# Catalytic Enantioselective Addition of Allylic Organometallic Reagents to Aldehydes and Ketones

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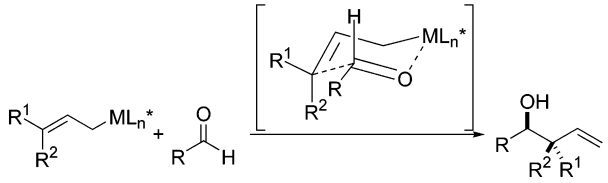
## 1. Introduction

The invention and development of new methods for the synthesis of complex molecules of both natural and unnatural origin remain an enduring challenge in organic chemistry. Over the past two decades one of the major efforts in this arena has been the controlled construction of open-chain systems bearing sequences of stereocenters. The allylmetal−aldehyde addition reaction has proven to be enormously successful for the synthesis these important structural subunits.[1−4] Some of the reasons for the popularity of the method are (1) the high degree of both diastereo- and enantioselectivity observed, (2) the extreme diversity of reagent reactivity based on metal, (3) the ability to access different stereodyads and triads, and (4) the latent functionality in the homoallylic alcohol product that makes the reaction ideal for synthetic planning. Moreover, the reactions are mechanistically intriguing, and their utility stimulated a important synergy between fundamental studies of stereochemistry and applications in target oriented synthesis.

Among the most common strategies to accomplish stereoselective introduction of an allyl group is the use of allylic organometallic reagents in which the metal is ligated by chiral modifiers. An important characteristic of these reagents is the excellent diastereocontrol observed. Because of the organizational features of the metal center, the chiral modifier is held in close proximity to the reacting nucleophile and electrophile, ensuring high stereochemical information transfer. In this category excellent results have been obtained from the use of chirally modified allylic borane[5] or allylic titanium[6] reagents (Scheme 1). Recently, the success of this approach has been extended to include allylic silanes[7,8,9] and allylic stannanes as well.[10,11]

**Scheme 1**

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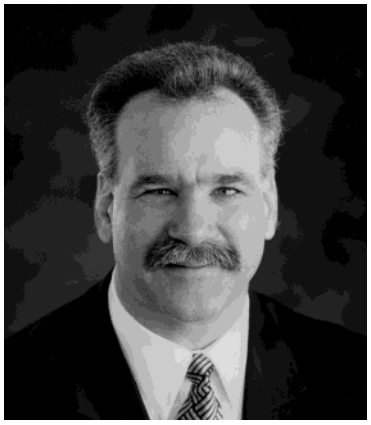
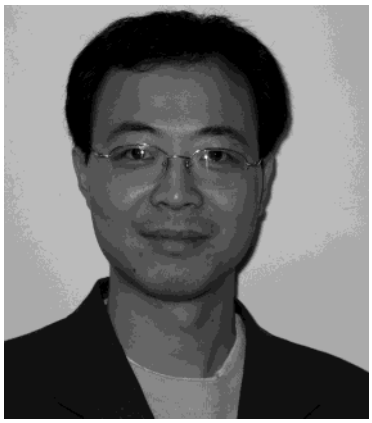


Scott E. Denmark was born in Lynbrook, New York on 17 June 1953. He obtained an S.B. degree from MIT in 1975 (working with Richard H. Holm and Daniel S. Kemp) and his D.Sc.Tech. (under the direction of Albert Eschenmoser) from the ETH Zürich in 1980. That same year he began his career at the University of Illinois. He was promoted to associate professor in 1986 and to full professor in 1987, and since 1991 he has been the Reynold C. Fuson Professor of Chemistry. His research interests include the invention of new synthetic reactions, exploratory organoelement chemistry, and the origin of stereocontrol in fundamental carbon–carbon bond forming processes. Professor Denmark is currently on the Board of Editors of *Organic Reactions* and *Organic Syntheses.* He is an Associate Editor of *Organic Letters* and is the Editor of *Topics in Stereochemistry*.

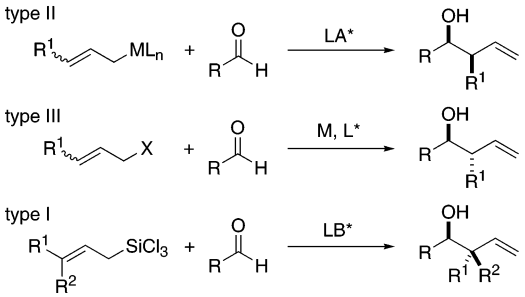


Jiping Fu was born in 1976 in Fujian, China. He received his B.S. degree in 1997 from the University of Science and Technology of China (USTC). He performed graduate studies in the University of Illinois at Urbana-Champaign under the supervision of Professor Soctt E. Denmark, during which he worked on chiral-phosphoramide-catalyzed enantioselective allylation reactions with allyltrichlorosilanes. He received his Ph.D. degree in 2002 and is currently carrying out postdoctoral research with Professor Eric N. Jacobsen at Harvard University.

Despite the high selectivity obtained and extensive application in synthesis, this approach requires a stoichiometric amount of the chiral ligand modifier. For inexpensive, readily available modifiers, this still represents a useful approach. However, there is little doubt that for both conceptual advances as well as practical applications, catalytic enantioselective methods hold tremendous appeal across the synthetic organic landscape. The development of enantioselective allylation under asymmetric catalysis has evolved more slowly than the cognate aldol reactions, but nevertheless, significant progress has been recorded in the past 10 years.[12] One of the most challenging problems associated with the development of catalytic enantioselective allylation is that the principal type of catalysis involves the use of Lewis acids with allylic silanes and stannanes. These type II reactions[4] give variable (though predominantly syn) diastereoselectivity with substituted reagents and thus are mostly useful for simple allylation. This problem has been substantially addressed by the advent of Lewis base catalysis with allylic trichlorosilane reagents which give excellent and predictable diastereoselectivity (type I reactions[4]) as well as enantioselectivity.

This review is organized around the overarching rubric of reaction type, which groups reagents into three main categories (Scheme 2):
(1) addition of allylic organometallic reagents (Si, Sn, B) catalyzed by chiral Lewis acids (type II reactions: predominantly syn diastereoselective independent of starting allylic geometry),
(2) addition of allylic organometallic reagents (Cr, Zn, In) generated in situ from the corresponding allylic halides catalyzed by chelating ligands (type III reactions: predominantly anti-selective independent of starting allylic geometry), and
(3) addition of allylic trichlorosilanes catalyzed by chiral Lewis bases (type I reactions: syn/anti diastereoselectivity reflects the *Z*/*E* ratio of the allylic geometry).

**Scheme 2**




Each section will commence with a general discussion of the mechanistic aspects of the addition, followed by a detailed presentation of the development and scope of chiral stereocontrolling reagents.

The extension of each type of method to the propargylation and allenylation of aldehydes as well as to the addition of ketones will be addressed separately. Finally, the application of catalytic enantioselective allylation in complex molecule synthesis will be presented to illustrate the utility of these methods. The literature in this review is comprehensively covered through the end of 2002, with additional references cited that appeared in the first quarter of 2003.

## *2. Chiral Lewis Acid-Catalyzed Addition of Allylic Silanes and Allylic Stannanes*

### 2.1. Mechanism and Stereochemical Course of Addition

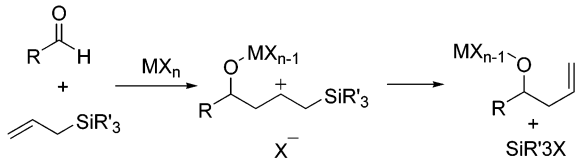
#### *2.1.1. General Mechanism of Addition*

The majority of catalytic enantioselective allylation reactions involve the chiral Lewis acid-catalyzed additions of allyltrimethylsilane (**1**) or allyltributylstannane (**2**) to aldehydes. In this process, the Lewis acid serves to activate the aldehyde toward nucleophilic attack as well as to direct the course of

addition. Although a detailed discussion of the mechanistic and stereochemical aspects of this addition is beyond the scope of this review, it is nonetheless important to present the salient features, as they are crucial to the understanding as well as development of asymmetric catalysts.

In general, the addition of allylic silanes to electrophiles has been established to be a stepwise process.[13] Thus, initial addition of an allylic silane to an activated aldehyde forms carbocation, which is stabilized by hyperconjugative overlap with the carbon−silicon bond (Scheme 3).[14] Cleavage of the silyl electrofuge then provides the homoallylic alcohol product.

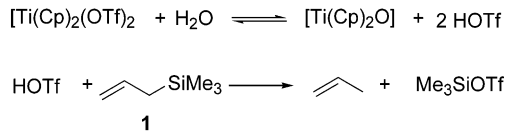
**Scheme 3**



Although many Lewis acids have been reported to promote the addition of allylic silanes to aldehydes, the reactions using only a catalytic amount of a Lewis acid were initially scarce. Moreover, in some of these reactions, the Lewis acid was actually found not to be responsible for the reaction.[15]

In a mechanistic investigation on the addition of allyltrimethylsilane to aldehydes catalyzed by Lewis acids such as $[Ti(Cp)_2(OTf)_2]$, $Ph_3C^+OTf^-$, and $Ph_3C^+ClO_4^-$, it was found that the reactive species is actually the electrofugal trimethylsilyl cation.[15] This possibility was first discussed and eliminated in the Lewis acid-catalyzed aldol reaction with trialkylsilyl enolates.[16,17] In the former study,[15] a trace amount of water in the reaction was shown to hydrolyze the Lewis acid to generate a Bronsted acid (Scheme 4). The Bronsted acid then reacts with allyltrimethylsilane to produce $Me_3SiOTf$ or $Me_3SiClO_4$, both of which are powerful catalysts for allylation.

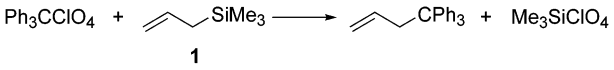
**Scheme 4**



Furthermore, dehydration of the solvent or addition of a hindered base to quench the acid does not necessarily prevent the formation of these silyl catalysts. In the case of $[Ti(Cp)_2(OTf)_2]$, upon activation of the aldehyde and addition of **1**, the metal alkoxide **i** and $Me_3SiOTf$ are produced (Scheme 5). To achieve a catalytic process, the metal must dissociate from the complex assisted by the silylation of the adduct. However, the silylation does not occur, and instead $Me_3SiOTf$ functions as highly reactive catalyst for the allylation. Thus, the reaction is actually a metal initiated, silyl-cation catalyzed process.

In the reaction with $Ph_3C^+ClO_4^-$, the silyl cation is generated by simple allylation of $Ph_3C^+ClO_4^-$ (Scheme 6), and the reaction rate for the addition of allylsilane to acetal could be quantitatively accounted for by invoking only $MeSi_3ClO_4$ catalysis.

**Scheme 6**



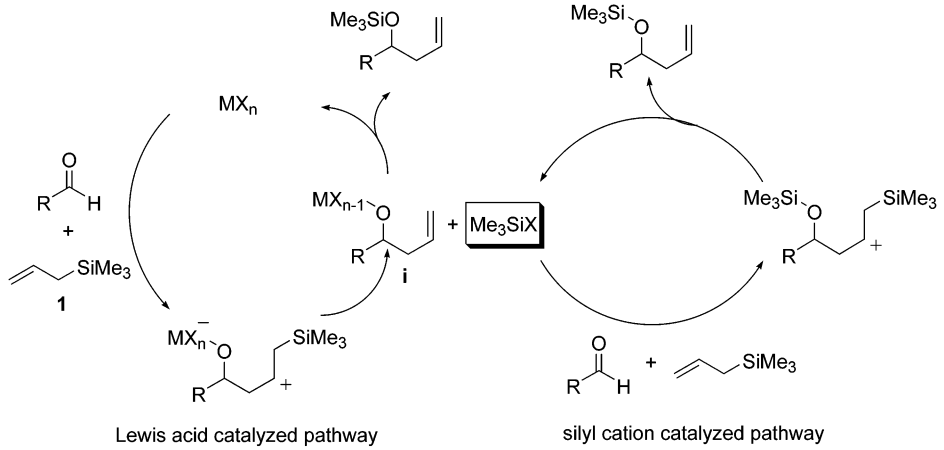
The mechanistic implications of such silyl-cation-catalyzed addition in asymmetric catalysis is significant. Highly enantioselective reactions require not only the asymmetric induction imposed by the chiral Lewis acid but also a minimum contribution from the nonselective catalysis by achiral species.

Such a competing pathway might not be as serious in the reaction with the more reactive allylstannanes. However, the overall rate of the reaction depends not only on the addition rate, but also on the efficiency of catalyst turnover. To facilitate the turnover event, various additives such as TMSCl, TBSCl,[18] *i*-PrSSiMe$_3$, *i*-PrSBEt$_3$, *i*-PrSAlEt$_2$, and $B(OMe)_3$[19,20,21] have been utilized.

### *2.1.2. Stereochemical Course of Addition*

**2.1.2.1. Lewis Acid−Aldehyde Complexes.** In this family of additions, the chiral Lewis acid serves both as a activator and the stereocontrolling agent. Understanding the structure of the Lewis acid·

**Scheme 5**



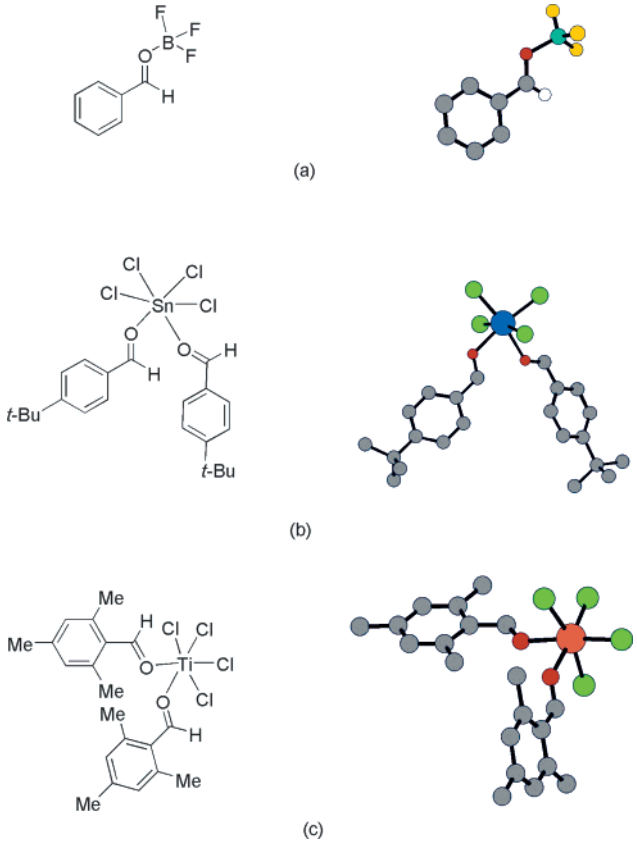



**Figure 1.** Chem 3D presentation of X-ray structure of (a) PhCHO·$BF_3$, (b) (4-*t*-$BuC_6H_4CHO)_2$·$SnCl_4$, and (c) (2,4,6-$Me_3C_6H_2CHO)_2$·$TiCl_4$.

aldehyde complex[22−24] is crucial because the geometrical and conformational preferences of this complex ultimately determine the stereochemical course of the reaction.

Of particular importance in the analysis of such complexes is the orientation of the M−O dative bond formed between the aldehyde and the Lewis acid. Solution and solid-state studies on Lewis acid·aldehyde complexes have provided ample evidence that the Lewis acid coordinates in the carbonyl plane syn to the formyl hydrogen. As shown in the X-ray crystal structure of the $BF_3$·benzaldehyde complex reported by Reetz, the Lewis acid is placed 1.59 Å from the carbonyl oxygen, along the direction of the canonical oxygen $sp^2$ lone pair and anti to the larger phenyl group (C−O−B 118.7°) (Figure 1a).[25] The evidence for this structure in solution was provided by a heteronuclear nOe NMR experiment, in which irradiation of the fluorines leads to a 5% enhancement of the aldehyde proton absorption. Similar coordination of a Lewis acid syn to the formyl hydrogen is also observed in the X-ray crystal structure of the (4-*t*-$BuC_6H_4CHO)_2$·$SnCl_4$ complex (Figure 1b).[26,27] In this structure, the two aldehydes coordinate in a cis fashion with an O−Sn−O angle of 78.9°. Similarly, the tin atom resides nearly in the plane of each carbonyl group (2° and 4° torsional angles) and anti to the aromatic rings (C−O−Sn 128.0° and 126.2°). In the (2,4,6-$Me_3C_6H_2CHO)_2$·$TiCl_4$ complex, the Ti atom adopts a similar orientation with respect to the aldehydes (Ti−O−C 134.4° and 133.7°, torsional angle Ti−O−C−H 8° and 14°).[28] Finally, in a novel indium complex with three benzaldehyde molecules $(C_6H_5CHO)_3$·$InCl_3$, the carbonyl groups are bonded in a similar fashion (In−O−C 125.0°, 125.5°, and 127.7°) in a *fac*-octahedral complex.[29]

In the development of Lewis acids for asymmetric catalysis, chiral ligands are used to modify the asymmetric environment of the metal centers. Thus, for the rational design of selective catalysts, knowledge of the orientation of the aldehyde with respect to chiral ligand is essential. However in most cases, the origins of the rate and stereochemical influence of the Lewis acid are still poorly understood, and little structural information (solid or solution state) on chiral Lewis acid aldehyde complexes is available. Nevertheless, in an attempt to provide a general rationalization for the stereochemical course of reactions of aldehydes complexed with Lewis acids, Corey introduced the hypothesis of formyl C−H···X (X = O or F) hydrogen bonding as an additional organizing element (Figure 2).[30]

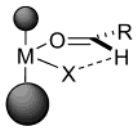


**Figure 2.** Formyl hydrogen bonding as an organizing element.

X-ray structures of the aldehyde·$BF_3$ complexes reveal that one of the fluorine atoms on the Lewis acid eclipses the formyl hydrogen (Figure 3).[25] Such orientation of fluoride has been previously rationalized by Reetz as a contribution from a generalized anomeric effect in which electrons from the noncomplexed lone pair on the aldehyde oxygen interact with the antibonding orbital of the eclipsed B−F or B−O bond.[25,31] Corey, however, suggests that the H···F distances in these complexes are within the sum of the van der Waals radii (2.67 Å) and proposes the existence of a hydrogen bonding interaction between the formyl hydrogen and the eclipsed coplanar fluoride.[30] Similarly, in the X-ray structures of [catecholborane·$(DMF)_2]^+$ $Br^-$ (H···O distance 2.46 Å) and [2-(*N*,*N*-dimethylamino)phenoxyborane·(DMF)]$^+$ $I^-$ (H···O distances 2.41 Å, 2.59 Å), the H···O distances are well below the sum of the van der Waals radii (2.71 Å). Thus, the existence of C−H···O hydrogen bonds in these complexes is also postulated. The notion of C−H hydrogen bonding to heteroatoms has been employed by Corey and coworkers as an organizational tool to formulate transition structure assemblies for many enantioselective reactions.[31−33] Although the working models do provide rationales for the observed enantioselectivities, the true origins of asymmetric induction still await further investigation.[34]

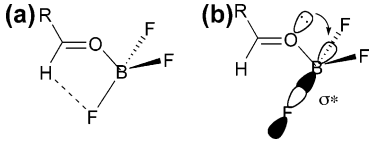
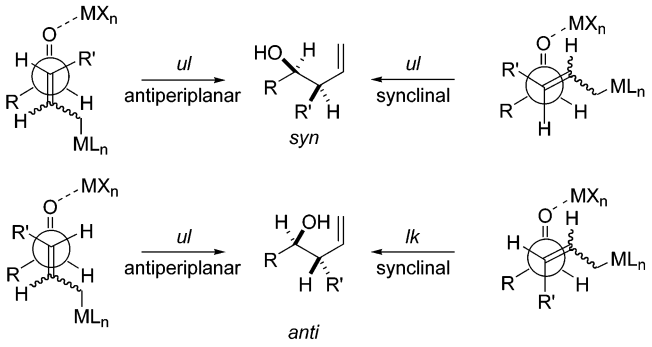



**Figure 3.** (a) Proposed hydrogen bonding in aldehyde·$BF_3$ complex. (b) Proposed anomeric effect in aldehyde·$BF_3$ complex.

