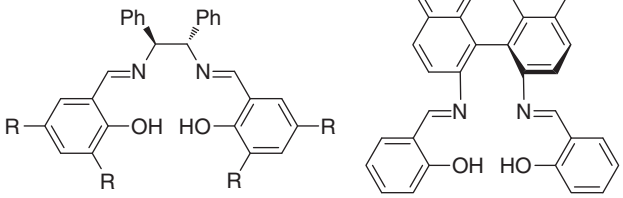
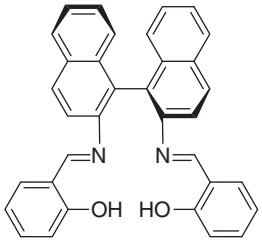


33 **34** **35**



36a R = H
36b R = Bu^t



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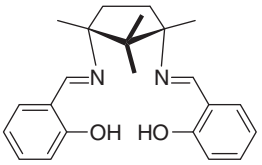

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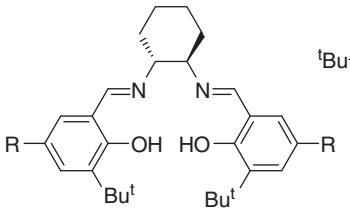
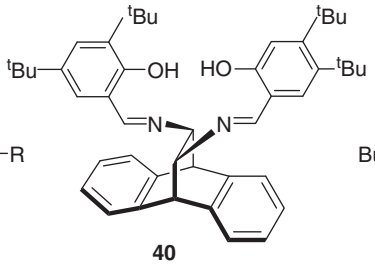


39a R = MeO
39b R = Bu^t



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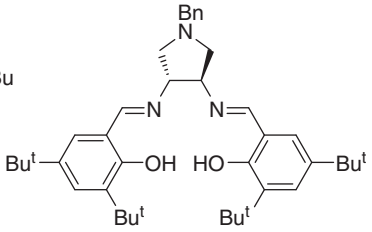

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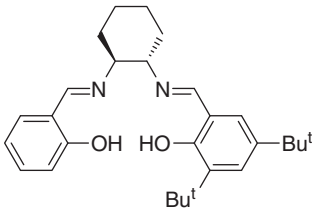

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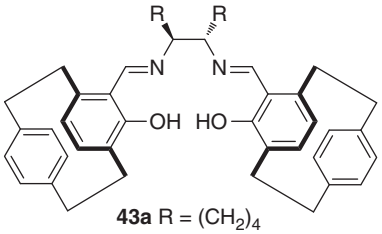
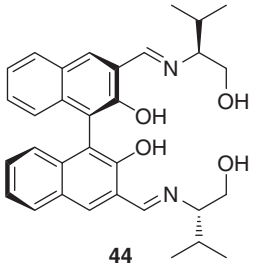


43a R = $(CH_2)_4$
43b R = H



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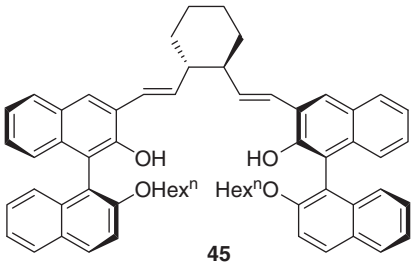

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Scheme 1

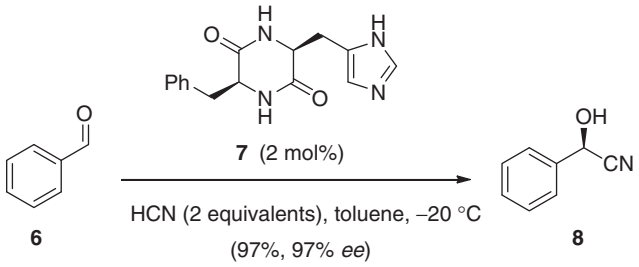
Table 1 Addition of HCN catalyzed by Ti (IV) complexes of **3** and **4**

No.	*R*	*Ligand*	*Time (h)*	*Temperature (°C)*	*Yield (%)*	*ee (%)*
i	*n*-C_6H_{11}	**3a**	8.5	−60	96	66 (*R*)
ii	Cyclohexyl	**3a**	1.5	−40	99	54 (*R*)
iii	2-Naphthyl	**3b**	7.5	−40	88	90 (*R*)
iv	3-$MeOC_6H_4$	**3b**	4	−40	80	85 (*R*)
v	2-Furyl	**3b**	7.5	−40	74	87 (*S*)
vi	3-$MeOC_6H_4$	**4**	41	−60	79	97 (*S*)
vii	2-MeC_6H_4	**4**	38	−60	96	92 (*S*)
viii	2-Naphthyl	**4**	84	−60	63	72 (*S*)
ix	(*E*)PhCH═CH	**4**	84	−60	40	62 (*S*)

1.18.3.1.2 Nonmetal-based catalysis

1.18.3.1.2.1 Peptide-catalyzed reactions

Cyclic peptides are known to catalyze the hydrocyanation of aldehydes since 1981.[10] As a typical example cyclo[(*S*)-His-(*S*)-Phe] **7** catalyzes the hydrocyanation of benzaldehyde **6** to provide mandelonitrile **8** in excellent yield and selectivity (equation 4). The reaction can be extended to a variety of aromatic aldehydes with *ee* greater than 80% and to aliphatic aldehydes, in these cases, with lower ee values. Interestingly, whereas compound **7** catalyzes the formation of (*S*)-cyanohydrins, the cyclic dipeptide cyclo[((*S*)-His-(*S*)-Leu)], in which the phenylalanine residue has been replaced by a leucine residue, promotes the formation of (*R*)-cyanohydrins.



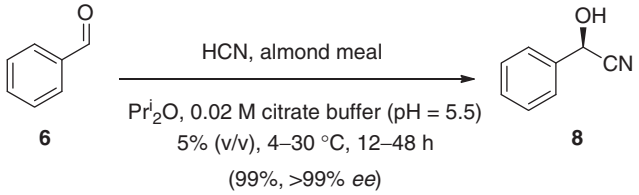
(4)

However, the main activity associated with this reaction during the past decade is devoted to the mechanism. Conformational studies based on NMR measurements have been carried out to determine the origin of the observed selectivity and several mechanisms have been proposed to explain the enantioselective autoinduction of the reaction. In 2009 the mechanism was studied in detail by computational quantum mechanics, molecular mechanics, and molecular dynamics methods[11] and it was discovered that a dimer is the actual catalyst, in which one imidazole ring is essential for delivery of the cyanide and the second imidazole group acts as an acid. Also the enantioselective autoinduction was found to be based on the incorporation of the product into the catalyst complex.

1.18.3.1.2.2 Enzymatic reactions

Hydroxynitrile lyases (HNLs, EC 4.1.2.x), also called oxynitrilases, are enzymes that catalyze the reversible condensation of hydrogen cyanide with aldehydes. HNLs constitute a branch of a much larger family of enzymes known as lyases and, in particular, aldehyde lyases a subcategory of carbon–carbon lyases. The synthesis of enantiomerically pure cyanohydrins catalyzed by HNLs has been reviewed recently.[12]

(*R*)-HNLs from several sources have been used for preparing optically active (*R*)-cyanohydrins from aromatic, heteroaromatic, and aliphatic aldehydes. The reaction may show some background reactivity corresponding to the nonenzymatic addition and because of it several reaction conditions have been investigated. The reaction performs well in aqueous buffer media although water–organic biphasic reactions are preferred in some case to achieve better enantioselectivities, particularly with difficult substrates, such as unsaturated aldehydes. By employing microaqueous conditions and almond meal as a source of (*R*)-HNL benzaldehyde **6** is transformed into (*R*)-mandelonitrile **8** in high enantioselectivity over a temperature range of 4–30 °C.[13] The reaction can be extended to other aliphatic, aromatic, and heteroaromatic aldehydes including fluorosubstituted benzaldehydes and it is amenable to a continuous processing in an industrial application (equation 5).

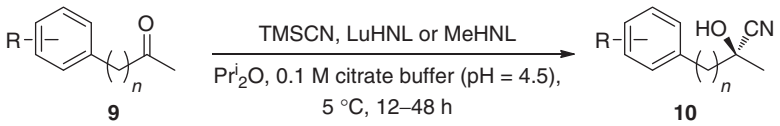


(5)

The obtention of stable, commercially available and highly efficient HNLs is of crucial importance. In particular, excellent results are obtained with immobilized HNLs entrapped in lens-shaped gels and in commercially available cross-linked aggregates.

The substrate tolerance of HNLs is highly restricted toward ketones when compared to structurally similar aldehydes. The use of recombinant enzymes, however, allows preparation of both (*R*)- and (*S*)-ketone cyanohydrins derived from cyclopentanones and heterocyclic saturated five- and six-membered ring ketones.

Methyl benzyl (or phenethyl) ketones **9** give rise to cyanohydrins **10** with good yields and enantioselectivities on treatment with hydrogen cyanide generated *in situ* from TMSCN and catalysis with flax HNL (*Lu*HNL) isolated from *Linum usitatissimum* or commercially available *Me*HNL (isolated from *cassava*). On the contrary, the reaction does not work with *Pa*HNL (isolated from almonds). Both yields and selectivities are dependent on the carbon chain length between the ketone and phenyl functional groups and the substitution (equation 6, Table 2). No reaction was observed in any case with substituted acetophenones.[14]



9 **10** (6)

Table 2 Addition of HCN catalyzed by hydroxynitrile lyases

No.	*n*	*R*	*LuHNL*		*MeHNL*	
			Yield (%)[a]	*ee (%)*	*Yield (%)*	*ee (%)*
i	1	2-Br	– (3)	– (<10)	44	97
ii	1	3-F	20 (47)	83 (59)	70	79
iii	1	3-Cl	24 (33)	89 (78)	71	93
iv	1	3-Br	37 (62)	99 (93)	61	93
v	1	3-Me	40 (61)	97 (91)	65	88
vi	1	3-CF_3	19 (44)	96 (95)	67	97
vii	1	3-MeO	31 (45)	99 (77)	53	92
viii	1	4-Br	9 (34)	93 (76)	77	90
ix	1	4-MeO	30 (59)	84 (66)	62	47
x	2	H	2 (15)	89 (40)	61	7
xi	2	4-OH	13 (41)	75 (36)	54	70
xii	2	4-MeO	1 (10)	99 (56)	68	14

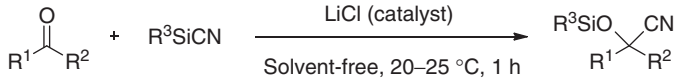
[a]Data for the reaction carried out at 20 °C are given in brackets.

1.18.3.2 Addition of Trimethylsilyl Cyanide

1.18.3.2.1 Metal-based catalysis

1.18.3.2.1.1 By group 1A and 2A elements

Lithium salts have demonstrated exceptional utility as catalysts in the cyanosilylation of aldehydes and ketones under solvent-free conditions. Solid lithium perchlorate is an efficient promoter under neutral conditions and lithium chloride added as a tetrahydrofuran (THF) solution catalyzes the addition of TMSCN to a variety of aldehydes and ketones with a substrate-to-catalyst molar ratio (S/C) as high as 10^5 (equation 7, Table 3).[15]



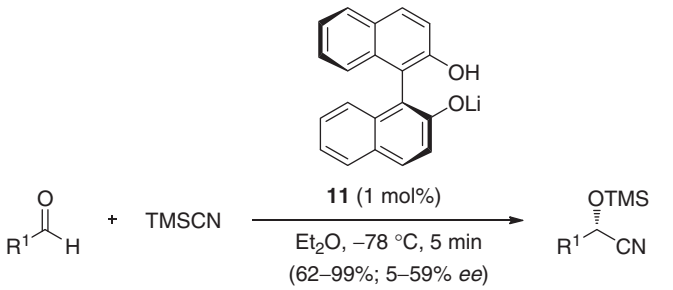
(7)

Lithium alkoxides catalyze the addition of TMSCN and sterically congested TBDMSCN to ketones including hindered substrates. The transition to optically active catalyst control is achieved with the monolithium salt of (*S*)-1,1′-bi-2-naphthol (BINOL) **11** that catalyzes the reaction with aldehydes with high efficiency but modest enantioselectivities (equation 8).[16]

Table 3 Addition of R_3SiCN catalyzed by LiCl under solvent-free conditions

No.	*R^1*	*R^2*	*R^3Si*	*S/C*[a]	*Time (h)*	*Yield (%)*[b]
i	Ph	H	Me_3Si	10 000	1	100
ii	Ph	H	Me_3Si	100 000	48	99
iii	Ph	H	Bu^nMe_2Si	10 000	5	100
iv	4-MeC_6H_4	H	Me_3Si	5 000	5	100
v	2-ClC_6H_4	H	Me_3Si	10 000	0.5	100
vi	2-ClC_6H_4	H	Bu^nMe_2Si	10 000	1	100
vii	4-ClC_6H_4	H	Me_3Si	10 000	0.6	100
viii	4-$MeOC_6H_4$	H	Me_3Si	5 000	6	100
ix	4-$CF_3C_6H_4$	H	Me_3Si	10 000	0.5	100
x	2-Naphthyl	H	Me_3Si	10 000	0.4	100
xi	(*E*)-PhCH═CH	H	Me_3Si	10 000	3	97
xii	(*E*)-PhCH═CH	H	Bu^nMe_2Si	5 000	8	100
xiii	(*E*)-*n*-C_5H_{11}CH═CH	H	Me_3Si	10 000	22	99
xiv	*n*-C_7H_{15}	H	Me_3Si	10 000	0.5	100
xv	Cyclohexyl	H	Me_3Si	10 000	0.5	100
xvi	Bu^t	H	Me_3Si	10 000	0.2	100
xvii	Bu^t	H	Bu^nMe_2Si	10 000	2	100
xviii	Ph	Me	Me_3Si	1 000	6	81
xix	Ph	Me	Me_3Si	100	3	100
xx	Bu^n	Bu^n	Me_3Si	1 000	6	80
xxi	Bu^n	Bu^n	Me_3Si	100	2.5	100

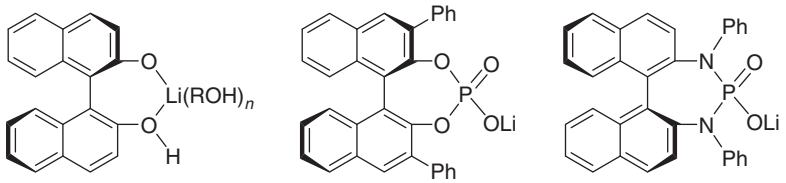
[a]Substrate/catalyst molar ratio.
[b]Determined by GC or ^1H NMR.



(8)

R = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-$MeOOC_6H_4$, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$CF_3C_6H_4$, 2-naphthyl, (*E*)-PhCH=CH, *n*-C_6H_{11}, cyclohexyl, Bu^t

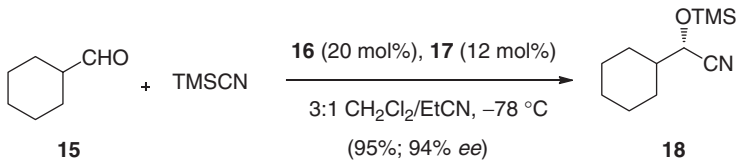
Increased enantioselectivities are obtained with lithium binaphtholate aqua and/or alcohol complexes **12**. These catalyst systems cannot be applied to the reaction with ketones which are more efficiently catalyzed at higher temperatures with lithium salts of phosphoric acids derived from (*R*)-BINOL **13** and (*S*)-2,2′-bis(diphenylphosphinoamino)-1,1′-binaphthyl (BINAM) **14**.[17] Interestingly, the same sense of induction toward (*R*)-isomers is observed for both **13** and **14** (**Figure 4**).



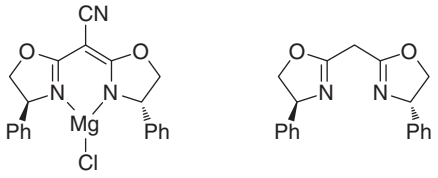
12 **13** **14**

Figure 4 BINOL and BINAM-based catalysts.

Cyanosilylation of cyclohexane carboxaldehyde **15** with TMSCN in the presence of 20 mol% of magnesium complex **16** affords the chiral cyanohydrin **18** in 85% yields and 65% *ee*. When bisoxazoline **17** is used as a cocatalyst the enantioselectivity is enhanced up to 94% *ee* (equation 9).[18] The reaction can be applied to a number of aliphatic aldehydes and good enantioselectivities are observed (up to 95% *ee*). The enhancement of the selectivity is probably because of the activation of both reactants by binding to chiral sites.



15 18

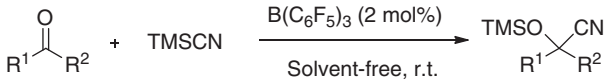


16 17 (9)

Calcination of the mineral hydrotalcite produces a basic mixed oxide of the composition $Mg_6Al_2O_8(OH)_2$ that catalyzes the addition of TMSCN to aldehydes and ketones. Incorporation of chiral organic molecules such as proline or BINOL to layered double hydroxides Mg–Al–NO_3 is also possible, but enantioselectivity is rather poor. A catalytic amount (2–10 mol%) of cesium fluoride also catalyzes silylcyanation of aldehydes and ketones in a reaction that takes place over 99% yield for 20 min and it is not affected by the electronic nature of the aldehyde substituent.[19]

1.18.3.2.1.2 By group 3A elements

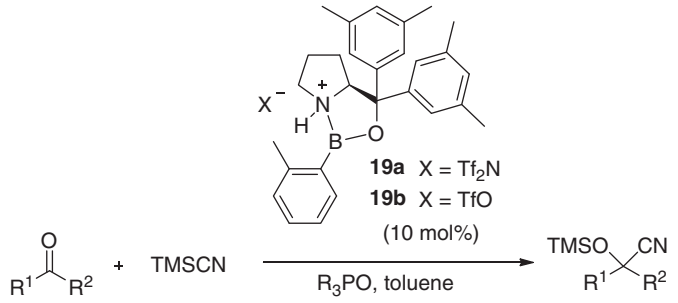
Cyanosilylation of aromatic aldehydes and ketones takes place at room temperature under solvent-free conditions in the presence of a catalytic amount of *tris*(pentafluorophenyl)borane; excellent yields in very short times of reaction are achieved (equation 10).[20]



R^1	R^2	Time (min)	Yield (%)	R^1	R^2	Time (min)	Yield (%)
Ph	Me	8	97	Ph	$(CH_3)_2CH$	10	96
4-ClC_6H_4	Me	15	98	Ph	Ph	25	89
3-ClC_6H_4	Me	15	91	2-Naphthyl	Me	4	97
2-ClC_6H_4	Me	35	81	Ph	H	5	94
2-$NO_2C_6H_4$	Me	60	68	4-$MeIC_6H_4$	H	10	94
4-$MeOC_6H_4$	Me	7	96	4-$MeOC_6H_4$	H	8	92
4-MeC_6H_4	Me	8	94	4-NCC_6H_4	H	15	91
$PhCH_2$	Et	10	98	(*E*)-PhCH=CH_4	H	35	87
$Ph(CH_2)_2$	Me	12	95	2-Furyl	H	50	78

(10)

Chiral oxazaboridinium ions **19** catalyze the enantioselective addition of TMSCN to both aldehydes and ketones in the presence of a phosphine oxide-type coreactant (equation 11, **Table 4**).[21] Under these conditions the reactive intermediate **20** is formed *in situ* from R_3PO and TMSCN leading to considerably higher *ee* values than does TMSCN alone. In general, high enantiomeric excesses are observed with the more electron-withdrawing substituents.



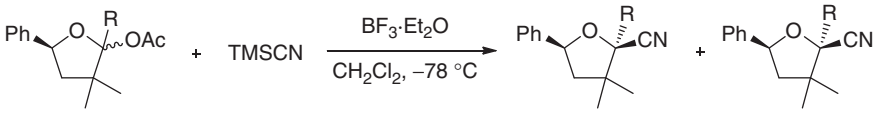
(11)

Table 4 Addition of TMSCN catalyzed by oxazaborolidinium ions **19**

No.	R^1	R^2	*Catalyst*	R^3PO[a]	*Temperature (°C)*	*Time (h)*	*Yield (%)*	*ee (%)*
i	Ph	H	**19a**	Ph_3PO	0	1.6	94	95
ii	2-MeC_6H_4	H	**19a**	Ph_3PO	0	3	95	91
iii	4-MeC_6H_4	H	**19a**	Ph_3PO	0	1.6	91	90
iv	4-CNC_6H_4	H	**19a**	Ph_3PO	0	6	98	97
v	Cyclohexyl	H	**19a**	Ph_3PO	0	1.6	97	90
vi	Bu^n	H	**19a**	Ph_3PO	0	1.6	96	91
vii	*n*-C_6H_{11}	H	**19a**	Ph_3PO	0	2	96	91
viii	Ph	Me	**19b**	$MePh_2PO$	25	14	77	83
ix	4-BrC_6H_4	Me	**19b**	$MePh_2PO$	45	10	73	81
x	4-$NO_2C_6H_4$	Me	**19b**	$MePh_2PO$	45	10	83	96
xi	4-$TfOC_6H_4$	Me	**19b**	$MePh_2PO$	45	10	79	95
xii	4-MeO	Me	**19b**	$MePh_2PO$	25	7	45	32
xiii	$(MeO)_2CH$	Me	**19b**	$MePh_2PO$	25	2	92	96
xiv	Cyclohexyl	Me	**19b**	$MePh_2PO$	25	3	95	85

[a] Ph_3PO (20 mol%); Me_2PhPO (11 mol%).

In the presence of boron trifluoride, TMSCN forms an anionic siliconate that delivers a cyano group to cyclic oxocarbenium ions. The high reactivity of the nucleophile is responsible for the observed low diastereoselectivity. This correlation between reactivity and stereoselectivity can explain the increase in diastereoselectivity observed with less reactive electrophiles. For instance, whereas addition to the oxocarbenium formed from acetal **21** takes place without any selectivity, the same reaction with the less reactive acetal **22** affords high diastereoselectivity (equation 12).[22]

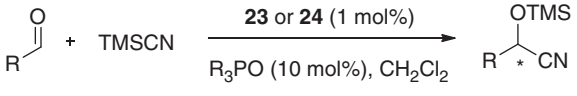


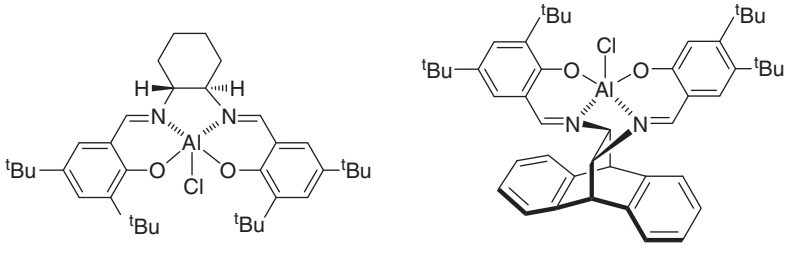
21 R = H
22 R = Ph

(63%, 54:45) for R = H
(96%, 95:5) for R = Ph

(12)

A series of aromatic and heteroaromatic *O*-(trimethylsilyl)cyanohydrins have been prepared by addition of TMSCN to the corresponding aldehydes using a catalyst generated *in situ* from (*S*,*S*)-2,6-bis(4′-isopropyloxazolin-2′-yl)pyridine (pybox) and aluminum(III) chloride. Ketone cyanohydrins are efficiently prepared using [Al(salen)]-catalyzed reactions in the presence of an *N*-oxide as a Lewis base. The chiral version of the reaction is achieved by chiral [Al(salen)]-complexes. Incorporation of achiral alkoxides ligands to the catalyst results in highly active catalytic systems (turn over number (TON) up to 470, turn over frequency (TOF) up to 140 h^{-1} at − 20 °C) for a variety of aryl alkyl ketones. The reaction with aldehydes also works well but uses phosphine oxides as the Lewis basic additives. Good enantioselectivities are obtained with Al(salen) **23** in the presence of triphenylphosphine oxide (Scheme 1). These results are enhanced by employing catalyst **24** in the presence of tri-*n*-butylphosphine oxide although the opposite enantiomer is preferentially obtained[23] (equation 13, Table 5).





23 **24**

(13)

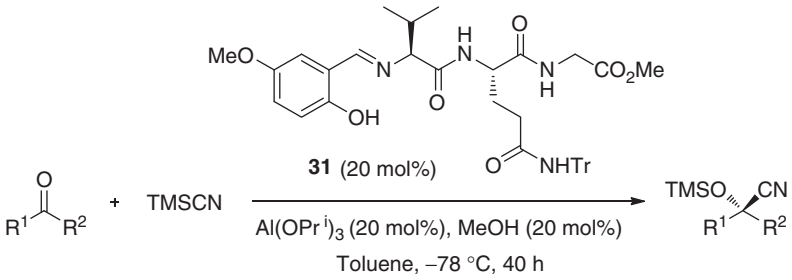
Mechanistic studies suggest a change in mechanism with increasing Lewis base concentration as the carbonyl compound becomes more electron deficient. Based on these analyses, the aluminum complex/Ph_3PO catalyst system is predicted to promote the reaction with ketones. The principle of dual activation catalysis has been applied with elaborated bifunctional catalysts

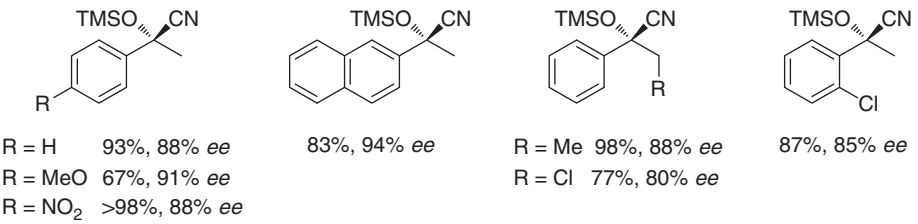
Table 5 Addition of TMSCN to aldehydes catalyzed by Schiff bases **23** and **24**

No.	R^1	*Catalyst*	R^3PO	*Temperature (°C)*	*Time (h)*	*Yield (%)*	*ee (%)*
i	Ph	**23**	Ph_3PO	−50	18	94	86 (*R*)
ii	4-ClC_6H_4	**23**	Ph_3PO	−50	18	96	86 (*R*)
iii	2-$MeOC_6H_4$	**23**	Ph_3PO	−50	18	92	82 (*R*)
iv	4-$MeOC_6H_4$	**23**	Ph_3PO	−45	22	94	72 (*R*)
v	4-$Bu^tC_6H_4$	**23**	Ph_3PO	−45	21	93	73 (*R*)
vi	4-$PhOC_6H_4$	**23**	Ph_3PO	−50	20	93	81 (*R*)
vii	(*E*)-PhCH=CH	**23**	Ph_3PO	−40	26	91	78 (*R*)
viii	2-Furyl	**23**	Ph_3PO	−50	18	93	78 (*R*)
ix	$Ph(CH_2)_2$	**23**	Ph_3PO	−50	21	93	79 (*R*)
x	Ph	**24**	$Oct^n{}_3PO$	10	16	93	86 (*S*)
xi	4-ClC_6H_4	**24**	$Oct^n{}_3PO$	10	14	86	70 (*S*)
xii	2-$MeOC_6H_4$	**24**	$Oct^n{}_3PO$	10	12	89	86 (*S*)
xiii	4-$MeOC_6H_4$	**24**	$Oct^n{}_3PO$	10	12	90	81 (*S*)
xiv	2-MeC_6H_4	**24**	$Oct^n{}_3PO$	10	12	94	80 (*S*)
xv	3-MeC_6H_4	**24**	$Oct^n{}_3PO$	10	12	92	88 (*S*)
xvi	4-MeC_6H_4	**24**	$Oct^n{}_3PO$	10	12	90	92 (*S*)
xvii	1-Naphthyl	**24**	$Oct^n{}_3PO$	10	12	85	76 (*S*)
xviii	2-Furyl	**24**	$Oct^n{}_3PO$	10	12	90	83 (*S*)
xix	(*E*)-PhCH=CH	**24**	$Oct^n{}_3PO$	10	12	89	78 (*S*)
xx	$Ph(CH_2)_2$	**24**	$Oct^n{}_3PO$	10	12	89	42 (*S*)

incorporating both the aluminum atom and the phosphorus unit. Catalysts **25**–**28** are successfully used in the cyanosilylation of aldehydes.[24] Good chemical yields (up to 92%) and high enantioselectivities (up to 99%) are observed. In the case of catalyst **28** a positive nonlinear effect is observed. Other bifunctional catalysts include carbohydrate derivatives **29** and **30**.[25] Good asymmetric induction is provided by **30** (up to 80% *ee*) with aldehydes and acetophenone (**Figure 5**).

Aromatic and aliphatic ketones are cyanosilylated in the presence of an Al-complex formed *in situ* from peptide **31** (equation 14).[26]





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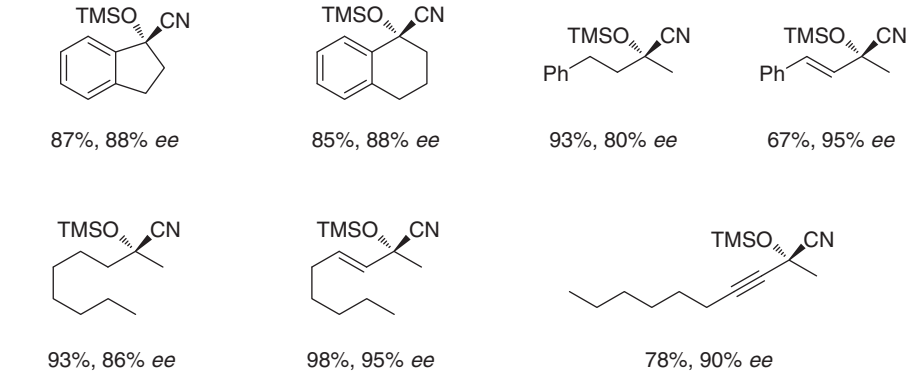


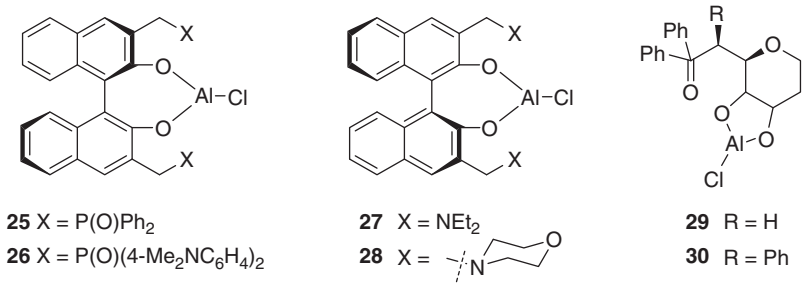


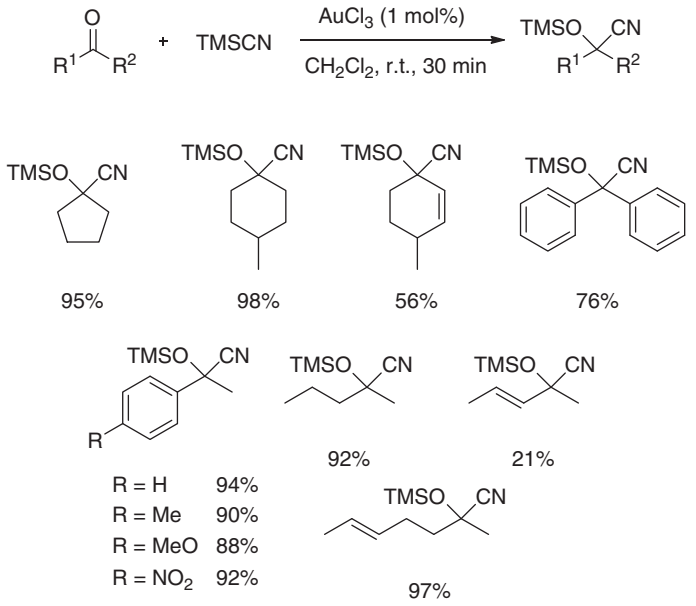
Figure 5 Bifunctional catalysts for the cyanosilylation of aldehydes.

The addition of TMSCN to aldehydes in water is catalyzed by indium trifluoride at room temperature; yields up to 95% are obtained. The same reaction with ketones is catalyzed by indium tribromide in dichloromethane as a solvent.