**Scheme 7**




**2.1.2.2. Addition of Allylic Silanes.** The Lewis acid plays a major role in the stereochemical course of the addition of allylic organometallic nucleophiles to the carbonyl group. For the two basic modes discussed herein, internal and external stereoinduction,[4] the structure and location of the Lewis acid fundamentally influence the approach of the allylmetal nucleophile. In formulating transition structure models for that approach, three basic stereochemical features need to be considered: (1) the mutual orientation of the two reacting $\pi$-systems with respect to each other (internal stereocontrol), i.e., the relative topicity of reactants that controls diastereoselectivity, (2) the orientation of the metal electrofuge with respect to the electrophile ($S_E2'$ selectivity), and (3) the selectivity for approach of the nucleophile to the diastereotopic faces of the complexed aldehyde. The constellation of steric interactions between the Lewis acid·aldehyde complex and the allylmetal nucleophile influences all three stereochemical features. Whereas the latter two factors are relevant to all additions, the former is only important for the addition of C(3)-substituted allylic species, in which the stereochemical consequences at the allylic terminus need to be considered as well. The transition structures developed to explain selectivities observed in these reactions have in addition identified the dihedral angle between the two reacting double bonds. To avoid eclipsing interactions, in two limiting arrangements, synclinal (60°) and antiperiplanar (180°) are considered (Scheme 7).

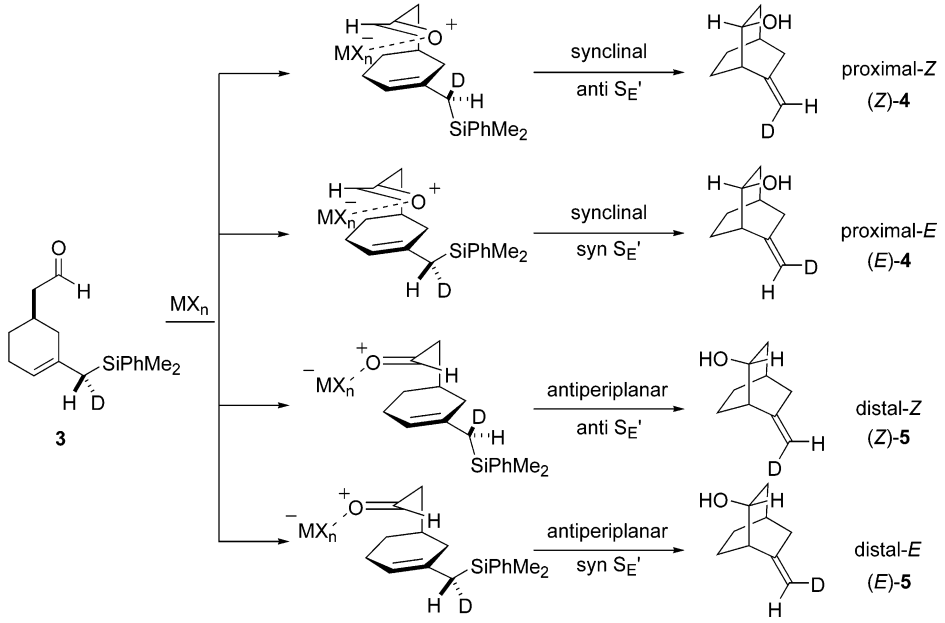
With regard to the diastereoselectivity in Lewis acid-catalyzed additions of 2-butenylsilanes, the syn homoallylic alcohol is the major product, independent of the geometry of the starting silanes (type II reaction[4]).[35−37] The stereochemical course of the addition has been studied in the cyclization of model **3** promoted by Lewis acids (Scheme 8).[38,39] In the model, the rigidity of **3** allows a clear correlation between product configuration and transition structure geometry. Thus, the ratio of epimeric products **4** to **5** directly reflects the preference of the double bond orientation. In addition, the position of the deuterium in the product can be established to determine if the reaction proceeds through a syn or anti $S_E'$ pathway. The ratio of proximal to distal products displays a strong Lewis acid dependence, which illustrates the influence of the Lewis acid on the synclinal and antiperiplanar transition structures. In these studies, the synclinal orientation of the double bonds is preferred, although to varying extent. Remarkably, in both proximal and distal products, (*Z*)-**4** and (*Z*)-**5** are obtained as the major isomers, which establishes that the reactions strongly favor the anti $S_E'$ pathway (Table 1).

**Table 1. Cyclization of 3 Promoted by Various Lewis Acids**

| entry | Lewis acid | proximal/distal (**4**/**5**) | **4** *Z*/*E* | **5** *Z*/*E* | proximal % anti $S_E'$ | distal % anti $S_E'$ |
|---|---|---|---|---|---|---|
| 1 | $BF_3$·$OEt_2$ | 75/25 | 94/4 | 94/6 | 100 | 100 |
| 2 | $SnCl_4$ | 60/40 | 91/9 | 94/6 | 97 | 100 |
| 3 | $CF_3SO_3H$ | 95/5 | 93/7 | 94/6 | 99 | 100 |
| 4 | $SiCl_4$ | 98/2 | 95/5 | – | 100 | – |

The synclinal arrangement of allylic silanes is also proposed by Bottoni in the studies on the addition of allyltrimethylsilane to aldehydes promoted by $BF_3$·$OEt_2$ (Figure 4).[40] On the basis of computational

**Scheme 8**



studies, Bottoni proposed an eight-membered transition structure with one of the fluorine atoms coordinating to the silicon. In this picture, the formation of the C−C and Si−F bonds and the breaking of the Si−C and B−F bonds occurs in a highly asynchronous, concerted manner. This proposal however, posits the operation of both syn and anti $S_E'$ pathways, which would be inconsistent with the experimentally established preference for anti $S_E'$ reactions of allylic trialkylsilanes.[39]

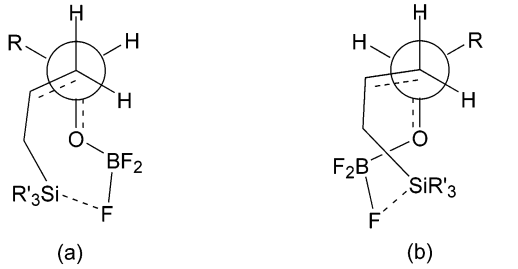
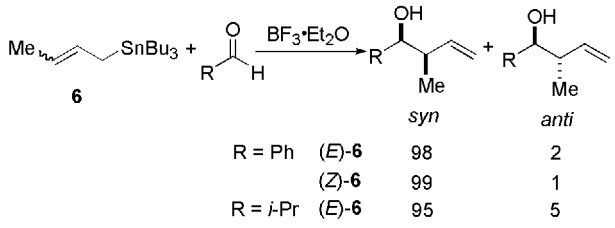



**Figure 4.** Proposed transition structure for the addition of allylsilane promoted by $BF_3$.

**2.1.2.3. Addition of Allylstannanes.** The Lewis acid-promoted addition of 2-butenylstannanes to aldehydes was first reported by Yamamoto in 1980.[41,42,43] In these additions, the syn homoallylic alcohol is the major product, independent of the geometry of the 2-butenylmetal reagent (Scheme 9). To explain the observed high diastereoselectivity, an acyclic transition structure is invoked in which the double bonds take up an antiperiplanar arrangement (Figure 5). It is proposed that the antiperiplanar transition structure (b) is favored because of the minimization of the steric interactions between the aldehyde R group and the $\gamma$-methyl group of **6**.

**Scheme 9**



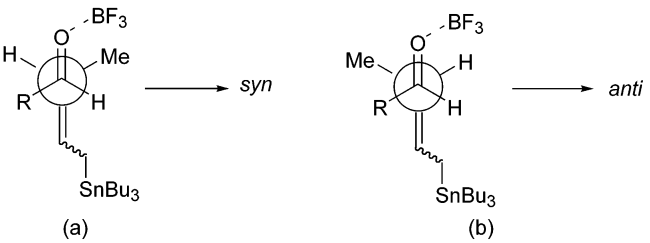




**Figure 5.** Antiperiplanar transition structures.

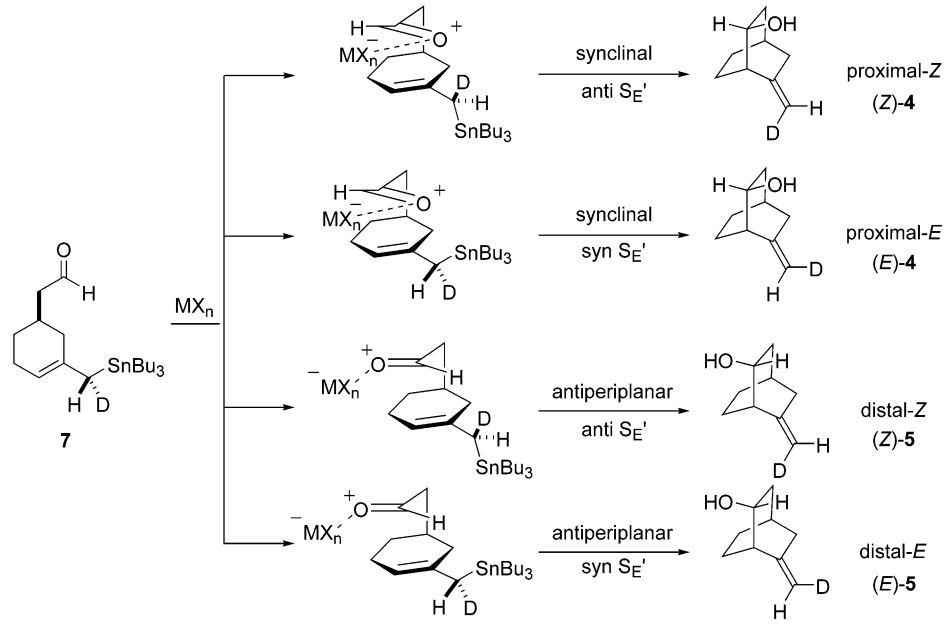
The synclinal transition structure, however, is favored in the Lewis acid-catalyzed cyclization of **7**, which was designed to evaluate the synclinal and antiperiplanar geometries (Scheme 10). Reaction of **7** with various Lewis acids results in the predominant formation of the proximal product **4**. The selectivities obtained with do not correlate with the size of the Lewis acid employed (Table 2). In addition, the *Z*/*E* ratio observed in the adduct **4** and **5** also reflect the preference of anti $S_E'$ over syn $S_E'$. As was observed in allylic silane model **3**, the (*Z*)-**4** and (*Z*)-**5** is obtained preferentially compared to (*E*)-**4** and (*E*)-**5**, establishing a preference of the anti $S_E'$ pathway.

**Table 2. Cyclization of 7 Promoted by Various Lewis Acids**

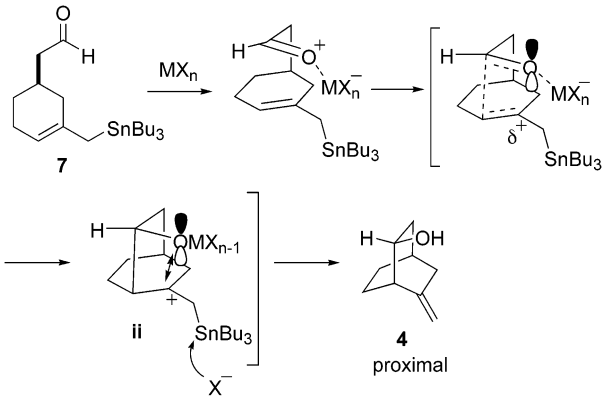
| entry | Lewis acid | proximal/distal (**4**/**5**) | **4** *Z*/*E* | **5** *Z*/*E* | proximal anti/syn $S_E'$ | distal % anti $S_E'$ |
|---|---|---|---|---|---|---|
| 1 | $TiCl_4$ | 88/12 | 89/11 | 95/5 | 94/6 | >99/1 |
| 2 | $SnCl_4$ | 94/6 | 86/14 | 95/5 | 91/9 | >99/1 |
| 3 | $BF_3$•$OEt_2$ | 86/14 | 92/8 | 95/5 | 97/3 | >99/1 |
| 4 | $CF_3SO_3H$ | 97/3 | 93/7 | | 98/2 | |
| 5 | $CF_3CO_2H$ | >99/1 | 93/7 | | 98/2 | |

Denmark proposed that the synclinal transition structure is favored because of stabilization by a

**Scheme 10**

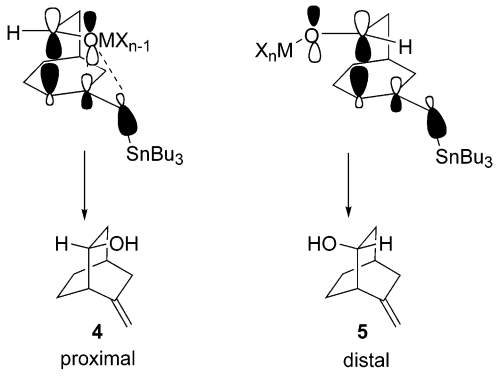


**Scheme 11**




subtle stereoelectronic effect.[44] First, the synclinal transition state would minimize the charge separation in the intermediate **ii** (Scheme 11). In addition, such an orientation also allows a secondary orbital interaction between the HOMO of the allyl group and the LUMO of the complexed aldehyde, which is absent in the antiperiplanar orientation (Scheme 12).

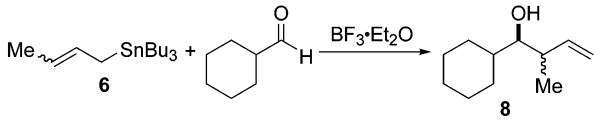
**Scheme 12**




Although the intramolecular addition models allow for an unambiguous correlation of product configuration with double bond orientation, they must limit the number of possible orientations.[45] However, support for synclinal transition structures in unbiased, and intermolecular additions is provided by Keck in systematic studies on the reaction between 2-butenylstannanes and aldehydes promoted by various Lewis acids.[46] The diastereoselectivity observed in the reaction is found to be highly dependent of the aldehyde structure, allylic stannane configuration, and the Lewis acid employed. Although the reactions are syn selective, much higher syn selectivity is observed with (*E*)-2-butenylstannanes. For example, in the reaction with cyclohexanecarboxaldehyde, syn selectivity decreases from 15/1 with (*E*)-**6** to only 1.4/1 with (*Z*)-**6** (Scheme 13).

Six limiting open transition structures with both antiperiplanar and synclinal arrangements are considered to explain the observed diastereoselectivity (Figure 6). If antiperiplanar transition structures are operative, allylic stannane (*Z*)-**6** should provide higher syn selectivity than (*E*)-**6** because the $Z_3$(S) transition structure would be more favored than $E_4$(S) arrangement, both leading to the syn adduct. Instead, Keck proposes that the reaction with (*E*)-**6** proceeds through

**Scheme 13**




| 6, *E*/*Z* | 8, *syn*/*anti* | 8, yield, % |
|---|---|---|
| 90/10 | 94/6 | 88 |
| 74/26 | 86/14 | 80 |
| 12/88 | 58/42 | 82 |

a synclinal arrangement $E_2$(S), which has no serious steric interactions, and also potentially benefits from secondary orbital overlap. In contrast, in the reaction with (*Z*)-**6**, both transition states allowing such overlap ($Z_1$(A), $Z_2$(S)) would also experience the steric interaction between $BF_3$ and the methylene carbon or the methyl group of the 2-butenylstannane. The lack of a uniquely favorable transition structure could

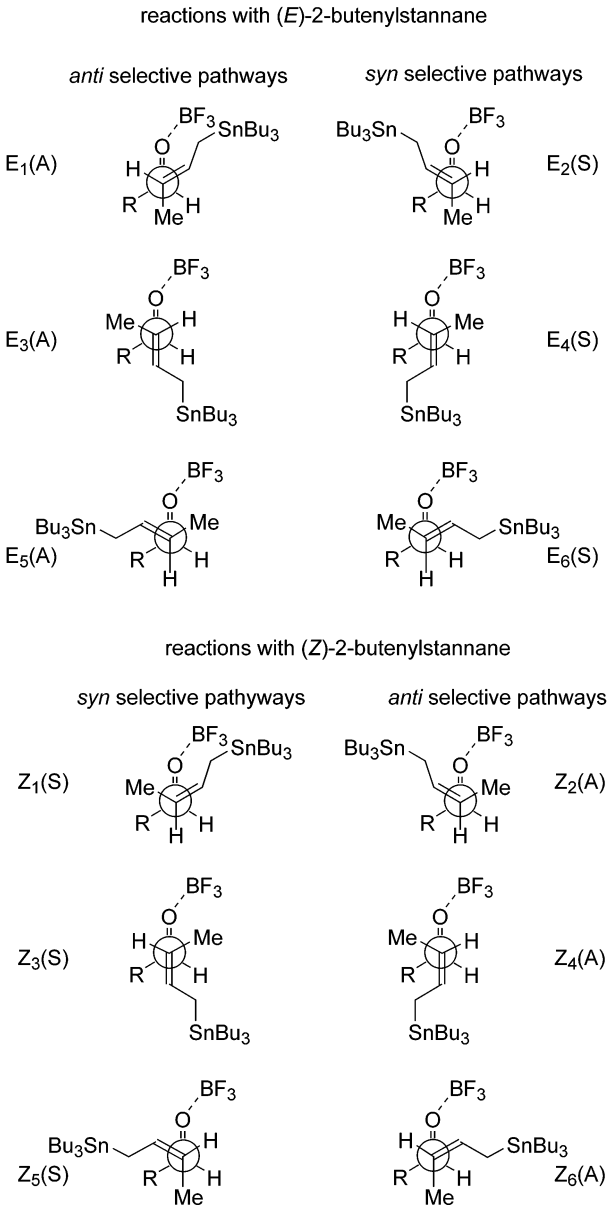



**Figure 6.** Transition structures for the addition of (*E*)- and (*Z*)-**6** to aldehydes promoted by $BF_3$•$OEt_2$.

explain the low selectivity observed in the addition of (*Z*)-**6**.

The stereochemical features of the Lewis acid promoted addition of allylstannanes/silanes to aldehydes can be summarized as follows: (1) the reaction proceeds through an open transition structure with an anti $S_E'$ arrangement of the metal with respect to the aldehyde regardless of the Lewis acid employed and (2) in the addition catalyzed by simple, achiral Lewis acids, the synclinal transition structures are favored from a combination of steric and stereoelectronic contributions. However, these studies have examined only simple achiral Lewis acids. In the reactions catalyzed by chiral Lewis acids, the size and shape of the chiral ligand and the structure of the complex will play a significant role. For example, it has already been noted that, under the influence of a chiral Lewis acid, the reaction can be anti selective.[47,48] Thus, a true understanding of the structure−selectivity correlation requires a detailed analysis of complete transition structure models that take into account all reaction components.

## 2.2. Chiral Lewis Acid-Catalyzed Allylation Reactions

In the view of the importance of chiral Lewis acids in asymmetric catalysis, especially in the enantioselective addition of nucleophiles to carbonyl groups,[49] it is not surprising that many chiral Lewis acids have been employed in the allylation reaction. The discussion of the various chiral agents used in this process is organized according to the nature of the central element.

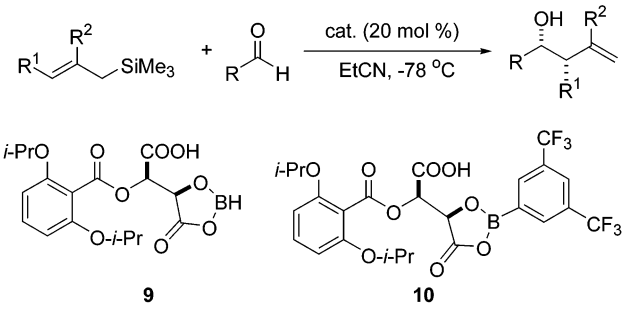
### *2.2.1. Chiral Acyloxy Borane (CAB)-Catalyzed Allylation Reactions*

The first examples of chiral Lewis acid-catalyzed enantioselective allylation of aldehydes were reported by Yamamoto in 1991 using chiral acyloxy borane (CAB) catalysts.[50] The CAB catalyst **9** is prepared by mixing borane·THF with mono(2,6-diisopropoxy)-benzoyltartaric acid. The structure of this complex is proposed to be a five-membered boronic ester. The catalyst is especially effective for the addition of substituted allylic silanes to aromatic aldehydes (Table 3, entries 1−3). With 20 mol % of **9**, a $\beta,\gamma$-disubstituted allylic trimethylsilane undergoes addition to benzaldehyde to give the syn (syn/anti 97/3) homoallylic alcohol with up to 98/2 er (Table 3, entry 1). High syn selectivities are observed regardless of the geometry purity of the starting silane. The addition to aliphatic aldehydes also affords the adducts with high selectivities, but with low yields (entry 2). When **1** is used, the reaction is much slower and less selective (entry 4).

A modified catalyst **10** prepared from the aryl boronic acid 3,5-(bistrifluoromethyl)phenylboronic acid in place of $BH_3$·THF improved both reactivity and enantioselectivity as shown in the addition of methallyltrimethylsilane (entries 3 and 5).[51]

The CAB catalyst has been further applied by Marshall in the addition of allylic stannanes (Table 4).[52] When a sub-stoichiometric amount (20 mol %) of CAB **9** is employed in the addition of substituted

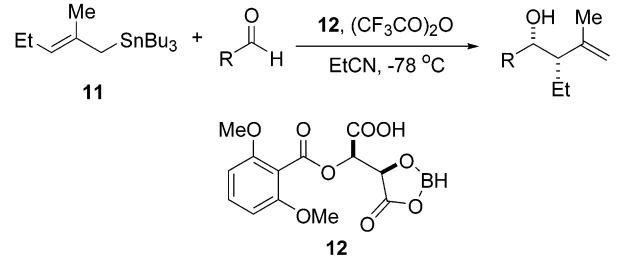
**Table 3. Addition of Allylsilanes Catalyzed by CAB**




| entry | $R^1$ | $R^2$ | R | cat. | yield, % | syn/anti | er |
|---|---|---|---|---|---|---|---|
| 1[a] | Me | Et | Ph | **9** | 74 | 97/3 | 98/2 |
| 2 | Me | Et | $C_3H_7$ | **9** | 36 | 95/5 | 93/7 |
| 3 | H | Me | Ph | **9** | 68 | − | 91/9 |
| 4[b] | H | H | Ph | **9** | 46 | − | 77.5/22.5 |
| 5 | H | Me | Ph | **10** | 99 | − | 94/6 |

[a] $E/Z$ = 65/35. [b] Reaction was done at −20 °C.

**Table 4. Addition of 11 Promoted by 12**



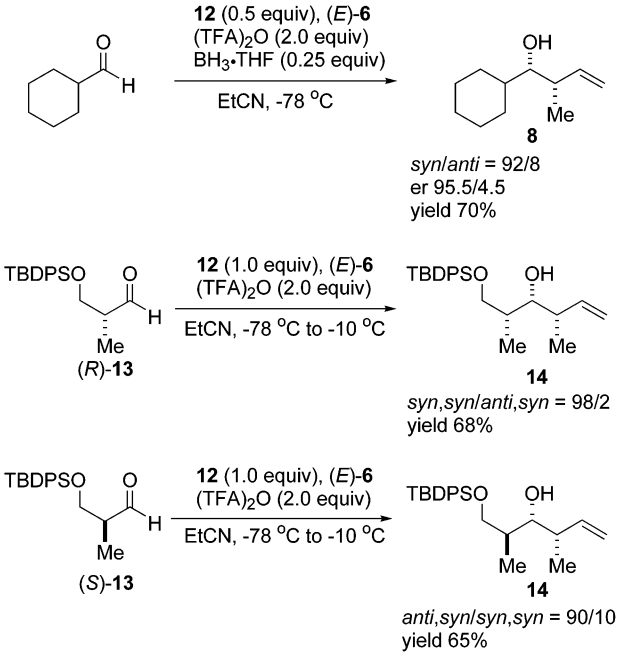

| R | **11** (equiv) | yield, % | syn/anti | er |
|---|---|---|---|---|
| Ph[a] | 0.2 | 40 | 93/7 | 89/11 |
| Ph | 1.0 | 99 | 90/10 | 92.5/7.5 |
| $n$-$C_3H_7$ | 1.0 | 61 | 97/3 | 90.5/9.5 |

[a] Reaction time 5 h with no $(CF_3CO)_2O$.

allylstannane **11** to benzaldehyde, only modest yield (40%) and enantioselectivity (er 89/11) are obtained. Optimized reaction conditions employ 1.0 equiv of **12** and 2.0 equiv of trifluoroacetic anhydride as the turnover reagent. Under these conditions, the addition of **11** to benzaldehyde produces the syn adduct in nearly quantitative yield and with good selectivity, whereas an aliphatic aldehyde affords comparable selectivity but lower yield (entry 3).

The combination of relative, internal, and external stereocontrol has been examined in the addition of 2-butenylstanne (*E*)-**6** to α-branched chiral and achiral aldehydes.[53] Under optimized reaction conditions (50 mol % of **12** and 2.0 equiv of $(CF_3CO)_2O$)), the addition of (*E*)-**6** to cyclohexanecarboxaldehyde affords *syn*-**8** (syn/anti 92/8) in 70% yield and 95.5/4.5 er. In the addition to chiral aldehyde (*R*)-**13**, the internal selectivity (under activation by $BF_3$·$Et_2O$) prefers the formation of *syn*,*syn*-**14** over *anti*,*syn*-**14** with a ratio of 90/10. Activation by the chiral CAB catalyst improves the selectivity for formation of *syn*,*syn*-**14** up to 98/2 (Scheme 14). In the unmatched case with (*S*)-**13**, the CAB catalyst overrides the intrinsic facial preference of aldehyde and affords *anti*,*syn*-**14** with 90/10 selectivity.

**Scheme 14**




To rationalize the stereochemical course of addition, Yamamoto proposed the importance of the $\pi$-facial bias in the aldehyde−Lewis acid complex in the asymmetric induction, although a clear picture of the origin of stereoselection was not presented.[51,54] A model that accounts for the selectivity observed has been proposed by Corey which invokes the formyl CH−O hydrogen bond.[31]

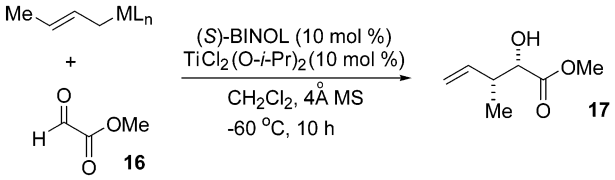
### 2.2.2. Titanium/BINOL-Catalyzed Allylation Reactions

One of the most extensively studied chiral Lewis acid-catalyzed allylation reactions employs titanium complexes of the readily available 1,1′-binaphthalene-2,2′-diol (BINOL) complexes, with Ti(IV) Lewis acids as the catalysts. The application of BINOL/Ti(IV) complexes in enantioselective allylation was first documented by Mikami in the addition of allylic silanes and stannanes to glyoxylates.[55] The catalyst is prepared in situ by mixing $TiCl_2(O\text{-}i\text{-}Pr)_2$ and (*S*)-BINOL in the presence of 4 Å molecular sieves. With 10 mol % of this catalyst, the addition of allylsilane (*E*)-**15** and allylstannane (*E*)-**6** to methyl glyoxylate **16** provides the syn adduct **17** in modest yield and diastereo- and enantioselectivity (Scheme 15). The reactions with simple allylsilane or allylstannane, **1** or **2**, however, are much less selective.

Although an antiperiplanar transition structure has been proposed by Mikami, the higher selectivity observed with (*E*)-**6** is better accounted for by a synclinal transition structure $E_2(S)$, as suggested by Keck (Figure 6).

The extension of the BINOL/Ti(IV) system to aliphatic and aromatic aldehydes was later independently reported by Umani-Ronchi/Tagliavini[56] and Keck.[57] In the procedure developed by Umani-Ronchi/Tagliavini,[56] the catalyst is prepared by combining $TiCl_2(O\text{-}i\text{-}Pr)_2$ with slightly more than 1.0 equiv of (*S*)-BINOL in $CH_2Cl_2$ at room temperature for 2 h in the presence of 4 Å molecular sieves (cat **a**, Table 5). The allylation of aldehydes is then carried

**Scheme 15**



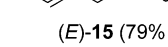
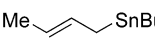
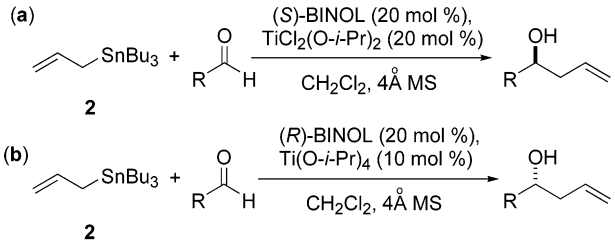

| allylic reagent | yield, % | *syn* (er) / *anti* (er) |
|---|---|---|
|  (*E*)-**15** (79% *E*) | 48 | 83 (80) / 17 (32) |
|  (*E*)-**6** (85% *E*) | 53 | 75 (84) / 25 (16) |

**Table 5. Addition of 2 to Aldehydes Catalyzed by BINOL/Ti(IV) Complexes**



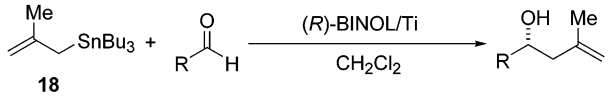

| entry | R | cat. | temp | time, h | yield, % | er |
|---|---|---|---|---|---|---|
| 1 | Ph | **a** | rt | 48 | 96 | 91/9 |
| 2 | Ph | **b** | rt | 3 | 85 | 94.4/5.6 |
| 3 | (*E*)-PhCH=CH | **a** | rt | 24 | 85 | 94.5/5.5 |
| 4 | (*E*)-PhCH=CH | **b** | rt | 43 | 77 | 92.5/7.5 |
| 5 | *c*-$C_6H_{11}$ | **a** | rt | 24 | 75 | 96.3/3.7 |
| 6 | *c*-$C_6H_{11}$ | **b** | 0 °C | 46 | 59 | 91.5/8.5 |
| 7 | $C_7H_{15}$ | **a** | −20 °C | 24 | 83 | 98.7/1.3 |
| 8 | $PhCH_2CH_2$ | **b** | 0 °C | 46 | 91 | 96.5/3.5 |

out with 20 mol % of this (*S*)-BINOL/Ti(IV) complex at −20 °C or room temperature. Both aliphatic and aromatic aldehydes afford the homoallylic alcohols in high yields and enantioselectivities (Table 5). The addition of molecular sieves is found to be extremely important for high reactivity and selectivity. These researchers find that upon mixing equimolar amounts of the BINOL/Ti(IV) complex with allyltributylstannane, a ligand exchange between the titanium complex and allylstannane **2** takes place. However, the resulting allyltitanium complex is not reactive toward aldehydes. Thus, it is proposed that a BINOL−Ti(IV)−allyl complex acts as a chiral Lewis acid that activates the aldehyde toward nucleophilic attack.[58]

Keck developed a similar allylation procedure using the (*R*)-BINOL/$Ti(O\text{-}i\text{-}Pr)_4$ complex as the catalyst.[57,59] In this procedure, the catalyst solution is prepared by combining $Ti(O\text{-}i\text{-}Pr)_4$ with 2.0 equiv of (*R*)-BINOL in dichloromethane solution for 5 min or 1 h, or by refluxing the solution for 1 h (cat **b**, Table 5).[57] The addition of allylstannane **2** to aldehydes catalyzed by 10 mol % of this complex provides the adducts in high yields and enantioselectivities (Table 5). α-Branched aldehydes such as cyclohexanecarboxaldehyde give the lowest yields and enantioselectivities.

The BINOL/Ti(IV) complexes are also effective for the addition of $\beta$-substituted allylic stannanes.[60−64] In the addition of methallylstannane **18**, the reaction condition for each aldehyde need to be optimized by examining four different procedures, including variation of catalyst preparation, reaction temperature, and reaction time.[60] Under the optimal reaction conditions, the adducts are obtained in excellent yields and selectivities (Scheme 16).

**Scheme 16**

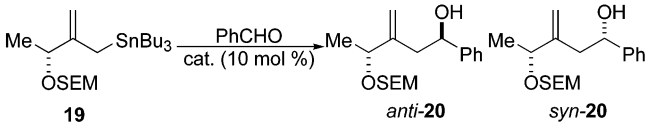



**18**

| R | yield, % | er |
|---|---|---|
| Ph | 95 | 98/2 |
| *c*-$C_6H_{11}$ | 50 | 92/8 |
| furyl | 99 | 99.5/0.5 |
| $PhCH_2CH_2$ | 97 | 99/1 |

The catalyst exhibits high stereocontrol (albeit in modest yield) in the addition of (*R*)-2-(1-silyloxyalkyl)-propenylstannane **19** to benzaldehyde.[64] As shown in Scheme 17, both 1,4-*anti*-**20** and 1,4-*syn*-**20** isomers could be obtained by using either (*R*)- or (*S*)-BINOL as the ligand.

**Scheme 17**



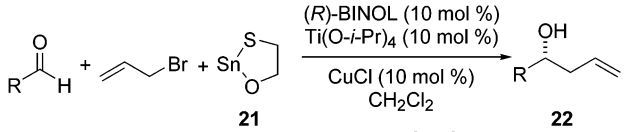

**19** *anti*-**20** *syn*-**20**

| cat. | yield, % | *anti*/*syn* |
|---|---|---|
| (*R*)-BINOL, $TiBr_2(O\text{-}i\text{-}Pr)_2$ | 40 | 92/8 |
| (*S*)-BINOL, $TiBr_2(O\text{-}i\text{-}Pr)_2$ | 30 | 12/88 |

Insight into the mechanism of addition has been provided by the demonstration of positive nonlinear effects in the BINOL/Ti(O-*i*-Pr)$_4$-catalyzed addition of **2**[65] and **18**.[60] This asymmetric amplification has been interpreted in terms of the "two-ligand model" involving the dimeric titanium complex $[BINOL]_2Ti_2X_4$, in which the meso dimer is less kinetically competent as a catalyst than the homochiral dimer.[65] On the basis of this two-ligand model, Corey has proposed that reaction of **2** with the complex results in an allyl−Ti(IV) complex in which the $Bu_3Sn$ group is attached to one of the BINOL oxygens causing dissociation of that oxygen from titanium.[31] Further coordination of aldehyde to this species forms the reactive, trigonal bipyramidal, hydrogen-bonded structure. A reaction through this transition structure would lead to the observed configuration of the homoallylic alcohol ((*R*) from (*R*)-BINOL). This transition structure, however, is valid only if the allylation actually occurs through an intermolecular allyl-transfer process.

The high selectivity and the broad substrate scope of the BINOL/Ti(IV) complexes have stimulated further engineering and modification of the catalytic system. Attempts to use allylic stannane reagents prepared in situ from allylic bromide and Sn(II) complexes such as **21** in the allylation reaction has been reported (Scheme 18).[66] This addition, however, gives much lower er compared to the reaction with **2**.

**Scheme 18**

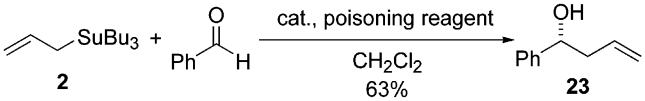



**21** **22**

R = $PhCH_2CH_2$ yield: 49%
er: 81.7/18.3

Faller has developed a chiral poisoning strategy for allylation with **2** using a combination of racemic BINOL and enantiopure diisopropyl D-tartrate (DIPT) (Scheme 19).[65] Although the (D)-DIPT/Ti(O-*i*-Pr)$_4$ complex does not catalyze the addition of **2** to benzaldehyde, a combination of racemic BINOL/Ti(O-*i*-Pr)$_4$ and (D)-DIPT/Ti(O-*i*-Pr)$_4$ does catalyze the allylation and provides the homoallylic alcohol **23** with high enantioselectivity. It was proposed that the (D)-DIPT/Ti(O-*i*-Pr)$_4$ complex selectively poisons the (*R*)-BINOL/Ti(IV) complex, leaving the (*S*)-BINOL/Ti(IV) complex as the reactive catalyst in solution.

**Scheme 19**



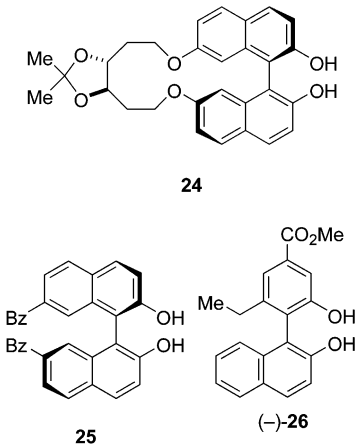

**2** **23**

er 95.5/4.5

cat.: (±)-BINOL (40 mol %), Ti(O-*i*-Pr)$_4$ (40 mol %)
poisoning reagent: (D)-DIPT (60 mol %), Ti(O-*i*-Pr)$_4$ (20 mol %)

Several groups have reported the modification of the chiral titanium complex with other BINOL ligands such as **24**,[67] **25**,[68] and (−)-**26**[69] (Chart 1). Yields and enantioselectivities comparable to those with the parent BINOL/Ti(IV) complex have been obtained.

**Chart 1**

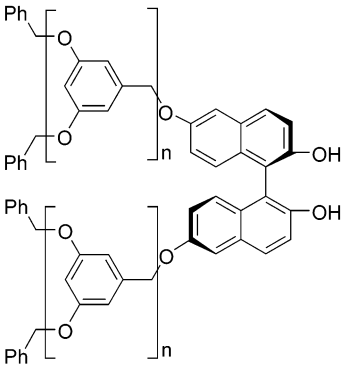



**24** **25** (−)-**26**

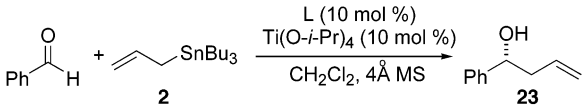
The synthesis and application of dendridic or polymeric BINOL ligands that could potentially benefit from easy separation from the reaction mixture are on record. A series of dendritic BINOL

ligands **27** has been employed in the formation of dendridic BINOL/Ti(IV) complexes.[70] In the allylation of benzaldehyde with **2**, the dendridic BINOL/Ti(IV) complexes show similar reactivities and selectivities to those with monomeric complex, although the yield with monomeric complex is much lower than that originally reported by Keck (Scheme 20).

**Scheme 20**



**27a**: n = 1; **27b**: n = 2; **27c**: n = 3



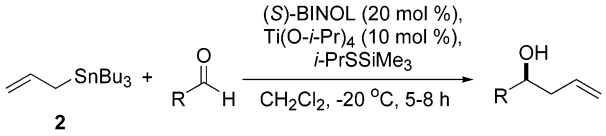

| L | yield, % | er |
|---|---|---|
| **27a** | 18 | 96/4 |
| **27b** | 36 | 94.5/5.5 |
| **27c** | 36 | 94/6 |
| (*R*)-BINOL | 31 | 93.5/6.5 |

On the other hand, a polymeric BINOL/Ti(IV) complex has been prepared from a polymeric BINOL linked at the 6,6′-positions. Interestingly this complex is ineffective in the allylation reaction.[71] It was proposed that due to the rigid structure of the polymer backbone, the titanium centers are isolated and the binaphthyl titanium units cannot dimerize to form the active catalyst.