1.18.3.2.1.3 By group 1B elements

Treatment of aldehydes and ketones with TMSCN in the presence of copper(II) triflate produces the corresponding cyanohydrins with high yields. The reaction with aliphatic aldehydes and ketones are faster (2–3 h) than those with aromatic aldehydes, which take 20–50 h to go on completion even in the best reaction conditions using acetonitrile as a solvent. However, a variety of aromatic, aliphatic and heterocyclic ketones undergo asymmetric trimethylsilylcyanation in the presence of a chiral-supported Cu(salen) complex and triphenylphosphine oxide as a cocatalyst. Various supports can be employed to render the insoluble the salen ligands; the best results are found with supported JandaJel jj–Cu(salen) complex, which affords the cyanohydrins in 83–96% yields and 52–84% *ee*.[27]

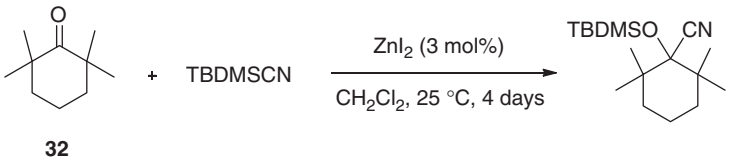
Gold(III) chloride is also an effective catalyst for the cyanosilylation of aldehydes and ketones. The reactions proceed under very mild conditions and low reaction temperatures and short reaction times are required with low catalyst loading (equation 15).[28]



(15)

1.18.3.2.1.4 By group 2B elements

Chiral nonracemic *β*-hydroxyketones can be cyanosilylated diastereoselectively with an excess of TMSCN in the presence of equimolar amounts of zinc(II) iodide and potassium cyanide. The initial products are not isolated but they are desilylated *in situ* to give cyanohydrins with complete diastereoselectivity. The sole presence of ZnI_2 in a catalytic amount is sufficient for promoting cyanosilylation of aldehydes and ketones including hindered substrates with different cyanating agents, such as *tert*-butyldimethylsilyl cyanide.[29] For instance, 2,2,6,6-tetramethylcyclohexanone **32** provides the corresponding silylated cyanohydrin in 92% yield after 4 days (equation 16).



32 (16)

Zn(II)-based interlinked 2D metallocycles capable of stacking to form an overall 3D structure catalyze the cyanosilylation of aromatic aldehydes. The catalyst can be reutilized without loss of activity.[30]

1.18.3.2.1.5 By group 4B elements

One of the most extensively studied chiral Lewis acid-catalyzed cyanosilylation reactions of aldehydes and ketones employs titanium complexes of readily available chiral Schiff bases with Ti(IV) Lewis acids as the catalysts. Usually, the catalyst is prepared *in situ* by mixing titanium(IV) tetraisopropoxide and the Schiff base in 1:1.1 ratios and in dichloromethane as a solvent. A considerable amount of work has been carried out on the cyanosilylation of benzaldehyde using Ti(IV)-complexes of Schiff bases and the reaction can be considered a benchmark for those catalysts (**Scheme 1**). Among the various mono-Schiff base ligands studied, compounds **33–35** show the best results (**Table 6**).[31] A remarkable rate enhancement is observed by the addition of Schiff bases to $Ti(OPr^i)_4$-catalyzed cyanosilylation of benzaldehyde. In particular, with compound **33** (**Table 6**, i) (*R*)-mandelonitrile is obtained with 67% *ee*. The enantioselectivity of the reaction is much influenced by the kind of Schiff bases in terms of substituents of the aromatic ring. The efficiency of the ligand also depends largely on the steric interactions between all players (aldehyde, ligand, and metal) but increasing the number of stereogenic centers around the metal, does not necessarily increase the enantioselectivity, which can be increased just by lowering the temperature (**Table 6**, ii). By preparing the catalyst from partially hydrolyzed $Ti(OPr^i)_4$ and the enantiomer of **33**, the reaction proceeds in excellent chemical yield and with high enantioselectivity (**Table 6**, iii) not only with benzaldehyde but also with other aromatic aldehydes and ketones. The reaction takes place with moderate enantioselectivity when **34** is used as a ligand in 1.1:1 ligand/$Ti(OPr^i)_4$ ratio (**Table 6**, iv). Although the *ee* value can be increased to 80% *ee* by using 100 mol% of catalyst, a higher enantioselectivity is observed when the ligand/$Ti(OPr^i)_4$ M ratio is 2:1 (**Table 6**, v). In general, it can be demonstrated that the presence of bulky and rigid groups in the ligand, as in **35** contributes to increase the enantioselectivity (**Table 6**, vi).

Table 6 Cyanosilylation of benzaldehyde catalyzed by Ti(IV) complexes of Schiff bases

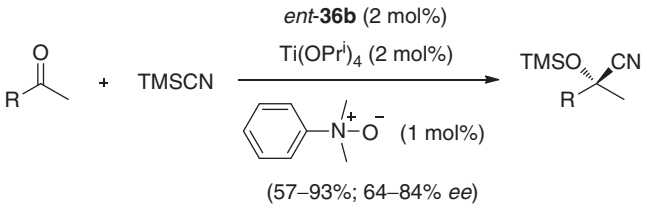
No.	*Mol%*	*Ligand*	*L/C*[a]	*Temperature (°C)*	*Time (h)*	*Yield (%)*	*ee (%)*
i	20	**33**	1.1:1	−30	44	90	67 (*R*)
ii	20	**33**	1.1:1	−78	36	67	85 (*R*)
iii	0.5	*ent*-**33**	1.1:1	r.t.	2	>99	89 (*S*)
iv	20	**34**	1.1:1	−80	60	85	53 (*S*)
v	20	**34**	2:1	−80	60	72	92 (*S*)
vi	20	**35**	1.1:1	−78	36	64	85 (*R*)
vii	10	**36a**	1.1:1	−78	24	72	87 (*R*)
viii	20	**37**	1.1:1	−40	60	86	68 (*R*)
ix	20	**38**	1.1:1	−45	12	97	66 (*S*)
x	20	**39a**	1.1:1	−80	24	95	76 (*S*)
xi	20	**39b**	1.1:1	−80	24	89	72 (*S*)
xii	10[b]	**39b**	1.1:1	r.t.	24	100[c]	86 (*S*)
xiii	20	**40**	1.1:1	−20	24	89	68 (*R*)
xiv	20	**41**	1.1:1	−30	24	99	88 (*R*)
xv	20	**36b**	1.1:1	−78	24	70	39 (*R*)
xvi	10	**42**	1.1:1	−80	24	65	90 (*R*)
xvii	10	**42**[d]	1.1:1	−80	24	59	94 (*R*)
xviii	10	**43a**	2.5:2	−78	120	90[c]	84 (*S*)
xix	10	**43b**	2.5:2	−78	120	90[c]	43 (*S*)
xx	20	**44**	2:1	6	4	100	86 (*R*)
xxi	10	**45**	1.2:1	−20	4	100	89 (*S*)

[a]Ligand/catalyst ratio.
[b]$TiCl_4$ is used as source of Ti(IV).
[c]Silylated cyanohydrin is obtained.
[d]Immobilized ligand.

Tetradentate *bis*-Schiff bases (salen ligands) are also excellent ligands to be used in the cyanosilylation of aldehydes and, again, the reaction with benzaldehyde is used as a control. A survey of symmetrical salen ligands reveals that the enantiomeric excess of the reaction is predominantly dependent on the aldehyde, with the best results being observed with electron-rich aromatic

aldehydes. Unsubstituted ligands **36a**, **37**, and **38** (Table 6, vii–ix) catalyze the cyanosilylation of benzaldehyde in good yields and moderate enantioselectivity.[13,32] Incorporation of bulky substituents at the aromatic rings as in the case of salen ligands **39**–**41** slightly increases the *ee* values (Table 6, x–xiv)[33] although the opposite effect accounts for **36b** (Table 6, xv). However, with unsymmetrical ligand **42**, 90% *ee* is achieved (Table 6, xvi). Indeed, a better result is achieved with immobilized **42** onto ordered mesoporous silica MCM-41 (Table 6, xvii). Incorporation of additional chirality to the salen ligand is also possible by replacing the aromatic rings with diverse chiral units. For example, ligand **43a** incorporating *p*-cyclophane moieties leads to a poor enantioselectivity (Table 6, xviii) whereas the corresponding ligand **43b** with an achiral ethylene bridge between the imine functions provides 84% *ee* (Table 6, xix). The BINOL-derived ligands **44** and **45** exhibit better stereocontrol in the reaction (Table 6, xx and xxi). Notably, in the case of salen ligand **45** when the 4-hydroxyl groups are unprotected the enantioselectivity drops considerably.

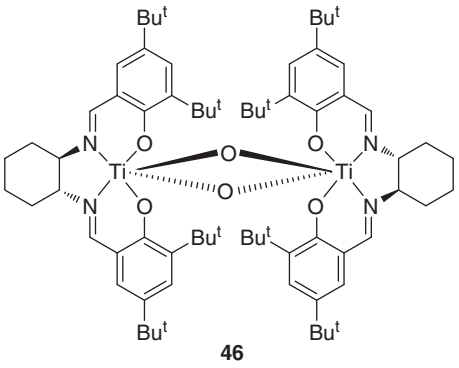
In the case of ketones a double activation is necessary and the presence of an *N*-oxide as cocatalyst results in a smooth reaction. The complex formed *in situ* between the enantiomer of salen ligand **36b** and $Ti(OPr^i)_4$ is used in a synergistic way with *N*,*N*-dimethylaniline *N*-oxide to activate ketones and TMSCN, respectively (equation 17).



(17)

R = Ph, 4-MeC_6H_4, 4-FC_6H_4, 2-FC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, $PhCH_2$, (*E*)-PhCH=CH

The ability of titanium(IV) complexes to form multinuclear aggregates clearly suggests the opportunity for dimeric Ti(salen) complexes, as demonstrated by mechanistic studies with ligands **39**. In fact, isolated complex **46** (characterized by X-ray crystallography), in which the titanium atoms are bridged by two oxygen atoms, promotes the cyanosilylation of aromatic aldehydes with high levels of asymmetric induction (up to 92% *ee*) (Figure 6).



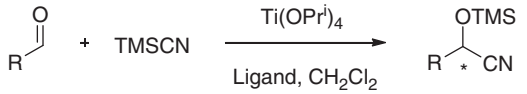
46

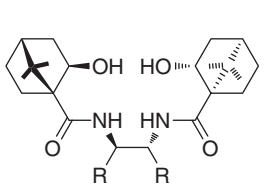
Figure 6 Dimeric catalyst for the cyanosilylation of aromatic aldehydes.

Lower enantioselectivities are observed for aliphatic aldehydes (up to 66%) and ketones (up to 72% *ee*). Interestingly, the reaction is complete within 1 h at room temperature by only employing 0.5 mol% of catalyst. Kinetic studies suggest that the catalytic cycle is based on complexes readily formed from species detected during the interaction of **46** with the reactants. The enhanced catalytic activity of **46** with respect to mononuclear complexes is explained on the possibility of simultaneously activating the aldehyde and TMSCN.

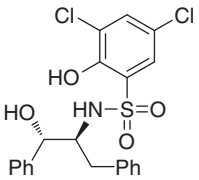
Tethering aromatic rings of **46** with different spacers results in an exceptionally efficient chiral catalysts for the enantioselective cyanosilylation of aldehydes, which produces cyanohydrins with turnover numbers from 1960 to 172 000 and up to 97% *ee*.[34] Titanium complexes formed with dimeric salen ligands derived from **41** with different length linkers are very active and promote enantioselective cyanosilylation of aromatic and aliphatic aldehydes (up to 86% *ee*) in 24 h at 0 °C with only 0.1 mol% of catalyst.[35]

Substitution of imine functionality by amino or amide groups results in more stable ligands that can be more easily recoverable. High levels of stereocontrol are achieved with ligand **47** in the reaction with aromatic and aliphatic aldehydes.[36] Similar results are found with ligands **48** and **49**, which can be used with a lower catalyst charge (equation 18, Table 7).

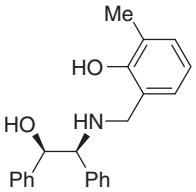




47a R = Ph
47b R = $(CH_2)_4$



48



49

(18)

Table 7 Cyanosilylation of aldehydes catalyzed by Ti(IV) complexes of ligands **47–49**

No.	*R*	*Mol%*	*Ligand*	*L/C*[a]	*Temperature (°C)*	*Time (h)*	*Yield (%)*	*ee (%)*
i	3-$PhOC_6H_4$	15	**47a**	16.5:15	−30	120	57	97.2 (*S*)
ii	4-$MeOC_6H_4$	15	**47a**	16.5:15	−30	120	53	96.6 (*S*)
iii	2-Naphthyl	15	**47a**	16.5:15	−30	120	76	96.2 (*S*)
iv	(*E*)-PhCH=CH	15	**47a**	16.5:15	−30	120	51	95.1 (*S*)
v	$Ph(CH_2)_2$	15	**47a**	16.5:15	−30	120	62	97.5 (*S*)
vi	2-MeC_6H_4	15	**47a**	16.5:15	−30	120	68	96.8 (*S*)
vii	Cyclohexyl	15	**47a**	16.5:15	−30	120	94	87.2 (*S*)
viii	Bu^i	15	**47a**	16.5:15	−30	120	96	88.5 (*S*)
ix	Ph	15	**47b**	16.5:15	−78	n.g.[b]	87	93 (*S*)
x	Cyclohexyl	15	**47b**	16.5:15	−78	n.g.[b]	90	>99 (*S*)
xi	Bu^i	15	**47b**	16.5:15	−78	n.g.[b]	92	97 (*S*)
xii	2-MeC_6H_4	15	**47b**	16.5:15	−78	n.g.[b]	80	94 (*S*)
xiii	3-$PhOC_6H_4$	15	**47b**	16.5:15	−78	n.g.[b]	78	95 (*S*)
xiv	4-$MeOC_6H_4$	15	**47b**	16.5:15	−78	n.g.[b]	72	99 (*S*)
xv	2-Naphthyl	15	**47b**	16.5:15	−78	n.g.[b]	78	99 (*S*)
xvi	(*E*)-PhCH=CH	15	**47b**	16.5:15	−78	n.g.[b]	74	97 (*S*)
xvii	$Ph(CH_2)_2$	15	**47b**	16.5:15	−78	n.g.[b]	73	97 (*S*)
xviii	Ph	10	**48**	1:1	−65	48	100	96 (*R*)
xix	4-ClC_6H_4	10	**48**	1:1	−65	48	93	90 (*R*)
xx	4-$MeOC_6H_4$	10	**48**	1:1	−65	48	100	94 (*R*)
xxi	2-$MeOC_6H_4$	10	**48**	1:1	−65	48	100	86 (*R*)
xxii	2-Naphthyl	10	**48**	1:1	−65	48	95	96 (*R*)
xxiii	1-Naphthyl	10	**48**	1:1	−65	48	100	77 (*R*)
xxiv	(*E*)-PhCH=CH	10	**48**	1:1	−65	48	100	93 (*R*)
xxv	Bu^i	10	**48**	1:1	−65	48	100	95 (*R*)
xxvi	Ph	5	**49**	1:1	−20	22	99	94
xxvii	4-MeC_6H_4	5	**49**	1:1	−20	15	90	93
xxviii	3-MeC_6H_4	5	**49**	1:1	−20	16	99	88
xxix	4-$MeOC_6H_4$	5	**49**	1:1	−20	14	98	93
xxx	3-$MeOC_6H_4$	5	**49**	1:1	−20	16	99	90
xxxi	4-FC_6H_4	5	**49**	1:1	−20	14	94	92
xxxii	2-ClC_6H_4	5	**49**	1:1	−20	15	99	76
xxxiii	3-ClC_6H_4	5	**49**	1:1	−20	20	98	90
xxxiv	4-ClC_6H_4	5	**49**	1:1	−20	15	98	87
xxxv	4-CNC_6H_4	5	**49**	1:1	−20	20	93	80
xxxvi	1-Naphthyl	5	**49**	1:1	−20	16	99	82
xxxvii	2-Naphthyl	5	**49**	1:1	−20	20	98	75
xxxviii	2-Furyl	5	**49**	1:1	−20	16	98	89
xxxix	(*E*)-PhCH=CH	5	**49**	1:1	−20	14	96	82
xl	(*E*)-MeCH=CH	5	**49**	1:1	−20	16	99	82
xli	*n*-C_6H_{13}	5	**49**	1:1	−20	16	99	57
xlii	$PhCH_2$	5	**49**	1:1	−20	14	98	72
xliii	$Ph(CH_2)_2$	5	**49**	1:1	−20	16	99	60

[a]Ligand/catalyst ratio.
[b]Not given.

The C_2-symmetric ligand **50** forms an effective catalyst with $Ti(OPr^i)_4$ for the enantioselective addition of TMSCN to several aromatic aldehydes with enantioselectivities of up to 98% *ee*.[37] The phosphorus-containing ligand **51** is employed in the same reaction and modest-to-good asymmetric induction (26–98% *ee*) is observed[38] (Figure 7).

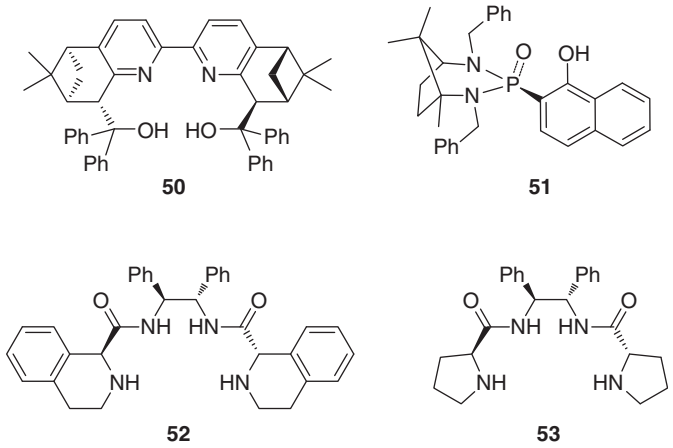
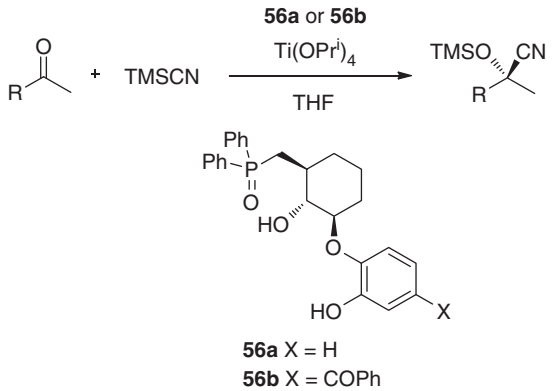


Figure 7 Chiral ligands for the Ti-catalyzed cyanosilylation of aldehydes and ketones.

Tetraaza ligands readily available by simple synthetic procedures are used to form bifunctional catalysts that are highly active and very efficient in the cyanosilylation of carbonyl compounds. The best results for aldehydes are obtained with ligand **52** (up to 92% *ee*) whereas the cyanosilylation of ketones performs better with **53** (up to 94% *ee*).

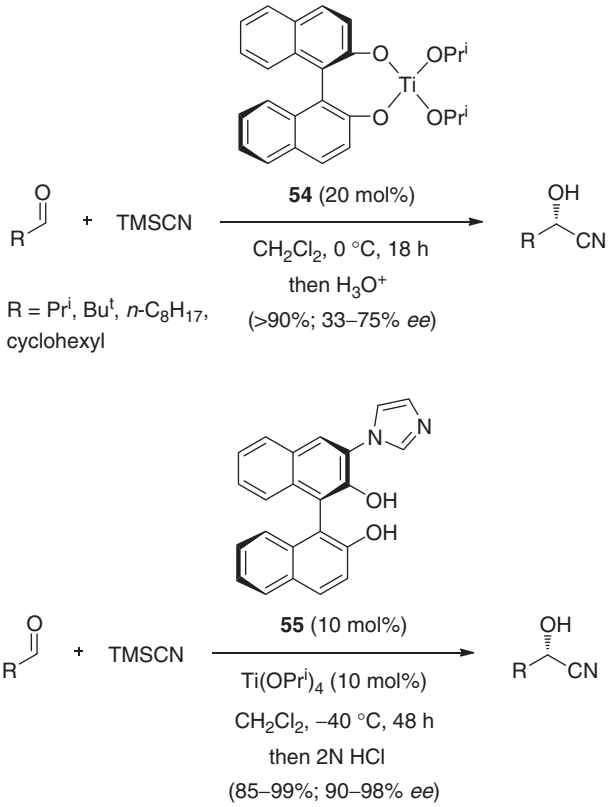
Aliphatic aldehydes undergo enantioselective cyanosilylation with TMSCN under catalysis with BINOL-derived titanium complexes **54** (Scheme 2).[39] On the contrary, the same reaction with aromatic aldehydes results in very low enantioselectivity (< 10% *ee*). Modest values of *ee* are obtained in the case of aromatic aldehydes by replacing BINOL with $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolan-4,5-dimethanol. Catalyst **54** is amenable to immobilization and with a Ti(IV) complex of a dendritically cross-linked BINOL polymer, the cyanosilylation of pivaldehyde shows 90% of conversion after 20 h and 72% *ee*. Both the reaction rate and the enantioselectivity are enhanced by incorporating into the ligand an imidazolyl unit at the 3-position of the binaphthol moiety. By employing bifunctional ligand **55** high yields (up to 99%) and enantioselectivities (up to 98% *ee*) are observed for both aromatic and aliphatic aldehydes (Scheme 2).[40]

The carbohydrate-derived bifunctional ligands **56** incorporating a catechol unit in their structures promote successful enantioselective cyanosilylation of methyl ketones.[41] Sterical and electronic studies reveal complex formed from **56b** as an improved catalyst for the reaction (equation 19, Table 8).



(19)

Cyanosilylation of ketones is also catalyzed by 2:1 complexes formed from *N*-oxides and $Ti(OPr^i)_4$. The asymmetric version of the reaction is achieved with chiral *N*-oxides as ligands such as **57**, which furnishes *O*-trimethylsilyl (TMS) cyanohydrins with enantiomeric excesses of up to 69% *ee*.[42] The reaction with aldehydes is also possible by utilizing *N*-oxides as bifunctional ligands and thus ligand **58** incorporating an additional *N*-oxide functionality furnishes the corresponding *O*-silylated cyanohydrins in yields up to 99% and good enantioselectivities (up to 80% *ee*) (Figure 8).

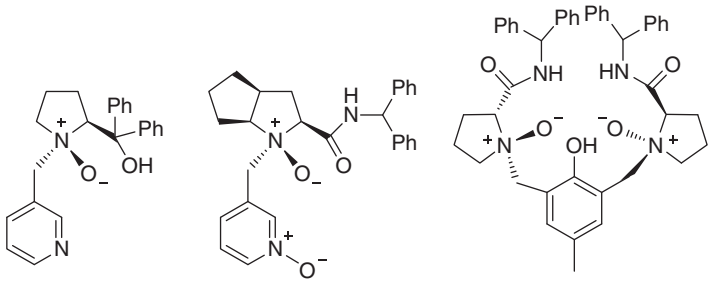


Scheme 2

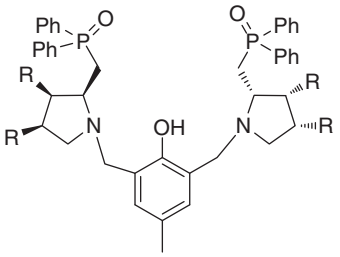
Table 8 Cyanosilylation of methylketones catalyzed by Ti(IV) complexes of **56**

No.	*R*	*Mol%*	*Ligand*	*Temperature (°C)*	*Time (h)*	*Yield (%)*	*ee (%)*
i	n-C_5H_{11}	10	**56a**	– 50	36	88	76
ii	n-C_5H_{11}	10	**56b**	– 58	44	71	88
iii	n-C_5H_{11}	2.5	**56b**	– 45	92	80	82
iv	Ph	2.5	**56b**	– 30	48	84	96
v	Ph	1	**56b**	– 20	88	92	94
vi	4-ClC_6H_4	1	**56b**	– 25	92	72	90
vii	Cyclohexyl	2.5	**56b**	– 30	70	91	93
viii	(E)-n-$C_5H_{11}CH{=}CH$	2.5	**56b**	– 30	92	72	90

The C_2-symmetric chiral *N,N′*-dioxide **59** is used in combination with 1 equivalent of $Ti(OPr^i)_4$ to efficiently catalyze the reaction with ketones in high yields with up to 92% *ee* under mild conditions. The reduced version of ligand **59** bearing two pyrrolidine units also forms active complexes with $Ti(OPr^i)_4$ that catalyze the enantioselective cyanosilylation of ketones in the presence of a phenolic *N*-oxide acting as a cocatalyst in a synergistic way. Incorporation of diphenylphosphine oxide units to the ligands results in the formation of bifunctional catalysts **60** which afford good yields (up to 82%) and enantioselectivities (up to 95%).[43] The formation of complexes between $Ti(OPr^i)_4$ and *o*-hydroxyarylphosphine oxides provides suitable catalysts for the asymmetric cyanosilylation of aromatic aldehydes, which performs with good to excellent enantioseletivities (up to 98% *ee*). Layered zirconium hydrogen phosphate exchanged with potassium ion to form $Zr(KPO_4)_2$ is a versatile effective and recyclable catalyst for the cyanosilylation of aldehydes and ketones under mild conditions (equation 20). Homogeneous catalysis is achieved with a zirconium complex derived from 2-*N*-(2-hydroxy-2-methylimino)-4-pentanone and $Zr(OPr^i)_4$. This catalyst (2 mol%) promotes the reaction with aromatic and aliphatic aldehydes in good chemical yields (75–100%) (equation 20).[44]

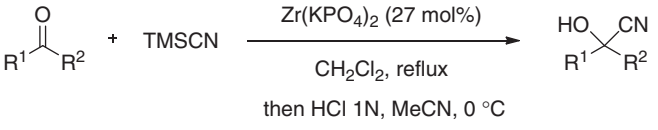


57 **58** **59**

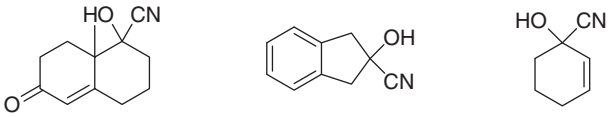


60a R = H
60b R = $(CH_2)_4$

Figure 8 Chiral *N,N′*-dioxides.



Ar		R		*n*	
Ph	98%	(*E*)-PhCH=CH	94%	1	98%
2-MeC_6H_4	88%	cyclohexyl	83%	2	98%
4-$MeOC_6H_4$	96%	*n*-C_6H_{13}	91%	3	95%
4-$NO_2C_6H_4$	88%				

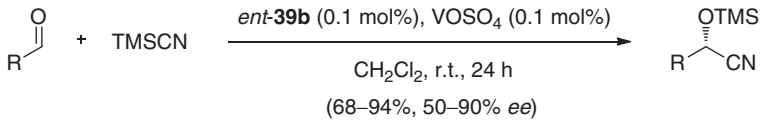


93% 86% 92%

(20)

1.18.3.2.1.6 By group 5B elements

The success of the Ti(IV)-salen catalyst systems stimulated significant efforts to improve both reactivity and enantioselectivity. Vanadium(V) complexes of ligand **39b** and its enantiomer have been investigated. The chiral (salen) VO catalyst formed from *ent*-**39b** is more enantioselective than the titanium-based systems and 0.1 mol% is sufficient to achieve a good conversion in the cyanosilylation of aromatic and aliphatic aldehydes (equation 21).[45]



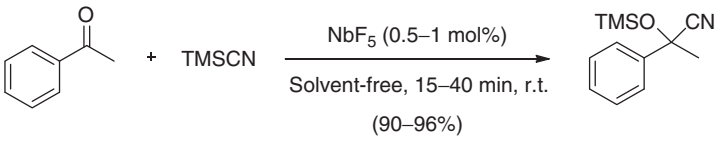
(21)

R = Ph, 4-MeOC$_6$H$_4$, 2-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, Et, ^{t}Bu

The counterion present in vanadium(V) salen complexes has a significant influence on the reactivity. For example, the chloride and fluoride complexes are 7 and 50 times more reactive than the ethylsulfonate complex. Also, the mechanism of the reaction catalyzed by vanadium complexes is more intriguing because of the ability of vanadium to undergo redox reactions.

Catalysts formed from **39b** and $VOSO_4$ can be converted into an efficient and recyclable catalyst by preparing polymeric salen ligands. The reaction can also be carried out in an efficient way in propylene carbonate using low catalyst loadings at room temperature.[46]

A catalytic amount of NbF_5 (1 mol%) under solvent-free conditions at room temperature is capable of catalyzing the cyanosilylation of ketones in a reaction of wide applicability.[47] The reaction takes place within 30 min and excellent yields are observed (equation 22). Aldehydes are more reactive and, under the same reaction conditions, produce the corresponding cyanohydrins in 10 min at room temperature in the presence of 0.5 mol% of NbF_5.

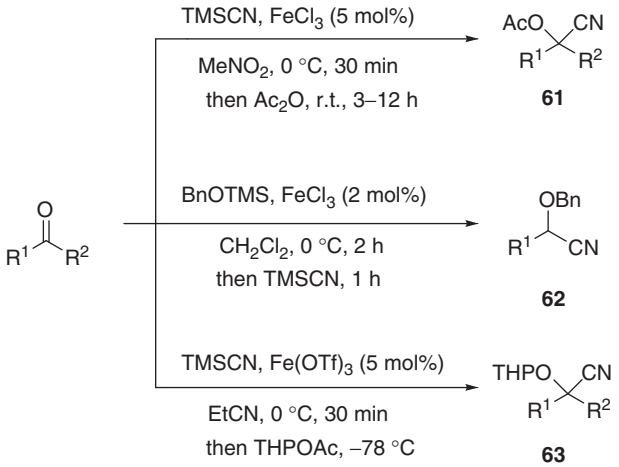


(22)

1.18.3.2.1.7 By group 8B elements

Reaction of aldehydes and ketones with TMSCN in the presence of a catalytic amount of $Cp(CO)_2FeMe$ (2.5 mol%) in THF at room temperature furnishes *O*-trimethylsilyl cyanohydrins in good chemical yields (up to 95%). The same reaction takes place under solvent-free conditions and catalysis with $Fe(Cp)_2PF_6$. Only 2.5 mol% of catalyst is needed for completing the reaction in 10 min at room temperature, both aldehydes and ketones showing a similar reactivity.

O-Protected cyanohydrins are versatile building blocks in organic synthesis. For this reason it is of a great importance to have different methods to prepare differentially protected cyanohydrins. In this context, it is possible to prepare cyanohydrin esters **61** in a one-pot procedure from the corresponding carbonyl compound on catalysis with iron(III) chloride (Scheme 3).[48] By using the same catalyst it is also possible to prepare in an efficient way cyanohydrin alkyl ethers **62** in a similar way. Acetal-type protected cyanohydrins **63** are obtained in reactions catalyzed by iron(III) triflate and subsequently treated with tetrahydropyran-2-yl acetate (Table 9).



Scheme 3

Potassium dodecatungstocobaltate ($K_5CoW_{12}O_{40} \cdot 3H_2O$) is a versatile and recyclable heterogeneous catalyst of wide applicability for the cyanosilylation of carbonyl compounds. The catalyst can be used several times without loss of activity and its insolubility in most solvents renders its recovery very easily.