In general, the allylation reaction catalyzed by the BINOL/Ti(IV) complexes is very slow and often requires extended reaction time, leading to irreproduciblity.[63,70,72] Recently Yu reported that the reaction rate could be enhanced by addition of a stoichiometric amount of an additive such as *i*-PrSSiMe$_3$, *i*-PrSBEt$_3$, *i*-PrSAlEt$_2$, and B(OMe)$_3$.[19,20,21] With 1.2 equiv of *i*-PrSSiMe and 10 mol % of the (*S*)-BINOL/Ti(IV) catalyst, the addition of **2** to hydrocinnamaldehyde affords **22** in 87% yield and 97/3 er after 4 h at −20 °C. Under the same reaction conditions without additive, **22** is obtained in 78% yield after 70 h. The use of *i*-PrSSiMe is generally applicable, and various aldehydes undergo allylation in high yields and enantioselectivities (Scheme 21). These additives are believed to facilitate the dissociation of the product from the reaction complex and thus accelerate the turnover of the catalyst.

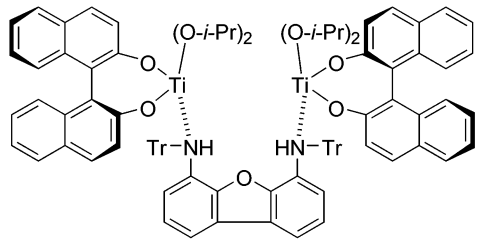
Maruoka has developed a new class of highly reactive and selective titanium complexes for the allylation of aldehydes.[73,74] The catalysts, prepared in situ by mixing Ti(O-*i*-Pr)$_4$, (*S*)-BINOL, and aromatic diamines, are proposed (without evidence) to be bidentate Ti(IV) complexes such as **28** and **29** (Chart 2). The efficiency of the catalyst is demonstrated in the allylation of cinnamaldehyde, a slow substrate in the addition of **2** catalyzed by the BINOL/Ti(IV) catalyst. With 3−5 mol % of catalysts **28** or **29**, the allylation proceeds in high yields and enantioselectivities, whereas the corresponding mono-Ti(IV) complexes such as **30** and **31** give much less satisfactory results under the same reaction conditions (Table 6). These bidentate catalysts are demonstrated to be effective for aromatic and aliphatic aldehydes as well. Recently, Maruoka has described the development of $\mu$-oxo bis(binaphthoxy)(isopropoxy)titanium complexes that display excellent enantioselectivities for the allylation of aldehydes with **2**. These complexes show enhanced reactivity with respect to monomeric BINOL/Ti(IV) catalysts and were also shown to be constitutionally stable (i.e., not in equilibrium with monomers or structurally isomeric dimers).[74b]

**Scheme 21**

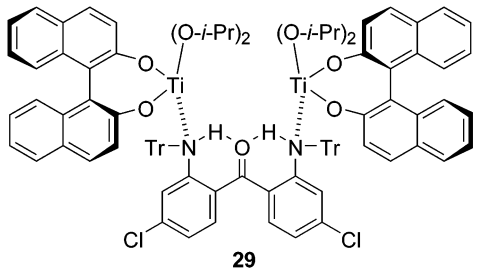



| R | yield, % | er |
|---|---|---|
| $PhCH_2CH_2$ | 87 | 97/3 |
| *c*-Hex | 75 | 92.5/7.5 |
| Ph | 91 | 98.5/1.5 |

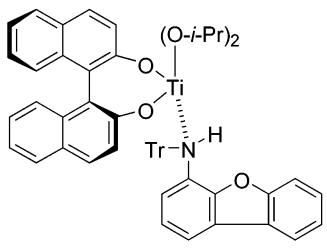
**Chart 2**



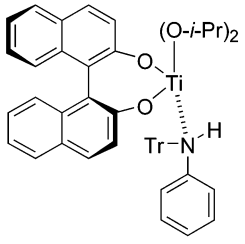

**28**




**29**

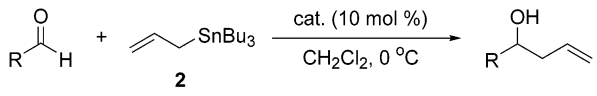



**30**




**31**

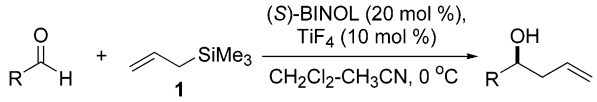
**Table 6. Addition of 2 to Aldehydes Catalyzed by Bidentate Ti Complexes**




| R | cat. | time, h | yield, % | er |
|---|---|---|---|---|
| (*E*)-PhCH=CH | **28** | 10 | 83 | 98/2 |
| (*E*)-PhCH=CH | **29** | 10 | 79 | 98.5/1.5 |
| (*E*)-PhCH=CH | **30** | 10 | 8 | 92.5/7.5 |
| (*E*)-PhCH=CH | **31** | 10 | 17 | 96/4 |
| Ph | **28** | 2.5 | 94 | 99/1 |
| $PhCH_2CH_2$ | **28** | 3 | 90 | 98.5/1.5 |

Because the BINOL/Ti(IV) catalysts are relatively weak Lewis acids, they found little use for promoting reaction with the less nucleophilic (and less toxic) allylic silanes. An elegant solution to this problem was devised by Carreira, who found that enhanced reactivity could be secured by the use of $TiF_4$ in place of Ti(O-*i*-Pr)$_4$ (Scheme 22).[75,76] With 10 mol % of the catalyst prepared in situ by mixing (*S*)-BINOL and $TiF_4$ in $CH_3CN$ solution, up to 97/3 er is obtained with α,α-disubstituted aldehydes. Simple aldehydes, however, give only modest enantioselectivities.

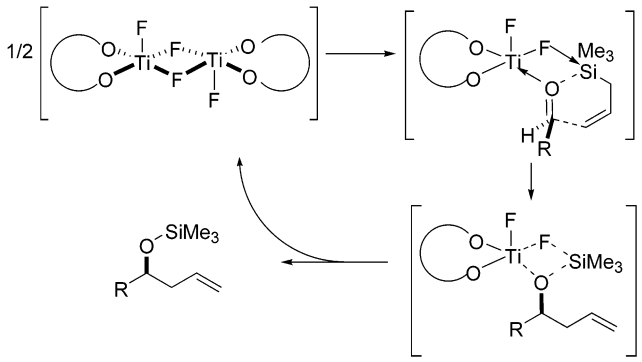
**Scheme 22**




| R | yield, % | er |
|---|---|---|
| $(CH_3)_3C$ | 91 | 97/3 |
| PhCHO | 85 | 90/10 |
| c-$C_6H_{11}$ | 72 | 80/20 |
| $PhCH_2CH_2$ | 69 | 80.5/19.5 |

Carreira attributed the high reactivity of the catalyst to two important factors: (1) the strong Lewis acidity of $TiF_4$ derived complexes and (2) the greater strength of the Ti−F bond compared to the Si−F bond which assists in catalyst turnover.[75] In addition, Duthaler proposed a ternary transition structure in which the electrophilic titanium center activates the aldehyde and the nucleophilic fluoride bridge to silicon increases the reactivity of allylsilane (Scheme 23).[77] A reaction that proceeds with this transition structure could directly give the silylated adduct with regeneration of the catalyst. This catalytic process also exhibits a positive nonlinear relationship between the enantiomeric of the BINOL and the resulting homoallylic alcohol. However, the Duthaler proposal in Scheme 23 invokes a "reservoir" model to explain this behavior rather than the "two-ligand" model proposed for the other BINOL/Ti(IV) systems.[65]

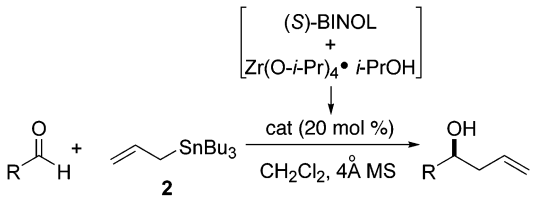
**Scheme 23**




### 2.2.3. Zirconium/BINOL-Catalyzed Allylation Reactions

The success of the BINOL/Ti(IV) catalyst systems naturally stimulated a significant effort to improve the reactivity limitations and to improve the scope of the process. In a logical extension, Tagliavini investigated the use of BINOL/Zr(IV) complexes for the addition of allyltributylstannane to aldehydes.[78,79] The catalyst (of unknown structure) prepared from (*S*)-BINOL and Zr(O-*i*-Pr)•*i*-PrOH is especially effective for the allylation of aromatic and unsaturated aldehydes (Table 7). It was proposed that the less crowed complex can better accommodate the sterically more demanding aromatic aldehydes. The allylation of cyclohexanecarboxaldehyde, however, produces a low yield, which is partially due to the competing Meerwein−Ponndorf−Verley-type reduction. A nonlinear relationship between the enantiopurity of the catalyst and that of the product is also observed, indicating a nonmonomeric catalyst structure.

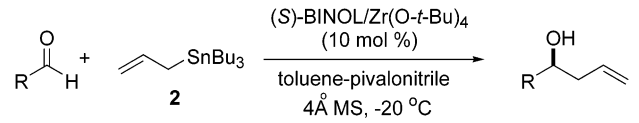
**Table 7. Addition of 2 to Aldehydes Catalyzed by the BINOL/Zr(IV) Complex**




| R | conditions | yield, % | er |
|---|---|---|---|
| Ph | −40 °C, 6 h | 79 | 96.4/3.6 |
| (*E*)-PhCH=CH | −20 °C, 3 h | 81 | 95.5/4.5 |
| *n*-$C_7H_{15}$ | 0 °C, 6 h | 58 | 93.6/6.4 |
| *c*-$C_6H_{11}$ | −20 °C, 6 h | 34 | 95.2/4.8 |

The efficiency of the BINOL/Zr(IV) catalyst was improved in a detailed study reported by Kurosu.[80] The addition of **2** to aldehydes was optimized by using a BINOL/Zr(O-*t*-Bu)$_4$ combination as the catalyst in toluene solution. Several critical effects were noted: (1) the reaction can proceed at −78 to −60 °C but requires 1.5 equiv of promoter to reach completion, (2) executing the reaction at 0 °C causes reduction of the aldehyde, (3) the addition of 4 Å molecular sieves minimizes the self-condensation of aldehydes, (4) the addition of pivalonitrile (10 mol %) has a beneficial effect on the enantioselectivity, and (5) an excess of **2** is necessary for high conversions. Under these optimized reaction conditions, a number of different aldehydes undergo allylation in high yields and enantioselectivities (Table 8).

**Table 8. Addition of 2 to Aldehydes Catalyzed by the BINOL/Zr(O-*t*-Bu)$_4$ Complex**

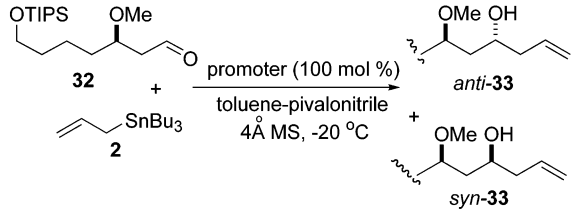



| entry | R | time, h | yield, % | er |
|---|---|---|---|---|
| 1 | Ph | 1.5 | 90 | 95/5 |
| 2 | (*E*)-PhCH=CH | 2.5 | 85 | 96.5/3.5 |
| 3 | $PhCH_2CH_2$ | 2.5 | 85 | 96.5/3.5 |
| 4 | $TBSOCH_2CH_2$ | 2.5 | 75 | 96/4 |
| 5[a] | $BnOCH_2CH_2$ | 2.5 | 88 | 96.5/3.5 |

[a] 20 mol % of catalyst was used.

The BINOL/Zr(O-*t*-Bu)$_4$ catalyst exhibits modest stereocontrol in the allylation of chiral *β*-hydroxy-aldehyde **32** (Scheme 24). In the matched case using (*R*)-BINOL/Zr(O-*t*-Bu)$_4$, the 1,3-diol, *anti*-**33** is obtained with 8.5/1 selectivity. In contrast, the unmatched case with (*S*)-BINOL/Zr(O-*t*-Bu)$_4$ catalyst gives *anti*-**33** only with a dr of 2.3/1.

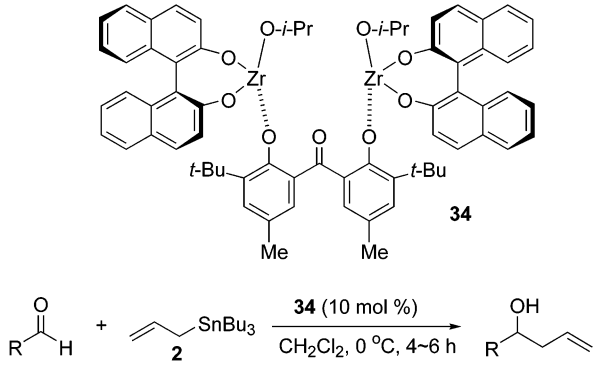
**Scheme 24**




| promoter | yield, % | *anti*/*syn* |
|---|---|---|
| (*S*)-BINOL-Zr(O-*t*-Bu)$_4$ | 90 | 2.3/1 |
| (*R*)-BINOL-Zr(O-*t*-Bu)$_4$ | 90 | 8.5/1 |

Maruoka has applied the ligand dimerization concept to generate a highly reactive, selective BINOL/Zr(IV) catalyst (with hypothetical structure **34**), which provides high yields and enantioselectivities for the allylation of various aldehydes (Scheme 25).[81] The use of Zr as the metal is essential for the high efficiency of the catalyst, as the bidentate complexes with other metals such as Ti and Hf give rather low yields and enantioselectivities.

**Scheme 25**

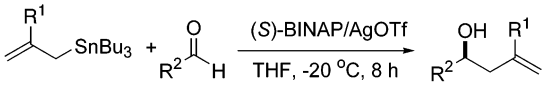



| R | yield, % | er |
|---|---|---|
| Ph | 91 | 97/3 |
| $PhCH_2CH_2$ | 82 | 97/3 |
| $C_7H_{15}$ | 76 | 96.5/3.5 |

### *2.2.4. Silver/BINAP-Catalyzed Allylation Reactions*

The 1,1′-binaphthyl skeleton is premier among the privileged enantioselective catalyst architectures and has already been shown effective in the use of BINOL derived catalysts. In a further evolution of this concept, Yamamoto developed silver/phosphine complexes as catalysts for the addition of allylic stannanes and allylic silanes to aldehydes.[82] Initially, it was found that the addition of **2** to benzaldehyde catalyzed by silver triflate is significantly accelerated by the addition of a phosphine ligand.[82] A survey of chiral phosphine ligands and silver salts revealed that the combination of (*S*)-2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl (BINAP) and silver triflate provides the best reactivity and selectivity. For example, a 5 mol % loading of the (*S*)-BINAP/AgOTf complex catalyzes the addition of **2** and **18** to aromatic aldehydes and gives the adducts with up to 98/2 er and 88% yield (Scheme 26). Lower yields are obtained when aliphatic aldehydes are used.

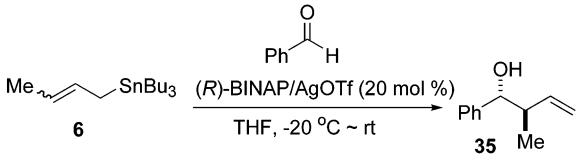
**Scheme 26**




| $R^1$ | $R^2$ | cat. (mol %) | yield, % | er |
|---|---|---|---|---|
| H | Ph | 5 | 88 | 98/2 |
| H | (*E*)-PhCH=CH | 15 | 83 | 94/6 |
| H | $PhCH_2CH_2$ | 20 | 47 | 94/6 |
| Me | Ph | 5 | 75 | 96/4 |

The addition of 2-butenylstannanes to benzaldehyde catalyzed by the BINAP/AgOTf complex was also studied (Scheme 27).[83] With 20 mol % of (*R*)-BINAP/AgOTf, the addition of 2-butenylstannane (*E*)-**6** to benzaldehyde provides *anti*-**35** (anti/syn, 95/5) in 56% yield and 97/3 er. The anti/syn ratio of the product is found to be independent of the geometrical composition of the starting 2-butenylstannane. These results are contrary to the selectivity observed in other Lewis acid-catalyzed additions of 2-butenylstannanes to aldehydes, in which the reaction generally is syn selective. This unusual anti selective stereoconvergence (type III reaction[4]) is rationalized

**Scheme 27**




| 6 *E*/*Z* | yield, % | *anti* (er) / *syn* (er) |
|---|---|---|
| 95:5 | 56 | 85 (97/3) / 15 (82/28) |
| 2:98 | 72 | 85 (95.5/4.5) / 15 (75/25) |
| 53:47 | 45 | 85 (97/3) / 15 (78.5/21.5) |

by invoking an antiperiplanar transition structure, which has the least steric interaction between the BINAP/Ag complex and the methyl group of the 2-butenylstannane (Figure 7). An alternative cyclic transition structure was also proposed, which may arise via transmetalation of the 2-butenylstannane to a 2-butenylsilver reagent. However, this pathway is still speculative since no transmetalation is observed when allylstannane is mixed with equimolar amount of BINAP/AgOTf complex.

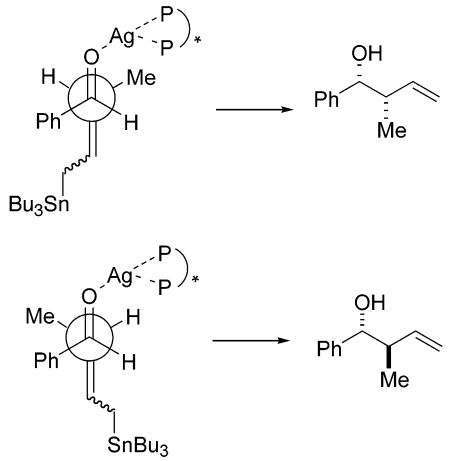



**Figure 7.** Transition structures for the addition of **6** catalyzed by BINAP/AgOTf.

The reactivity of the 2,4-pentadienylstannane **36** is also examined with this catalyst.[84] The addition to benzaldehyde affords the $\gamma$-pentadienylated product **37** with a 95/5 er (Figure 8). Due to the high $\gamma$-selectivity observed, it was concluded that the reaction proceeds via a cyclic transition structure since an acyclic transition structure in a Lewis acid-catalyzed process would likely lead to the $\epsilon$-adduct. Two possible cyclic transition structures are proposed. If the BINAP/Ag complex functions as a Lewis acid, the reaction could proceed through a six-membered cyclic model with both silver and tin coordinating to the aldehyde. An alternative mechanism involving transmetalation and a cyclic transition structure with a BINAP-coordinated silver is also proposed.[47] Because the absolute configuration of the

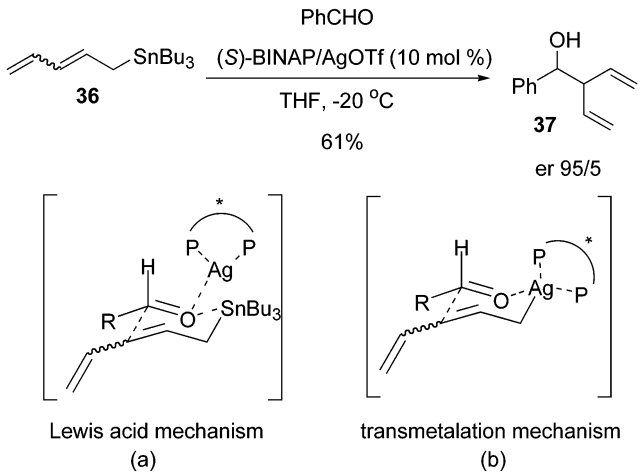
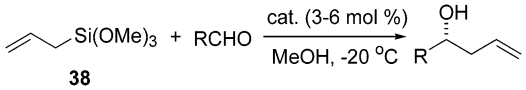



**Figure 8.** Transition structure for the addition of **36** catalyzed by BINAP/AgOTf.

products is not established, the correlation of reaction pathways for **6** and **36** cannot be assured.

Allyltrimethoxysilanes display sufficient reactivity to function as effective nucleophiles in allylation reactions catalyzed by the BINAP/silver salt complexes.[85] Interestingly, whereas the BINAP/AgOTf complex is ineffective here, the use of AgF in place of AgOTf produces satisfactory results. With 1.5 equiv of allyltrimethoxysilane **38** and 5 mol % of the BINAP/AgF complex in MeOH, benzaldehyde undergoes allylation in 84% yield and 96.5/3.5 er (Table 9). Employing (*R*)-*p*-Tol-BINAP gives similar yields and enantioselectivities compared to those obtained with (*R*)-BINAP. The interaction of the fluoride with the trialkoxysilane moiety is proposed to be important for the high reactivity observed with AgF complex in this case.

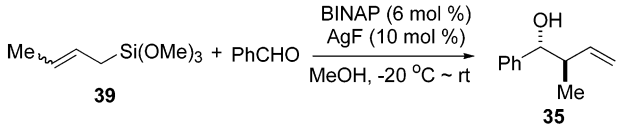
**Table 9. Addition of 38 to Aldehydes Catalyzed by Chiral Phosphine/Silver Complexes**



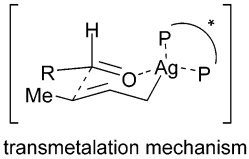

| cat. | R | yield, % | er |
|---|---|---|---|
| (*R*)-BINAP/AgF | Ph | 84 | 96.5/3.5 |
| (*R*)-*p*-Tol-BINAP/AgF | Ph | 80 | 97/3 |
| (*R*)-*p*-Tol-BINAP/AgF | (*E*)-PhCH=CH | 93 | 89/11 |
| (*R*)-*p*-Tol-BINAP/AgF | 2-furyl | 70 | 91.5/8.5 |

Extension of this protocol to the addition of 2-butenyltrimethoxysilanes **39** revealed that anti adducts are obtained with high diastereoselectivities and enantioselectivities regardless of the geometric composition of the silanes (Scheme 28). In an effort to elucidate the reaction mechanism, it was found that upon mixing **39** with the BINAP/AgF complex and DMF in $CH_3OD$ solvent, no peaks of the 2-butenylsilanes are observed in $^1H$ NMR spectrum. Thus, a transmetalation mechanism is proposed (in contrast to the reactions with 2-butenylstannanes) which involves a fast isomerization of 2-butenylsilver reagent prior to the addition to aldehyde through a closed, chairlike transition structure. The reaction, however, has not yet been extended to aliphatic aldehydes.

**Scheme 28**




| **39** *E*/*Z* | yield, % | *anti* (er) : *syn* (er) |
|---|---|---|
| 83:17 | 77 | 92 (98/2) : 8 (81/19) |
| <1:99 | 82 | 94 (97/3) : 6 (80/20) |
| 45:55 | 99 | 93 (97/3) : 7 (80/20) |




transmetalation mechanism

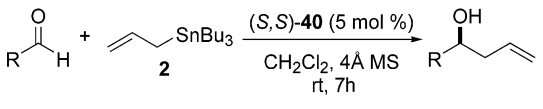
Other variations of the chiral phosphine/silver complex systems (with **2**) include the development of aqueous reaction conditions[86] and the use of a chiral diphenylthiophosphoramide as the ligand.[87] Neither of these modifications has led to significant improvements compared to the original process.

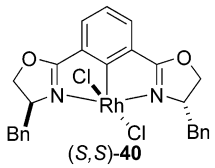
### 2.2.5. Rhodium-Catalyzed Allylation Reactions

The use of chiral rhodium complexes as catalysts in the enantioselective allylation was initially reported by Nuss.[88] With 1 mol % of Rh(COD)[(−)-(DIOP)]$BF_4$, the addition of **2** to benzaldehyde provides the adduct in high yield, albeit with little asymmetric induction (17%).

Better results were obtained by Nishiyama, who developed chiral bis(oxazolinyl)phenylrhodium(III) complexes as the catalysts for the addition of allylic stannanes to aldehydes.[48,89] With 5 mol % of (*S*,*S*)-**40**, the addition of **2** to aldehydes provided the homoallylic alcohols in good yields but still modest enantioselectivities (Scheme 29). The sense of asymmetric induction observed with (*S*,*S*)-**40** is rationalized by a transition structure in which the nucleophile approaches from the *Si*-face of the complexed aldehyde because of the shielding of the *Re*-face by the oxazoline substituent. This model is presented in detail below in the discussion of catalyzed additions with (*E*)- and (*Z*)-**6**.

**Scheme 29**



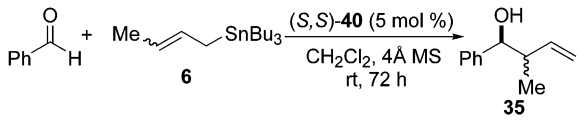




| R | yield, % | er |
|---|---|---|
| Ph | 88 | 80.5/19.5 |
| (*E*)-PhCH=CH | 98 | 88.5/11.5 |
| $PhCH_2CH_2$ | 84 | 81.5/18.3 |

The addition of 2-butenylstannes **6** catalyzed by (*S*,*S*)-**40** is slightly anti-selective, independent of the geometrical composition of the stannanes (Figure 9).[48] In analyzing the usual anti selectivity observed, several antiperiplanar and synclinal transition structures are considered. Among these, the antiperiplanar transition structures are proposed to be favored because the synclinal arrangements (c, d) engender steric interactions between the stannane moiety and the catalyst (Figure 9). Of the two antiperiplanar transition structures **a** and **b**, reaction through **a** leading to the anti adduct may be favored due to the steric repulsion between the methyl group on **6** and the chloride on the catalyst in **b**. Clearly the ligands on the Lewis acid have a profound effect on the coordination geometry and influence the diastereoselectivity.

### 2.2.6. Zinc-Catalyzed Allylation Reactions

Zinc(II) complexes with chiral bisoxazolines **41**,[90] **42**,[91] or bipyridine **43**[92] as ligands have been employed in the addition of **2** to aldehydes. These reactions produce the homoallylic alcohols with high yields, but with modest enantioselectivities (Table 10).




| 6, *E*/*Z* | yield, % | *anti*(er)/*syn*(er) |
|---|---|---|
| 95/5 | 77 | 71 (78.5/21.5)/29 (54/46) |
| 2/98 | 85 | 63 (80/20)/37 (53.5/46.5) |

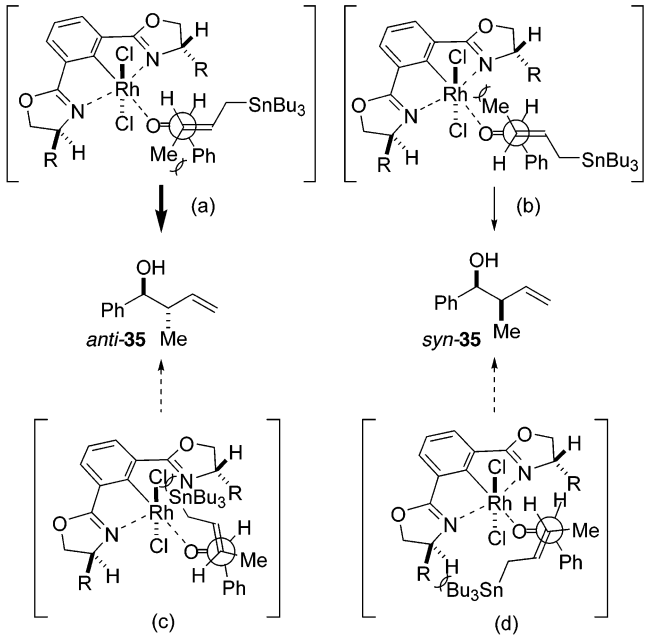
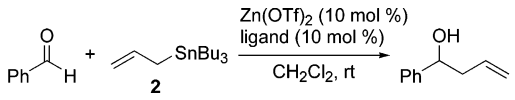
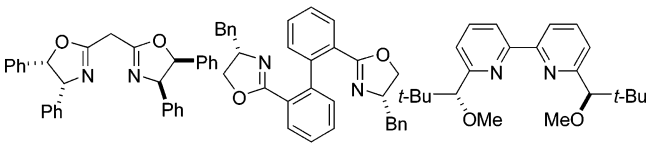



**Figure 9.** Proposed transition structures for the addition of **6** catalyzed by (*S*,*S*)-**40**.

**Table 10. Addition of 2 to Benzaldehyde Catalyzed by Chiral Zinc Complexes**



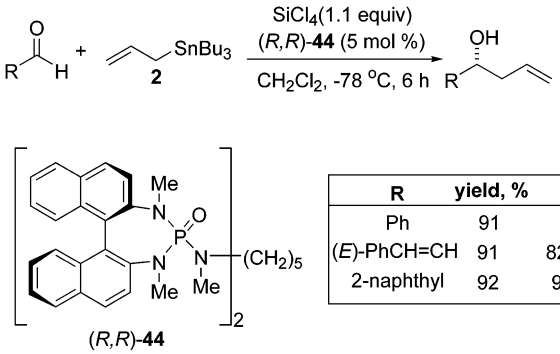

| entry | ligand | time, h | yield, % | er |
|---|---|---|---|---|
| 1 | **41** | 30 | 80 | 67.5/32.5 |
| 2 | **42** | 72 | 54 | 61/39 |
| 3 | **43** | 21 | 92 | 69.5/30.5 |

### 2.2.7. Silicon Tetrachloride/Bisphosphoramide-Catalyzed Allylation Reactions

The chiral Lewis acid catalysts described so far are generated by the combination of a strong Lewis acid ($BH_3$, $TiCl_2$(O-*i*-Pr)$_2$, $TiF_4$, AgF) with a chiral ligand either in situ or in separate preparation. Recently, Denmark has developed a novel method for the generation of a chiral Lewis acid by activation of a weak Lewis acid with a chiral Lewis base.[93] This activation has been achieved by combination of $SiCl_4$ and a catalytic amount of chiral phosphoramide. Whereas $SiCl_4$ does not promote the addition of

addition of **2** to benzaldehyde, the action of a catalytic amount of chiral phosphoramide (*R*,*R*)-**44** significantly enhances the reaction rate, allowing the addition to take place at −78 °C. With 5 mol % of (*R*,*R*)-**44**, up to 97/3 er is achieved in the addition of **2** to benzaldehyde (Scheme 30). Aliphatic aldehydes, however, do not provide addition products.

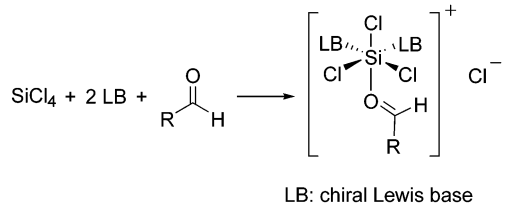
**Scheme 30**




| R | yield, % | er |
|---|---|---|
| Ph | 91 | 97/3 |
| (*E*)-PhCH=CH | 91 | 82.5/17.5 |
| 2-naphthyl | 92 | 96.5/3.5 |

Interestingly, the bisphosphoramide (*R*,*R*)-**44** provides higher enantioselectivity than bisphosphoramides with other tether lengths. This observation supports the hypothesis that two phosphoramides are involved in the rate and stereochemistry determining steps. For silicon to accommodate two phosphoramides and the aldehyde in a hexacoordinate array, ionization of a chloride anion must be proposed. Thus, the origin of activation by phosphoramide has been attributed the formation of cationic, silicon species (Scheme 31).

**Scheme 31**




### *2.2.8. Chiral Lewis Acid-Catalyzed Addition of Allylborane Reagents*

Chirally modified allylic boranes are among the most successful reagents for type I reactions.[4] The Lewis acidity of the boron atom, ease of modification with chiral ligands, and organized transition structures lead to high yields and selectivities. It is thus surprising to find that external Lewis acids can enhance the rate of reaction of allylic boronates. Although the enantioselectivities are not yet competitive with other methods, the diastereoselectivity with 2-butenylboronates is striking. Moreover, the novelty of the reactions and the potential for asymmetric catalysis certainly warrants discussion here.

Whereas the reaction of allylboronate **45** with benzaldehyde requires 14 days at room temperature to reach completion, Hall and co-workers discovered that the reaction rate could be enhanced by the addition of 10 mol % of a Lewis acid (Figure 10).[94] Among the Lewis acids surveyed, $Cu(OTf)_2$, $Sc(OTf)_3$, and $Yb(OTf)_3$ provide the greatest rate enhancement. Furthermore, the diastereomeric ratio of the product **46** correlates well with the geometric composition of the allylboronates. This has been observed previously in the uncatalyzed reaction of **45** with aldehydes,[95] which suggests a closed, chairlike transition structure.

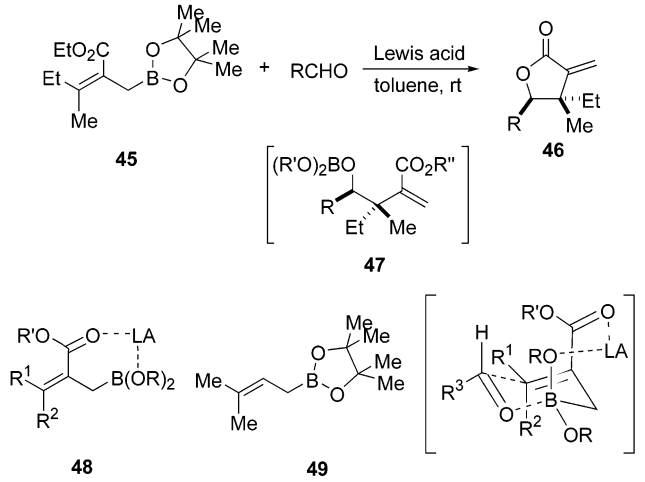


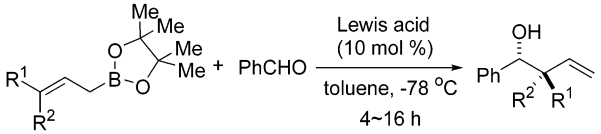

**Figure 10.** Proposed transition structures for the addition of **45** catalyzed by Lewis acid.

In a study to elucidate the origin of activation by Lewis acids, it was found that a mixture of the allylic boronate and $Sc(OTf)_3$ forms a defined 1/1 complex, the structure of which is suggested to be the chelated complex **48** (Figure 10). These observations led to a proposed transition structure which involves a seven-membered metal-activated complex assembled within the usual chairlike transition structure. It is proposed that the coordination of the Lewis acid to one of the alkoxy groups increases the Lewis acidity of the boron atom, which enables it to coordinate to the aldehyde. The importance of the 2-alkoxycarbonyl group is demonstrated by comparison to the rate of addition with allylboronate **49**, in which the magnitude of the enhancement in the presence of a Lewis acid is smaller than that observed for **45**. The decrease in half-life of reaction between the catalyzed ($Sc(OTf)_3$) and the uncatalyzed reaction is about 35 times for **45** and only 3 times for **49**.

In an independent study, Ishiyama reported that the rate difference between the catalyzed and uncatalyzed addition of allylic boronates **50** to aldehydes is found to be significant at −78 °C (Table 11).[96] Whereas the addition of **50a** to benzaldehyde does not proceed at all in the absence of a Lewis acid at −78 °C, a variety of Lewis acids such as $AlCl_3$ and $Sc(OTf)_3$ do catalyze the reaction to afford the corresponding homoallylic alcohol. Furthermore, the addition of (*E*)- or (*Z*)-2-butenylboronic esters **50b** and **50c** to benzaldehyde produces the syn and anti homoallylic alcohols with high diastereoselectivities. The potential for achieving asymmetric induction has been demonstrated with the use of the $Et_2AlCl$/BINOL complex. With 10 mol % of this complex, the addition of 2-butenylboronic esters to benzaldehyde produces the homoallylic alcohols with high dia-

stereoselectivities, although the yields and enantioselectivities are only modest. The origin of activation in this case, however, still remains unclear.

**Table 11. Addition of Allylboronates to Benzaldehyde Catalyzed by Lewis Acids**




**50a**: $R^1$ = H, $R^2$ = H;
**50b**: $R^1$ = Me, $R^2$ = H;
**50c**: $R^1$ = H, $R^2$ = Me

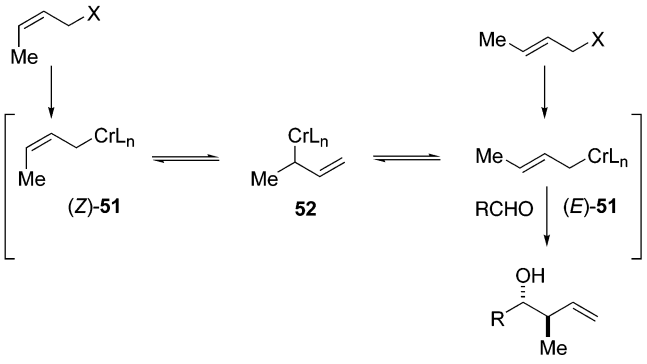
| boronate | Lewis acid | yield, % | anti/syn | er |
|---|---|---|---|---|
| **50a** | $AlCl_3$ | 88 | – | – |
| **50a** | $Sc(OTf)_3$ | 80 | – | – |
| **50b** | $AlCl_3$ | 92 | 99/1 | – |
| **50c** | $AlCl_3$ | 87 | 2/98 | – |
| **50b** | $Et_2AlCl$/BINOL | 40 | 99/1 | 75.5/24.5 |
| **50c** | $Et_2AlCl$/BINOL | 19 | 2/98 | 54/46 |

## *3. Catalytic Enantioselective Allylation with Allylic Halides*

### 3.1. Chromium-Mediated Allylation Reactions

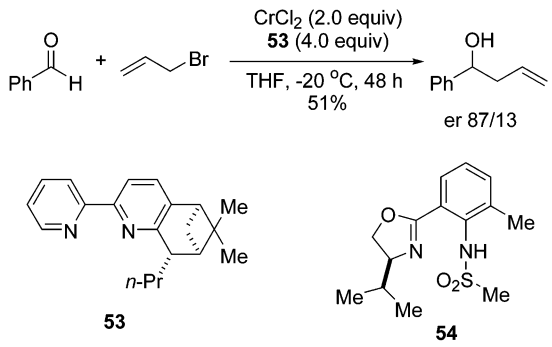
The generation of allylic organometallic reagents in situ from allylic halides and various metals is synthetically advantageous because it does not require the preparation, isolation and handling of toxic or sensitive reagents. One of the most useful examples of this class is the chromium-mediated addition of allylic halides to aldehydes,[97] which was first reported by Hiyama.[98] The addition of 2-butenyl halides to aldehydes produces the anti homoallylic alcohols regardless of the geometry of the starting alkene (Scheme 32). The convergent anti-diastereoselectivity (type III reactions[4]) is explained by isomerization of the (*Z*)-2-butenylchromium reagent (*Z*)-**51** to the (*E*)-2-butenylchromium reagent (*E*)-**51** via the intermediate 1-butenylchromium species **52** followed by the addition to aldehydes through a closed, chair-like transition structure.

**Scheme 32**



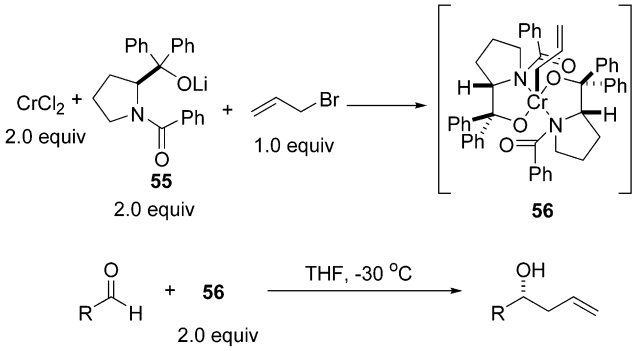

The development of an asymmetric variant of these additions first employed chiral pyridine ligands for the allylic chromium reagents (Scheme 33).[99] The allylation of benzaldehyde was carried out with 2.0 equiv of allylic bromide, 2.0 equiv of $CrCl_2$, and 4.0 equiv of the chiral pyridine **53** to give the homoallylic alcohol in 51% yield and 87/13 er. Recently, Kishi also applied sulfonamide ligands such as **54** in these additions.[100,101] The enantioselectivities however, still remain modest.