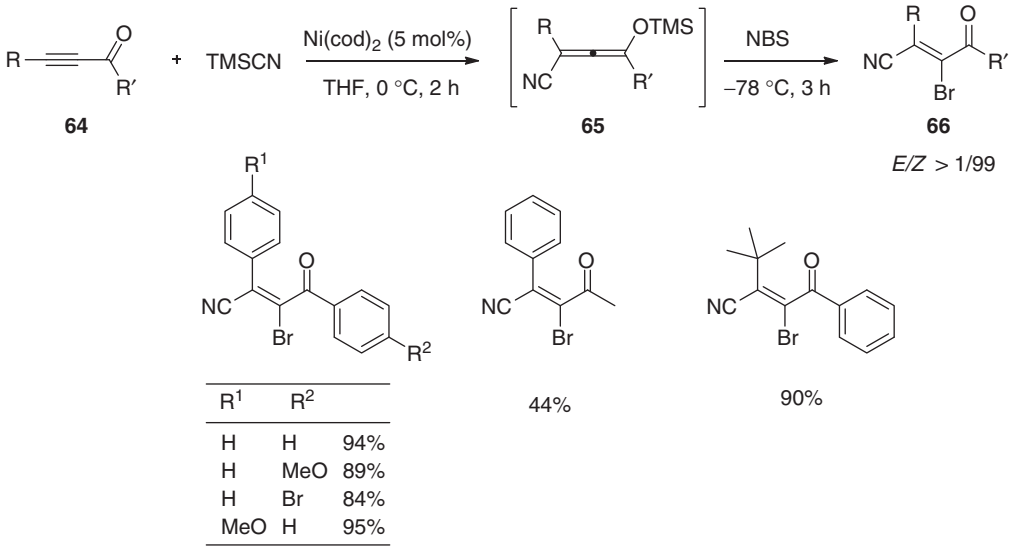
Table 9 Cyanosilylation of aldehydes and ketones catalyzed by Fe(III) (Scheme 3)

No.	R^1	R^2	***61*** *(Yield, %)*[a]	***62*** *(Yield, %)*[b]	***63*** *(Yield, %)*[c]
i	Ph	H	94	98	95
ii	2-MeC_6H_4	H	82	96	86
iii	3-MeC_6H_4	H	80	70	75
iv	4-MeC_6H_4	H	91	95	90
v	2,4,6-$Me_3C_6H_2$	H	91	88	90
vi	4-$MeOC_6H_4$	H	56	–	93
vii	4-BrC_6H_4	H	95	83	86
viii	4-$MeCOC_6H_4$	H	73	87	–
ix	4-$Me_2OCC_6H_4$	H	93	51	90
x	1-Naphthyl	H	85	–	94
xi	2-Naphthyl	H	89	70	92
xii	$Ph(CH_2)_2$	H	89	–	88
xiii	$PhCH_2CH(Me)$	H	–	–	78
xiv	Cyclohexyl	H	91	–	–
xvi	Bu^t	H	62	–	80
xvii	(*E*)-PhCH═CH	H	–	87	85
xviii	$PhCH_2$	Me	80	–	74
xix	Ph	Me	79	–	79
xx	$(CH_2)_4$		91	–	88
xxi	$(CH_2)_5$		90	–	88

[a]TMSCN, $FeCl_3$ (5 mol%), then Ac_2O.
[b]BnOTMS, $FeCl_3$ (2 mol%), then TMSCN.
[c]TMSCN, $Fe(OTf)_3$, then THPOAc.

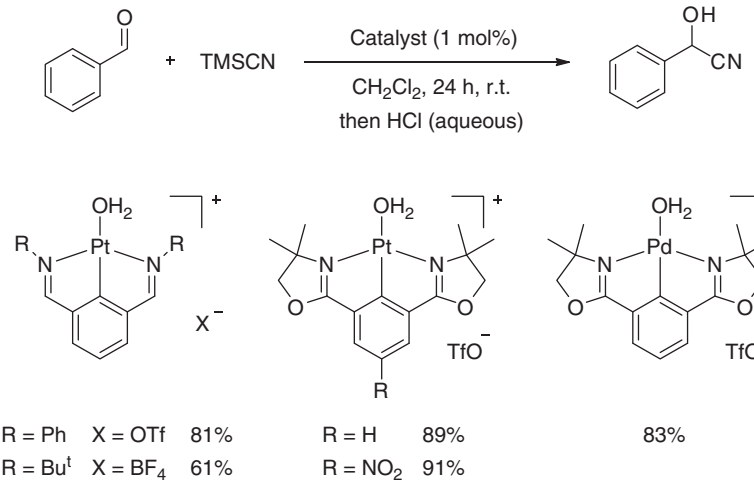
Several anionic Co(III) complexes of optically active amino acids, bearing a lithium cation in the external sphere, act as suitable catalysts in the reaction of TMSCN with aromatic aldehydes. However, although conversion is very high (>90%) the observed enantioselectivities are only modest (up to 42% *ee*).

The conjugate addition of cyanide to ynones **64** is catalyzed by Ni(0) to give *β*-cyanosiloxyallenes **65** in quantitative yield.[49] Compounds **65** are not isolated and they are further transformed into *α*-bromo-*γ*-cyano tetrasubstituted enones **66** as illustrated in Scheme 4.



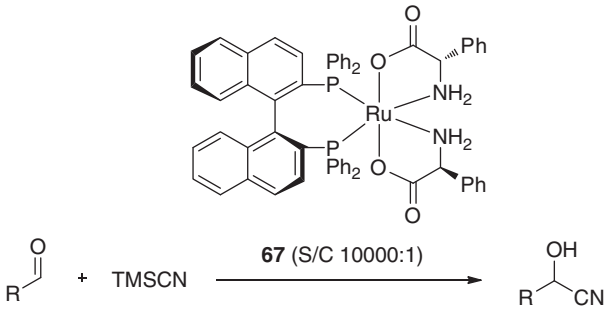
Scheme 4

Platinum and palladium NCN-pincer complexes catalyze the cyanosilylation of aromatic and aliphatic aldehydes at room temperature.[50] Several catalysts function equally well in the cyanosilylation of benzaldehyde (equation 23). Although dichloromethane is commonly used as a solvent, it can be replaced by toluene. The chiral version of the reaction using homochiral catalysts still shows good conversions but very low enantioselectivity (<15% *ee*).



(23)

Combination of chiral ruthenium complex **67** with lithium carbonate results in high catalytic activity in the reaction of aromatic and aliphatic aldehydes with TMSCN.[51] Thus, at S/C ratio of 10 000:1 the reaction can be effected in 91–99% yield and up to 98% *ee* (equation 24, **Table 10**). In the case of benzaldehyde the reaction goes to completion when an S/C ratio of 1 000 000:1 is used at $-40\,^{\circ}C$ for 24 h.



(24)

Table 10 Cyanosilylation of aldehydes catalyzed by **67**

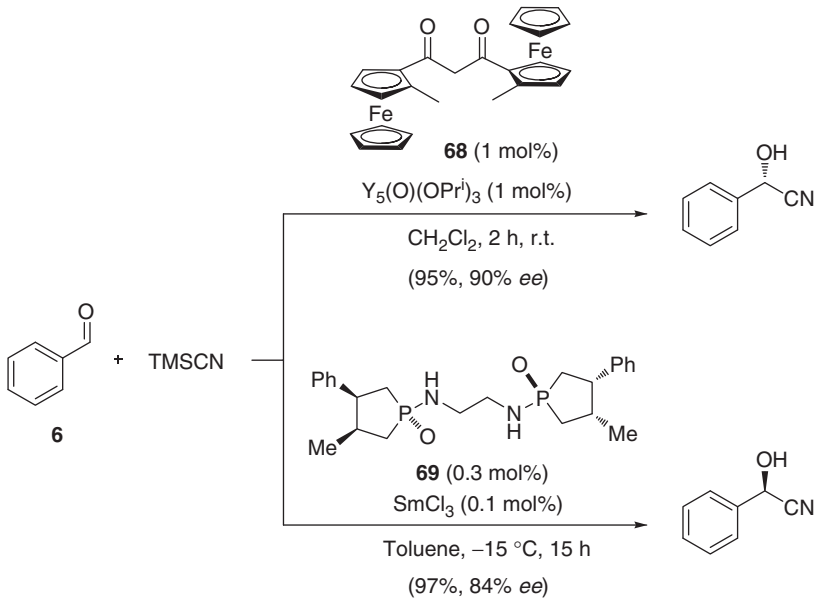
No.	*R*[1]	*Solvent*	*Temperature (°C)*	*Time (h)*	*Yield (%)*	*ee (%)*
i	Ph	Et_2O	−78	12	98	97
ii	2-MeC_6H_4	Et_2O	−78	24	99	96
iii	2-FC_6H_4	Et_2O	−78	18	97	96
iv	2-ClC_6H_4	Et_2O	−78	12	97	94
v	3-MeC_6H_4	Et_2O	−70	12	99	97
vi	3-ClC_6H_4	Et_2O	−78	12	98	98
vii	3-BrC_6H_4	Et_2O	−78	12	98	98
viii	3-$MeOC_6H_4$	Et_2O	−70	24	97	95
ix	4-$Me_2OCC_6H_4$	Et_2O	−70	24	95	97
x	4-MeC_6H_4	Et_2O	−70	12	96	97
xi	4-ClC_6H_4	Et_2O	−78	12	98	94
xii	4-$CF_3C_6H_4$	Et_2O	−70	24	99	96
xiii	4-$MeOC_6H_4$	Et_2O	−70	18	97	95
xiv	1-Naphthyl	Et_2O	−70	18	97	93
xvi	2-Furyl	Et_2O	−78	18	91	93
xvii	3-Pyridyl	Et_2O	−78	18	94	93
xviii	Bu^t	Bu^{t}OMe	−78	18	92	95
xix	Cyclohexyl	Bu^{t}OMe	−78	18	97	88
xx	*n*-C_5H_{11}	Bu^{t}OMe	−78	18	98	70
xxi	(*E*)-PhCH=CH	Bu^{t}OMe	−78	18	93	91
xxii	1-Cyclohexenyl	Bu^{t}OMe	−70	18	92	93

It is worth noting that the cyanation of aliphatic aldehydes shows higher enantioselectivities in *tert*-butyl methyl ether than in diethyl ether. The same reaction can be carried out with α-ketoesters but using lithium phenoxide as an additive. Under these conditions cyanation reactions take place, at S/C ratio of 1000:1, in high yields and enantioselectivities (up to 99% *ee*).[52] The use of xylyl-BINAP instead of BINAP provides better enantioselectivities in some cases.

1.18.3.2.1.8 By rare earth elements

Rare earth salts catalyze the cyanosilylation of aldehydes and ketones; several compounds such as ytterbium(III) triflate, samarium diiodide, and scandium triflate have demonstrated their utility. The high coordination capacity of lanthanides means that the reactions can be effected with a broad range of ligands. Silylene-bridged lanthanide complexes are very efficient catalysts for the cyanosilylation of aldehydes and ketones achieving conversions of up to 99%. Immobilization of scandium(III) triflate is possible by using a silica-supported aminoalcohol and a series of lanthanides including samarium, neodymium, and praseodymium can be incorporated into tetraazaligands to form Ln–N complexes that provide quantitative conversions. The use of chiral ligands allows the preparation of enantioenriched cyanohydrins. Chiral europium complexes promote enantioselective reactions of TMSCN with aldehydes. Complexes formed between lanthanide trichlorides and pybox ligands are active catalysts in the enantioselective cyanosilylation of aldehydes. However, although high conversions are obtained (up to 97%), modest enantiomeric excesses are observed (up to 67% *ee*) with the exception of ytterbium trichloride that provides enantioselectivities up to 89% *ee*.

Higher enantioselectivities are obtained with chiral Lewis acids derived from yttrium and samarium. The enantioselective cyanosilylation of benzaldehyde is catalyzed by yttrium isopropoxide and [*R,R*]-*bis*-(2-methylferrocenyl)-propane-1,3-dione **68** or by the complex formed by samarium trichloride and *bis*-phosphoramidate **69** (Scheme 5).[53]

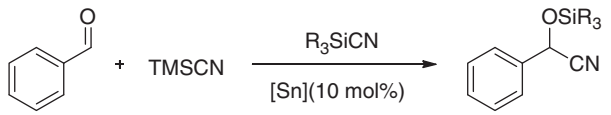


Scheme 5

Although the yttrium-catalyzed reaction affords (*S*)-cyanohydrin, the samarium-catalyzed one provides the (*R*)-cyanohydrin. The same behavior is also observed with other aromatic aldehydes. However, with aliphatic aldehydes, the (*R*)-enantiomer is obtained in the case of the yttrium-catalyzed reaction.

1.18.3.2.1.9 By other elements

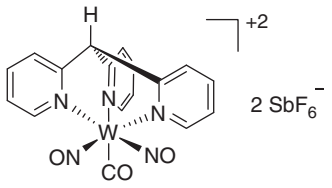
Bismuth bromide is a highly active catalyst for the cyanation of carbonyl compounds. The modification of the reaction using bismuth trichloride and L-tartrate as a chiral cocatalyst results in moderate enantioselectivities (up to 72% *ee*). Several tin species are capable of catalyzing the cyanosilylation of aldehydes. Tributyltin cyanide and dibutyltin dibromide (or dichloride) act as an effective catalysts and in all cases good yields are obtained (equation 25).[54]



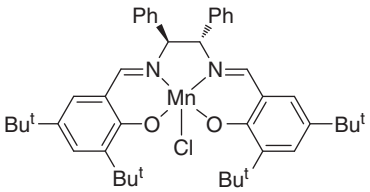
(25)

Bu_3SnCN	neat, 17 h, r.t.	94% (R = Et)
Bu_2SnCl_2	neat, 0.5 h, 0 °C	97% (R = Me)
Bu_2SnBr_2	THF, 24 h, r.t.	78% (R = Me)

The stable tungsten complex **70** catalyzes the addition of TMSCN to both aldehydes and ketones to good yields (up to 91%) in a reaction that does not require aqueous work-up, thus facilitating isolation of *O*-silylated adducts. The asymmetric version of the reaction is achieved with Mn(salen) complexes like **71** (Figure 9). Up to 62% *ee* is obtained by carrying out the reaction in the presence of triphenyl phosphine oxide, which act as a Lewis base. This double activation also works with ketones, which give up to 85% *ee*.[55]



70



71

Figure 9 W and Mn catalysts for the addition of TMSCN to aldehydes and ketones.

1.18.3.2.1.10 By inorganic solid acids

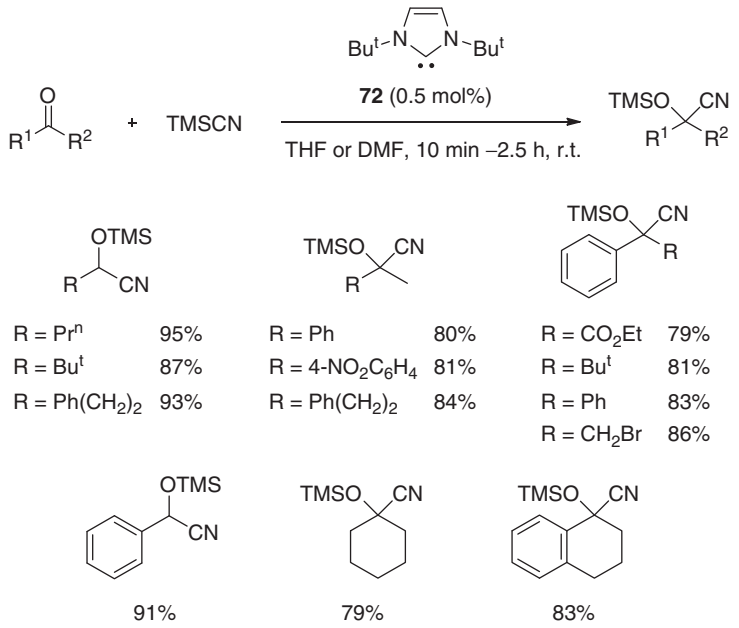
Inorganic solid acids such as Sn(IV)-ion-exchanged montmorillonite catalyze the cyanosilylation of carbonyl compounds including sterically bulky substrates. Montmorillonite K10 also promotes the reaction with aromatic and aliphatic aldehydes (up to 92% yield) and the environmentally benign dodecatungstophosphoric acid ($H_3PW_{12}O_{40}$) facilitates the process under solvent-free conditions in 5–10 min. A great variety of substrates can be cyanosilylated including hindered ketones; for example, the reaction of acetophenone takes place in 5 min and 96% yield. Phosphomolibdic acid supported on silica gel catalyzes the addition of TMSCN to various aldehydes in most cases with yields over 93%; the catalyst can be recovered and reutilized several times without loss of activity. Similarly, metal-free silica-supported perchloric acid catalyzes the same reaction in high yields and short reaction times.

The cyanation of aldehydes is considerably accelerated in the presence of the heterogeneous mesoporous aluminosilicate Al–MCM-41 (Si/Al = 20) and it proceeds quantitatively at 0 °C in 5 min.[56] This catalyst is much more active than amorphous SiO_2–Al_2O_3 having the same Si/Al ratio. By replacing aluminum with erbium, the reaction can be carried out under solvent-free conditions; the Er(III)-MCM-41 catalyst presents excellent turnover numbers (up to TON = 181) and frequencies (up to TOF = 228).

1.18.3.2.2 Nonmetal-based catalysis

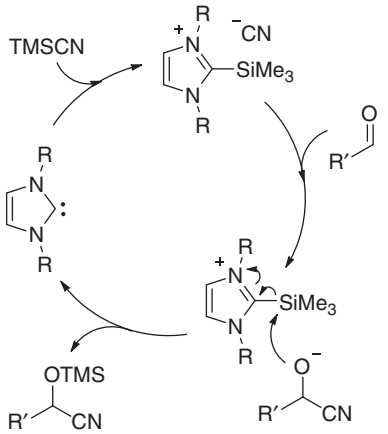
1.18.3.2.2.1 By Lewis bases and related compounds

N-Heterocyclic carbenes (NHCs) are capable of catalyzing effectively cyanosilylation of carbonyl compounds. In the presence of only 0.01–0.05 mol% of NHC **72**, conversions up to 99% are achieved.[57] Under the conditions illustrated in equation 26, hindered ketones are cyanated in good yields.



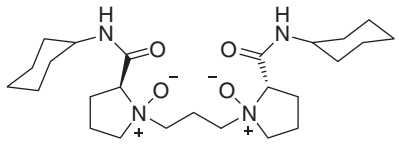
(26)

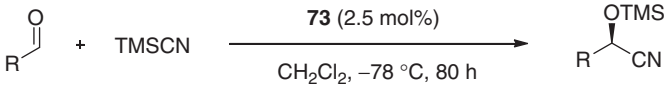
NHC can be generated *in situ* from the corresponding imidazolium salt and a base like potassium *tert*-butoxide and similar results are obtained for aldehydes and ketones. As a Lewis base catalyst, it is postulated that the NHC activates TMSCN by forming an intermediate 2-(trimethylsilyl)imidazolium cyanide salt that transfers, in an efficient way, the cyanide to the carbonyl compound (Scheme 6).



Scheme 6

A variety of *N*-oxides have been well-established as nucleophilic organocatalysts in several organic reactions. Promising results are achieved with *N*-methylmorpholine *N*-oxide in the cyanosilylation of aldehydes and ketones. An asymmetric version of the reaction is achieved with enantiomerically pure proline-based *N,N′*-dioxides **73** and **74**. Compound **73** catalyzes the addition of TMSCN to aldehydes in good yields and moderate enantioselectivities (equation 27).[58]



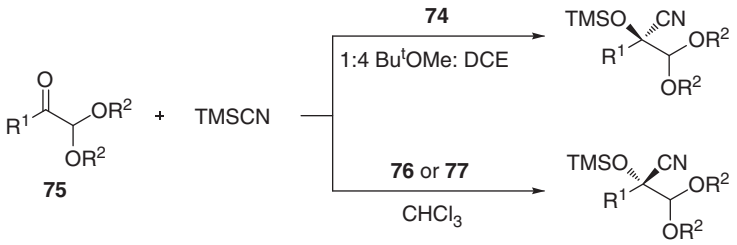


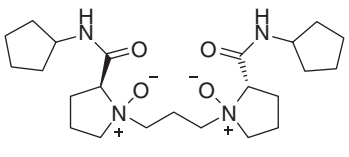
(27)

R	Yield (%)	*ee* (%)
Ph	92	73
4-MeC_6H_5	69	69
3-MeC_6H_5	80	71
4-$MeOC_6H_5$	57	64
3-$MeOC_6H_5$	78	69
3-$PhOC_6H_5$	74	71
4-FC_6H_5	70	69

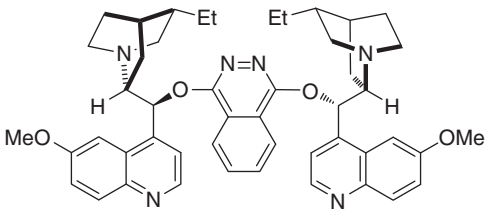
R	Yield (%)	*ee* (%)
2-ClC_6H_5	83	67
3-ClC_6H_5	90	66
4-ClC_6H_5	63	65
1-Naphthyl	92	59
2-Naphthyl	79	71
2-Furyl	59	53
$PhCH_2$	68	62

The reaction with α,α-dialkoxy ketones **75** is catalyzed by **74** and higher yields (up to 99%) and enantioselectivities (up to 93% *ee*) of (*R*)-cyanohydrins are obtained (Scheme 7).[59] The regioselective 1,2-addition of TMSCN to (*E*)-1,1,1-trifluoro-4-ethoxybut-3-en-2-one takes place in quantitative yield in less than 1 min in the presence of tertiary amines like triethylamine, Hunig's base, 4-(dimethylamino)pyridine (DMAP), and (+)-*N*-methylephedrine. The asymmetric cyanosilylation of acetophenone can be carried out using cinchona alkaloids as catalysts, but only 10% *ee* is achieved. The reaction of benzaldehyde with TMSCN in the presence of chiral amines (*S*)-α-methylbenzylamine, (1*S*,2*R*)-*N*-methylephedrine, (–)-strychnine, and $(DHQD)_2PHAL$ **76** produces only racemic product or low enantioselectivity (less than 30% *ee*) depending on the solvent. However, cinchona-derived alkaloids **76** and **77** give excellent yields and high enantiomeric excesses of (*S*)-cyanohydrins in the reaction with acetal ketones **75** (Scheme 7, Table 11). Thus, catalysts **76** and **77** are complementary to catalyst **74**.

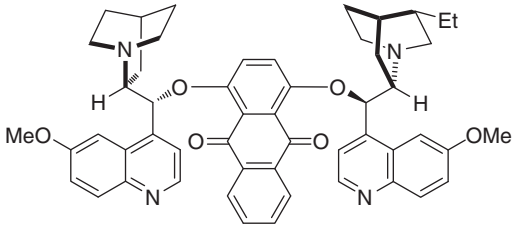




74



$(DHQD)_2PHAL$ **75**



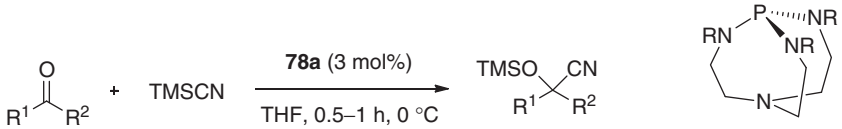
$(DHQ)_2AQN$ **76**

Scheme 7

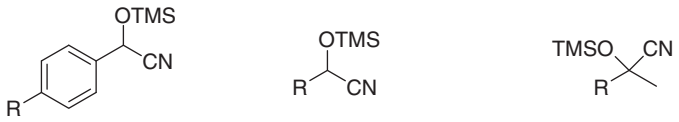
Table 11 Cyanosilylation of α,α-dialkoxy ketones **75**

No.	R^1	R^2	*Catalyst (mol%)*	*Temperature (°C)*	*Time (h)*	*Yield (%)*	*ee (%)*
i	Ph	$PhCH_2$	**74** (10)	– 45	10	99	92
ii	4-ClC_6H_4	$PhCH_2$	**74** (10)	– 45	10	83	88
iii	3-ClC_6H_4	$PhCH_2$	**74** (10)	– 45	10	99	93
iv	4-FC_6H_4	$PhCH_2$	**74** (10)	– 45	6	99	89
v	3-FC_6H_4	$PhCH_2$	**74** (10)	– 45	10	92	87
vi	3-$NO_2C_6H_4$	$PhCH_2$	**74** (10)	– 45	10	99	85
vii	4-MeC_6H_4	$PhCH_2$	**74** (10)	– 45	36	73	90
viii	4-$MeOC_6H_4$	$PhCH_2$	**74** (10)	– 45	20	99	90
ix	3,4-$DiMeC_6H_3$	$PhCH_2$	**74** (10)	– 45	36	94	88
x	1-Naphthyl	$PhCH_2$	**74** (10)	– 45	20	85	93
xi	2-Furyl	$PhCH_2$	**74** (10)	– 45	12	99	90
xii	(*E*)-PhCH═CH	Pr^i	**74** (10)	– 45	10	92	92
xiii	(*E*)-4-ClC_6H_4CH═CH	Pr^i	**74** (10)	– 45	10	88	87
xiv	(*E*)-4-$NO_2C_6H_4CH$═CH	Pr^i	**74** (10)	– 45	6	99	93
xvi	(*E*)-4-$MeOC_6H_4CH$═CH	Pr^i	**74** (10)	– 45	20	85	90
xvii	(*E*)-2-PyC_6H_4CH═CH	Pr^i	**74** (10)	– 45	10	95	85
xviii	Me	Pr^i	**74** (10)	– 45	10	90	92
xix	Ph	Et	**76** (2)	– 50	19	98	90
xx	4-$MeOC_6H_4$	Et	**76** (2)	– 50	18	94	97
xxi	4-ClC_6H_4	Et	**76** (2)	– 50	18	96	98
xxii	4-ClC_6H_4	Et	**76** (10)	– 50	40	99	94
xxiii	(*E*)-PhCH═CH	Pr^n	**76** (2)	– 50	16	93	91
xxiv	(*E*)-4-$MeOC_6H_4CH$═CH	Pr^n	**76** (2)	– 50	18	92	90
xxv	(*E*)-4-$MeOC_6H_4CH$═CH	Pr^n	**76** (10)	– 30	21	96	92
xxvi	(*E*)-4-ClC_6H_4CH═CH	Pr^n	**76** (2)	– 50	18	95	92
xxvii	(*E*)-2-PyC_6H_4CH═CH	Pr^n	**76** (2)	– 50	18	97	93
xxviii	PhC≡C	Et	**76** (2)	– 50	19	93	96
xxix	PhC≡C	Ph	**75** (10)	– 30	21	96	93
xxx	Bu^nC≡C	Bu^n	**76** (2)	– 50	18	94	95
xxxi	Me	Pr^n	**76** (2)	– 50	46	97	92
xxxii	Me	Pr^n	**75** (10)	– 50	88	95	96
xxxiii	$Ph(CH_2)_2$	Pr^n	**76** (2)	– 50	24	96	97
xxxiv	Bu^n	Et	**76** (2)	– 50	18	92	90
xxxv	Pr^i	Et	**76** (2)	– 40	94	81	94

Nonionic phosphazanes like **78** are able to catalyze the addition of TMSCN to aldehydes and ketones (equation 28) through a reaction that involves the intermediacy of phosphorus–silicon adducts as demonstrated by ^{29}Si-NMR spectroscopy.

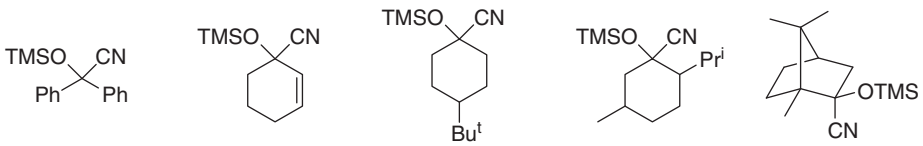


78a R = Me
78b R = Pr^i



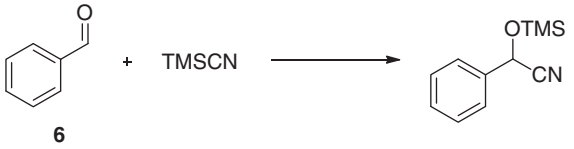
R = H	92%	R = 2-Naphthyl	83%	R = Ph	94%
R = MeO	94%	R = 2-Furyl	84%	R = (*E*)-PhCH=CH	86%
R = Cl	68%	R = Cyclohexyl	90%	R = 4-$EtO_2CC_6H_4$	88%
R = CN	59%	R = $Ph(CH_2)_2$	92%	R = *n*-C_8H_{17}	90%
		R = *n*-C_6H_{13}	95%		

(28)



91% 54% 89% (*dr* 84:16) 94% (*dr* 66:34) 33%

High yields in very short reaction times (3 min) are obtained by using elemental iodine as a catalyst. Only 0.2 mol% of iodine is needed for achieving chemical yields up to 97%. By using iodine as a catalyst, the reaction is carried out under neutral conditions; the same effect is achieved by utilizing a neutral π-nucleophile like 1-methoxy-2-methyl-1-(trimethylsiloxy) propene **79**, which in addition can be used under solvent-free conditions (equation 29).[60] Trimethylsilyl *bis*(fluorosulfonylamide) **80** can also be employed as a catalyst. Introduction of chirality can be done by using a chiral sulfoxide; however, modest enantioselectivities (up to 61% *ee*) are obtained with aldehydes.



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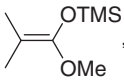
I_2 (0.2 mol%), CH_2Cl_2, 3 min, r.t. (95%) (29)

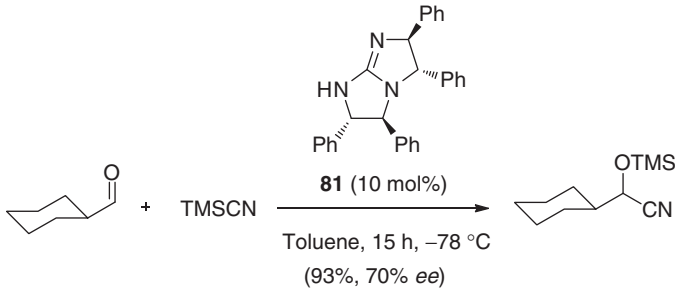


79, (10 mol%), neat, 2 h, r.t. (>95% yield)

$TMSN(SO_2F)_2$, (1 mol%), CH_2Cl_2, 15 min, –78 °C (>95% yield)

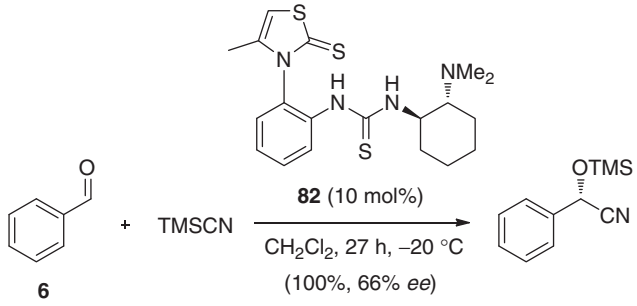
80

Guanidine fulfills the requirements to act as a Lewis base organocatalyst in the reaction of carbonyl compounds with TMSCN. Tetramethylguanidine is a highly efficient catalyst for cyanosilylation of aldehydes and ketones. The reaction proceeds smoothly with 0.1 mol% of catalyst under solvent-free conditions and yields up to 99% are obtained. By using chiral guanidines like **81**, enantioselective reactions are carried out and good to moderate enantiomeric excesses are obtained (equation 30).[61]



(30)

Optically active thioureas **82** and **83** containing a dialkylamino group are used for the enantioselective cyanosilylation of aldehydes and ketones, respectively (**Scheme 8**).[62]



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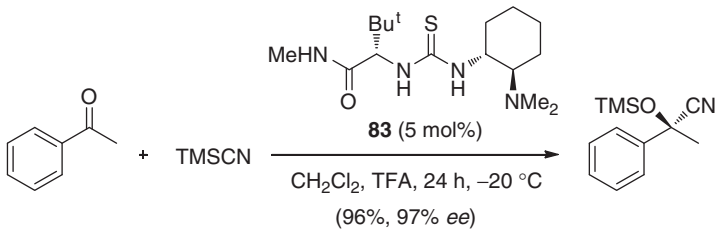
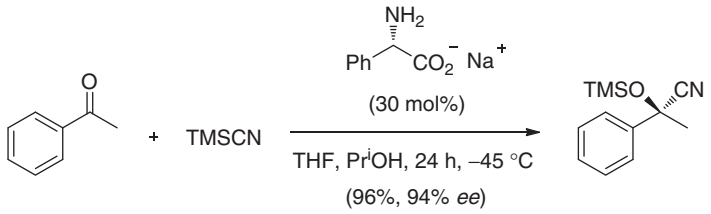


Scheme 8

The reaction with ketones catalyzed by **83** is considerably more selective than the reaction with aldehydes catalyzed by **82**. In both cases a bifunctional role, consisting in activating TMSCN by the dialkylamino group and the carbonyl by the thiourea, moiety can be attributed to the catalysts.