**Scheme 33**




Kibayashi reported improved enantioselectivity by the use of the chiral (dialkoxyallyl)chromium(III) reagent derived from proline (Scheme 34).[102] The allyl chromium reagent **56** is prepared by combining the lithium alkoxide **55** and $CrCl_2$ followed by treatment with allyl bromide. The addition of this allylic chromium reagent to aldehydes was then carried out at −30 °C. Whereas electron-poor aromatic aldehydes give up to 99/1 er, much lower selectivities are obtained with aliphatic and electron rich aromatic aldehydes.

**Scheme 34**







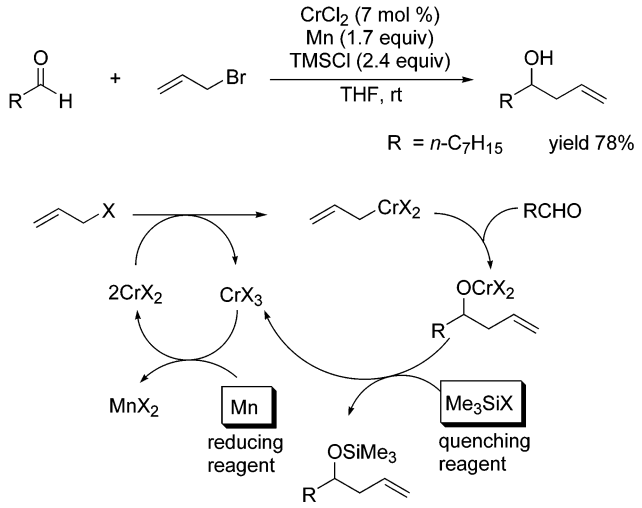
| R | yield, % | er |
|---|---|---|
| 4-$MeOC_6H_4$ | 84 | 74.5/25.5 |
| $C_6H_5$ | 62 | 91/9 |
| 4-$ClC_6H_4$ | 47 | 99/1 |
| $PhCH_2CH_2$ | 60 | 80.5/19.5 |

These results show that chromium reagents modified with chiral ligands are able to provide some level of asymmetric induction. However, these procedures require a stoichiometric amount of the chiral ligands (4.0 equiv) as well as the toxic chromium salts.

Significant progress toward a catalytic process was reported by Fürstner (Scheme 35).[103,104] With a stoichiometric amount of manganese as the bulk reducing reagent and TMSCl as the quenching and

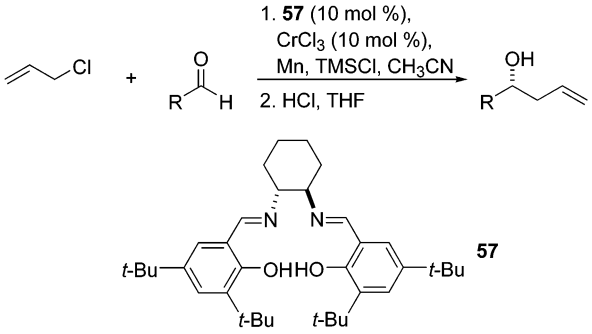
turnover reagent, the addition of allylic halides such as allyl bromide to aldehydes can be achieved with only a catalytic amount of $CrCl_2$.

**Scheme 35**




Umani-Ronchi has recently adapted this process to achieve the first catalytic, enantioselective variant of this reaction.[105,106] In this study, a chiral chromium salen complex is employed, and details of the preparation of the catalyst are found to be crucial for high selectivity and reactivity (Scheme 36). An optimized procedure requires the in situ reduction of the anhydrous $CrCl_3$ to $CrCl_2$ with an excess of Mn, followed by complexation with the salen ligand **57** in the presence of $Et_3N$ (20 mol %) to form the chiral [Cr(salen)] complex. The addition of allylic halides to aldehydes is then conducted at room temperature with 10 mol % of the complex. Among the allylic halides surveyed, allyl chloride provides the adduct with the best yield and enantioselectivity. Both aromatic and aliphatic aldehydes react under those conditions, and up to 94.5/5.5 er is obtained in the addition to cyclohexanecarboxaldehyde. However, the yields of the addition are only modest, which is partly due to the competing pinacol coupling reaction.

**Scheme 36**




| R | yield, % | er |
|---|---|---|
| Ph | 67 | 92/8 |
| $c$-$C_6H_{11}$ | 42 | 95/5 |
| $PhCH_2CH_2$ | 45 | 88.5/11.5 |

The catalytic system has been extended to the addition of 2-butenyl halides to aldehydes (Figure 11).[107] While 2-butenyl chloride does not react, modest yield could be obtained when more reactive 2-butenyl bromide (**58**) is used. The diastereoselectivity observed is highly dependent on the ratio of the salen ligand **57** to $CrCl_2$ and not on the geometrical composition of the 2-butenyl bromide. The reaction is, as expected, anti-selective (90/10) in the absence of ligand but, surprisingly, switches to syn selectivity in the presence of **57**. Selectivity as high as 83/17, syn/anti is obtained in the presence of **57** (**57**/Cr, 2/1), and the syn product has an er of 94.5/5.5.

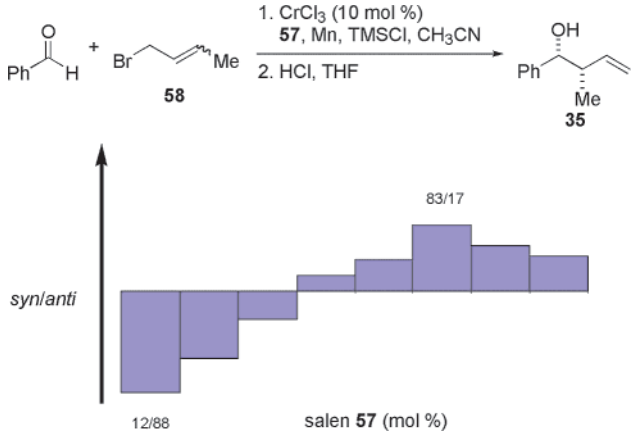
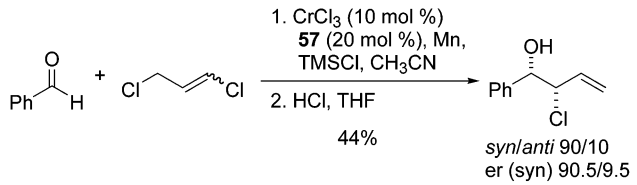



**Figure 11.** Dependence of diastereoselectivity on the ratio of salen/$CrCl_2$.

To explain the need for a second equiv of the salen ligand, a transition structure has been proposed in which one molecule of [Cr(salen)-allyl] and one molecule of [Cr(salen)X] work synergistically in the stereo-differentiating step.[108] The involvement of more than one salen ligand is supported by nonlinear effect and kinetics studies. An acyclic transition structure in which the aldehyde is coordinated by the weakly acidic [Cr(salen)X] moiety is proposed to explain the observed syn-selective addition.

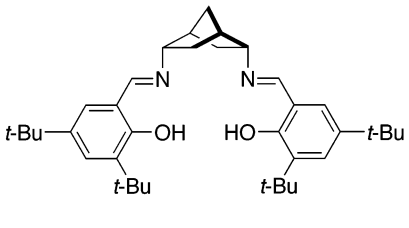
The Cr/salen complex also catalyzes the addition of 1,3-dichloropropene to aromatic aldehydes and provides the syn chlorohydrin adduct in modest yield and selectivity (Scheme 37).[109]

**Scheme 37**

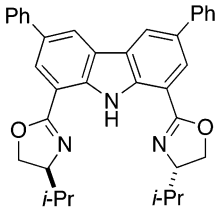



Paterson has recently reported the use of an analogous salen catalyst **59** for enantioselective allylation and vinylation of aldehydes with modest to high enantioselectivities (Chart 3).[110] In addition, Nakada has developed a bis(oxazolinyl)carbazole ligand **60** (Chart 3) for enantioselective allylation and methallylation.[111] This ligand is notable because it forms a stable, recylcable chromium complex and affords generally high yields and enantioselectivities.

**Chart 3**




**59**

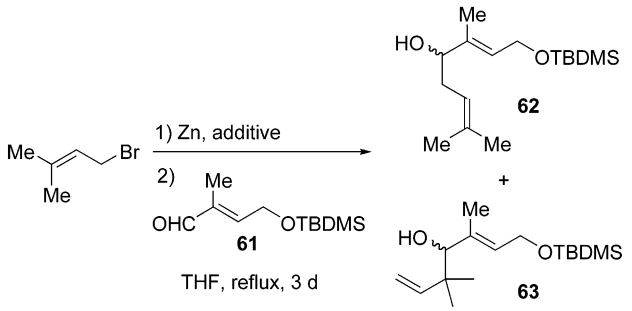


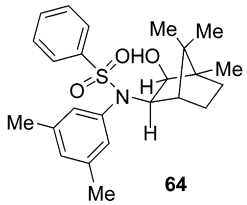

**60**

## 3.2. Zinc-Mediated Allylation

The enantioselective addition of organozinc reagents to aldehydes is one of the most well studied enantioselective organometallic processes.[112] However, the use of allylic zinc reagents as the nucleophiles has not been well developed. Hong and coworkers recently reported an asymmetric α-selective addition of prenylzinc to unsaturated aldehyde **61** (Table 12).[113] The use of prenylzinc alone produces predominately the γ-adduct **63**. In the presence of HMPA (15 equiv), although the initial addition affords the γ-adduct, after refluxing the reaction mixture for 3 days, the α-adduct **62** is isolated in high yield. These observations suggested a reversible γ-addition but an irreversible formation of the α-adduct. To achieve asymmetric induction, several chiral ligands were surveyed, and it was found that the α-adduct **62** could be obtained in up to 97/3 er in the presence of 1.5 equiv of **64**. However, the enantioselectivity decreases to 86/14 when only 0.2 equiv of ligand is used.

**Table 12. Addition of Prenyl Bromide to 61 Mediated by Zinc**



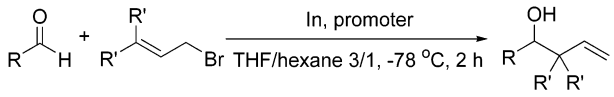

**64**

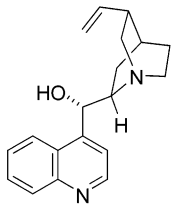
| additive, (equiv) | **62**/**63** | **62**, er | yield, % |
|---|---|---|---|
| none | 7/93 | | 90 |
| HMPA (15) | 94/6 | | 89 |
| **64** (1.5), HMPA (15) | 94/6 | 97/3 | 87 |
| **64** (0.2), HMPA (15) | 94/6 | 86/14 | 87 |

## 3.3. Indium-Mediated Allylation

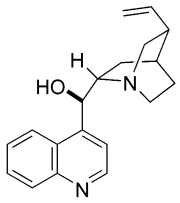
An enantioselective allylation of aldehydes with allylic halides mediated by indium has been reported.[114] With a stoichiometric amount of chiral ligands such as (+)-cinchonine **65** and (−)-cinchonidine **66**, allylindium reagents, generated in situ from an allylic bromide and indium powder, undergo addition to aldehydes and provide the homoallylic alcohols in high yields (Table 13). The enantioselectivities, however, are only modest, though in one case, up to 95/5 er is observed in the prenylation of benzaldehyde. Attempts to use a sub-stoichiometric amount of chiral ligands results in much lower enantioselectivity.

**Table 13. Addition of Allylic Bromides to Aldehydes Mediated by Indium**




**65**




**66**

| R | R′ | promoter | yield, % | er (*R*/*S*) |
|---|---|---|---|---|
| Ph | Me | **65** | 98 | 12/88 |
| Ph | Me | **66** | 99 | 95/5 |
| *n*-$C_8H_{17}$ | H | **66** | 69 | 21.5/78.5 |

## *4. Chiral Lewis Base-Catalyzed Addition of Allylic Trichlorosilanes*

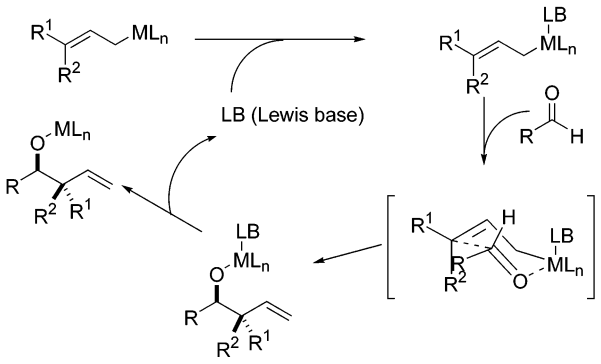
Although high enantioselectivities have been achieved in the allylation catalyzed by chiral Lewis acids, the advantages of catalysis are significantly offset by the lack, in general, of diastereocontrol because of the nonrigid nature of the transition structure for most additions. A mechanistically distinct process that addresses the problem of relative diastereocontrol is the Lewis base-catalyzed addition of allylic trichlorosilanes to aldehydes.[115] The demonstration that Lewis bases promote this addition in a fundamentally different way than Lewis acids activate the addition of allylic trialkylsilanes and stannanes provided the crucial foundation for the invention of a new enantioselective process that would have greater stereochemical control and generality.

## 4.1. Lewis Base-Promoted Allylation

The general scheme by which Lewis bases activate allyltrihalometal reagents begins by coordination of the base to the central, electrophilic element (Scheme 38). The resulting complex retains sufficient Lewis acidity to coordinate the aldehyde, and the ternary complex of allylmetal, aldehyde, and chiral Lewis base reacts through a closed transition structure. This reactive intermediate could provide an opportunity to control diastereoselectivity as well as to allow the chirality of the chiral Lewis base to be expressed at the reaction field. Finally, the dissocia-

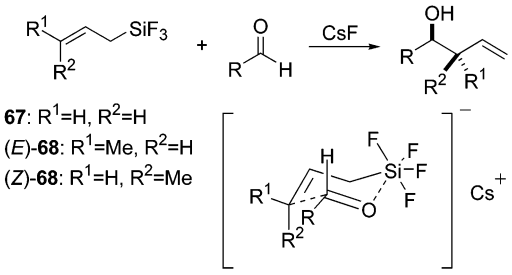
tion of the Lewis base from the product trichlorosilyl ether is required for catalyst turnover so it can reenter the cycle. This turnover event is made possible by the noncovalent association between the chiral Lewis base and chlorosilane substrate.

**Scheme 38**



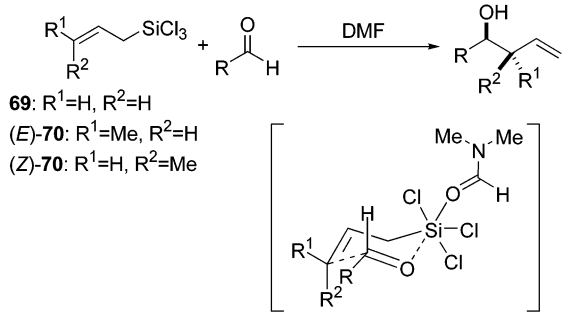

The use of anionic activators or strong donor solvents in the allylation of aldehydes has been pioneered by Sakurai[116,117] and Kobayashi.[118−120] Sakurai reported that the addition of allylic trifluorosilanes **67** to aldehydes could be promoted by fluoride ion as well as by catecholates to provide homoallylic alcohols with high regioselectivities (Scheme 39).[116,121,122] Most importantly, the addition of 2-butenylsilanes (*E*)- and (*Z*)-**68** is highly diastereoselective; (*E*)-**68** provides the anti-homoallylic alcohol, and the (*Z*)-**68** provides the syn-homoallyl alcohol. Thus, it is proposed that the reaction proceeds through a closed, chairlike transition structure organized around the silicon.

**Scheme 39**




In a related study, Kobayashi and co-workers described the stereoselective allylation of aldehydes with allylic trichlorosilanes **69** in dimethylformamide (Scheme 40).[118−120] In this system as well, the 2-butenyltrichlorosilanes ((*E*)- and (*Z*)-**70**) reacted

**Scheme 40**

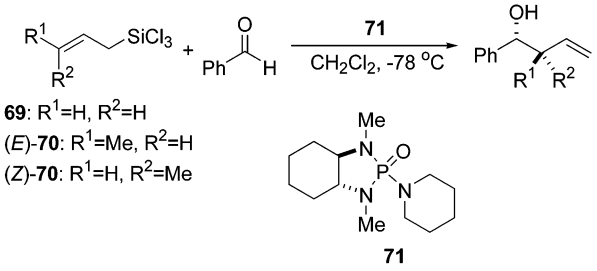



stereospecifically, thus permitting the formulation of a closed, chairlike transition structure through activation by DMF.

## 4.2. Chiral Phosphoramide-Catalyzed Allylation Reactions

The ability of silicon to expand its coordination number to accommodate the Lewis base and aldehyde clearly suggested the opportunity for asymmetric catalysis. The use of chiral Lewis bases as promoters for the asymmetric allylation and crotylation was first demonstrated by Denmark in 1994 (Table 14).[123] With a stoichiometric amount of chiral phosphoramide **71** derived from (*R*,*R*)-*trans*-1,2-cyclohexanediamine as the promoter, the addition of allyltrichlorosilane (**69**) to benzaldehyde provides the homoallylic alcohol in high yield, yet with modest enantioselectivity (er 80/20). More importantly, the addition of (*E*)- and (*Z*)-**70** affords the anti and syn adducts, respectively, with high diastereoselectivities, which clearly supports the operation of a closed, chairlike transition structure for these additions as well. The potential for a catalytic process is demonstrated by the use of 0.1 equiv of promoter. After 24 h at −78 °C, the product is isolated in 40% yield and with slightly lower er (76.5/23.5).

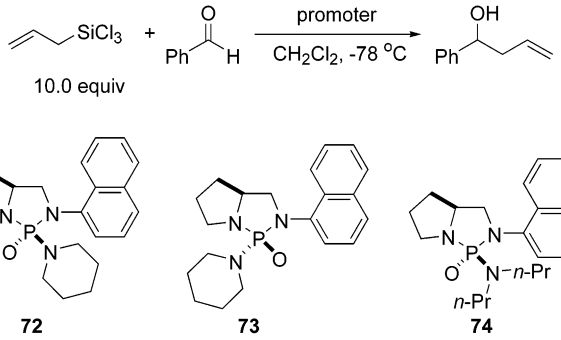
**Table 14. Addition of Allylic Trichlorosilanes to Benzaldehyde Promoted by (*R*,*R*)-71**




| silane | **71**, equiv | yield, % | anti/syn | er |
|---|---|---|---|---|
| **69** | 1.0 | 80 | − | 80/20 |
| (*E*)-**70** | 1.0 | 68 | 98/2 | 83/17 |
| (*Z*)-**70** | 1.0 | 72 | 2/98 | 80/20 |
| **69** | 0.1 | 40 | − | 76.5/23.5 |

Iseki reported an improvement in the addition selectivity by the use of chiral phosphoramides derived from (*S*)-proline.[124,125] A stoichiometric amount of phosphoramide **72** effectively promotes the allylation of benzaldehyde with 10 equiv of **69** and provides the adduct with 74% yield and 85.5/14.5 er (Table 15). The selectivity is highly dependent on the configuration on the phosphorus atom and the substituents on the nitrogen. For example, in contrast to the results form **72**, only 5% yield and 64.5/35.5 er are obtained with the diastereomeric phosphoramide **73**. Furthermore, by changing the exocyclic nitrogen substituent from a piperidinyl to a dipropylamino group in phosphoramide **74**, the enantiomeric adduct is formed with similar selectivity. The promoter is also effective at 10 mol % loadings, although it requires exceedingly long reaction time (7 days) and a 10-fold excess of **69**.

**Table 15. Addition of 69 to Benzaldehyde Catalyzed by 72−74**




| promoter | loading, equiv | time, h | yield, % | er, (*R*/*S*) |
|---|---|---|---|---|
| **72** | 1.0 | 6 | 74 | 85.5/14.5 |
| **73** | 1.0 | 6 | 5 | 64.5/35.5 |
| **74** | 1.0 | 6 | 84 | 7.5/92.5 |
| **72**[a] | 0.1 | 168 | 67 | 92.5/7.5 |

[a] Reaction in THF.

The low reactivity and selectivity observed in chiral Lewis base promoted allylation as well as the dependence of enantioselectivity on the promoter loading has been addressed by Denmark in a mechanistic investigation.[126] From a combination of nonlinear effect and kinetics studies, the reaction promoted by **71** is found to be second-order in phosphoramide though a first-order, less selective pathway can be competitive at lower phosphoramide concentration. Postulating the involvement of two phosphoramides in the transition structure requires the ionization of one chloride ion to produce a hexacoordinate cationic silicon species. The involvement of ionic species as intermediates is also supported by the effect of ammonium salts on the reactivity of **69** reported by Berrisford.[127] In the reaction of **69** with benzaldehyde, the addition of 1.0 equiv of *n*-$Bu_4N^+I^-$ slightly enhances the reaction rate. This rate enhancement may be explained by an increase in the ionic strength of the medium, which stabilizes the charged intermediates. Thus, the origin of activation with phosphoramides is suggested to be the enhanced Lewis acidity of the silicon in the cationic complex together with the increased nucleophilicity of the allyl group.

The generalized transition structures for the cationic reaction pathways involving one or two phosphoramides are shown in Figure 12. In the monophosphoramide pathway, the reactive intermediate is proposed to be a trigonal bipyramidal pentacoordinate siliconate, whereas in the diphosphoramide pathway, an octahedral hexacoordinate siliconate is

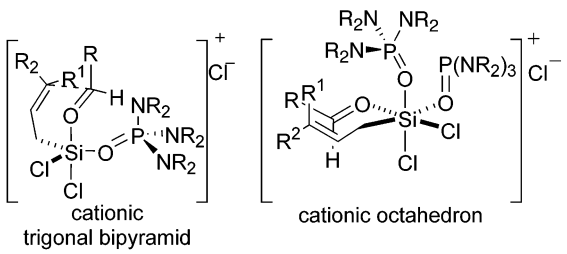
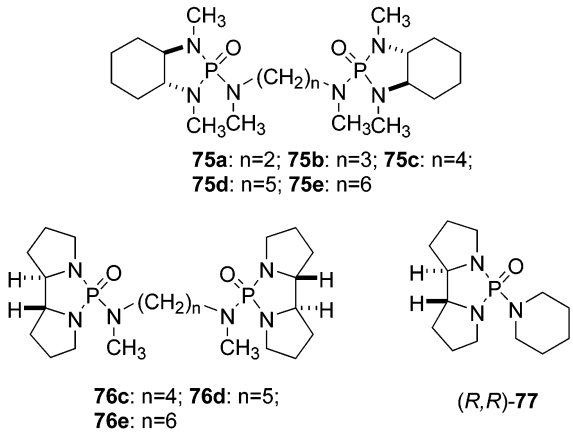



**Figure 12.** Penta- and hexacoordinate cationic silicon assemblies.

suggested. It is clear that the enantioselectivity obtained from the former pathway would be less than that in the latter because of the diminished influence of a single chiral promoter compared to the influence to two chiral ligands.

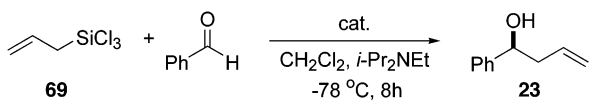
Although mechanistically intriguing, the dual pathways have adverse effects on the rate and selectivity of the process. First, because the reaction is second-order in the catalyst, the rate falls off as the square of catalyst concentration. Second, at lower concentration, a competing, less selective (one phosphoramide) pathway can compromise the overall reaction selectivity. The dilemma of dual mechanistic pathways has been addressed by the use of bisphosphoramides **75** with the expectation of increasing the effective concentration of the second catalyst molecule through proximity (Chart 4).[126] A systematic investigation of the tether reveals that the highest er (up to 86/14) is provided by bisphosphoramide **75d**, in which the two basic functions are separated by a five-methylene unit.

**Chart 4**




The enantioselectivity is further improved with the use of bisphosphoramide (*R*)-(*l*,*l*)-**76d** based on the (*R*,*R*)-2,2′-bispyrrolidine skeleton.[128] The bisphosphoramide (*R*)-(*l*,*l*)-**76d** catalyzed the allylation of benzaldehyde at 5 mol % loading to give the homoallylic alcohol in high yield and enantioselectivity. For this series as well, the dimer with a five-methylene tether provides superior selectivity and enantioselectivity compared to the bisphosphoramides (*R*)-(*l*,*l*)-**76c** and (*R*)-(*l*,*l*)-**76e** (with different tether lengths) and the monophosphoramide (*R*)-**77** (Table 16). The strong cooperativity of the dimers and the enhanced selectivity compared to (*R*)-(*l*,*l*)-**77**

**Table 16. Addition of 69 to Benzaldehyde Catalyzed (*R*)-(*l*,*l*)-76 and (*R*,*R*)-77**

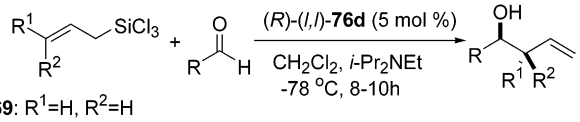



| cat., (mol %) | er | yield, % |
|---|---|---|
| **76a** (5) | 59/41 | 54 |
| **76b** (5) | 93.5/6.5 | 85 |
| **76c** (5) | 83.5/16.5 | 58 |
| **77** (20) | 78/22 | 56 |

supports the hypothesis of a two-phosphoramide pathway. In these additions, 5.0 equiv of *i*-PrNEt is used as an additive, the role of which has been proposed to help catalyst turnover.[129]

With a 5 mol % loading of (*R*)−(*l*,*l*)-**76d**, aromatic, heteroaromatic, and unsaturated aldehydes all undergo allylation in good yields and selectivities (Table 17). The additions of (*E*)-**70** and (*Z*)-**70** are also highly diastereoselective and enantioselective. Moreover, $\gamma$-disubstituted allylic trichlorosilane **78** provides prenylation products with excellent enantioselectivities. The *Z*-substituent has a beneficial effect on the selectivity, as evidenced by the highly selective syn-crotylation and prenylation process.

**Table 17. Addition of Allylic Trichlorosilanes to Aldehydes Catalyzed by (*R*)-(*l*,*l*)-76**

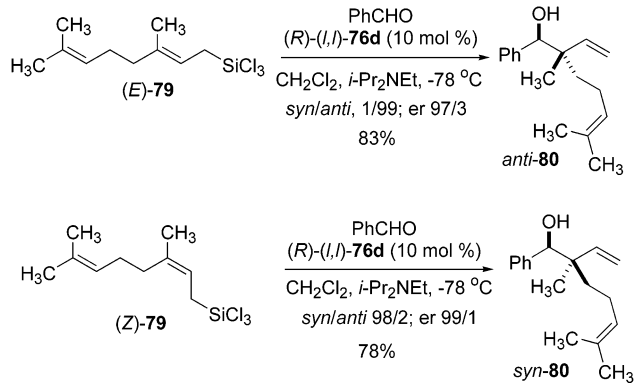



**69**: $R^1$=H, $R^2$=H
(*E*)-**70**: $R^1$=Me, $R^2$=H
(*Z*)-**70**: $R^1$=H, $R^2$=Me
**78**: $R^1$=$R^2$=Me

| silane | R | yield, % | syn/anti | er |
|---|---|---|---|---|
| **69** | Ph | 85 | | 93.5/6.5 |
| **69** | (*E*)-$C_6H_5CH$=CH | 86 | | 90.5/9.5 |
| **69** | 2-furyl | 59 | | 90.5/9.5 |
| (*E*)-**70** | Ph | 82 | 1/99 | 93/7 |
| (*E*)-**70** | (*E*)-$C_6H_5CH$=CH | 57 | 1/99 | 90/10 |
| (*Z*)-**70** | Ph | 89 | 99/1 | 97/3 |
| (*Z*)-**70** | (*E*)-$C_6H_5CH$=CH | 78 | 99/1 | 94/6 |
| (*Z*)-**70** | (*E*)-$C_6H_5CH$=C($CH_3$) | 62 | 95/5 | 96/4 |
| (*Z*)-**70** | 2-furyl | 82 | 99/1 | 97.5/2.5 |
| **78** | Ph | 89 | | 98/2 |
| **78** | (*E*)-$C_6H_5CH$=CH | 70 | | 94/6 |
| **78** | 2-furyl | 71 | | 97.5/2.5 |

This allylation method has been applied to construct quaternary stereogenic centers by the addition of unsymmetrical $\gamma$-disubstituted allyltrichlorosilanes to aldehydes (Scheme 41).[128] The trisubstituted silanes (*E*)- and (*Z*)-**79** are synthesized from corresponding alcohol in geometrically pure form in two steps.[120,128] The catalyzed addition of these reagents to benzaldehyde provides the adducts *anti*-**80** and *syn*-**80** with excellent diastereo- and enantioselectivities (Scheme 41), which represents the first catalytic, enantioselective generation of stereogenic quaternary carbon centers by the allylation reaction.

**Scheme 41**




To understand the correlation of bisphosphoramide structure and reaction selectivity, solution and solid-state studies on the bisphosphoramide·$SnCl_4$ complexes have been carried out.[130] The formation of *cis*-configured, octahedral 1/1 bisphosphoramide·$SnCl_4$ complexes is supported by both crystallographic and solution NMR studies. On the basis of the X-ray crystallographic analysis of **76d**·$SnCl_4$, a transition structure has been proposed to explain the observed selectivities. In putative reactive complex, the allyl group is proposed to reside trans to the phosphoramide, rendering it more nucleophilic. At the same time, the aldehyde is coordinated trans to the chloride to increase its electrophilicity. Thus, in the hypothetical arrangement a (Figure 13) is not favored because of the steric interaction between the allyl group, in particular, the Z-substituent on the allylsilane and the $\beta$-pyrrolidine ring. Thus, the reaction proceeds through transition structure **b** (Figure 13) to give the observed homoallylic alcohol with *S* configuration at the hydroxyl center. The strong interaction between the *Z*-substituent and the $\beta$-pyrrolidine ring also explains the beneficial effect of the *Z*-substituent on the enantioselectivity observed in the syn-crotylation and prenylation reactions. The solution and solid-state structure studies also revealed that the unique features of (*R*)-(*l*,*l*)-**76d** are its ability to function as a bidentate ligand and thus bring the chiral environment close to the reaction center along with the highly asymmetric environment created by the 2,2′-bispyrrolidine backbone.

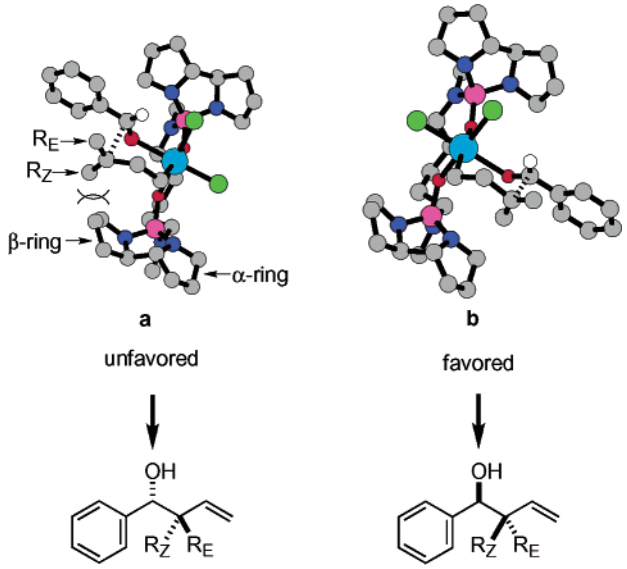


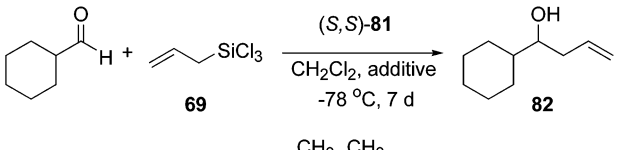

**Figure 13.** Proposed transition structures for the addition of allylic trichlorosilanes catalyzed by (*R*)-(*l*,*l*)-**76d**.

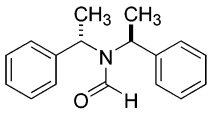
## 4.3. Chiral Formamide-Catalyzed Allylation Reactions

Following on the original observation by Kobayashi that DMF (as solvent) promoted the allylation of aldehydes with **69**, Iseki developed chiral DMF analogues for enantioselective additions.[131,132] A stoichiometric amount of chiral formamide (*S*,*S*)-**81** promotes the allylation of cyclohexanecarboxaldehyde to give the adduct (*R*)-**82** in 81% yield and 84/17 er

after 7 days at −78 °C using 10 equiv of allylic trichlorosilane (Table 18, entry 1). Interestingly, when a catalytic amount of (*S*,*S*)-**81** is used, the enantiomeric product (*S*)-**82** is obtained in low yield and selectivity (entry 2). A change in the sense of enantioselectivity is clearly indicative of the operation of dual catalytic pathways for formamides as well. In this case, however, the two pathways (one and two formamide) give enantiomeric products. The addition of HMPA is found to be beneficial for both the reaction and rate and selectivity. With 1.0 equiv of HMPA as an additive, the enantioselectivity increases to 98/2 er, and it is rather insensitive to the promoter loading (entry 3, 4). Under the optimized reaction conditions, with 20 mol % of (*S*,*S*)-**81**, 1.0 equiv of HMPA, and 1.5 equiv of allylic trichlorosilane in propionitrile at −78 °C for 14 days, the adduct could be obtained in 80% yield and 99/1 er. The addition of 2-butenylsilanes is even more sluggish, requiring 21 days for complete reaction. The diastereoselectivity and enantioselectivity are quite high for (*E*)-**70** but less so for (*Z*)-**70**. A transition structure with both HMPA and formamide bound to silicon is proposed to account for the effect of HMPA on both reactivity and enantioselectivity. However, this model is not consistent with a nonlinear effect observed in the reaction catalyzed by (*S*,*S*)-**81**.

**Table 18. Addition of Allyltrichlorosilane Promoted by (*S*,*S*)-81**[a]



(*S*,*S*)-**81**

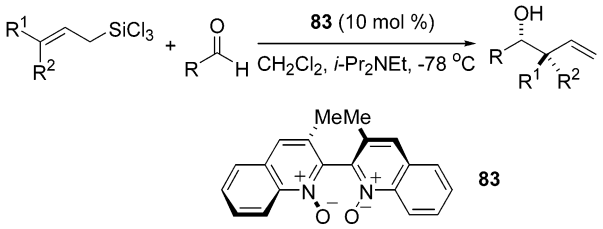
| entry | (*S*,*S*)-**81**, equiv | HMPA, equiv | er (*R*/*S*) | yield, % |
|---|---|---|---|---|
| 1 | 1.0 | − | 84/16 | 81 |
| 2 | 0.1 | − | 34/66 | 12 |
| 3 | 1.0 | 1.0 | 98/2 | 89 |
| 4 | 0.25 | 1.0 | 97/3 | 33 |
| 5[b] | 0.2 | 1.0 | 99/1 | 80 |

[a] Reaction done in $CH_2Cl_2$ with 10.0 equiv of **69**. [b] Reaction done in $C_2H_5CN$ solvent for 14 days with 1.5 equiv of **69**.

## 4.4. Chiral N-Oxide-Catalyzed Allylation Reactions

Chiral *N*-oxides have emerged as another class of highly selective catalysts for the addition of allylic trichlorosilanes.[129,133,134] With 10 mol % of biquinoline *N*,*N*-dioxide **83**, the addition of **69** to benzaldehyde affords the adduct with 94/6 er (Scheme 42).[129] The addition of 5.0 equiv of *i*-$Pr_2NEt$ dramatically accelerates the reaction, allowing high yield to be obtained at 10 mol % loading of the catalyst. High diastereoselectivities are observed in the addition of (*E*)- and (*Z*)-2-butenylsilanes, suggesting a six-membered, chairlike transition structure.

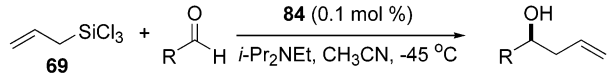
**Scheme 42**



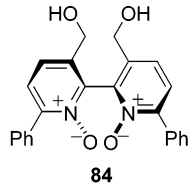

| silane | yield, % | *anti*/*syn* | er |
|---|---|---|---|
| **69**: $R^1 = R^2 = H$ | 85 | - | 94/6 |
| (*E*)-**70**: $R^1$ = Me, $R^2$ = H | 68 | 97/3 | 93/7 |
| (*Z*)-**70**: $R^1$ = H, $R^2$ = Me | 64 | 1/99 | 92/8 |

Hayashi has developed the more reactive bis-*N*-oxide **84** for the addition of **69** to aromatic aldehydes. With this catalyst, high conversion is achieved with as low as 0.1 mol % loading (Scheme 43).[134] The observed enantioselectivity is highly dependent on the electronic nature of the aldehyde. Whereas up to 97/3 er is obtained with electron-rich aldehydes, electron-deficient aldehydes produce much lower selectivities. The high reactivity observed with **84** is ascribed to possible $\pi-\pi$ stacking between the phenyl group at the 6,6′-position and the aromatic ring of the aldehyde in the transition structure.

**Scheme 43**




| R | yield, % | er |
|---|---|---|
| Ph | 95 | 92/8 |
| 4-$MeOC_6H_4$ | 96 | 97/3 |
| 4-$CF_3C_6H_4$ | 83 | 78/22 |

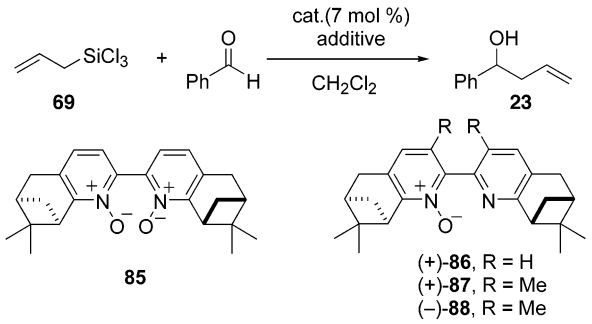


**84**

In a further modification of the bipyridyl motif, Kocovsky reported the use of 2,2′-bipyridiyl *N*-monoxides as catalysts for the allylation reaction (Table 19).[133] Whereas the bis-*N*-oxide **85** derived from (+)-nopinone catalyzes the addition with rather low er (70.5/29.5) and yield (18%), much higher selectivity (er 94.5/5.5) is obtained with the corresponding *N*-monoxide (+)-**86**. The yield is further optimized by carrying out the reaction below −60 °C and by the addition of *n*-$Bu_4N^+I^-$. It is proposed that the preferred geometry of the ligand in the transition structure is dictated by the twist about 2,2′-bipyridyl axis, which in turn is controlled by the configuration of the terpene moieties. Because the atropoisomers of **86** could not be isolated, methyl groups at the 3,3′-positions are introduced to increase the rotation barrier. This allows the isolation of atropoisomerically pure mono *N*-oxide (+)-**87** and (−)-**88**. In the allylation reaction, 10 mol % of (+)-**87** affords the adduct with up to 99/1 er and 72% yield. In contrast, the atropoisomeric monoxide (−)-**88** provides the opposite enantiomer with slightly lower enantioselectivity, thus supporting the hypothesis that the

asymmetric induction is controlled by the configuration at the 2,2′-bipyridyl bond.