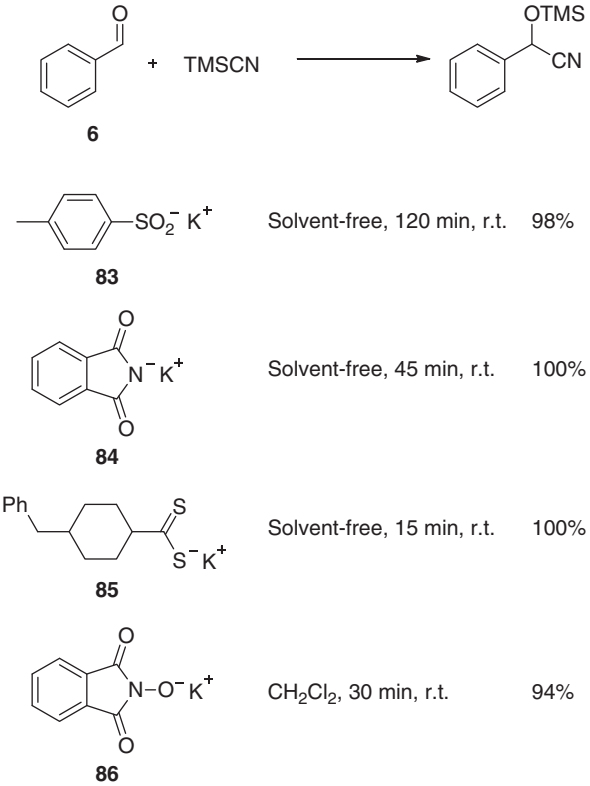
1.18.3.2.2.2 By ionic salts and related species

Chiral amino acid salts catalyze the addition of TMSCN to ketones. After examination of several aminoacids and counterions the sodium salt of phenylglycine works particularly well with acetophenones (equation 31);[63] the scope of the reaction can be extended to other aromatic and aliphatic ketones with good results (up to 97% *ee*). Based on NMR experiments it is hypothesized that the mechanism of activation is similar to that exerted by *N*-oxides and phosphine oxides, that is, by activating TMSCN. Milder conditions and shorter reaction times are achieved with sodium salts of L-aspartate and L-hisitidine. With the latter excellent yields (up to 92%) are obtained, but in both cases enantioselectivities are rather lower than with sodium L-phenylglycine.



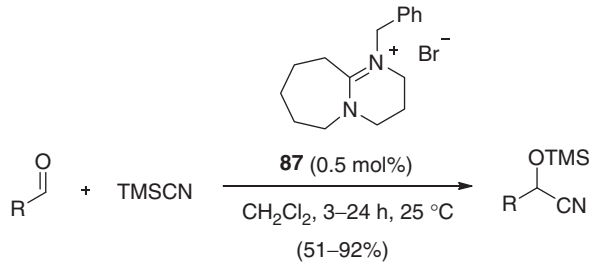
(31)

Potassium *p*-toluenesulfinate **83** promotes the addition of TMSCN to carbonyl compounds in essentially quantitative yield under solvent-free conditions. Aliphatic, aromatic, and heterocyclic aldehydes and ketones can be cyanosilylated by this environmentally friendly and highly efficient way. Potassium phthalimidate **84** is an alternative that allows preparation of silylated cyanohydrins in excellent chemical yields (equation 32).[64] Still under solvent-free conditions it is possible to use potassium 4-benzylpiperidine dithiocarbamate **85** as a suitable catalyst of the reaction. All these potassium salts show a wide scope on the substrate and afford the adducts in near quantitative yields.



(32)

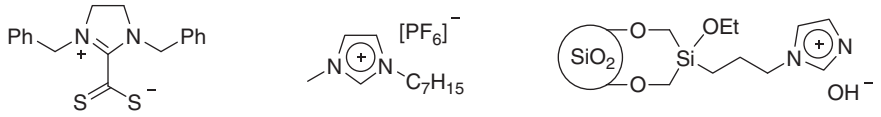
Similar results are obtained with tetrabutylammonium phthalimide *N*-oxyl **86**. Other tetraalkyl ammonium salts like tetrabutylammonium cyanide and tetraethylammonium 2-(carbamoyl)benzoate also catalyze the reaction with high efficiency. Among several basic ammonium salts, monoquaternized base **87** is the best catalyst for the cyanosilylation of aldehydes. A wide range of substrates including aromatic and aliphatic compounds show a good reactivity, the most reactive being aromatic aldehydes with electron-withdrawing substituents (equation 33).[65]



(33)

Similar results are obtained with methyltriphosphonium iodide as a catalyst. This catalyst however, fails to promote the addition of TMSCN to ketones and the more reactive benzyltriphosphonium chloride should be used. The reaction is influenced by the groups attached to the phosphorus atom but particularly by the nature of the counterion. Although iodides and bromides provide low conversions, yields up to 92% are obtained with the corresponding chlorides.

Imidazolium carbodithioates like **88** (Figure 10) catalyze the reaction with aldehydes in dichloromethane with complete conversion and good chemical yields. By using ionic liquid **89** as a catalyst the same process is achieved in the absence of any solvent and with silica-immobilized catalyst **90** is possible to extend the reaction to ketones. Under these conditions aldehydes react in virtually quantitative yield in 0.5–1 h with only 2.8 mol% of catalyst.

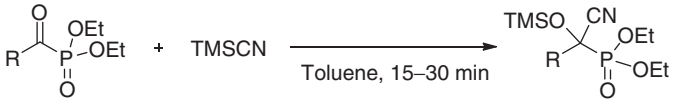


88 **89** **90**

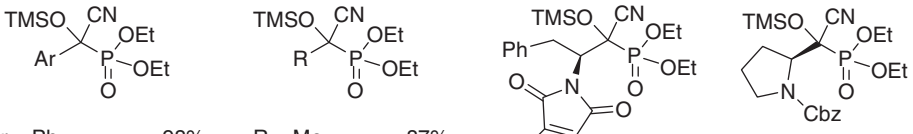
Figure 10 Ionic liquids as catalysts for the addition of TMSCN to aldehydes.

1.18.3.2.3 Uncatalyzed reactions

In general, carbonyl compounds do not react – or react very slowly – with TMSCN in the absence of any catalyst. An exception to this behavior is observed for the highly reactive acylphosphonates **91**. These compounds undergo nucleophilic addition of TMSCN without the influence of a catalyst (equation 34).[66]



91



Ar = Ph	98%	R = Me	87%
Ar = 4-FC_6H_4	98%	R = Cyclohexyl	97%
Ar = 4-$MeOC_6H_4$	97%	R = Pr^i	94%
Ar = 4-ClC_6H_4	97%		
Ar = 2-MeC_6H_4	98%		

83% 93%

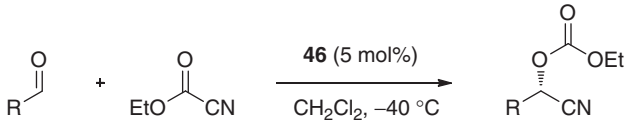
(34)

The addition of TMSCN to aldehydes in the absence of any additive and any solvent takes place in good yields in short reaction times (< 30 min) when carried out at 200 °C using microwave irradiation. The same reaction conditions serve for cyanosilylation of chalcones and related enones.

1.18.3.3 Addition of Acyl Cyanides

1.18.3.3.1 Metal-based catalysis

Cyanoformate esters (ROCOCN) are a safer and less expensive alternative to both hydrogen cyanide and TMSCN. They react with aldehydes and ketones to give cyanohydrin carbonates. The reaction can be catalyzed by tributyltin cyanide without solvent or in polar solvents, such as acetonitrile or *N*,*N*-dimethylformamide (DMF). Chiral Lewis acid promoted additions of EtOCON to carbonyl compounds give varying degrees of enantioselectivity depending on the Lewis acid and the aldehyde/ketone appendages. The addition of ethyl cyanoformate to aromatic aldehydes catalyzed by bimetallic titanium complex **46** furnishes cyanohydrin carbonate in good enantioselectivity (up to 99% *ee*). Lower values were observed with aliphatic aldehydes (up to 84% *ee*)[67] (equation 35, Table 12).



(35)

Table 12 Addition of ethylcyanoformate to aldehydes

No.	*R*[1]	*Time (h)*	*Yield (%)*	*ee (%)*
i	Ph	18	90	95
ii	4-$MeOC_6H_4$	18	92	95
iii	3-$MeOC_6H_4$	17	94	99
iv	2-$MeOC_6H_4$	48	95	98
v	2-MeC_6H_4	48	95	94
vi	4-$CF_3C_6H_4$	6	84	76
vii	4-ClC_6H_4	68	96	94
viii	(*E*)-PhCH=CH	45	99	94
ix	*n*-C_8H_{17}	22	54	84
x	Pr^i	20	88	79
xi	Cyclohexyl	18	82	79
xii	Bu^t	48	69	76

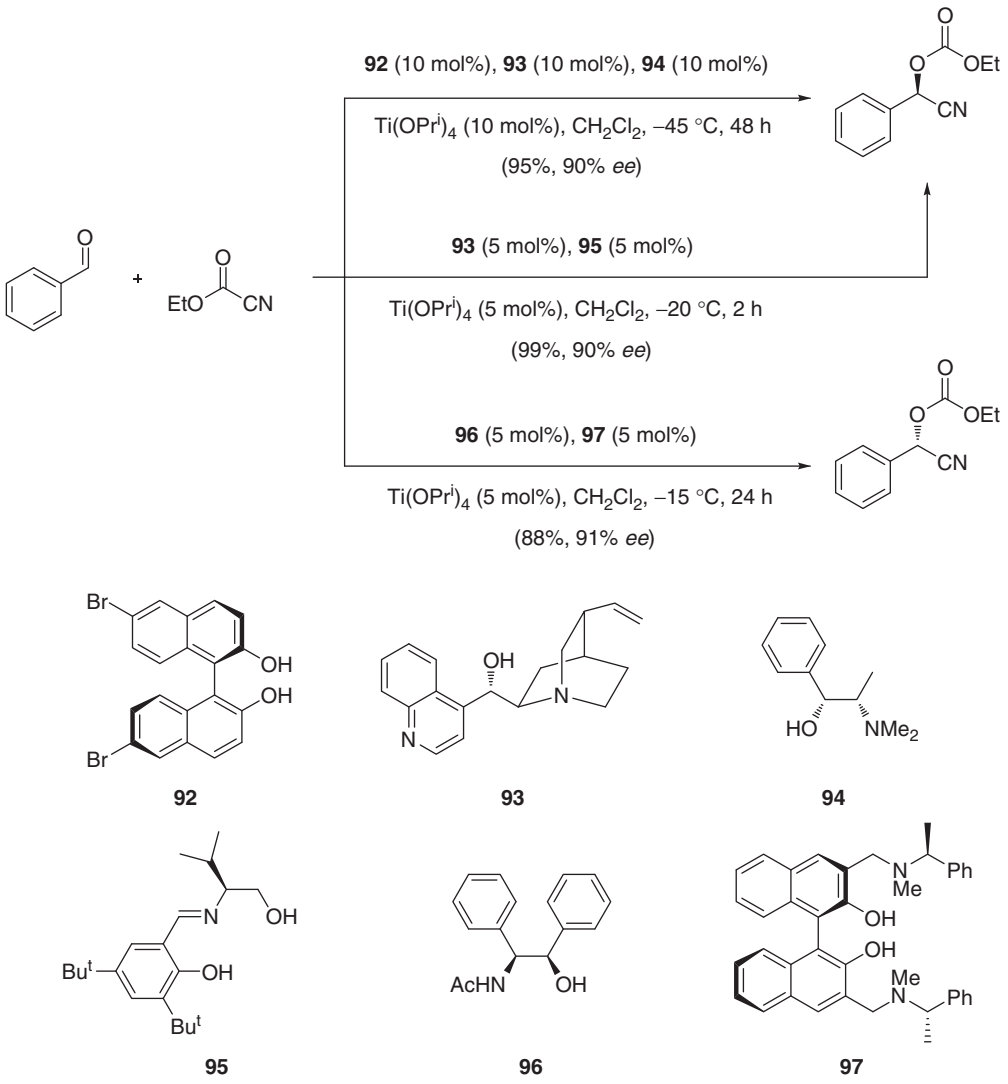
When mononuclear salen–Ti$(OPr^i)_4$ complex formed *in situ* from **39b** is the promoter, the amount of ethyl cyanoformate is crucial for obtaining good yields and enantioselectivities. Although excellent values are obtained from 1.25 to 1.75 equivalents, a decrease to 1.0 equivalent, or an increase to 2.0 equivalents is capable of reducing the isolated yield notably.[68] The corresponding complex between **39b** vanadium(V) provides excellent yields (up to 97%) and enantioselectivities (up to 97% *ee*) when imidazole or hydrotalcite are used as cocatalysts.[69] Modest enantioselectivities are obtained by employing chiral C_2-symmetric *N*,*N*′-dioxide ligands similar to **59**.

Efficient enantioselective additions can be realized with aldehydes and ethyl cyano formate using a multicomponent bifunctional catalytic system elaborated with the combination of BINOL **92**, cinchonine **93**, (1*R*,2*S*)-(–)-*N*-methylephedrine **94** and Ti$(OPr^i)_4$. It is proposed that the complex of **92** with Ti(IV) acts as the Lewis acid to activate the carbonyl group and the tertiary amine of ligands **93** and **94** act as Lewis bases to activate the ethylcyano carbonate. All the ligands and Ti$(OPr^i)_4$ are used in the same catalytic amount of 10 mol% (Scheme 9). An identical result is obtained by using 5 mol% of **93** and **95** in the presence of 5 mol% of Ti$(OPr^i)_4$. The opposite enantiomer is prepared with the same catalytic amounts of ligands **96** and **97**.[70]

The reaction promoted by 1 mol% of the heterobimetallic complex **98** requires water, *tris*(2,6-dimethoxyphenyl)phosphine and butyllithium as achiral additives to achieve high reactivity (up to 99%) and enantiomeric excesses (up to 98% *ee*).[71] However, with solid **99** and in the presence of 10 mol% of cinchonine (*S*)-cyanohydrin carbonates are obtained under mild conditions ($-20\ ^\circ C$) in excellent yields (up to 99%) and enantioselectivities (up to 95% *ee*)[72] (Figure 11).

Another efficient catalytic system is formed by bimetallic complex **46** and achiral or chiral Lewis base, which allows the addition of α-ketonitriles to aldehydes furnishing *O*-acylated cyanohydrins in high yields (up to 90%) and enantioselectivities (up to 94% *ee*).[73]

Reactions of aldehydes with benzoyl cyanide are possible under catalysis by BINOLAM–Ti(IV) complexes. The catalyst prepared *in situ* plays a Lewis acid–Brønsted base dual role that favors the obtention of (*R*)-*O*-benzoyl cyanohydrins in good yields and moderate enantioselectivities (equation 36, Table 13).



Scheme 9

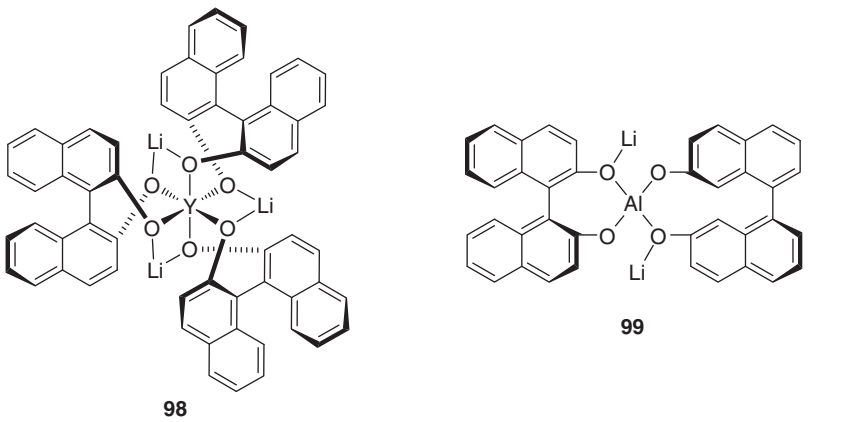
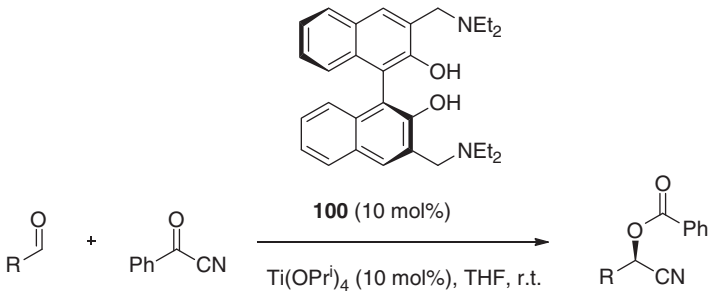


Figure 11 Bimetallic catalysts.

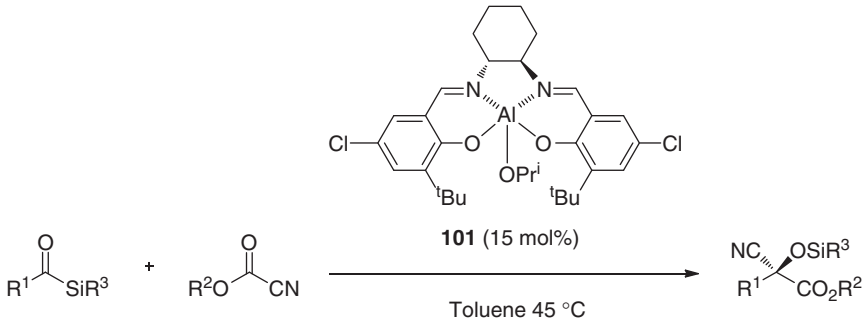


(36)

Table 13 Addition of benzoylcyanide to aldehydes

No.	*R*[1]	*Time (h)*	*Yield (%)*	*ee (%)*
i	Ph	6	90	68
ii	4-MeC_6H_4	21	76	58
iii	4-ClC_6H_4	18	85	58
iv	2-Furyl	7	89	56
v	3-Pyridyl	22	93	38
viii	(*E*)-PhCH═CH	6	87	68
ix	*n*-C_6H_{13}	12	80	56
x	$Ph(CH_2)_2$	3	93	66

A number of aryl acylsilanes and cyanoformate esters react smoothly under catalysis of salen aluminum complex **101**. Good yields and moderate enantioselectivities are obtained (equation 37), the catalytic system showing significant remote electronic and concentration effects[74] (Table 14).



(37)

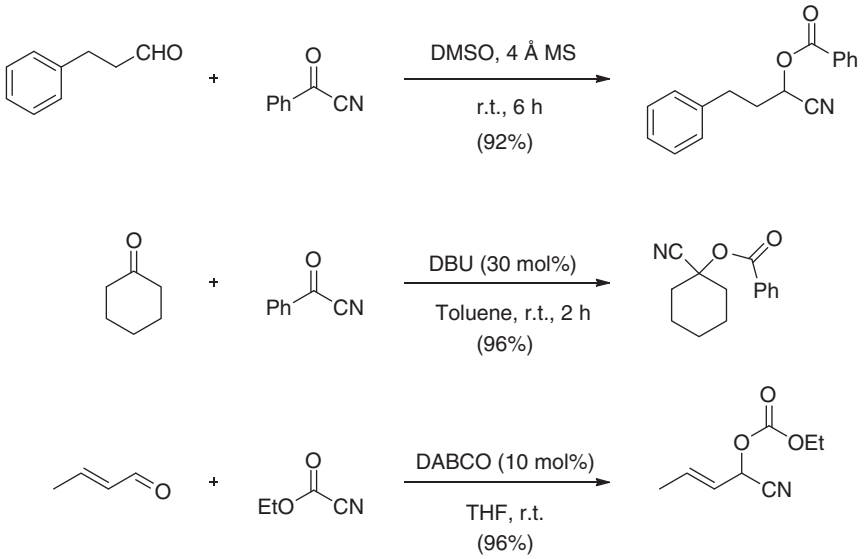
Table 14 Addition of alkylcyanoformates to acylsilanes

No.	*R*[1]	*R*[2]	*SiR*[3]	*Yield (%)*	*ee (%)*
i	Ph	Bn	$SiEt_3$	83	79
ii	Ph	Bn	$SiBu^tMe_2$	82	64
iii	Ph	Et	$SiEt_3$	93	77
iv	4-MeC_6H_4	Bn	$SiEt_3$	79	80
v	2-Naphthyl	Bn	$SiEt_3$	90	62
vi	4-$MeOC_6H_4$	Bn	$SiEt_3$	84	82
vii	4-ClC_6H_4	Bn	$SiEt_3$	87	64
viii	4-ClC_6H_4	Et	$SiEt_3$	87	61
ix	4-FC_6H_4	Bn	$SiEt_3$	81	78
x	4-CNC_6H_4	Bn	$SiEt_3$	70	64

1.18.3.3.2 Nonmetal-based catalysis

Potassium carbonate promotes addition of various acyl cyanides to aldehydes in acetonitrile–water in good yields (75–95%). In the presence of molecular sieves in dimethylsulfoxide (DMSO), the addition of benzoyl cyanide to aldehydes takes place with no

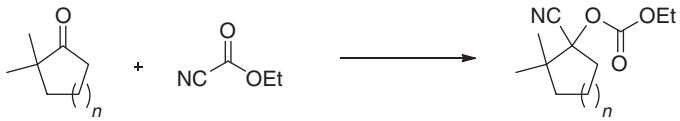
catalyst. However, the presence of a Lewis acid, such as 1,8-diazabicycloundec-7-ene (DBU) is required in the reaction with ketones. By using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base, α,β-unsaturated aldehydes form cyanohydrin carbonates in good yields, only 1,2-addition being observed (Scheme 10).



Scheme 10

In the presence of a catalytic amount (10 mol%) of DMAP the reaction with aromatic and aliphatic aldehydes and ketones takes place under solvent-free conditions in 15–90 min and *O*-protected cyanohydrins are obtained in good yields. Similar results are obtained by carrying out the reaction in an ionic liquid, but the reaction needs more time to go on completion.

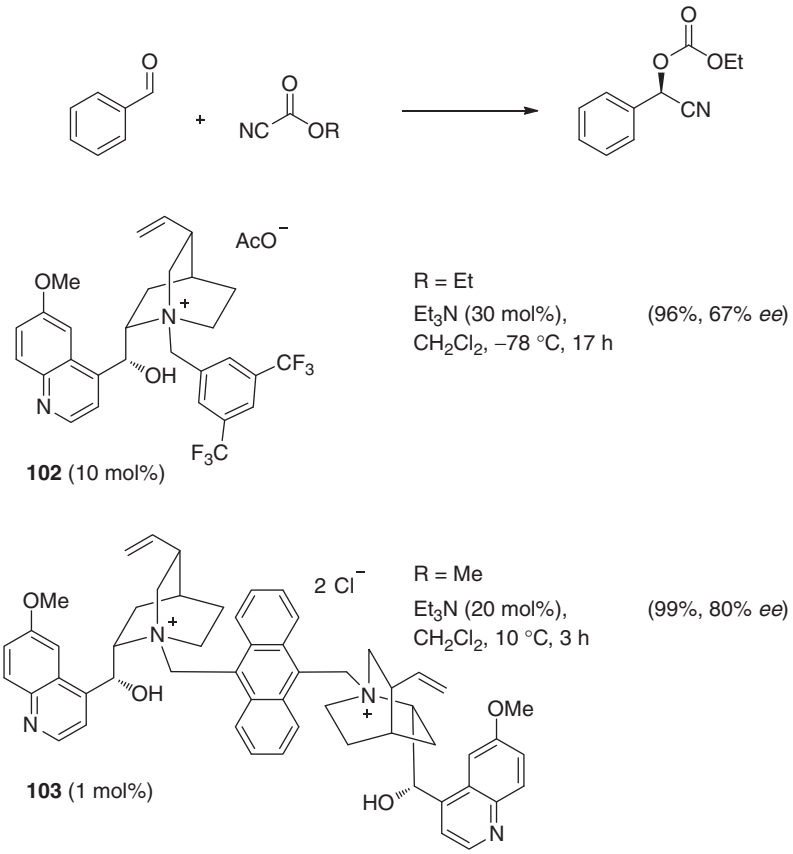
The chemoenzymatic reaction between ethyl cyanoformate and benzaldehyde catalyzed by the hydroxynitrile liase from *Prunus amygdalus* provides (*R*)-mandelonitrile in excellent enantioselectivity (>99% *ee*).[75] Enantioselective reactions are also possible by using chiral Lewis bases. Dialkyl ketones undergo cyanocarbonylation under catalysis with cinchona alkaloid derivatives providing direct access to quaternary centers. For example, the reaction with hindered ketones is catalyzed by $(DHQ)_2AQN$ **76** furnishing the corresponding adducts in good yields and enantioselectivities (equation 38).[76]



(38)

$n = 1$	$(DHQ)_2AQN$ **76** (15 mol%), –24 °C, 4 h	(76%, 95% *ee*)
$n = 2$	$(DHQ)_2AQN$ **76** (30 mol%), –12 °C, 5 h	(53%, 92% *ee*)

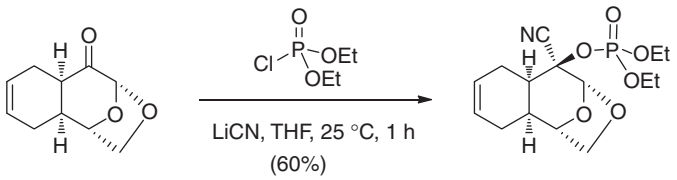
When ethyl cyanocarbonate is reacted with aldehydes in the presence of quaternary ammonium salt **102** and triethylamine, (*R*)-cyanohydrin carbonates are obtained with moderate enantioselectivities (up to 72% *ee*) (equation 39). Dimeric dimethylanthracenyl-derived cinchonidine ammonium salt **103** shows a higher efficiency. Only 1 mol% of catalyst working at 10 °C is enough to achieve enantioselectivities of up to 88% *ee* with quantitative yields (equation 39).[77]



(39)

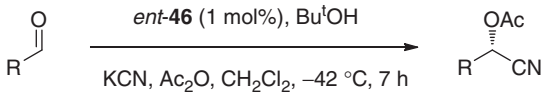
1.18.3.4 Addition of Cyanide Alkaline Salts

The classical examples in the area of cyanation of carbonyl compounds originate from the work involving the uncatalyzed addition of lithium, sodium, and potassium cyanide. Protected cyanohydrins are obtained when the reaction is carried out in the presence of reagents, such as trimethylsilyl chloride or acyl chloride. Similarly, the addition of lithium cyanide in the presence of a dialkyl chlorophosphate affords the corresponding cyanophosphates (equation 40).[78]



(40)

Optically active cyanohydrins are obtained by using potassium cyanide as a cyanide source in enzymatic reactions. Actually, the HNL enzyme catalyzes the addition of HCN as discussed in previous sections. The enantioselective addition of potassium cyanide to aldehydes employing bimetallic species as catalysts are highly attractive because of the convenient access to the catalyst components along with the simplicity of the reaction, which can be carried out in the presence of acetic anhydride to afford *O*-acetyl cyanohydrins (equation 41, Table 15).[79] The reaction, however, does not work with ketones under the conditions illustrated in equation 41. A mechanistic rationale has been proposed for the reaction, based on X-ray analysis of iron–salen complexes structurally related to bimetallic complex **46**.[80]

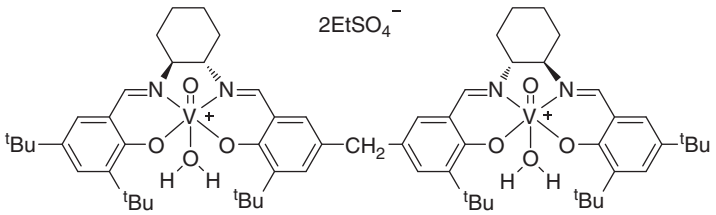


(41)

Table 15 Addition of potassium cyanide to aldehydes

No.	R^1	*Yield (%)*	*ee (%)*
i	Ph	92	89
ii	4-$MeOC_6H_4$	74	93
iii	3-$MeOC_6H_4$	99	93
iv	4-$PhOC_6H_4$	99	89
v	4-FC_6H_4	99	93
vi	2-FC_6H_4	86	82
vii	3-FC_6H_4	99	89
viii	2-ClC_6H_4	89	88
ix	$Ph(CH_2)_2$	79	82
x	Pr^i	62	72
xi	Bu^t	90	60

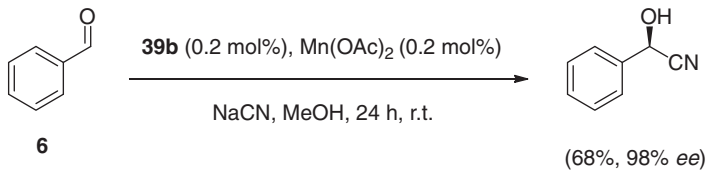
The reaction with aldehydes is also catalyzed by polymeric salen–Ti (IV) or V (V) complexes and it can be carried out with aldehydes attached to Wang resin achieving high enantioselectivities (up to 91% *ee*). Comparable results are obtained with sodium cyanide, the vanadium catalyst **104** (Figure 12) being found to be better than the titanium catalyst **46**.[81]



104

Figure 12 Dimeric vanadium catalyst.

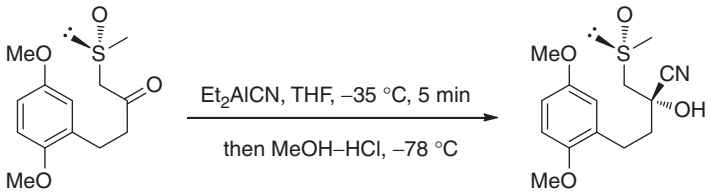
A combination between the reaction catalyzed by **46** and further enzyme-mediated resolution of the obtained enantioenriched (*R*)-*O*-acetylcyanohydrins allow obtention of those compounds in a very high enantioselectivity (up to >99% *ee*). The addition of sodium cyanide to aromatic aldehydes is also catalyzed by a catalyst generated *in situ* from manganese(II) acetate and the chiral Schiff base ligand **39b**. The reaction takes place with excellent chemical yield and enantioselectivity at room temperature in 24 h with only 0.2 mol% of catalyst (equation 42).[82]



6 (68%, 98% *ee*) (42)

1.18.3.5 Addition of Diethyl Aluminum Cyanide

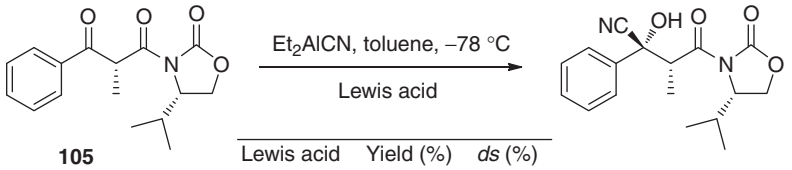
The reaction of chiral nonracemic *β*-ketosulfoxides with diethylaluminum cyanide provides a method for preparing optically active functionalized cyanohydrins of synthetic interest. The reaction does not work with aldehydes unless $ZnBr_2$ is used as a catalyst. With aromatic ketones and aldehydes, a remote stereocontrol is possible and $Yb(OTf)_3$ and $Y(OTf)_3$ are preferred as catalysts. The order of the addition of the reagents is critical to obtain good yields and thus, a solution of the carbonyl derivative should be added dropwise into a solution of diethylaluminum cyanide. The reaction has been utilized in the context of anthracyclinone synthesis giving rise to excellent diastereoselectivities (equation 43).[83]



(97%, *ds* >99%)

(43)

The addition to β-ketoamides **105** also takes place with good diastereoselectivities but only when $ZnBr_2$ or Et_2AlCl are used as additives. The high diastereoselectivity observed is explained based on the formation of a rigid chelate which orientates the cyanide entry from the opposite side to the α-methyl group (equation 44).[84]

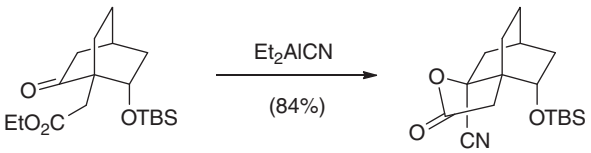


105

Lewis acid	Yield (%)	*ds* (%)
$ZnBr_2$	82	98
Et_2AlCl	79	95
None	63	80

(44)

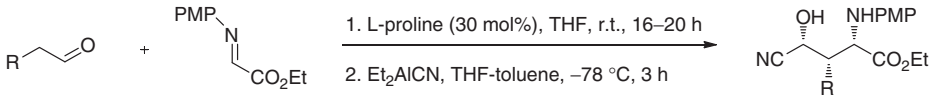
In the case of rigid systems, a complete selectivity is observed. That is the case of ketone **106**, which on treatment with diethylaluminum cyanide affords not only the cyanohydrin, but also effects an intramolecular cyclization to furnish **107**, an advanced intermediate toward the synthesis of the natural product maoecrystal V (equation 45).[85]



106 **107**

(45)

The reaction of α-dibenzylamino aldehydes with diethylaluminum cyanide in toluene at −78 °C affords preferentially *anti* adducts. However, when the cyanide reagent is employed in a one-pot asymmetric Mannich-hydrocyanation reaction *syn* adducts are obtained (equation 46, Table 16).[86]



(46)

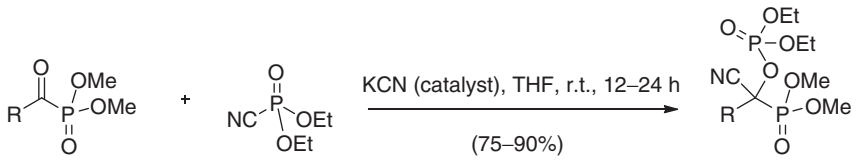
Table 16 Organocatalytic addition of diethylaluminum cyanide

No.	R^1	*Yield (%)*	*ee (%)*
i	Ph	40	94
ii	Bu^t	60	93
iii	$n\text{-}C_5H_{11}$	68	98
iv	$n\text{-}C_6H_{13}$	65	98
v	$PhCH_2$	62	>99
vi	$TBSO(CH_2)_3$	42	>99
vii	$(E)\text{-}CH_3(CH_2)_4CH{=}CHCH_2$	40	>99

1.18.3.6 Addition of Dialkylcyanophosphonates

The cyanophosphorylation of carbonyl compounds have been of interest for some time and it is known for a range of aldehydes and ketones. The earliest examples for this class involve the addition of diethylcyanophosphate catalyzed by a cyanide salt, typically lithium cyanide.

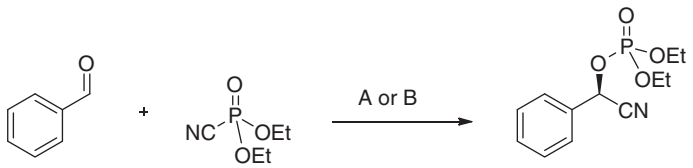
Acylphosphonates **108** are transformed into phosphonocyanohydrin *O*-phosphonates **109** by treatment with diethyl cyanophosphonate in the presence of a catalytic amount of potassium cyanide (equation 47).[87]



108 **109** (47)

R = Me, Et, Bu^t, cyclohexyl, Ph, 4-MeC_6H_4, 4-MeOC_6H_4, 4-FC_6H_4, 4-MeC_6H_4

NHCs can also act as nucleophilic catalysts in the cyanophosphorylation of aldehydes. Although good chemical yields are obtained, an asymmetric version of the reaction has not still been developed. The enantioselective cyanophosphorylation of aldehydes is possible with the bifunctional aluminum catalyst **27** derived from (*S*)-BINOLAM. The addition of diethyl cyanophopshate to aromatic aldehydes in the presence of 10 mol% of **27** furnishes the corresponding (*R*)-cyanohydrin-*O*-phosphate in good yields (87–90%) and high enantioselectivities (up to 98% *ee*). With heterobimetallic Ytterbium lithium complex **98**, the same enantiomeric induction is observed and similar results are obtained (equation 48).[88]



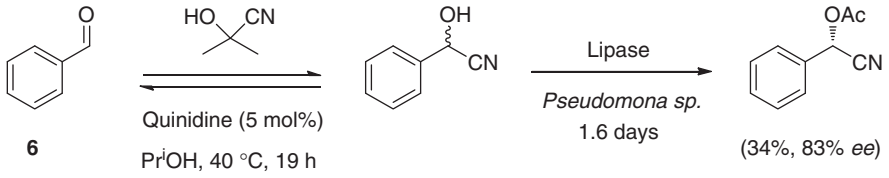
6 (48)

A: **27** (10 mol%), toluene, r.t., 4 h (89%, 98% *ee*)

B: **98** (10 mol%), H_2O (30 mol%), BuLi (10 mol%), (1,6-di$MeOC_6H_3)_3PO$ (10 mol%), THF, –78 °C, 2 h (89%, 98% *ee*)

1.18.3.7 Addition of Acetone Cyanohydrin

Acetone cyanohydrin is a rather more practical reagent than hydrogen cyanide, which is very volatile and highly toxic. However, the reactivity of acetone cyanohydrin is lower than other cyanide reagents and catalysts are required to complete the reaction. The transhydrocyanation reaction can be promoted by tertiary amines and Amberlite IRA-904, an anion-exchange resin (OH^- form). When coupled *in situ* with lipase-catalyzed kinetic resolution, optically active cyanohydrin acetates are obtained in excellent yields (up to 100%) and enantioselectivities (up to 94% *ee*).[89] The racemization of cyanohydrins can also be induced by other bases such as quinidine as illustrated in Scheme 11.



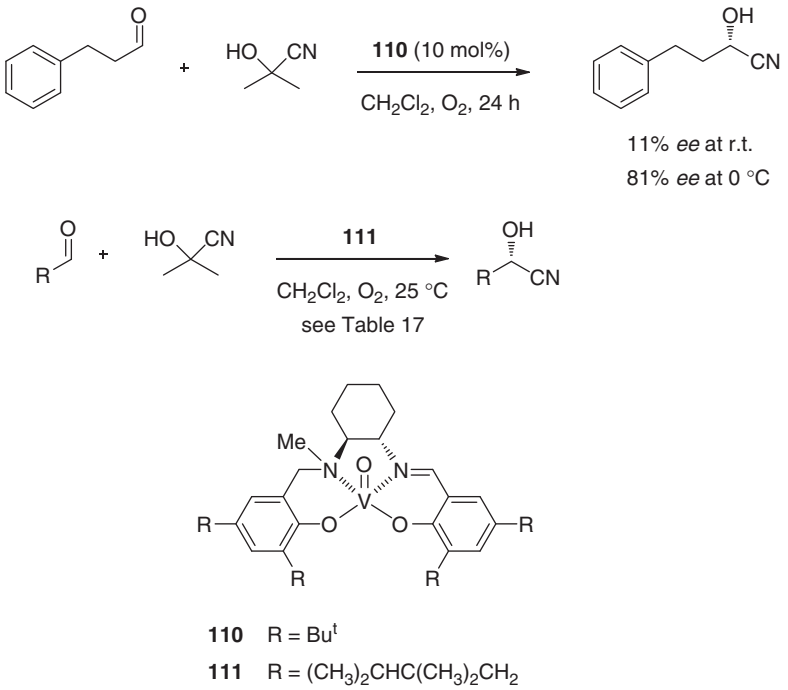
6

Scheme 11

Immobilization of the enzyme leads to an improvement of both the enantioselectivity and the reaction times for the dynamic kinetic resolution. Different solvents and acetate donors can be employed to develop an efficient dynamic resolution process. The enzymatic hydrolysis of cyanohydrin acetates can be done in an enantioselective way furnishing unprotected cyanohydrins. By using subtilisin A the kinetic resolution is (*S*)-selective, whereas *Candida rugosa* lipase is (*R*)-selective.[90]

The transhydrocyanation from acetone cyanohydrin to aldehydes and ketones is also catalyzed by Lewis acids. Typically, titanium(IV) and lanthanoid alkoxides catalyze efficiently the reaction providing the corresponding cyanohydrins. Catalysts prepared from samarium(II) halides, butyllithium, and sodium cyclopentadiene in the presence of THF ($Cp_2Sm(THF)_2$) are

effective at mediating the direct acetylcyanation of aldehydes with acetone cyanohydrin and isoprenyl acetate. Enantioenriched nonprotected cyanohydrins are prepared from aliphatic aldehydes using acetone cyanohydrin in the presence of vanadium-(salen) catalysts **110** in a reaction that is highly dependent on the temperature. With **111**, only 0.2–0.4 mol% of catalyst is necessary to achieve good values of enantioselectivity at room temperature for aliphatic aldehydes (Scheme 12).[91] Aromatic substrates, however require higher amounts of catalyst and show poorer enantioselectivity (Table 17).

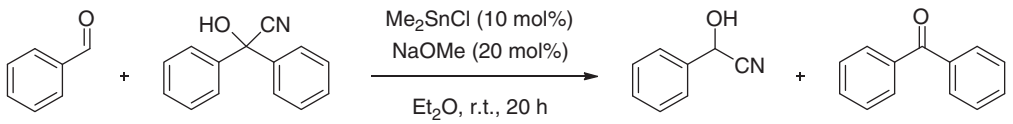


Scheme 12

Table 17 Organocatalytic addition of diethylaluminum cyanide

No.	*R*[1]	*Mol%*	*Time (h)*	*Yield (%)*	*ee (%)*
i	$Ph(CH_2)_2$	0.2	6.5	95	89
ii	*n*-C_7H_{15}	0.2	7	92	91
iii	Bu^t	0.2	3	87	89
iv	$BnO(CH_2)_3$	0.4	7	87	89
v	Pr^i	0.4	4	85	94
vi	Cyclopentyl	0.4	3	92	92
vii	Cyclohexyl	0.4	2	92	95
viii	Bu^t	0.4	2	89	93
ix	Ph	1.5	6	66	29

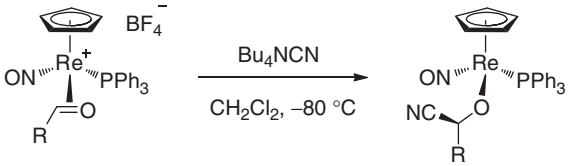
In a similar way to acetone cyanohydrin other ketone cyanohydrins can be used as a cyanide source. For example, benzophenone cyanohydrin transfers cyanide to aromatic aldehydes in the presence of a catalytic amount of organotindimethoxide catalysts formed *in situ* (equation 49).[92]



(49)

1.18.3.8 Addition of Other Cyanide Reagents

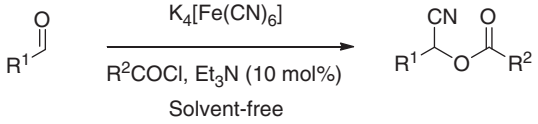
The reaction of chiral rhenium aldehyde complexes with tetrabutylammonium cyanide affords optically active cyanohydrin alkoxide complexes in good yields albeit moderate diastereoselectivities (equation 50).[93]



(50)

The addition of tetraethylammonium cyanide, in the presence of magnesium dibromide etherate, to α-alkoxy aldehydes takes place with good chemical yields and *syn* selectivity. Improved results are achieved by using $Et_4NAg(CN)_2$ as a cyanide source. With this reagent the reaction is highly dependent on the amount of catalyst. Under optimized conditions (5.0 equivalents of $MgBr_2 \cdot Et_2O$, $-78\ ^\circ C$, CH_2Cl_2) diastereomeric ratios of up to 24:1 are obtained.[94]

Potassium hexacyanoferrate (II) is an environmentally benign cyanide source that can be used for the direct cyanoaroylation of aldehydes in the presence of triethylamine as a catalyst under solvent-free conditions (equation 51). The major advantage of the method outlined in equation 51 is that it avoids the use of toxic and hazardous reagents providing an efficient and versatile approach to *O*-acyl cyanohydrins.[95]



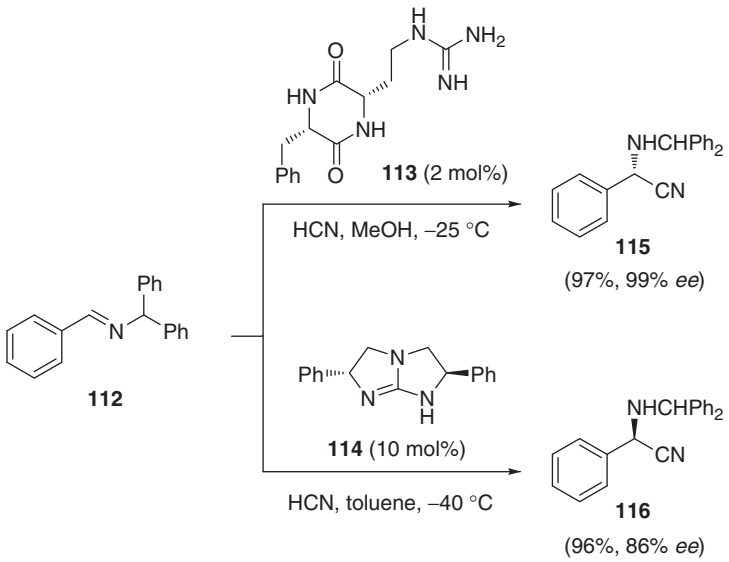
(51)

1.18.4 Addition of Cyanide to Imines and Related Compounds

1.18.4.1 Addition to Imines

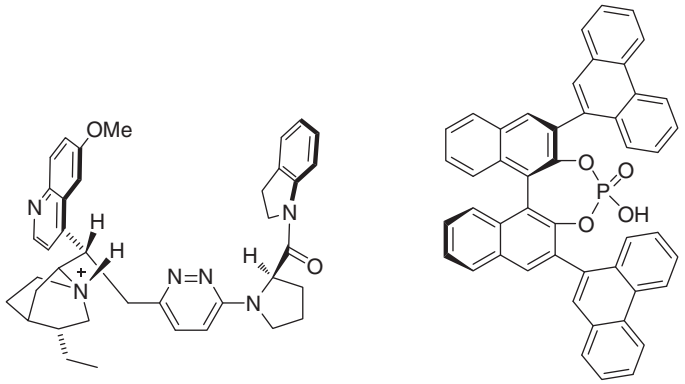
1.18.4.1.1 Addition of hydrogen cyanide

The direct uncatalyzed hydrocyanation of imines with hydrogen cyanide is rapid at ambient temperature, takes hours at 0 °C and it is completely blocked at −70 °C; such a dependence of temperature allows the use of catalysts to promote not only a rapid reaction at low temperature, but also enantioselective processes. One of the first examples is given by the addition of hydrogen cyanide to aromatic and aliphatic aldimines catalyzed by cyclic dipeptide **113** bearing a guanidino unit in its structure.[96] Although enantioselectivities of up to >99% *ee* are found for aromatic substrates, aliphatic and electron-poor substituted arylimines lead to poor values (<10% *ee*). The chiral bicyclic guanidine **114** is also an effective catalyst for the reaction, demonstrating that the guanidino functionality is alone sufficient for catalytic activity.[97] Interestingly, catalysts **113** and **114** are complementary providing enantiomeric α-aminonitriles **115** and **116** (Scheme 13).



Scheme 13

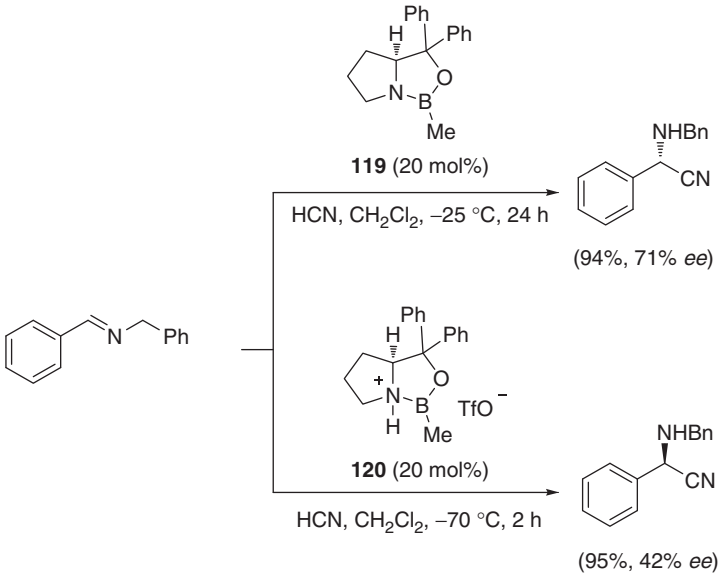
Brønsted acid catalysts have been investigated in the addition of hydrogen cyanide to imines. These acid-mediated reactions are remarkable because of the high level of enantioselectivity they display. Thus, the addition of hydrogen cyanide to *N*-allylbenzaldimines using 10 mol% of **117** affords after *in situ* trifluoroacetylation protected α-aminonitriles in high enantioselectivities.[98] The reaction of aromatic aldimines with 5 mol% of **118**, however, afforded α-aminonitriles in good yield albeit moderate selectivities (up to 80% *ee*)[99] (Figure 13).



117 **118**

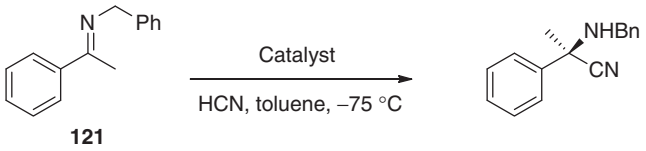
Figure 13 Brønsted acid catalysts.

An interesting reversal of enantioselectivity in the addition of hydrogen cyanide to imines is found with oxazaborolidines. Although catalyst **119** promotes the formation of (*S*)-enantiomers, the protonated form **120** favors the formation of (*R*)-enantiomers in a more rapid reaction but with lower enantioselectivity[100] (Scheme 14).



Scheme 14

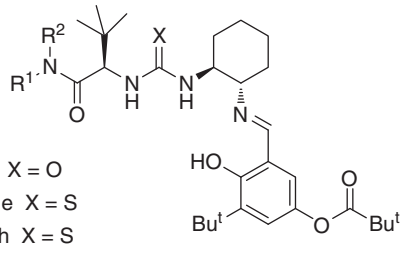
The enantioselective organocatalytic addition of hydrogen cyanide to ketimines is achieved by using easy accessible and recyclable Schiff base catalyst. Urea **122** catalyzes the hydrocyanation of imine **121** to give the corresponding α-aminonitrile in 90% *ee*. The reaction can be applied to a variety of acetophenones substituted at the aromatic ring (equation 52).[101]



121

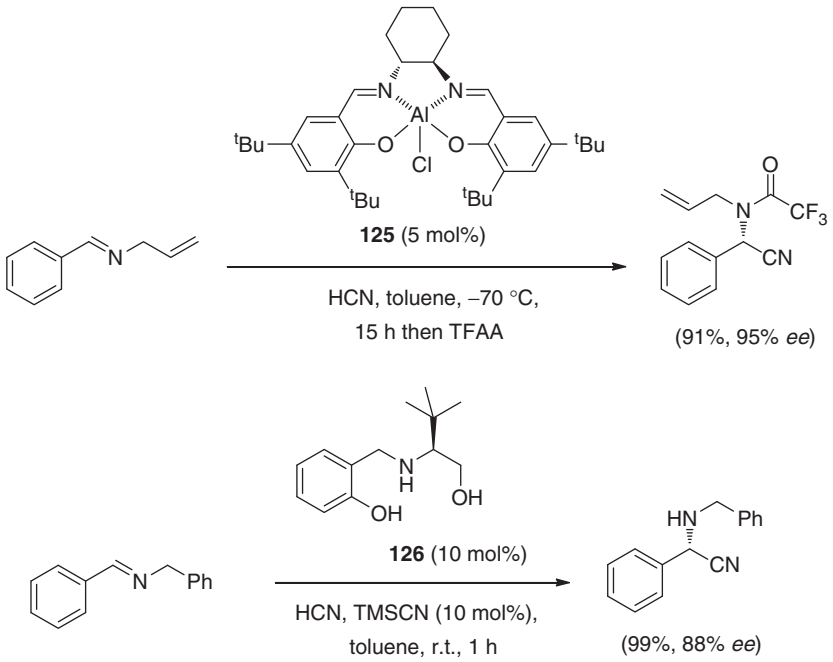
122 (2 mol%): (97%, 90% *ee*)
123 (1 mol%): (>95% yield, 97% *ee*)

(52)



122 R^1 = H R^2 = Bn X = O
123 R^1 = Me R^2 = Me X = S
124 R^1 = Me R^2 = Ph X = S

Further optimization of the catalyst led to thiourea **123**, which is more efficient and provides higher enantioselectivities. Similarly, thiourea **124** catalyzes hydrocyanation of *N*-allylbenzaldimines in quantitative yield and high enantioselectivity (up to 98% *ee*). One of the earliest examples of the use of a metal catalyst in the hydrocyanation of imines is the addition of hydrogen cyanide to *N*-allylbenzaldimines mediated by 5 mol% of chiral (salen) Al(III) complex **125** (Scheme 15).[102] Exchange of aluminum by vanadium provides another catalyst for the addition of HCN to *N*-benzyl aromatic aldimines.[103]



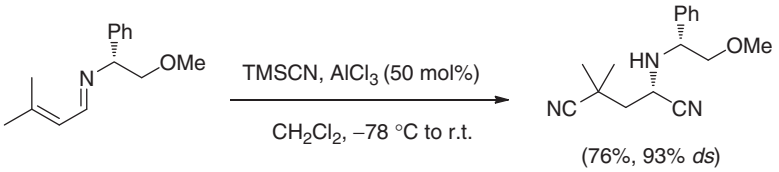
Scheme 15

Chiral nonracemic heterobimetallic complexes like *ent*-**99** catalyze the addition of hydrogen cyanide to aldimines and ketimines in high conversion rates and enantioselectivities (up to 95% *ee*).[104] Excellent values of enantioselectivity (up to 98% *ee*) are also observed in the reaction promoted by a catalyst formed *in situ* from partially hydrolyzed titanium alkoxides and ligand **126**. Under these reaction conditions the hydrocyanation takes place in 1 h by using a 1:1 mixture of TMSCN and HCN as cyanide source.[105]

1.18.4.1.2 Addition of trimethylsilyl cyanide

Optically active α-aminonitriles are obtained through cyanosilylation of *N*-substituted lactaldehyde imines with TMSCN in the presence of a Lewis acid. A variety of Lewis acids, including zinc(II) iodide, trimethylsilyl triflate, and dimethylzinc can be used, providing good yields and acceptable *syn* diastereoselectivity (up to 86%). Other Lewis acids such as trimethylaluminum, lithium perchlorate, and diethylaluminum chloride furnish the same product but in markedly lower chemical yield. Zinc(II) chloride also catalyzes the addition of TMSCN to unstable aldimines obtained from *N*-protected aminoaldehydes and *C*-protected amino acids and indium(III) triflate promotes the addition of TMSCN to aromatic aldimines. The addition of TMSCN to *N*-benzyl aldimines and ketimines catalyzed by 10 mol% of the heterobimetallic aluminum complex **99** affords *N*-benzyl-α-aminonitriles in low enantioselectivity (up to 32% *ee*). Similar results are obtained with *N*-diphenylphosphinoyl ketimines employing a chiral zirconium complex as catalyst. Although the reaction performs with good chemical yields, modest enantioselectivities are obtained. However, the corresponding scandium heterobimetallic complex gives rise to enantioselectivities of up to 91% *ee*.

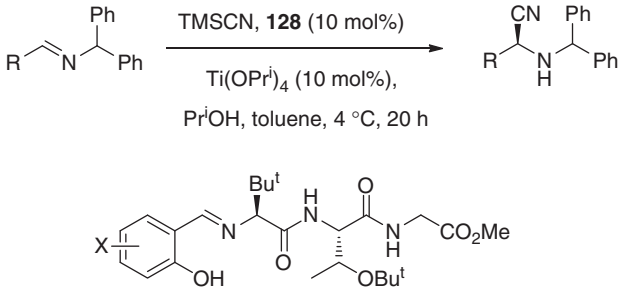
A double nucleophilic addition of TMSCN to α,β-unsaturated aldimines is promoted by aluminum trichloride to give 2-aminopentanedinitriles. An asymmetric version of the reaction is achieved by using chiral auxiliaries as illustrated in equation 53.



(53)

In the presence of a mixture of ketenesilyl(thio)acetal and TMSCN, the former gives the conjugate addition and the latter the 1,2-addition[106] in a reaction that can be employed as a key step in the synthesis of 2,4,5-trisubstituted pyrroles. The same process is also catalyzed by titanium(IV) isopropoxide.

The addition of TMSCN to aromatic aldimines is catalyzed by Ti-tripeptide Schiff base complexes.[107] The reaction is highly efficient and proceeds with excellent enantioselectivity when ligands **128** are employed (equation 54, **Table 18**).



(54)

128a X = 5-MeO
128b X = 3,5-diCl
128c X = 3,5-diBr

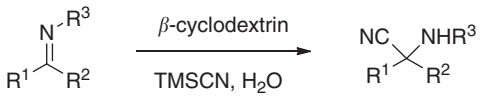
Table 18 Addition of TMSCN to imines

No.	R^1	*Catalyst*	*Yield (%)*	*ee (%)*
i	Ph	**128a**	82	>99
ii	2-ClC_6H_4	**128b**	85	>99
iii	2-BrC_6H_4	**128b**	93	>99
iv	4-$MeOC_6H_4$	**128b**	99	94
v	2-Naphthyl	**128a**	80	>99
vi	1-Naphthyl	**128a**	87	>99
vii	Bu^t	**128c**	97	85

The same system affords excellent results with α,β-unsaturated imines. Both aliphatic and aromatic substrates give regio- and enantioselective cyanide addition to furnish unsaturated aminonitriles of synthetic utility. By using cinchona alkaloids as ligands excellent yields and enantiomeric excesses are also observed with both aldimines and ketimines.[108]

Organometallic platinum and palladium NCN-pincer complexes catalyze the trimethylsilylcyanation of imines in a similar way to aldehydes, as mentioned in previous sections (see Section 1.18.3.2.1.7, equation 23). The same reaction is catalyzed by molybdenum(II) tetraacetate activated with molecular oxygen and dibutyltin bromide. Heterogeneous catalysis is also a valid approach for the trimethylsilylcyanation of imines. Both a recyclable silica-based scandium(III) interphase catalyst and a cadmium(II)-(4,4′-bipyridine) complex are successfully employed in promoting addition of TMSCN to imines.[109]

In some instances, imines mirror aldehydes in their reactions with TMSCN. Lewis base catalysts can be used to promote the formation of α-aminonitriles. For example, a chiral diamine enhances the modest diastereoselectivity observed in the addition of TMSCN imines bearing a chiral auxiliary at the nitrogen atom.[110] β-Cyclodextrins facilitate a biomimetic cyanation of imines in water furnishing α-aminonitriles in quantitative yields (equation 55).[111] In this reaction, the catalyst can be recovered and reutilized for five consecutive runs without appreciable change in the yield and purity of the products. Chiral *N*-oxides, used in stoichiometric amounts, can also promote the reaction although with moderate enantioselectivities (Table 19).

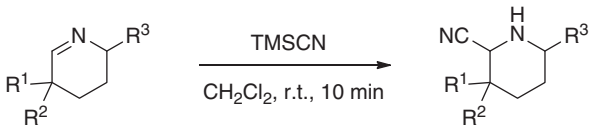


(55)

Table 19 Addition of TMSCN to imines catalyzed by β-cyclodextrin

No.	*R*[1]	*R*[2]	*R*[3]	*Time (h)*	*Yield (%)*
i	Ph	H	Ph	1	98
ii	Ph	H	4-FC_6H_4	1	98
iii	Ph	H	2-MeC_6H_4	1	96
iv	Ph	H	2-$MeOC_6H_4$	1	95
v	Ph	H	$PhCH_2$	1.5	92
vi	4-BrC_6H_4	H	Ph	1	98
vii	4-ClC_6H_4	H	4-FC_6H_4	1	98
viii	4-MeC_6H_4	H	Ph	1	96
ix	4-MeC_6H_4	H	Ts	1	94
x	2,4,6-TriMeC_6H_2	H	Ph	1	94
xi	4-$MeOC_6H_4$	H	Ph	1	96
xii	2,4-Di$MeOC_6H_3$	H	Ph	1	94
xiii	4-AllyloxyC_6H_4	H	Ph	1	95
xiv	4-$NO_2C_6H_4$	H	Ph	2	90
xv	(*E*)-PhCH═CH	H	Ph	2	90
xvi	1-Naphthyl	H	4-FC_6H_4	1	92
xvii	2-Naphthyl	H	Ph	1	95
xviii	$C_{10}H_{20}$	H	Ph	2	90
xix	Ph	Me	Ph	2	94
xx	4-MeC_6H_4	Me	Ph	2	94
xxi	2-Naphthyl	Me	Ph	2	92
xxii	Bu^t	Me	Ph	2	90

Depending on the substrates, the addition of TMSCN to imines does not need any catalyst and the reaction takes place spontaneously under different reaction conditions. Although the reaction goes on completion with α-alkoxyimines at room temperature, fluorinated imines required prolonged heating in an alcohol as a solvent to achieve good chemical yields. Cyclic imines present a higher reactivity and the reaction can be carried out smoothly at room temperature in just 10 min (equation 56, Table 20).[112]

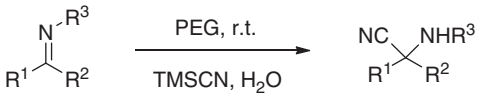


(56)

Polyethylenglycol in water constitutes an environment friendly medium for the reaction, which takes place with a variety of substrates including aldimines and ketimines (equation 57, Table 21). The polyethylenglycol can be recovered and reused for five consecutive runs.[113]

Table 20 Uncatalyzed addition of TMSCN to cyclic imines

No.	R^1	R^2	R^3	*Yield (%)*	*dr*
i	Me	Me	H	92	–
ii	Et	Et	H	97	–
iii	$-(CH_2)_5-$	H	96	–	–
iv	Me	Me	Me	100	58:42
v	Me	Me	Et	100	63:37
vi	Me	Me	Ph	92	85:15
vii	$-(CH_2)_5-$		Me	100	76:24
viii	$-(CH_2)_5-$		Ph	93	–
ix	Me	Pr^n	H	95	53:47



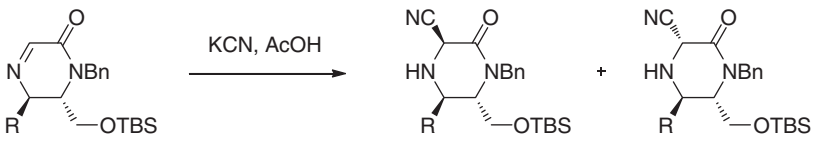
(57)

Table 21 Addition of TMSCN to imines in water

No.	R^1	R^2	R^3	*Time (h)*	*Yield (%)*
i	Ph	H	Ph	3	94
ii	Ph	H	4-FC_6H_4	3	94
iii	Ph	H	$PhCH_2$	5	88
iv	4-BrC_6H_4	H	2-$MeOC_6H_4$	3	92
v	4-ClC_6H_4	H	Ph	3	94
vi	4-MeC_6H_4	H	4-FC_6H_4	3	90
vii	4-MeC_6H_4	H	Ts	3	90
viii	2,4,6-$TriMeC_6H_2$	H	Ph	3.5	88
ix	4-$MeOC_6H_4$	H	Ph	3	90
x	2,4-$DiMeOC_6H_3$	H	Ph	3.5	86
xi	4-$AllyloxyC_6H_4$	H	Ph	3.5	90
xii	4-$NO_2C_6H_4$	H	Ph	5	84
xiii	(*E*)-PhCH═CH	H	Ph	5	82
xiv	2-Naphthyl	H	Ph	3	90
xv	$C_{10}H_{20}$	H	Ph	5	85
xvi	Ph	Me	Ph	4	88
xvii	4-MeC_6H_4	Me	Ph	4.5	86
xviii	C_6H_{10}	–	Ph	5	84

1.18.4.1.3 Addition of other cyanide reagents

The addition of potassium cyanide to iminoketopiperazines **129** in acetic acid furnishes diastereomeric mixtures of adducts. α-Aminonitriles **130** are valuable compounds because of their similarity to the piperazine core of saframycin A, an anti-proliferative compound (equation 58).[114]

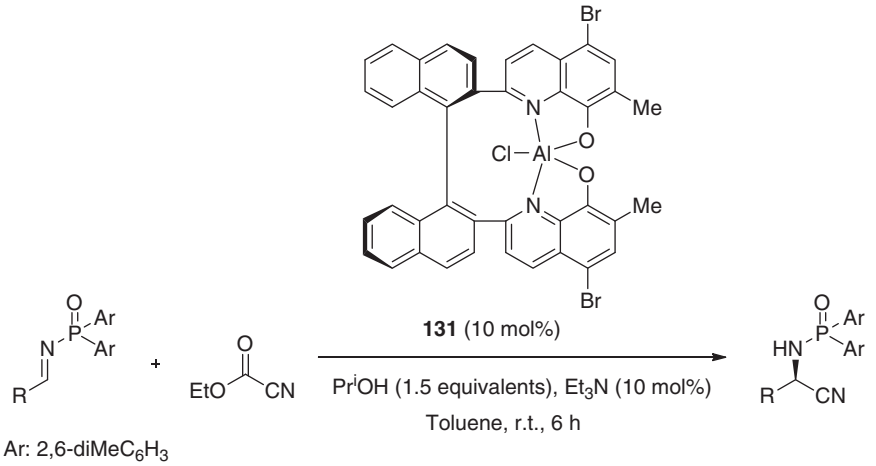


129 **130a** **130b**

(58)

R	**130a : 130b**	Yield (%)
$PhCH_2CH_2$	69 : 31	40
Pr^i	64 : 36	63

Tetrabutylammonium cyanide reacts with ruthenium complexes of α,β-unsaturated imines in a regioselective way to give the corresponding 1,2-adducts. The acylcyanation of imines catalyzed by tethered *bis*(8-quinolinolato)aluminum complex **131** is carried out at room temperature and excellent enantioselectivities are obtained. The reactions need the presence of an equimolar amount of isopropanol to avoid catalyst inhibition by the product. Also, a tertiary amine, i.e., triethylamine, is necessary to enhance both yield and enantiomeric excess (equation 59, Table 22).[115]

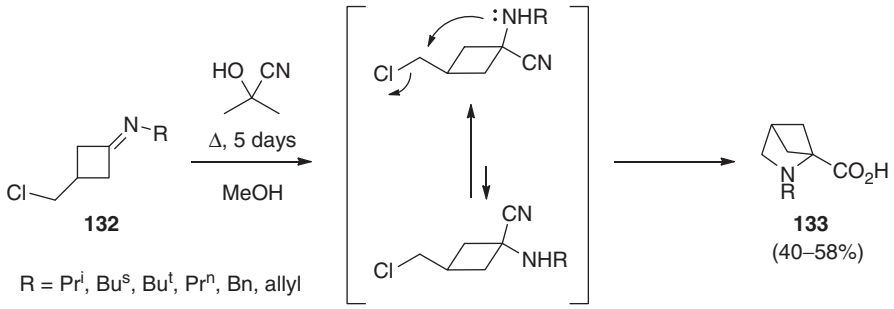


(59)

Table 22 Addition of TMSCN to imines catalyzed by **131**

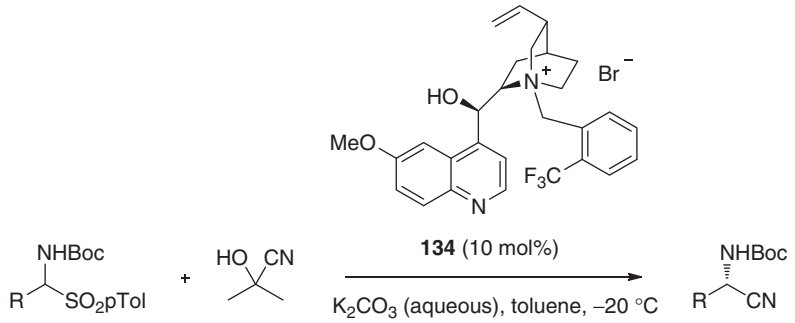
No.	*R*[1]	*Yield (%)*	*ee (%)*
i	Ph	96	97
ii	4-BrC$_6$H$_4$	92	94
iii	4-ClC$_6$H$_4$	88	93
iv	4-FC$_6$H$_4$	85	94
v	2-Furyl	99	96
vi	2-Thienyl	93	96
vii	3-MeOC$_6$H$_4$	99	98
viii	2-MeC$_6$H$_4$	99	98
ix	4-MeOC$_6$H$_4$	88	95
x	4-MeC$_6$H$_4$	93	97
xi	1-Naphthyl	82	95
xii	2-Naphthyl	80	94
xiii	(*E*,*E*)-MeCH=CHCH=CH	85	90
xiv	Bu^t	94	90

The reversible addition of acetone cyanohydrin to imines **132** is favored by heating the reaction mixture in methanol, thus inducing a further cyclization to bicyclic stable compounds **133** (Scheme 16).[116] The reaction also takes place with optically active aromatic aldimines at low to ambient temperature, but with modest diastereoselectivities and the requirement that triethylaluminum be used.



Scheme 16

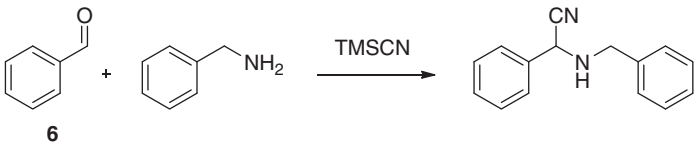
Under chiral phase-transfer catalysis conditions and using quinine derived catalyst **133**, the reaction between acetone cyanohydrin and *N*-Boc imines generated *in situ* from α-amido sulfones takes place with excellent yields and good enantioselectivities (equation 60).[117]



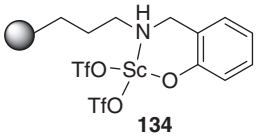
(60)

1.18.4.1.4 Three-component Strecker reactions

The three-component Strecker reaction is an important and rather attractive C–C bond forming reaction because of its atom economy, simplicity, and availability of starting materials. The reaction between an aldehyde, an imine, and a cyanide source like TMSCN or acetone cyanohydrin proceeds smoothly in the presence of either a Lewis acid (e.g., copper(II) triflate) or a Lewis base (e.g., triethylamine) catalyst to provide the corresponding α-aminonitriles. In the presence of Preyssler's heteropolyacid ($H_{14}[NaP_5W_{30}O_{110}]$) excellent yields are obtained with TMSCN. Similar results are obtained by employing montmorillonite KSF clay, which provides α-aminonitriles in excellent yields under mild conditions. At room temperature, 10 mol% of $NbCl_5$ can also be used as a suitable catalyst. In the same way good results are obtained with 2 mol% of rhodium(III) iodide and a silica-based scandium(III) interphase catalyst **134** (equation 61).[109a,118] The reaction is amenable to be implemented in a continuous flow reactor (**Table 23**).



6

Reaction conditions	Yield (%)
$RhI_3{\cdot}H_2O$ (2 mol%), CH_3CN, r.t., 10 min	97
$NbCl_5$ (10 mol%), CH_3CN, r.t., 1 h	90
Montmorillonite KSF, 3.5 h, CH_2Cl_2, r.t.	90
$H_{14}[NaP_5W_{30}O_{110}]$, CH_3CN, reflux, 4.5 h	95
 (5 mol%), CH_2Cl_2, r.t., 14 h	99

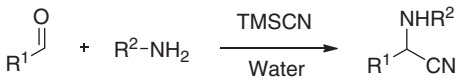
134

(61)

Table 23 Addition of acetone cyanohydrin to *N*-Boc imines

No.	*R^1*	*Yield (%)*	*ee (%)*
i	$Ph(CH_2)_2$	95	68
ii	$PhCH_2$	95	79
iii	Me	85	78
iv	Et	88	80
v	Pr^i	92	82
vi	Bu^t	85	88
vii	C_6H_{13}	95	72
viii	Bu^i	90	68
xiv	Cyclohexyl	95	50

Amino acid-derived α-aminonitriles are obtained in methanol as a solvent and in the presence of zinc(II) chloride. Catalysis with Lewis bases is also possible. For example, condensation of aromatic and aliphatic aldehydes with *p*-anisidine in the presence of magnesium sulfate and DBU affords α-aminonitriles in up to 90% chemical yield.[65] The reaction can also be carried out in water without any catalyst under nontoxic and environmentally friendly conditions.[119] A variety of alkyl and aryl aldehydes and amines can be used, and in all cases good yields are obtained (equation 62, **Table 24**).

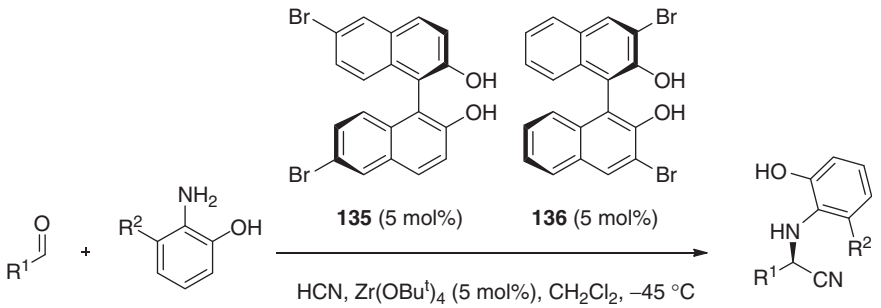


(62)

Table 24 Three-component Strecker reaction in water

No.	R^1	R^2	*Time (h)*	*Yield (%)*
i	Ph	Ph	4	95
ii	2-$NO_2C_6H_4$	Ph	8	95
iii	4-FC_6H_4	Ph	12	70
iv	4-$MeOC_6H_4$	Ph	4	70
v	1-Naphthyl	Ph	4	71
vi	4-OHC_6H_4	Ph	8	65
vii	(*E*)-PhCH=CH	Ph	12	76
vii	Pr^i	$PhCH_2$	12	68
viii	Cyclopropyl	$PhCH_2$	12	70
ix	2-MeC_6H_4	$PhCH_2$	12	64
x	2-BrC_6H_4	$PhCH_2$	12	72
xi	2-Thienyl	Ph	12	87
xii	2-MeC_6H_4	Ph	12	86
xiii	Cyclopropyl	Ph	12	74
xiv	Pr^i	Ph	12	72
xv	Ph	2-$MeOC_6H_4$	12	92
xvi	2-BrC_6H_4	Ph	12	91
xvii	4-ClC_6H_4	Ph	12	63
xviii	3-$PhOC_6H_4$	Ph	12	60
xix	Ph	$PhCH_2$	12	83
xx	2-CF_3-5-ClC_6H_3	Ph	12	90
xxi	2-F-4-BrC_6H_3	Ph	12	95
xxii	3-Methyl-2-thienyl	Ph	12	94

The use of hydrogen cyanide as cyanide source is possible in the presence of a catalytic amount of a chiral zirconium catalyst (equation 63).[120] The chiral zirconium catalyst is formed *in situ* from $Zr(OBu^t)_4$, (*R*)-6-Br-BINOL **135**, and (*R*)-3-Br–BINOL **136**, the combination of both ligands being essential for achieving good values of *ee* (equation 63, **Table 25**).



(63)

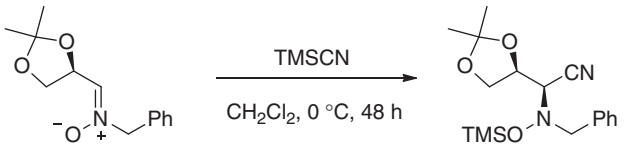
Table 25 Three-component Strecker reaction catalyzed by a zirconium complex

No.	R^1	R^2	*Yield (%)*	*ee (%)*
i	Ph	H	80	86
ii	1-Naphthyl	H	83	85
iii	Bu^i	Me	99	94
iv	C_8H_{17}	Me	83	90
v	$Ph(CH_2)_2$	Me	85	94
vi	Pr^i	Me	94	90
vii	Cyclohexyl	Me	95	94
viii	Bu^n	Me	100	86

The reaction of hydrogen cyanide with biphenyl-2,2′-dicarboxaldehydes and ammonia or methyl amine provides cyclic dinitriles in a diastereoselective way, through a reaction in which the stereoselection is controlled by the chiral twist of the biaryl axis. Kinetic studies of cyanide addition to imines conclude that cyanide addition to iminium ions formed by protonation of the imine is an extremely favorable process with high values for K_{HCN} (ca. 10^4 dm^3 mol^{-1}).[121] In a similar way to imines, acyl cyanide can be used as a cyanide source in the presence of a catalytic amount of thiourea **123**. The reaction employing acetone cyanohydrin is also possible by carrying out the reaction in a closed vessel and in the presence of triethylamine and methanol as a solvent.[122]

1.18.4.2 Addition to Nitrones

The nucleophilic addition of potassium cyanide 5- and 6-membered cyclic nitrones can be carried out under ultrasound activation or in an acidic medium. A variety of chiral α-hydroxyamino nitriles are prepared in good yields and high diastereoselectivities by using chiral nonracemic nitrones as starting materials.[123] Several cyanide reagents, including lithium cyanide, tetrabutylammonium cyanide, TMSCN, and diethylaluminum cyanide are employed, the best results being obtained with TMSCN and diethylaluminum cyanide. For example, D-glyceraldehyde-derived nitrone **137** undergoes a complete diastereoselective addition of TMSCN (equation 64). The reaction takes 48 h in dichloromethane as a solvent but it can be considerably accelerated by precomplexing the nitrone with diethylaluminum chloride.



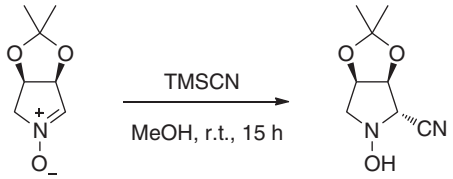
137 **138** (84%, *ds* ≥ 95%) (64)

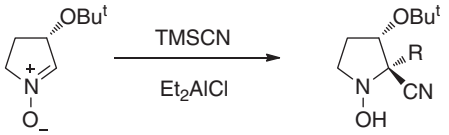
With the more reactive cyclic nitrones, the reaction with TMSCN in dichloromethane to provide *O*-silyl-α-hydroxyaminonitriles, proceeds in quantitative yield and complete diastereoselectivity. Moreover, in the presence of an activating reagent of the nitrone such as diethylaluminum chloride or TMSOTf, the reaction goes on completion in 5 min. If the reaction is carried out in methanol the same excellent results are observed and the desilylated α-hydroxyamino nitriles are obtained (Scheme 17).[124] With more hindered cyclic ketonitrones, longer reaction times are needed even in the presence of a promoter like trimethylaluminum.[125]

1.18.4.3 Addition to Iminium Salts

Trimethylsilyl cyanide adds to cyclic iminium ions generated *in situ* from either α-hydroxy or α-methoxytosylamides and Lewis acids, which also serve to catalyze the cyanide addition. Among the Lewis acids employed to promote the reaction tin(IV) chloride is the most powerful one, whereas titanium(IV) chloride and boron trifluoride etherate are less efficient. Diethylaluminum cyanide reacts with iminium salts generated through oxidation of ketene silyl acetals to provide α-cyano aminoesters **138** (Scheme 18).[126]

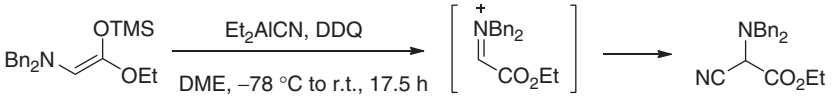
Trapping of an iminium ion with potassium cyanide serves to prepare a synthetic intermediate en route to camphotecin.[127] The oxidation of various amine substrates with tropylium ion affords iminium ions that undergo addition of potassium cyanide to afford the corresponding α-aminonitriles in good yields (equation 65, Table 26).[128]





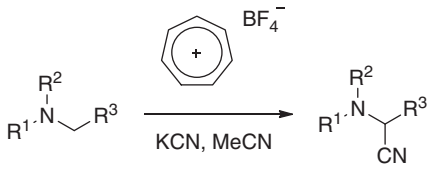
R	Reaction conditions	Yield (%), *ds*
H	CH_2Cl_2, 0 °C, 5 min	100, *ds* ≥ 95%
Ph	THF, –20 °C, 2 h	95, *ds* = 92%

Scheme 17



138 (80%)

Scheme 18



(65)

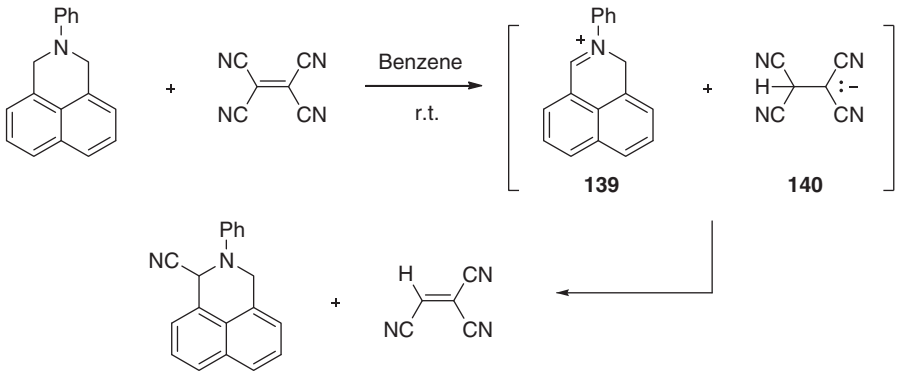
Table 26 Addition of cyanide to iminium ions

No.	R^1	R^2	R^3	*Temperature (°C)*	*Time (h)*	*Yield (%)*
i	$PhCH_2$	Bu^i	Pr^i	120	12	78
ii	4-$NO_2C_6H_4CH_2$	Bu^i	Pr^i	120	12	77
iii	4-$MeOC_6H_4CH_2$	Bu^i	Pr^i	100	12	43
iv	2,4,6-$TriMeC_6H_2CH_2$	Me	H	80	12	71
v	Allyl	Bu^i	Pr^i	23	0.25	73
vi	MeO_2CCH_2	Bu^i	Pr^i	12	12	75
vii	$PhCH_2$	Me	H	80	12	34
viii	$PhCH_2$	$PhCH_2$	Ph	80	12	42

Tetracyanoethylene can be used as a cyanide source in the reaction with conjugated iminium ions like **139**. The iminium ion is formed as a consequence of a net hydride abstraction by tetracyanoethylene from the precursor. In addition to **139**, tetracyanoethanide **140** is formed, delivering a cyanide ion to **139** (Scheme 19).[129]

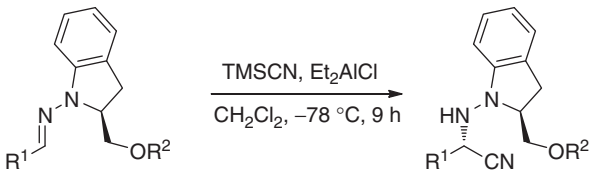
1.18.4.4 Addition to Hydrazones

The trimethylsilylcyanation of hydrazones usually proceeds through the intermediacy of Lewis acids, which act as catalysts. Both TMSCN and tributyltin cyanide can be utilized as cyanide source, and when diethylaluminum cyanide is used, no catalyst is



Scheme 19

required. The reaction of aliphatic hydrazones with TMSCN in the presence of a catalytic amount of hafnium triflate leads to formation of α-hydrazinonitriles. With hydrazones bearing a chiral group at one nitrogen atom high diastereoselectivities are obtained in the presence of diethylaluminum chloride (equation 66, **Table 27**).[130] Similar results are obtained by using titanium(IV) chloride and indium(III) triflate.[131]

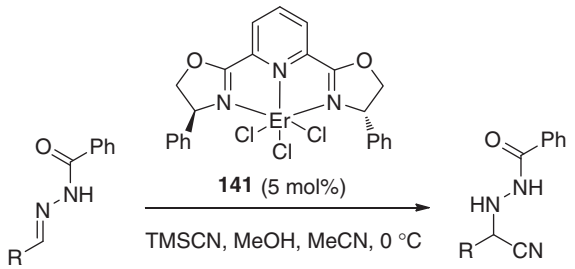


(66)

Table 27 Addition of TMSCN to hydrazones

No.	R^1	R^2	*Yield (%)*	*ds (%)*
i	Bu^t	Me	82	94
ii	Bu^t	$MeOCH_2$	73	92
iii	Bu^t	TBS	67	82
iv	Pr^i	Me	91	96
v	Bu^n	Me	80	90
vi	Et	Me	87	90
viii	$TsO(CH_2)_4$	Me	85	90

Enantioselective additions are achieved with catalyst **141** easily prepared from the pybox ligand and erbium trichloride. By using 2.0 equivalents of TMSCN and methanol, to generate hydrogen cyanide *in situ*, good to excellent enantioselectivities (up to 97% *ee*) are obtained (equation 67, **Table 28**).[132]



(67)

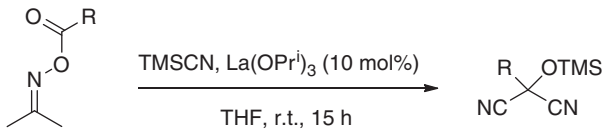
The addition of TMSCN to cyclic hydrazones is better carried out in the presence of titanium(IV) chloride. The reaction is employed for preparing (3*R*,5*R*)-5-hydroxypiperazic acid, a component of polyoxypeptins and piperazimycin A.[133]

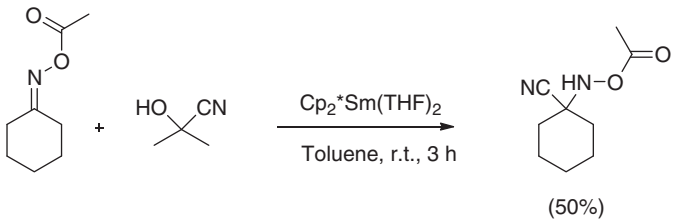
Table 28 Addition of TMSCN to hydrazones catalyzed by **141**

No.	*R^1*	*Time (h)*	*Yield (%)*	*ee (%)*
i	4-$Me_2NC_6H_4$	3	85	97
ii	4-$BnOC_6H_4$	2	92	93
iii	Ph	2	96	90
iv	2-Naphthyl	3	93	88
v	3,4-$DiMeOC_6H_3$	3	90	85
vi	3,4,5-$TriMeOC_6H_2$	3	87	80
vii	3-$BnOC_6H_4$	2	90	83
viii	3-$MeOC_6H_4$	2	96	79
xix	4-MeC_6H_4	2	98	80
x	1-Naphthyl	2	99	76
xi	2,4,6,-$TriMeC_6H_2$	3	89	76
xii	4-ClC_6H_4	3	94	84
xiii	Ph_2CH	2	98	69
xiv	Bu^t	2	98	66
xv	$PhCH_2$	2	99	31

1.18.4.5 Addition to Oximes

Oxime ethers react with TMSCN in the presence of $La(OPr^i)_3$ to give unexpected α-trimethylsiloxy dinitriles in excellent yields (Scheme 20).[134]





Scheme 20

However, the reaction with acetone cyanohydrin in the presence of $Cp^*Sm(THF)_2$ provides the expected *O*-acyl-α-hydroxyaminonitrile.[135] The same reaction promoted by $Sm(OPr^i)_3$ takes place with only 30% yield.

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1.19 Carbonyl and Imine Activation

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Glossary

Cation–π interaction Cation–π interaction is a noncovalent molecular interaction between a cation and the face of an electron-rich π system such as benzene ring.

Density functional theory (DFT) Density functional theory is the most popular and versatile quantum mechanical modeling method used in physics and chemistry.

^{1}H, ^{15}N Heteronuclear single quantum coherence (^{1}H, ^{15}N HSQC) ^{1}H, ^{15}N HSQC is a 2D-NMR experiment to obtain a 2D chemical shift correlation map between directly bonded ^{1}H and ^{15}N. The ^{1}H, ^{15}N HSQC experiment can be performed using the natural abundance of the ^{15}N isotope.

Hydrogen bond The hydrogen bond is the interaction between a hydrogen atom and an electronegative atom. The hydrogen bond is stronger than a van der Waals interaction, but weaker than covalent or ionic bonds.

Organocatalyst Organocatalyst is an organic catalyst consisting of carbon, hydrogen, nitrogen, oxygen, and other nonmetal elements found in organic compounds.

pK_a The logarithmic constant, pK_a, is equal to $-\log_{10}K_a$ (p$K_a = -\log_{10}K_a$). Acid dissociation constant, K_a, is written as a quotient of the equilibrium concentrations ($K_a = [A^-][H^+]/[HA]$).

1.19.1 Introduction

Hydrogen bonding plays a central role in many biological systems, for example, in the folding and oligomeric complexation of proteins as well as biosynthesis and metabolism catalyzed by biocatalysts. In a similar manner to enzymatic biocatalysis, the utilization of hydrogen bonding in organic synthesis has become a subject of recent research, leading to the discovery of novel small molecule-based catalysis, organocatalysis, for a broad spectrum of asymmetric transformations. There have been many reviews that highlight organocatalysis.[1,2]

Organocatalysts can be classified into covalent organocatalysts (proline derivatives, 4-dimethylaminopyridine, N-heterocyclic carbene, imidazolidinones, etc.)[2] and noncovalent organocatalysts (diols, (thio)ureas, phosphoric acids, *N*-oxide, phase-transfer onium salts, etc.) by means of the mode of activation (Figure 1). Although organocatalysis relies on various noncovalent interactions such as π–π stacking, cation–π, ionic, hydrophobic interactions as well as hydrogen bonding, many of noncovalent organocatalysts have been developed as hydrogen-bond donors, displaying the effective and unique hydrogen bonding activation modes.[1]

This chapter highlights the activation of C═O and C═N bonds and the nucleophilic additions to these π-bonds by noncovalent organocatalysts, such as hydrogen-bonding catalysts and Brønsted acids including the ionic electrophile activation via counter anion recognition. Recently, the highly enantioselective addition reactions to the substrates having a C═O or C═N bond have been achieved by the newly developed chiral catalysts[1,2] (*see* Chapters 1.17, 1.18, 2.07, 2.13, and 4.03).

1.19.2 Differences between Hydrogen-Bonding Catalysts and Brønsted Acid Catalysts

In recent years, noncovalent organocatalysts have been mainly developed as hydrogen-bond or proton donors. Although it is difficult to make a clear distinction between hydrogen-bonding catalysts and Brønsted acid catalysts, particularly general Brønsted acid catalysts, the differences of these catalysts will be addressed. Hydrogen bond X–H…A **1** forms between the polarized X–H bond of hydrogen-bond donor (X–H) and the electronegative hydrogen-bond acceptor atom (A) (Figure 2).[3] The catalysts forming this interaction are called hydrogen-bonding catalysts. Hydrogen bonds are flexible with regard to bond length and angle. The typical bond length of a normal hydrogen bond is 1.5–2.2 Å, although stronger or weaker hydrogen bonds also exist.[4] When

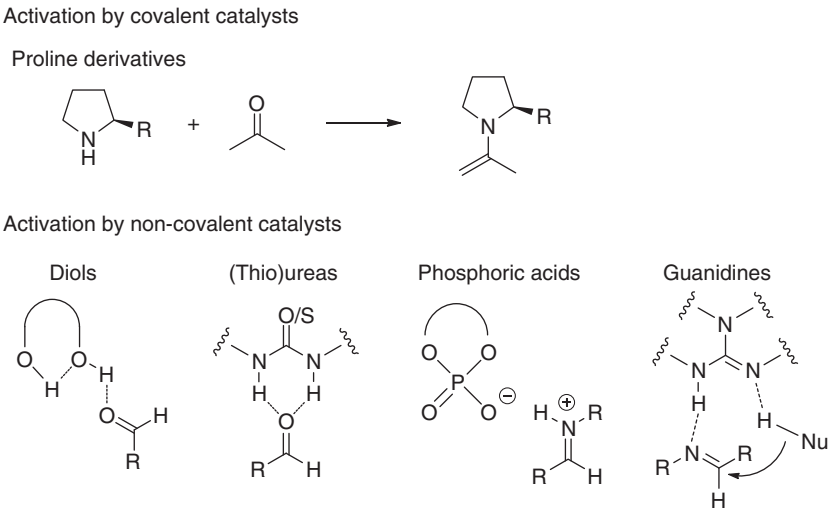


Figure 1 Organocatalytic mode of activation.

X–H is a stronger acid, the proton transfer from proton donor (X–H) to acceptor atom (A) occurs to give an ion pair **3** via the hydrogen-bonded complexes **1** and **2**. In general, the catalysts forming this activated ion pair are called Brønsted acid catalysts. However, there is an equilibrium between hydrogen-bond complexes **1** and **2** and an ion pair **3**; thus, the differences between hydrogen-bonding catalysts and Brønsted acid catalysts are not often clear.

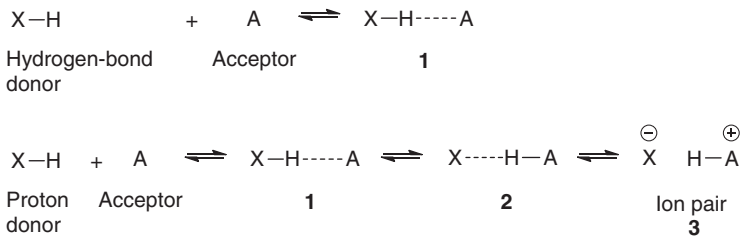


Figure 2 Nucleophilic addition to C═O and C═N bonds.

Nucleophilic addition to carbonyl compounds or imines can be accelerated by employing hydrogen-bonding catalysts or Brønsted acid catalysts (Figure 3). These catalysts might be simply distinguished in the point of view of proton transfer from catalysts. In hydrogen-bonding catalysis, a direct proton transfer from the catalyst to the product (or substrate) will not occur. In other words, the proton (H^b) of the catalyst will not be removed by the substrate throughout the reaction. In contrast, Brønsted acid catalyst directly transfers its proton (H^b) into the product.

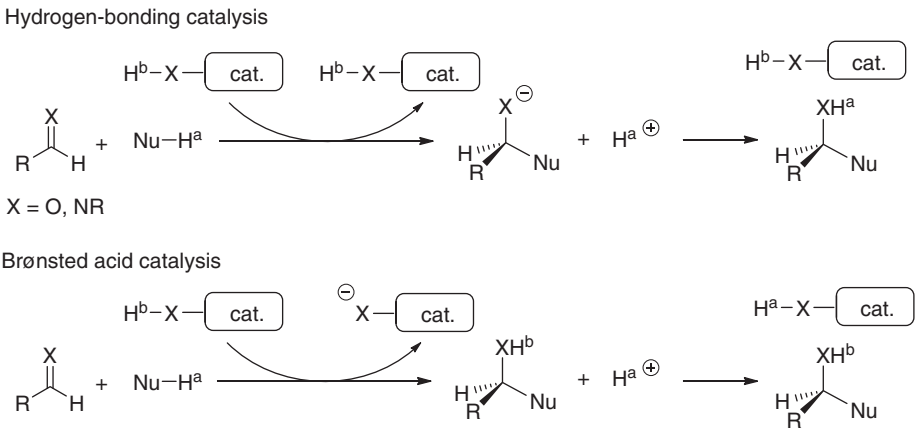


Figure 3 Continuous proton transfer.

The hydrogen-bonding catalysts affect the reaction rates by decreasing the lowest unoccupied molecular orbital level of carbonyl compounds or imines and by stabilizing the transition states. The strength of hydrogen-bond becomes larger with a negatively charged acceptor than a neutral acceptor.[5] As shown in Figure 4(a), the hydrogen-bond of a water molecule with a hydroxyl anion is almost three times stronger than that with another water molecule in gas phase. Therefore, the catalysts would be bound more strongly to the charged transition states than neutral substrates (Figure 4(b)). In the case of the additions of a weak nucleophile to C=O bond, the hydrogen-bonding catalysts promote the reaction by binding to the negatively charged oxygen atom in the rate-determining tetrahedral transition states.[6]

In contrast to hydrogen-bonding catalysis, the proton transfer from catalysts to electrophiles takes place in Brønsted acid catalysis.[7] Brønsted acid catalysis can be classified into two types, based on whether proton transfer occurs to the substrate ground

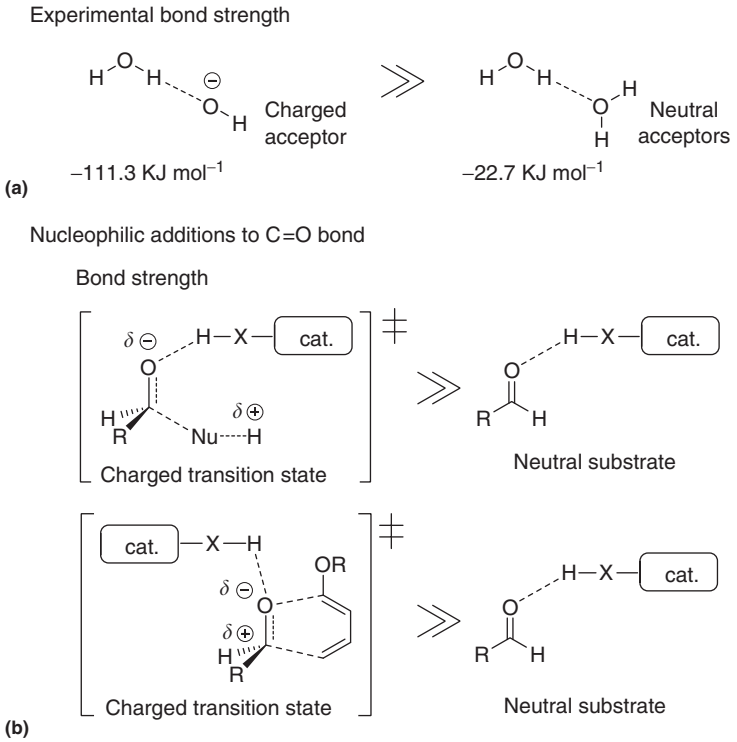


Figure 4 Bond strength of hydrogen bond to negatively charged species.

state or to the addition transition state (Figure 5). In the former case (Type 1), the substrate is significantly protonated before nucleophilic attack. In Type 1, the substrate is in a fast equilibrium with its conjugate acid which reacts slowly with nucleophile; thus, the catalyst contributes to the reaction rate acceleration by shifting the equilibrium into an ion pair. In the latter case (Type 2), rate-determining step is the proton-transfer step. The proton is transferred into the transition state of the rate-determining step. Therefore, the reactions are initiated by the formation of hydrogen bond, which leads to a distinct proton transfer. The proton

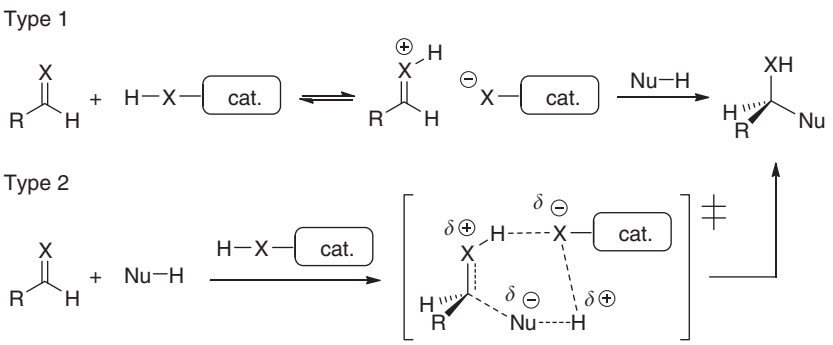


Figure 5 Brønsted acid catalysis.

transfer in this Brønsted acid catalysis is closely related to the stabilization of the transition states in hydrogen-bonding catalysis; thus, it is frequently difficult to make a clear distinction between hydrogen-bonding catalysts and Brønsted acid catalysts.

Nucleophilic attack to carbonyl compounds or imines takes place either by way of a hydrogen-bond complex or an ion pair. In general, the combination of weakly acidic catalysts and neutral electrophiles leads to the hydrogen-bond-catalyzed reactions, whereas use of stronger acid catalysts with basic electrophiles results in the Brønsted acid-catalyzed reactions. The diols and (thio)ureas are classified into hydrogen-bonding catalysts. The combination of such neutral acid catalysts and neutral carbonyl compounds, aldehyde or ketone leads to the formation of hydrogen-bond complexes (Figure 1). The nucleophilic addition using these catalysts proceeds without the formation of ion pairs. In contrast, phosphoric acids are generally classified into Brønsted acid catalysts. The combination of such stronger acid catalysts and basic imines is assumed to lead to the formation of ion pairs, iminium salts, before or coincident with the nucleophilic attack.

1.19.3 Activation of Carbonyl Compounds and Imine Derivatives

This section highlights the activation models and the mechanical investigations including transition states supported by computational methods or X-ray studies. The reviews on quantum mechanical calculations are provided.[8]

1.19.3.1 Activation by Hydrogen-Bonding Organocatalysts

Catalytic functions of hydrogen-bonding organocatalysts are the activation of substrates and the stabilization of transition states or intermediates. Like an oxyanion hole of enzymes, hydrogen bonds have the ability to activate the C═O or C═N bond of substrates by polarization. Hydrogen bonds also stabilize the negative charges in transition states or intermediates when charge separation occurs during the reaction. Therefore, the investigation into transition states is of importance in a hydrogen-bond-mediated catalysis.

α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanol (TADDOL) is a hydrogen-bonding organocatalyst which catalyzed the hetero Diels–Alder reaction between aldehyde **4** and Danishefsky's diene **5a** (Figure 6). As the possible activation of benzaldehyde, the starting complex **A1** with a single hydrogen bond and the starting complex **A2** with double hydrogen bonds are shown. Diols such as TADDOL are well known to form an intramolecular hydrogen bond. Computational structure optimizations of the starting

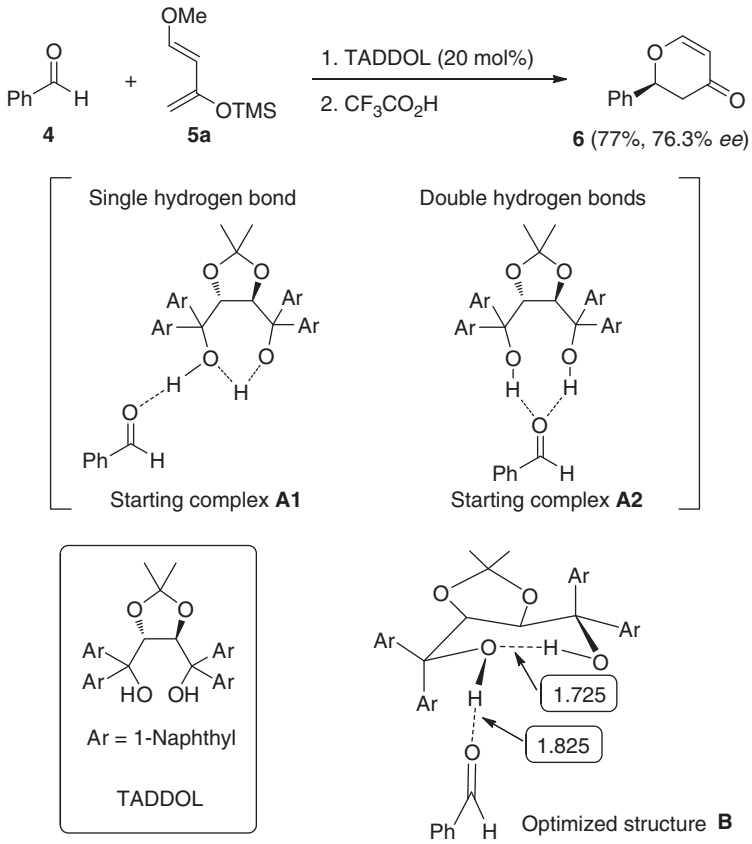


Figure 6 Hydrogen bonding between TADDOL and aldehyde.

complexes support the complex **A1** activated by single hydrogen bond as reported by Ding and coworkers.[9] In the optimized structure **B**, the length of the intermolecular single hydrogen bond is 1.825 Å, which is in the range of the moderate or normal hydrogen bond. Consequently, a single hydrogen bond between one hydroxyl group of (*R*,*R*)-1-Np-TADDOL and oxygen atom of aldehyde is regarded to be the driving force of this catalytic system.

The TADDOL-catalyzed reaction was studied theoretically in the model system using **4** and **5b** (Figure 7). The calculation results indicated that the reaction proceeds via a concerted mechanism through the transition state structure **C**, in which the single hydrogen bond length is normal 1.612 Å. The enantioselectivity was also rationalized by the computational analysis of the relative energies of TADDOL-binding transition state structures.

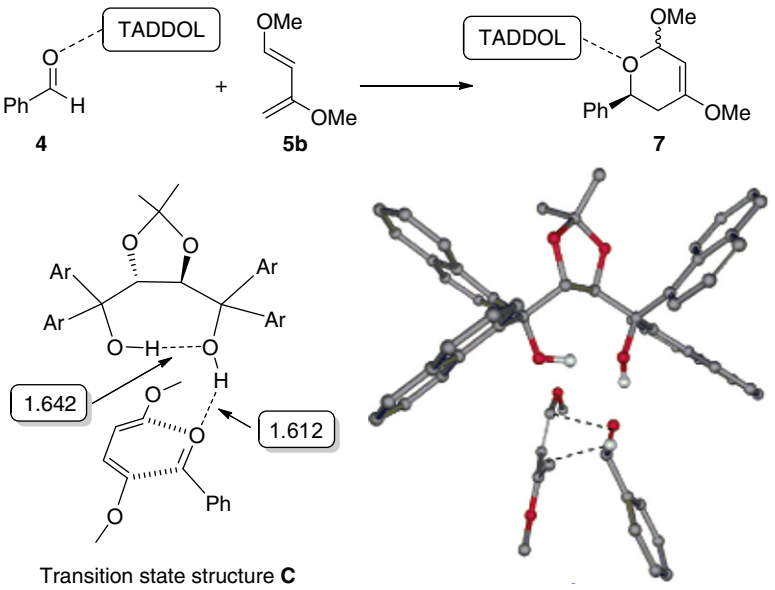


Figure 7 Transition state in the model system.

Yamamoto and coworkers reported that the 1,1′-biaryl-2,2′-dimethanol (BAMOL) derivatives are highly effective catalysts for enantioselective hetero Diels–Alder reactions between aldehydes **8** and aminosiloxydiene **9a** (Figure 8).[10] An X-ray crystal structure of a complex of benzaldehyde and 2,2′-*bis*-(diphenylhydroxymethyl)binaphthylene reveals an intramolecular hydrogen

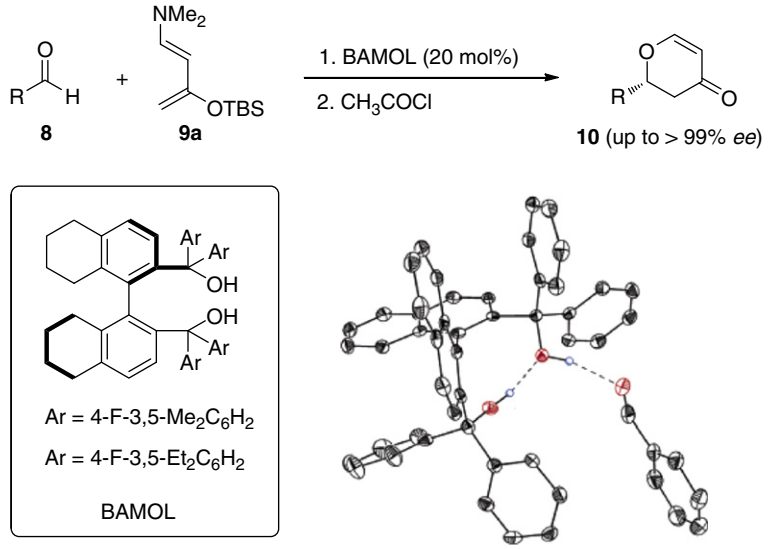
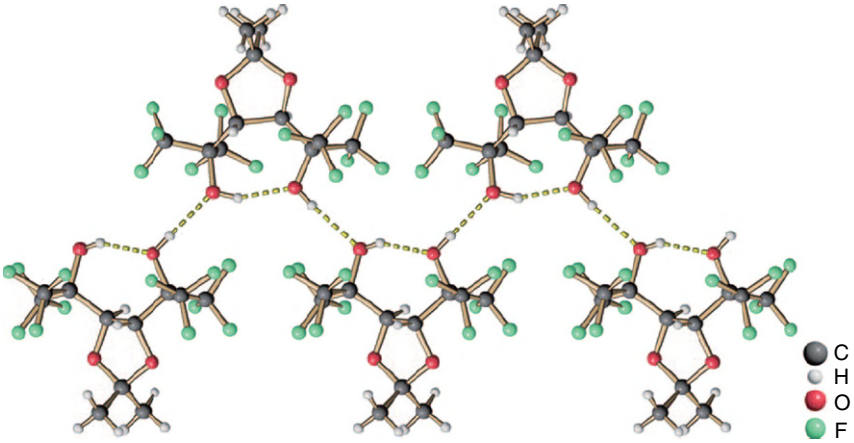


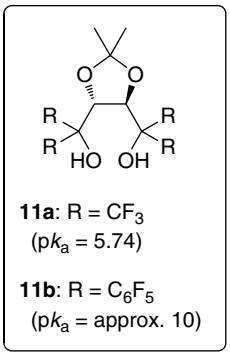
Figure 8 BAMOL-catalyzed reaction and X-ray crystal structure.

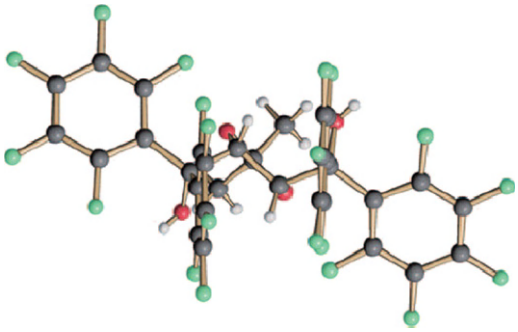
bond between the two hydroxyl groups of the catalyst and an intermolecular hydrogen bond between the catalyst and benzaldehyde.

The pK_a values of **11a** and **11b** were determined by Berkessel and coworkers (Figure 9).[11] Although a pK_a value for fluorinated TADDOL analog **11a** is expected to be in the range of a pK_a value of 17.2 for 1,1,1,3,3,3-hexafluoro-2-propanol [$(CF_3)_2HCOH$], **11a** had a pK_a value of 5.74. This large increase in acidity can be explained by the X-ray crystal structure of **11a**, which reveals an intramolecular hydrogen bond between two hydroxyl groups of **11a**. The intramolecular hydrogen bond enhances the polarity of the second hydroxyl group and stabilizes the anion resulting from deprotonation. In contrast, this effect of OH-acidification by hydrogen bonding was not observed in tetrakis-pentafluorophenyl derivative **11b**, which had a pK_a value of approximately 10. As revealed by the X-ray crystal structure of **11b**, there is no interaction between the hydroxyl groups of **11b** because of stacking of two pentafluorophenyl group. Thus, no hydrogen bond-induced acidification was observed.



X-ray crystal structure of **11a**





X-ray crystal structure of **11b**

Figure 9 pK_a values and X-ray crystal structures.

Houk et al. studied the TADDOL-catalyzed reaction between benzaldehyde **4** and aminosiloxydiene **9b** through the combined use of molecular mechanics and our Own N-layered Integrated molecular Orbital and molecular Mechanics (B3LYP/6–31G(d):AM1) calculations and identified the origins of stereoselection (Figure 10).[12] The lowest energy transition state structure is given. This transition structure benefits from the presence of a stabilizing CH–π interaction (3.19 Å) between the aldehyde CH and the pseudoequatorial naphthalene ring of TADDOL.

Urea and thiourea derivatives are hydrogen-bonding organocatalysts. Etter and coworkers reported that diaryl ureas possessing electron-withdrawing substituents readily form cocrystals with a variety of hydrogen-bond acceptors, such as carbonyl compounds (Figure 11).[13] This study inspired the impressive development of chiral (thio)urea catalysts.

In recent years, significant advances have been made in bifunctional thiourea catalysis, in which a variety of hydrogen bond interactions are proposed. For example, Takemoto et al. developed the bifunctional thiourea catalyst **12** for enantioselective Michael addition of 1,3-dicarbonyl compounds to nitroolefins.[14] Pápai et al. investigated the mechanism of the model system using **13** and **14** through density functional theory (DFT) calculations.[15] Two transition states **D1** and **D2** are given in Figure 12.

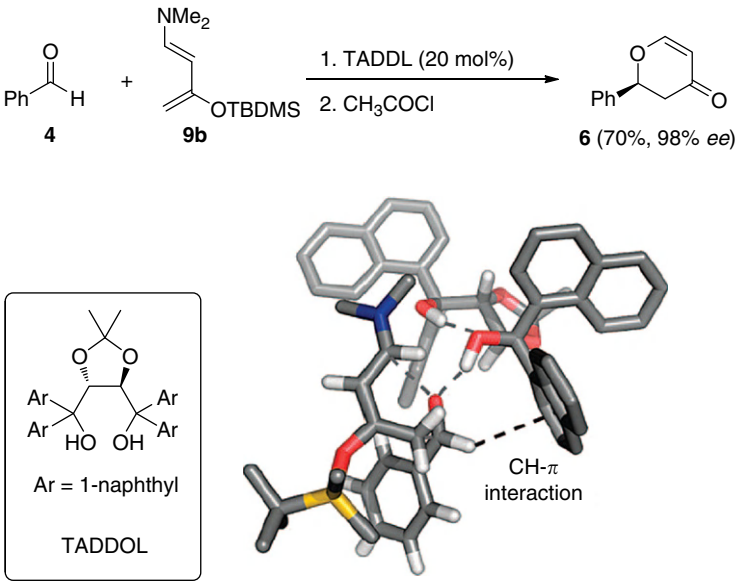


Figure 10 TADDOL-catalyzed reaction and transition state structure.

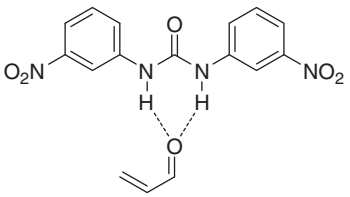


Figure 11 *Bis*-hydrogen-bonding interaction of urea.

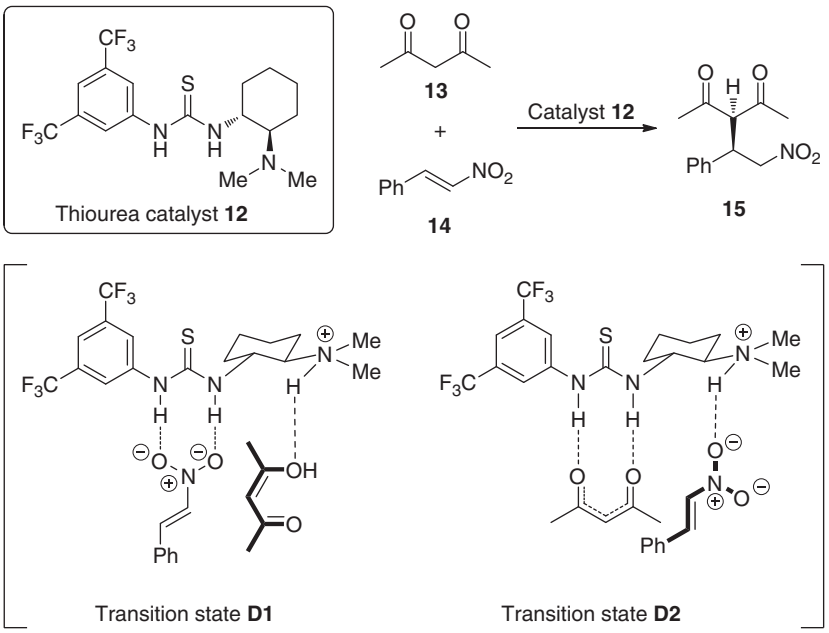


Figure 12 Two transition states in bifunctional thiourea-catalyzed reaction.

The activation barrier for **D2** was calculated to be only 2.2 kcal mol^{-1}, which is 2.7 kcal lower than the barrier for **D1** (4.9 kcal mol^{-1}). This calculation predicts that the reaction proceeds predominantly via transition state **D2**.

The reaction between a carbonyl compound and a nitroalkane, known as the Henry (or nitroaldol) reaction, was investigated by Hiemstra's group (Figure 13).[16] When the bifunctional thiourea catalyst **16a** having *Cinchona* alkaloid moiety was employed, the reaction of benzaldehyde **4** with nitromethane afforded the corresponding nitroalcohol **17** in 92% *ee*. Himo et al. reported a DFT investigation of this reaction using an analog **16b** of *Cinchona* thiourea **16a**.[17] The first step of Henry reaction is the deprotonation of nitromethane by the quinuclidine nitrogen, the most basic site in the catalyst. The optimized structures of the stationary points for the proton transfer are given as structures **I**–**III** in Figure 13. The deprotonation of nitromethane is proposed to be accelerated by the coordination of the nitro group to the thiourea moiety shown as **I** and **II**. The resulting nitromethide is stabilized by the protonated catalyst through hydrogen bonding as shown as **III** and the starting complex **E**. The calculation results indicated the energetically most accessible transition state structure **F** for the carbon–carbon bond-forming step (Figure 14). In this structure, two hydrogen bonds between benzaldehyde and thiourea moiety were observed and these lengths are normal 1.79 and 1.84 Å.

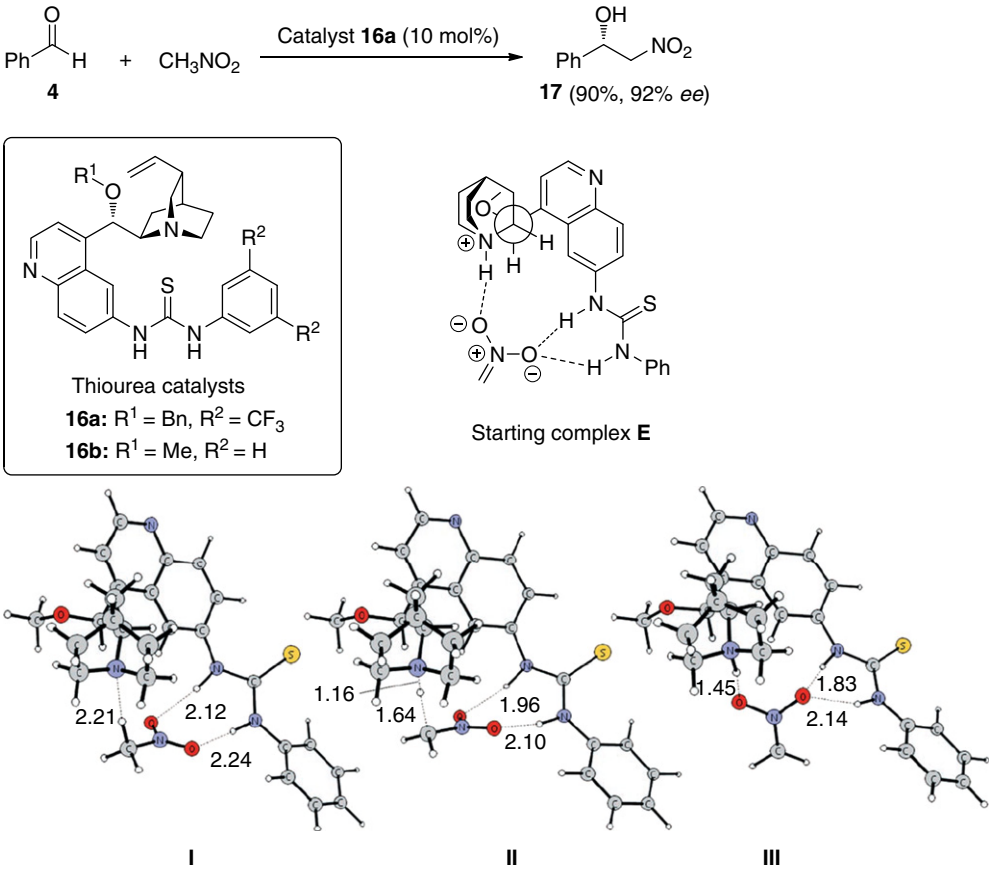
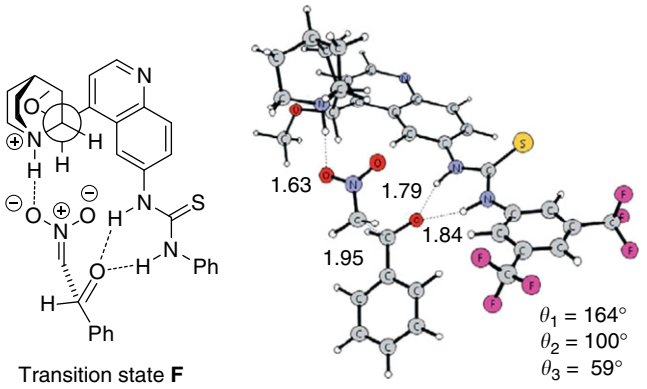


Figure 13 Bifunctional thiourea-catalyzed Henry reaction and generation of starting complex. (Nitromethane bidentately coordinated to the thiourea of the catalyst (**I**); Transition state for the proton transfer (**II**); Nitromethide coordinated to the quinuclidinium and the thiourea (**III**).)

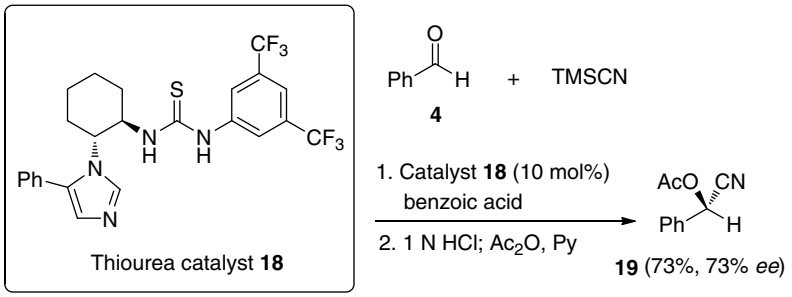
Schreiner et al. reported the bifunctional thiourea catalyst **18** for the enantioselective cyanosilylation of aldehydes with trimethylsilyl cyanide (TMSCN) (Figure 15).[18] Investigation to explore the role of the two NH protons of thiourea was carried out by using ^{1}H, ^{15}N heteronuclear single quantum coherence (^{1}H, ^{15}N HSQC) experiment along with Nuclear Overhauser Effect Spectroscopy and Rotating Overhauser enhancement and Exchange Spectroscopy experiments in CD_2Cl_2 (Figure 14). In HSQC spectrum for the complex between thiourea catalyst **18** and 2,6-dimethylbenzoic acid as an additive, the NH signal at $\delta(^{15}N)$ – 251.0 ppm (light blue) appears as an intense peak, indicating that the exchange of this NH proton slowed down due to an intermolecular hydrogen bond with 2,6-dimethylbenzoic acid, whereas the NH signal at $\delta(^{15}N)$ – 253.5 ppm (dark blue) appears as a weak cross peak in the correlation spectrum, because of the broad NH proton signal.

Mechanistic investigation was also carried out by using DFT computations. The computations for the ternary complex between thiourea **18**, benzoic acid, and benzaldehyde **4** showed that the free thiourea NH proton coordinates the carbonyl oxygen atom of



Transition state **F**

Figure 14 Transition state in Henry reaction.



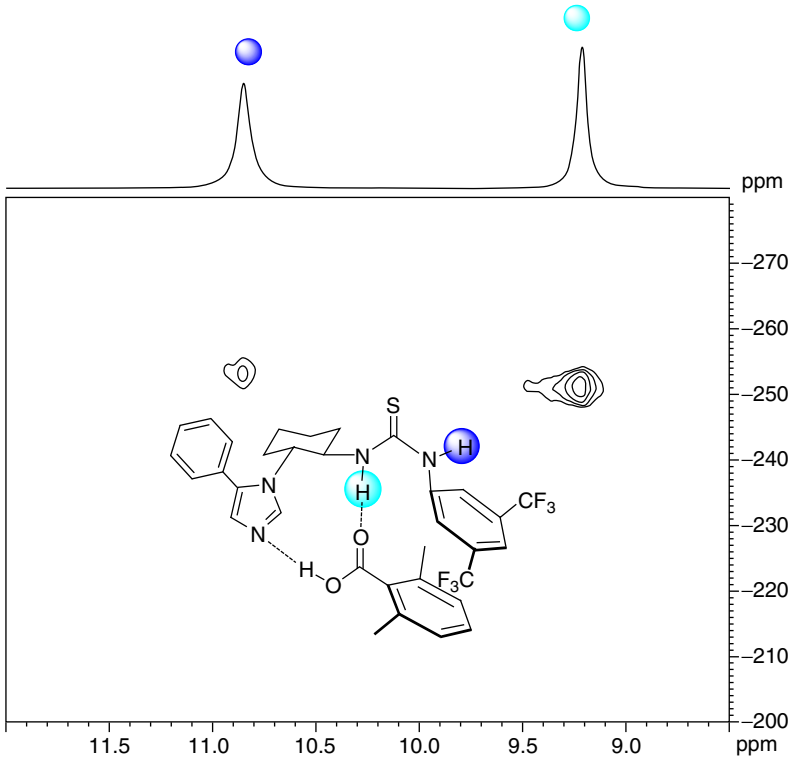


Figure 15 Enantioselective cyanosilylation and ^{1}H, ^{15}N HSQC spectrum for the complex between **18** and 2,6-dimethylbenzoic acid.

the benzaldehyde **4** (Figure 16). This interaction is additionally aided by a CH–π interaction between the *ortho* proton of *N*-aryl group and the phenyl ring of benzaldehyde,[19] which is 2.626 Å distance.

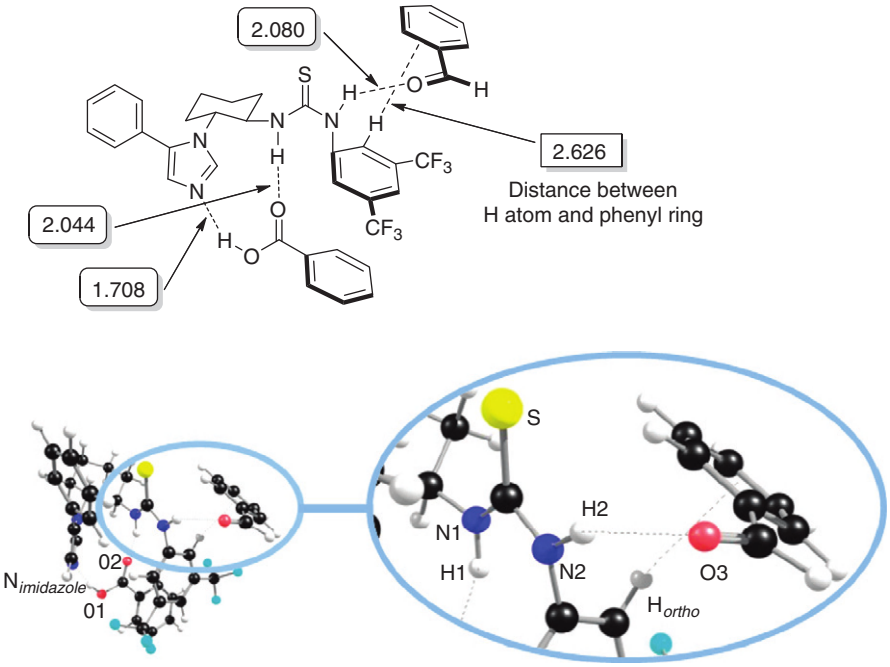


Figure 16 Ternary complex for cyanosilylation reaction.

The chiral bicyclic guanidine **20** promoted Strecker reaction as reported by Corey's group (Figure 17).[20] The addition of hydrogen cyanide (HCN) to achiral *N*-benzhydrylimine **21** gave the amino nitrile **22** in 86% *ee*. As possible reaction pathways, both the additions of HCN and the addition of hydrogen isocyanide (HNC) were proposed, although the isomerization of HCN to HNC has very high energy barriers.[21] Han and coworkers investigated the model reaction of methanimine using DFT with the B3LYP method.[22] They show that the bicyclic guanidine could catalyze the isomerization between HCN and HNC. The pathway through the isomerization and the addition of HNC to methanimine was lower in energy than the pathway through the addition of HCN to methanimine. Although HNC is much less stable than HCN,[23] it is more reactive. As the activation of C═N bond, the starting complex **G** binds to methanimine by the amino hydrogen atom of guanidine. Additionally, the other nitrogen atom of guanidine attracts the proton of HNC. The calculation suggests that the reaction most likely proceeds via the transition state structure **H** to give the product complex **I**.

The amine catalyst **23**, derived by the introduction of L-phenylalanine into the bispidine framework, catalyzed the aldol-type reaction as reported by Feng's group (Figure 18).[24] The weak acidic additives, such as HCO_2H were shown to be suitable for this reaction, affording the product with excellent enantioselectivities, whereas stronger acids, such as trifluoroacetic acid and TsOH, made the reaction sluggish with only trace product. In this reaction, the enamine complex would be formed between acetone and the primary amino group of catalyst **23**. The transition state structure **J** for the aldol-type addition between methyl benzoylformate **24** and acetone was theoretically calculated. The keto group of benzoylformate **24** is activated by hydrogen bond with the protonated piperidine moiety. The favored transition state **J** leading to the major *R* product shows a shorter distance (1.726 Å) between the protonated piperidine and the C═O bond of **24** compared with that of the disfavored transition state leading to the *S* product, indicating a stronger hydrogen bond-interaction.

1.19.3.2 Activation by Brønsted Acid Organocatalysts

The stronger acids, particularly Brønsted acid organocatalysts, are suitable for catalyzing the nucleophilic addition to basic imines. The reaction of imines leads to an increase in basicity at the nitrogen atom in the transition state of a rate-determining step; thus, Brønsted acid catalysts are capable of stabilizing the transition state structure.

Brønsted acid-assisted chiral Brønsted acid catalyst **26** was designed and synthesized by Ishihara and Yamamoto's group (Figure 19).[25] As mentioned in the pK_a values of TADDOL analogs **11a** and **11b** (Figure 9), the increase in acidity of catalysts is induced by intramolecular hydrogen bond. They expected the suitable activation of C–H or O–H bond of **26** by intramolecular

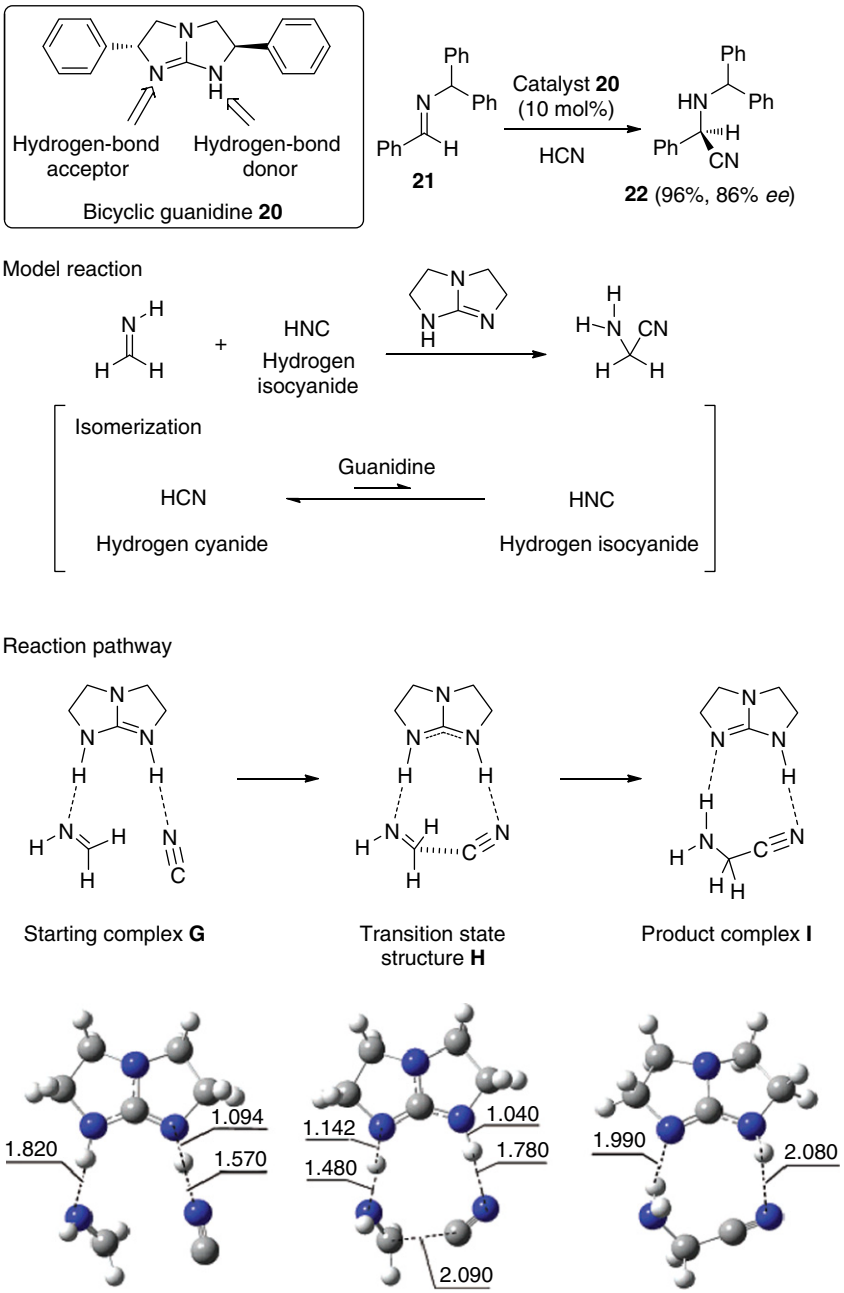


Figure 17 Strecker reaction using guanidine catalyst and the model reaction to study the mechanism.

hydrogen bond as indicated by the activation forms **K1** and **K2**. Particularly, the activation of a substrate by more acidic *bis*(triflyl)methyl proton of form **K1** is assumed to be important. The structure of **26** was confirmed by single crystal X-ray analysis. In the solid state, the length of the intramolecular hydrogen bond between H5A atom and O2 atom is 2.305 Å (for the form **K1**), whereas the length of the hydrogen bond between H21A atom and O5 atom is 3.267 Å (for the form **K2**). This catalyst **26** was applied to the enantioselective Mannich-type reaction of ketene silyl acetals with aldimines.[25]

Chiral phosphoric acids **27** were reported as novel Brønsted acid organocatalysts independently by Akiyama's and Terada's group (Figure 20).[26] The phosphoric acid catalysts **27** are bearing both Brønsted-acidic site and Lewis-basic site, which play a crucial role in the activation of electrophilic and nucleophilic reaction components.

Akiyama's group reported the enantioselective Mannich-type reaction of aldimine **28** and ketene silyl acetal using chiral 1,1′-bi-2-naphthol- based phosphoric acids **27a** (Figure 21).[27] Yamanaka and Akiyama performed the theoretical investigation based on computational analysis using an analogous catalyst **27b**.[28] The calculations support that the reaction occurs by a double hydrogen-bonding pathway over single hydrogen-bonding pathway. The double hydrogen-bonding complex **L1** is the favored

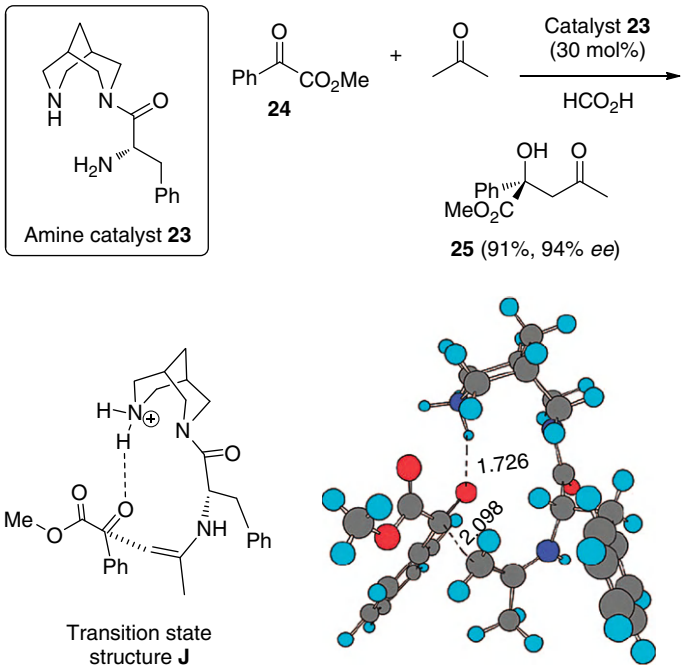


Figure 18 Aldol-type reaction using amine catalyst.

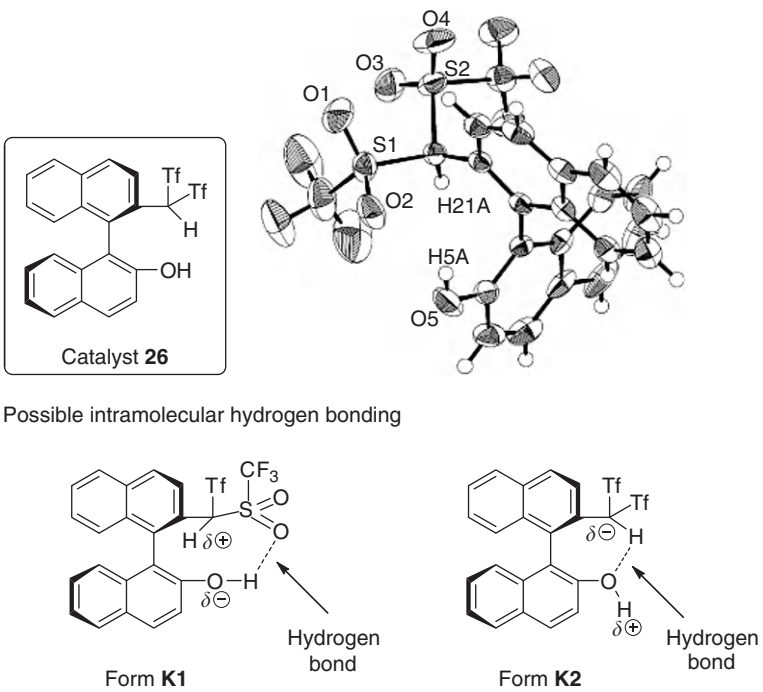


Figure 19 Brønsted acid-assisted chiral Brønsted acid catalyst and X-ray crystal structure.

starting complex. The proton transfer from phosphoric acid **27b** to the nitrogen atom of C═N bond occurs to give the stable iminum complex **L2** before nucleophilic addition of ketene silyl acetal, because aldimine **28** has stronger basic character.

Terada's group reported that chiral phosphoric acid has extremely high catalytic activity for the direct Mannich reaction between *N*-Boc-protected imine **30** and acetyl acetone (Figure 22).[29] The computational analysis had shown that the hydrogen-bonding complex **M** is more stable than other complexes.[30] In the complex **M**, the length of the N–H bond is 1.67 Å, whereas the

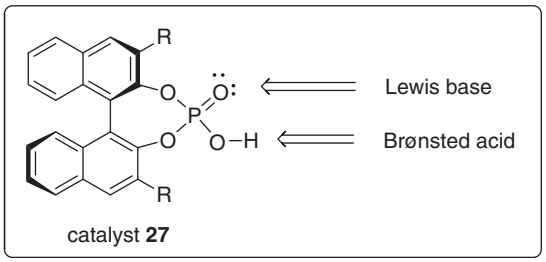


Figure 20 Chiral phosphoric acids.

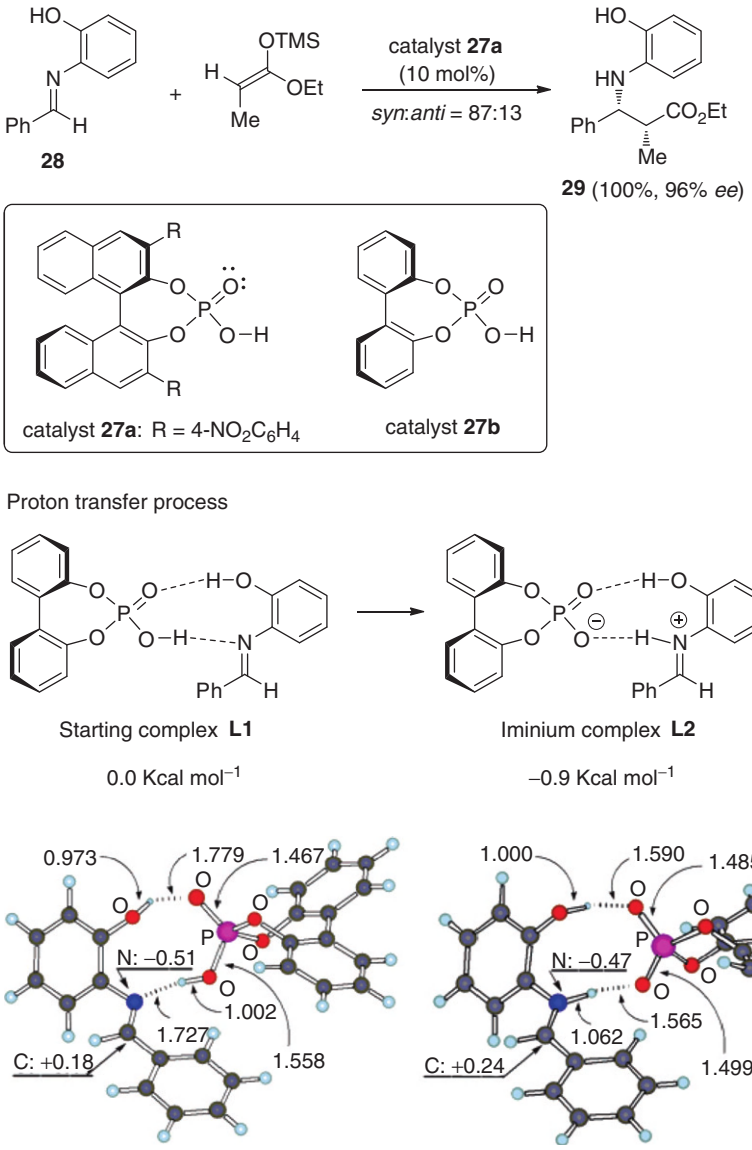


Figure 21 Mannich-type reaction and the formation of iminum complex.

length of the O–H bond is 1.02 Å. It means that the acidic proton in **27** keeps its connection to the chiral phosphoric acid and the formation of protonated substrate is not observed.

Gong's group reported that the chiral phosphoric acid **27d** has mediated the 1,3-dipolar cycloaddition of benzylideneindoline **31** with azomethine ylide generated from aldehyde **32** and diethyl aminomalonate **33** (Figure 23).[31] The calculation studies were

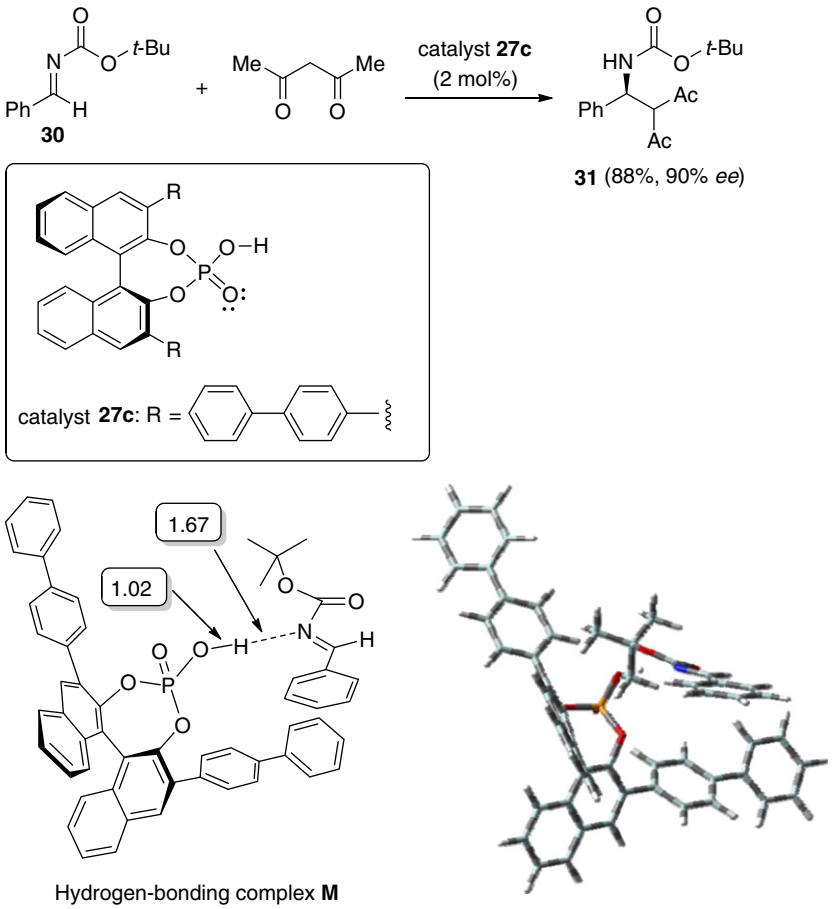


Figure 22 Reaction of Boc-imine and the starting complex.

performed by using model catalyst **27e** instead of catalyst **27d**. In the lowest-energy transition structure **N**, both the methyleneindoline and the azomethine ylide are hydrogen-bonded to the catalyst.

Electrospray ionization mass spectrometry (ESI-MS) is an analytical technique that is rapidly and widely growing as an important tool in molecular analysis. Schrader and List reported that ESI-MS can be used to detect key intermediates in the phosphoric acid-catalyzed cascade reaction.[32] Recently, Rueping and Gschwind reported that nuclear magnetic resonance spectroscopy can be used to distinguish hydrogen bonding and ion pairing in the activation of imines by a phosphoric acid.[33] These studies would help to identify the activation of imines by Brønsted acid organocatalysts.

1.19.3.3 Activation by Ion Pair Formation with Organocatalysts

The electrophile activation by ion pair formation is extremely attractive (Figure 24).[34] Jacobsen's group demonstrated that thiourea catalysts can recognize the *in situ* generated counter anions by hydrogen bonding and activate the ionic electrophilic intermediates such as an iminium or oxonium ion.

The chiral thiourea **35a**-catalyzed Pictet–Spengler reaction of **36** was reported by Jacobsen and coworkers (Figure 25).[35] They found that the *in situ* generation of *N*-acyliminium ion **O** was the key to achieve the high stereocontrol and good chemical efficiency. They studied the Pictet–Spengler-type cyclization of *β*-indolylethyl hydroxylactam **38** for understanding the mechanism and gained the important insights into the mechanism.[36] In this proposal mechanism, thiourea catalyst plays the role of an anion receptor to form the chiral ion pair **P** between *N*-acyliminium and chloride-thiourea complex. The catalyst would promote cyclization by abstracting a chloride in the rate-determining step; thus, they calculated the ground-state structure of a thiourea-complex **Q** binding to the chloride of the hydroxyllactam (Figure 26).

The 4-pyrenyl-substituted chiral thiourea catalyst **41** was developed for the enantioselective polycyclization of hydroxylactam **42** (Figure 27).[37] Hydrogen-bond-mediated ionization of the *in-situ* generated chlorolactam by thiourea catalyst would generate an ion pair. This catalyst **41** was designed not only to bind a chloride anion, but also to engage stabilizing cation–*π* interactions which play the principal role in asymmetric induction (Figure 28).

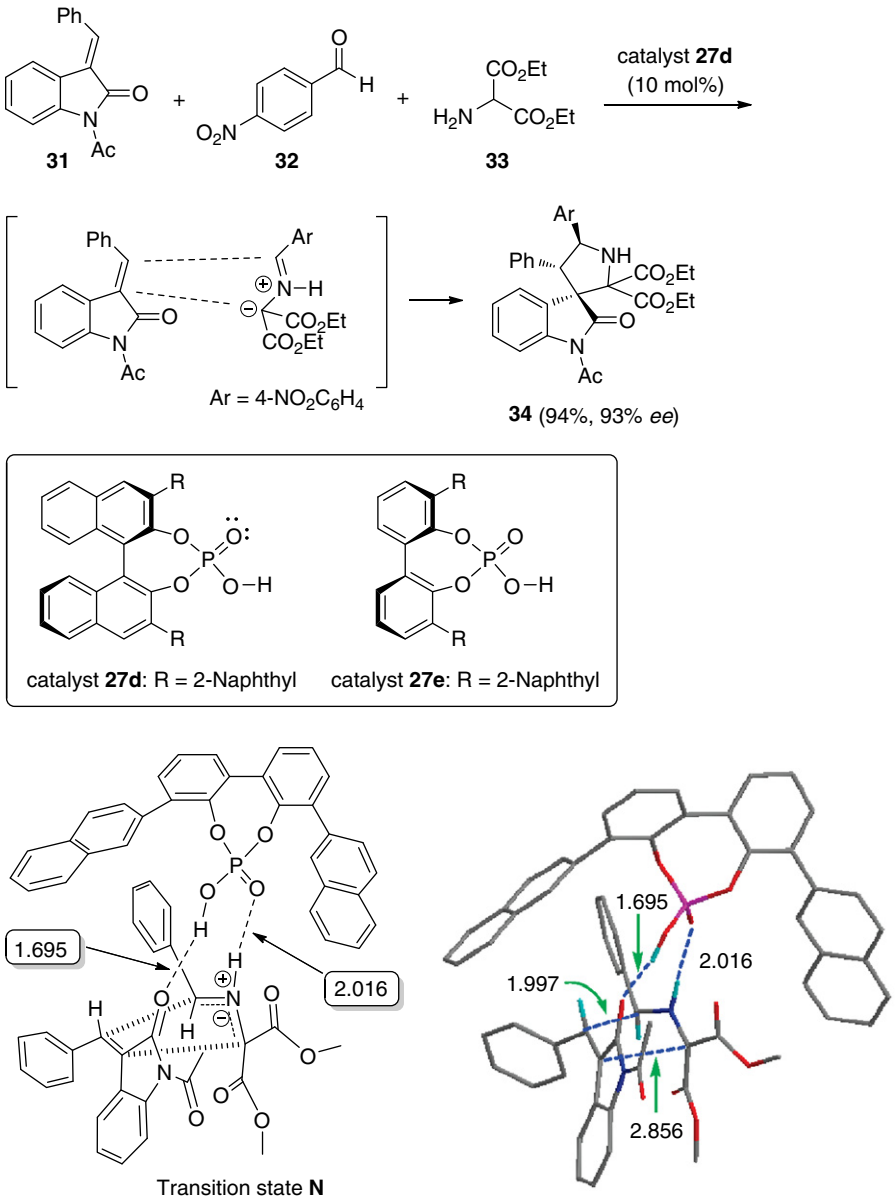


Figure 23 Three-component 1,3-dipolar cycloaddition and transition state structure.

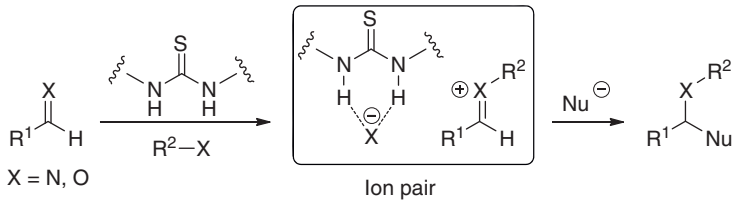


Figure 24 Ionic electrophile activation with counter anion recognition by organocatalysts.

The thiourea-catalyzed asymmetric Strecker reaction, hydrocyanation of imines, was intensively investigated by the group of Jacobsen.[38] Recently, they reported that the simple chiral thiourea 44 was a powerful catalyst for the asymmetric Strecker reaction even when inexpensive KCN was used as cyanide source (Figure 29).[39]

In their preliminary study, they proposed the mechanistic model in which thiourea functionality binds imino group. In 2009, the detailed kinetic and computational study on thiourea-catalyzed Strecker reaction was reported for understanding the

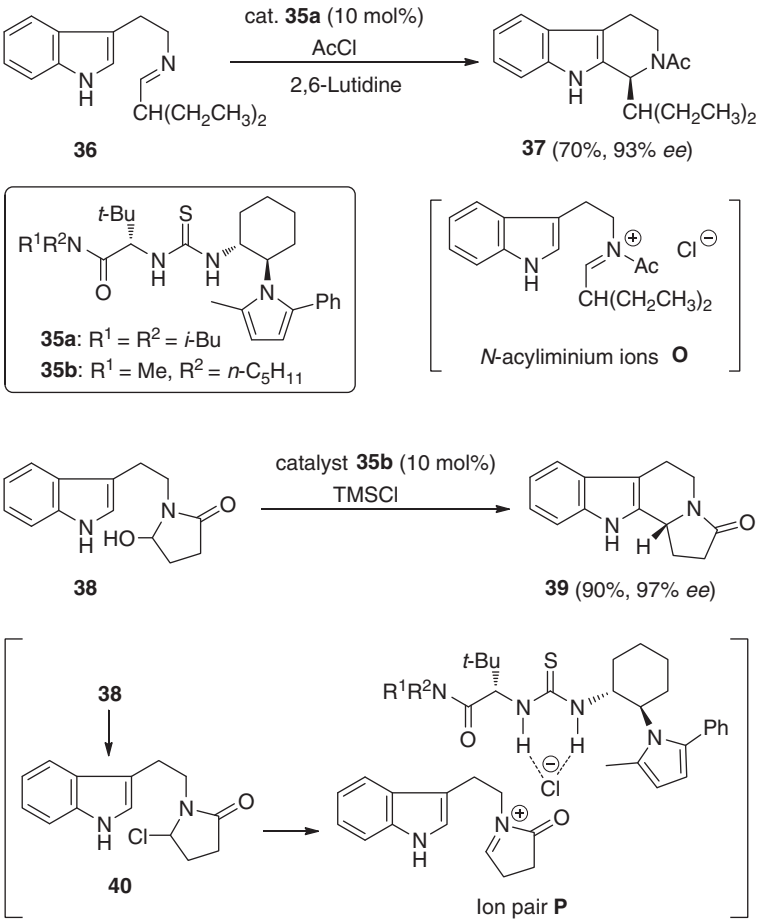


Figure 25 Chiral thiourea-catalyzed Pictet–Spengler reaction.

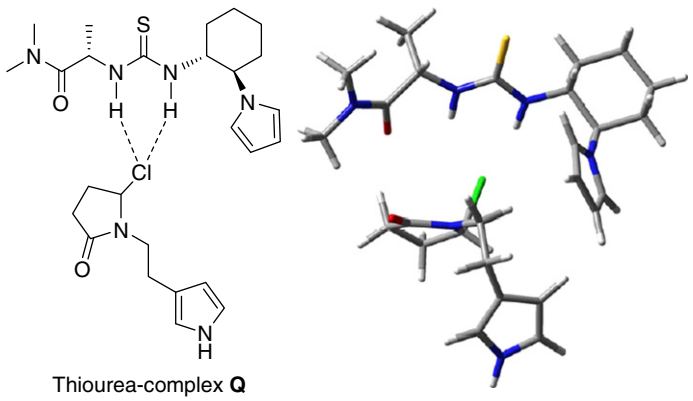


Figure 26 DFT computational ground state structure of thiourea-complex.

mechanism.[40] They showed that the binding of thiourea hydrogens to cyanide anion was favored, rather than an activation of the imine electrophile. The enantioselectivity is attributed to a larger stabilization of the iminium in the transition state structure **R** leading to the major *R*-enantiomer (Figure 30). The interaction between cyanide ion and thiourea was also proposed by List's group in their study on the three-component acylcyanation of aldimines.[41]

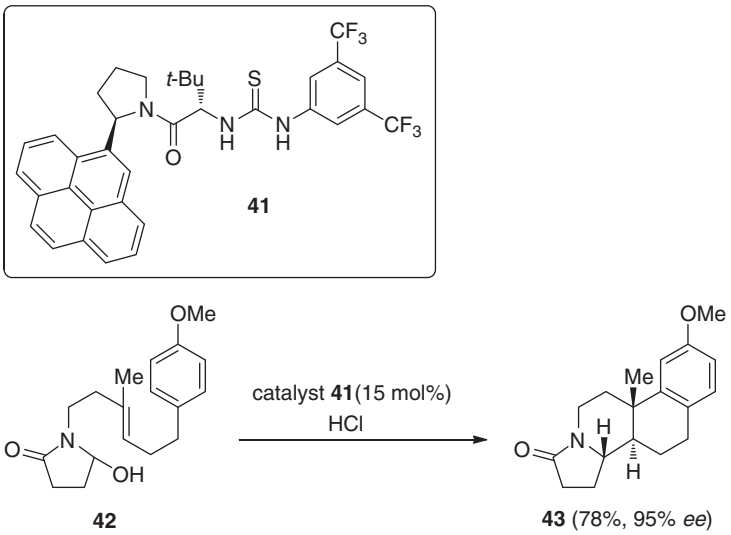


Figure 27 Chiral thiourea-catalyzed Pictet–Spengler reaction.

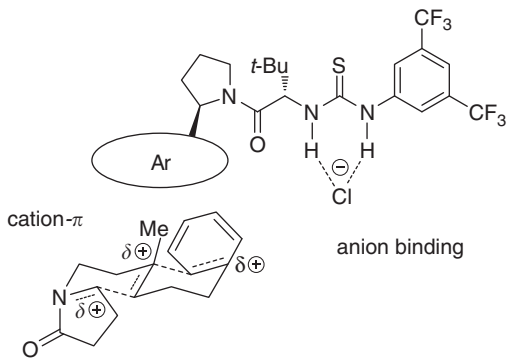


Figure 28 Ion pair formation and cation–π interactions.

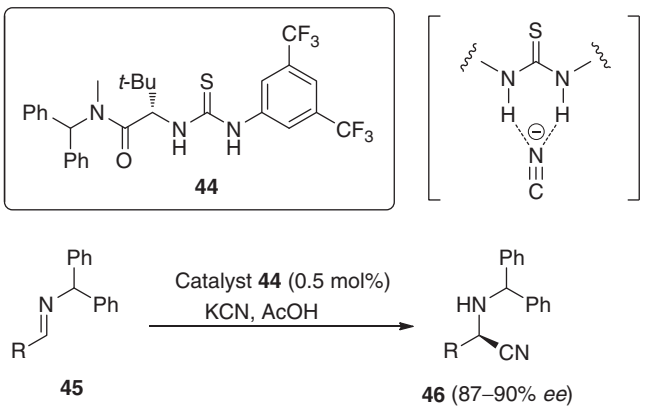


Figure 29 Chiral thiourea-catalyzed asymmetric Strecker reaction.

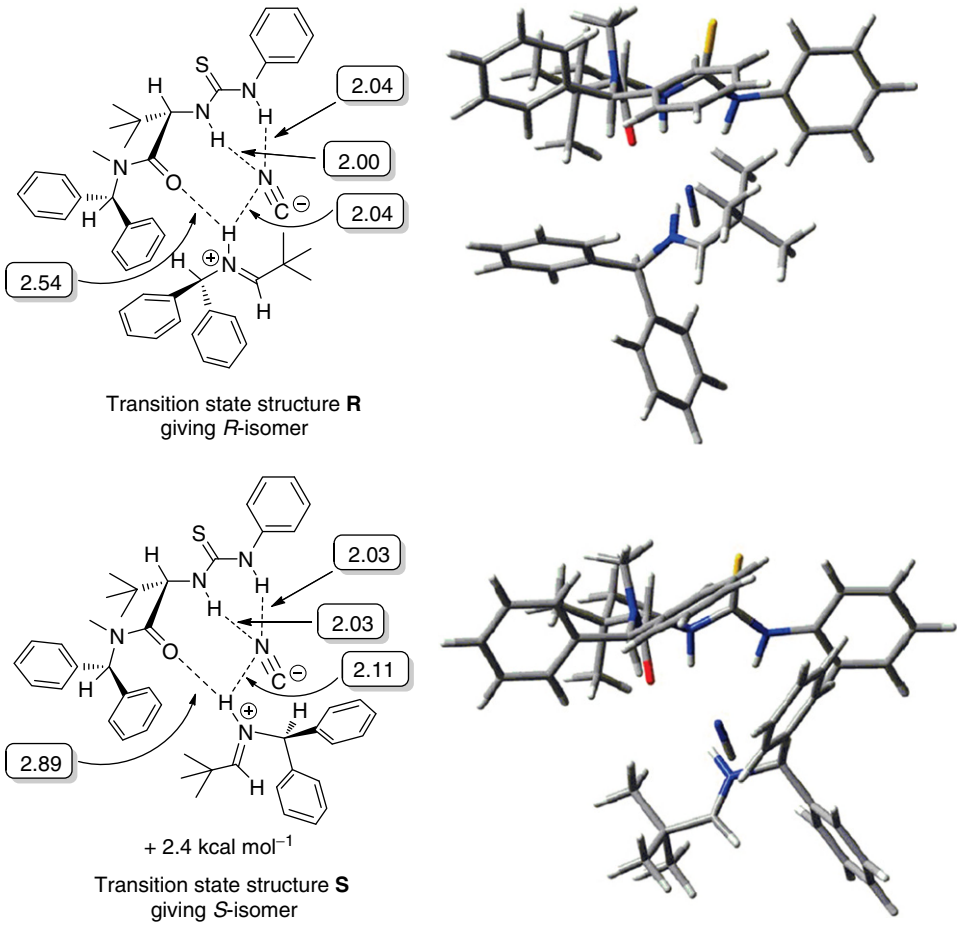


Figure 30 Transition state structures for asymmetric Strecker reaction.

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