**Table 19. Addition of 69 to Benzaldehyde Catalyzed by N-Oxides**

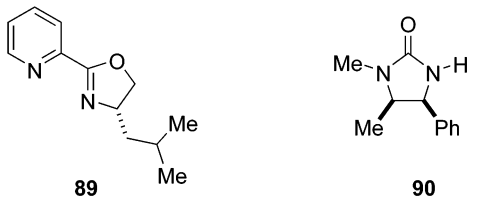



| entry | cat. | temp, °C | time, h | yield, % | er, (*R*/*S*) |
|---|---|---|---|---|---|
| 1 | **85** | −90 | 48 | 18 | 70.5/29.5 |
| 2 | (+)-**86** | −90 | 48 | 41 | 5.5/94.5 |
| 3[a] | (+)-**86** | −60 | 24 | 78 | 5/95 |
| 4[a] | (+)-**87** | −60 | 12 | 72 | 1/99 |
| 5[a] | (−)-**88** | −60 | 24 | 67 | 91/9 |

[a] 1.0 equiv of *n*-$Bu_4N^+I$ is used as an additive.

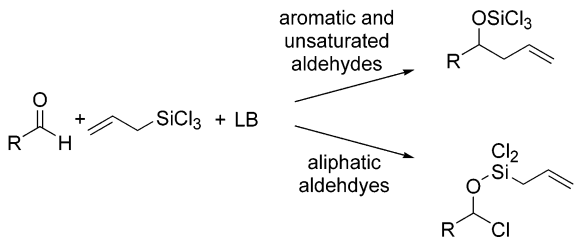
Other chiral Lewis bases such as diamine **89**[135] and urea **90**[136] have been reported as promoters for these allylations, and modest enantioselectivities have been obtained (87/13 er for **89** and 58/42 er for **90**) in the addition of **69** to benzaldehyde (Chart 5).

**Chart 5**




The most significant limitation in the chiral Lewis base-catalyzed additions is the inability to engage aliphatic aldehydes as substrates. Mechanistic studies reveal that the activation of allylic trichlorosilanes requires the coordination of two Lewis bases and ionization of a chloride anion. Aliphatic aldehydes have been shown to combine reversibly with the chloride resulting in the formation of α-chloro silyl ethers, which precludes the addition of the allylic nucleophile (Scheme 44).[137] Although the existence of this equilibrium between the aldehyde and α-chloro silyl ether allows the isolation of adduct after extended reaction time,[131,132] a highly efficient protocol has yet to be achieved.

**Scheme 44**

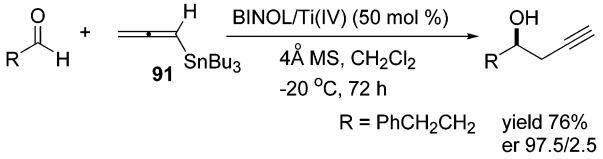



## 5. Propargylation and Allenylation of Aldehydes

Mechanistically, the addition of allenic or propargylic reagents[138] to aldehydes closely resembles the corresponding reaction with allylic metal reagents. Thus, many allylation methods have been further extended to propargylation and allenylation.

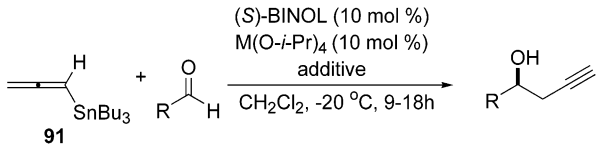
The enantioselective propargylation of achiral aldehydes with allenyl stannane **91** promoted by a stoichiometric amount of the BINOL/Ti(IV) complex was first reported by Keck.[139] The reaction, however, is much slower than the allylation under the same reaction conditions. Nonetheless, high yields and enantioselectivities could be obtained using either 100 or 50 mol % of the promoter after an extended period of time (Scheme 45). The lower reactivity of the allenylstannane could be due to the development of positive charge at an sp carbon during the electrophilic addition to the allenyl moiety.[139]

**Scheme 45**




As was seen in the allylation reactions, the rate of propargylation is significantly enhanced when a stoichiometric amount of *i*-$PrSBEt_2$[140] or $B(OMe)_3$[21] is added. This modification allows a catalytic amount of Lewis acid to be used (Table 20). Both BINOL/Ti(IV) and BINOL/Zr(IV) complexes could be employed in the addition, although the BINOL/Ti(IV) catalyst provides marginally higher enantioselectivities. In addition, sterically hindered and aromatic aldehydes give lower yields than linear aliphatic aldehydes.

**Table 20. Addition of Allenyltributylstannane to Aldehydes Catalyzed by the BINOL/M(IV) Complex**



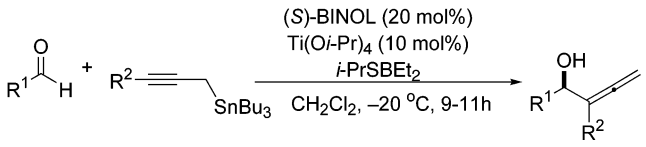

| R | M | additive | yield, % | er |
|---|---|---|---|---|
| $PhCH_2CH_2$ | Ti | *i*-$PrSBEt_2$ | 86 | 97/3 |
| $PhCH_2CH_2$[a] | Ti | $B(OMe)_3$ | 72 | 98.5/1.5 |
| $PhCH_2CH_2$ | Zr | *i*-$PrSBEt_2$ | 72 | 96/4 |
| $Me_2CHCH_2$ | Ti | *i*-$PrSBEt_2$ | 61 | 97.5/2.5 |
| *c*-$C_6H_{11}$ | Ti | *i*-$PrSBEt_2$ | 73 | 95.5/4.5 |
| $C_6H_5$ | Ti | *i*-$PrSBEt_2$ | 52 | 96/4 |

[a] BINOL (20 mol %), Ti(O-*i*-Pr)$_4$ (10 mol %), 0 °C, 9 h.

Under similar conditions, propargylic stannanes also successfully add to aldehydes to provide the allenic alcohols in high yields and selectivities (Table 21).[141] β-Branched aldehydes such as isovaleraldehyde provide the lowest yield and enantioselectivity.

An interesting regioselectivity convergence is observed in these reactions using either allenic or propargylic stannanes.[141] For example, the addition

**Table 21. Addition of Propargylic Stannanes to Aldehydes Catalyzed by the BINOL/Ti(IV) Complex**



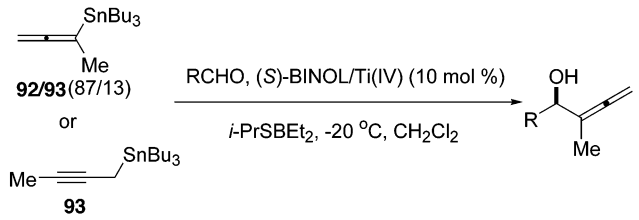

| $R^1$ | $R^2$ | yield, % | er |
|---|---|---|---|
| $PhCH_2CH_2$ | Me | 85 | 96.5/3.5 |
| $PhCH_2CH_2$ | Et | 77 | 98/2 |
| $PhCH_2CH_2$ | Pr | 71 | 96.5/3.5 |
| $Me_2CHCH_2$ | Me | 62 | 90.5/9.5 |
| Ph | Me | 74 | 95/5 |

of either allenic stannane **92** or propargylic stannane **93** affords the same allenic alcohols in comparable yields and enantioselectivities (Scheme 46). In contrast, the homopropargylic alcohols **95** are the major products when the unsubstituted allenyl stannane **91** or propargylic stannane **94** is used (Scheme 47). These results are explained by an equilibrium between the allenic stannane and propargylic stannane prior to the addition to the aldehyde (Scheme 48). Thus, the regioselectivity of the addition depends on the thermodynamic stability of the tin reagents as well as steric interactions in the transition structure with either allenic or propargylic stannane isomers.

A highly enantioselective propargylation of aromatic and unsaturated aldehydes using the chiral Lewis acid generated from $SiCl_4$ and a chiral phosphoramide has been described (Scheme 49).[93] With 5 mol % of bisphosphoramide (*R*,*R*)-**44** and a stoichiometric amount of $SiCl_4$, the addition of **91** to aldehydes proceeds at −78 °C to give the homopropargylic alcohols in high yields and enantioselectivities.

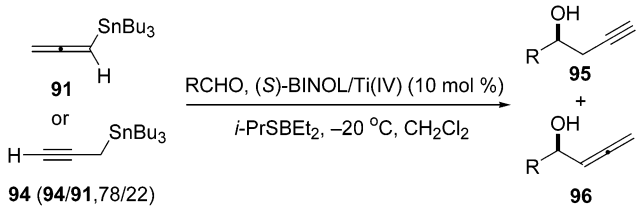
Allenic trimethylsilanes also function as propargylation reagents. Evans reported the addition of allenic trimethylsilanes **97** to ethyl glyoxylate with the bis(oxazolinyl)pyridine-scandium triflate catalyst (*S*,*S*)-**98** (Scheme 50).[142] With 10 mol % of (*S*,*S*)-**98**, various allenic trimethylsilanes undergo addition to ethyl glyoxylate and provide the homopropargylic alcohols in high yields and enantioselectivities. When allenic silane **99** bearing a bulkier silyl group is used, a [3+2] cycloaddition adduct **100** is obtained instead,

**Scheme 46**



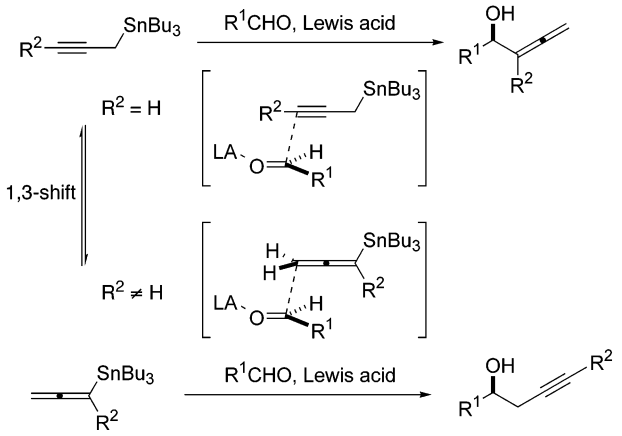

| | R | yield, % | er |
|---|---|---|---|
| **92** | $PhCH_2CH_2$ | 81 | 95.5/4.5 |
| | $n$-$C_6H_{13}$ | 78 | 96/4 |
| **93** | $PhCH_2CH_2$ | 85 | 96.5/3.5 |
| | $n$-$C_6H_{13}$ | 97 | 96/4 |

**Scheme 47**

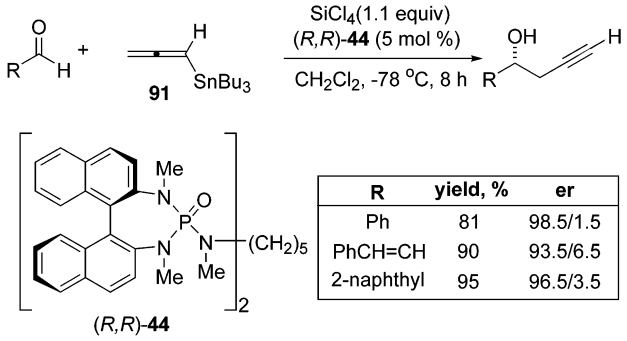



| | R | 95/96 | yield, % | er |
|---|---|---|---|---|
| **91** | $PhCH_2CH_2$ | >98:2 | 86 | 97/3 |
| | $n$-$C_6H_{13}$ | >98:2 | 75 | 96/4 |
| **94** | $PhCH_2CH_2$ | 89:11 | 71 | 95.5/4.5 |
| | $n$-$C_6H_{13}$ | 87:13 | 70 | 96/4 |

**Scheme 48**

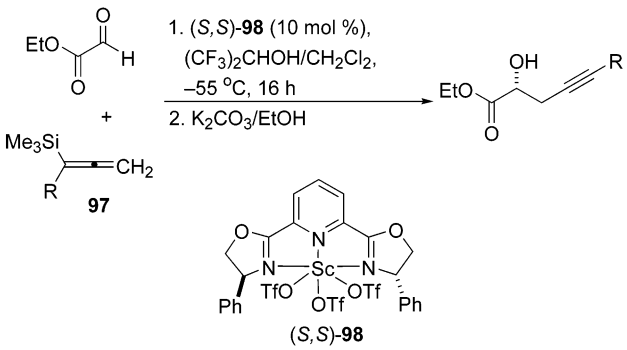



**Scheme 49**



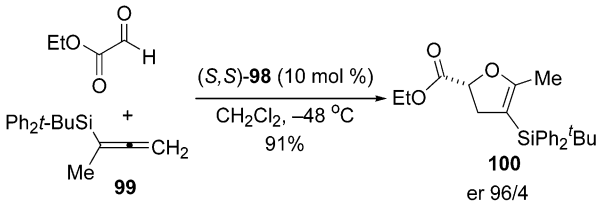

| R | yield, % | er |
|---|---|---|
| Ph | 81 | 98.5/1.5 |
| PhCH=CH | 90 | 93.5/6.5 |
| 2-naphthyl | 95 | 96.5/3.5 |

**Scheme 50**

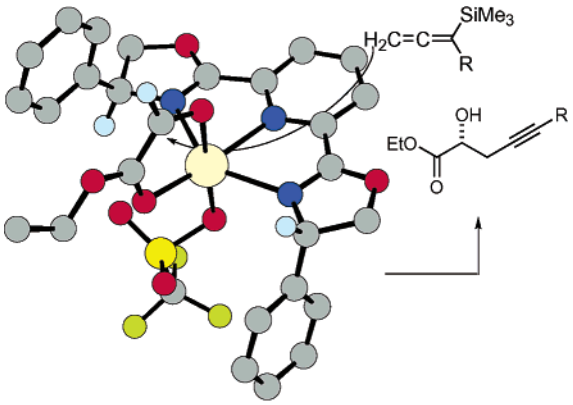



| R | yield, % | er |
|---|---|---|
| Me | 95 | 99/1 |
| Bu | 90 | 97/3 |
| $c$-$C_6H_{11}$ | 95 | 95/5 |
| Ph | 63 | 98.5/1.5 |

**Scheme 51**




also in high enantiopurity (Scheme 51). The stereochemical course of addition could be rationalized by a model based on the X-ray structure of the catalyst complex (Figure 14). It is proposed that the aldehyde is bound in the apical rather than the equatorial position to achieve a stronger activation of the carbonyl group. Thus, the addition of the allenic silane from the *Re* face is favored, as the *Si* face is effectively shielded by a phenyl group on the ligand.

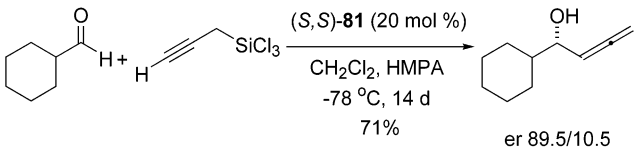



Sc[(*S,S*)-Ph-pybox(Ethyl glyoxylate)](OTf)$^{2+}$ complex

**Figure 14.** Proposed transition structure for the addition of allenylsilanes catalyzed by (*S,S*)-**98**.

The use of allenyl- and propargyltrichlorosilanes as effective agents for enantioselective additions to aldehydes under Lewis base catalysis has been reported.[143,144] With 20 mol % of formamide (*S,S*)-**81** and 1.0 equiv of HMPA, propargyltrichlorosilane adds to aliphatic aldehydes to give the allenic alcohols in modest yields and enantioselectivities after 14 days at −78 °C (Scheme 52). Although the starting propargyltrichlorosilane contains 25 mol % of allenyltrichlorosilane, the allenic alcohols are the major products observed, which indicates the lower reactivity of allenic trichlorosilane.

**Scheme 52**



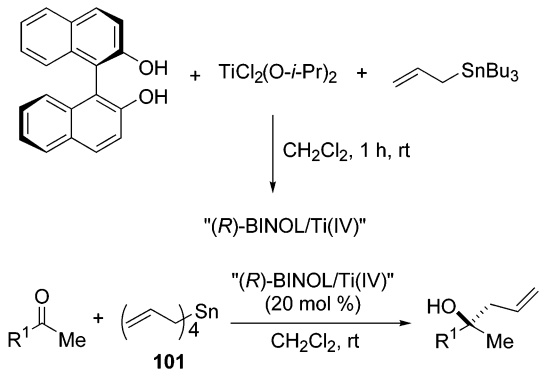

The use of propargyl chloride for the in situ generation of an asymmetric, chromium propargylation reagent has been described.[145] The addition of propargyl chloride to aldehydes in the presence of the salen ligand **57** (under condition developed for the allylation reaction) gives the homopropargylic alcohols in modest yields and enantioselectivities.

## 6. Allylation of Ketones

As is anticipated by the lesser reactivity of ketones (compared to aldehydes) toward nucleophilic addition, the number of methods for enantioselective construction of tertiary alcohols by this approach is very limited.

In extension of their studies on the BINOL/Ti(IV)-catalyzed allylation reaction, Tagliavini et al. developed a procedure that allows the allylation of ketones with tetraallylstannane (**101**) as the nucleophile.[146] The catalyst is prepared in situ by mixing equimolar amounts of BINOL, $TiCl_2(O\text{-}i\text{-}Pr)_2$, and 2.0 equiv of **2** (Scheme 53). With 20 mol % of this complex, the addition of **101** to ketones provides the adducts in good yields, albeit with modest enantioselectivities. When (*R*)-BINOL was used, the *Re* face of ketone is attacked, which is the same pathway seen in the allylation of aldehydes.

**Scheme 53**



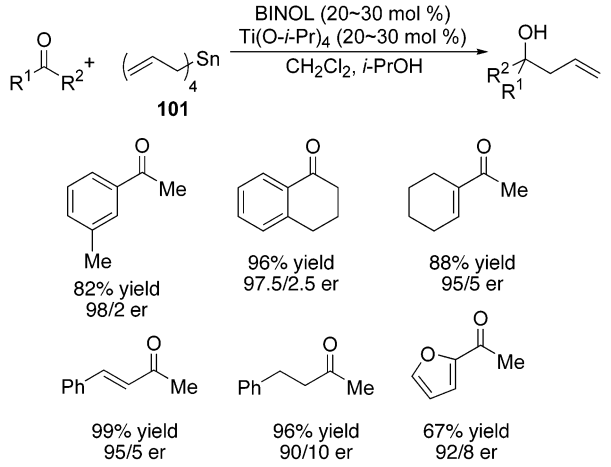

| $R^1$ | yield, % | er |
|---|---|---|
| Ph | 77 | 82.5/17.5 |
| 2-naphthyl | 87 | 75.5/24.5 |
| (*E*)-PhCH=CH | 83 | 75.5/24.5 |
| *n*-$C_6H_{13}$ | 89 | 64.5/35.5 |

The enantioselectivity of this process is significantly enhanced if the catalyst is prepared directly from BINOL/$Ti(O\text{-}i\text{-}Pr)_4$, and 2-propanol is used as an additive.[147] Under optimal conditions with 20 equiv of 2-propanol and 20−30 mol % of the catalyst, **101** adds to various ketones and produces the tertiary homoallylic alcohols with high enantioselectivities (Scheme 54). Although **101** is generally used in excess, up to 92% conversion could be obtained with only 0.25 equiv of **101**, which suggests that all allyl groups are active. The structure of the catalyst, the mechanism of the addition, and the role of alcohol additive remain uncertain.

Maruoka has applied the use of "dimerizing ligands" to the allylation of aryl ketones using the BINOL/Ti(IV) complex **28**.[74c] With 30 mol % of **28** and 1.0 equiv **101**, the allylation of methyl aryl and alkyl ketones affords the adducts with up to 98% yield and 96/4 er.

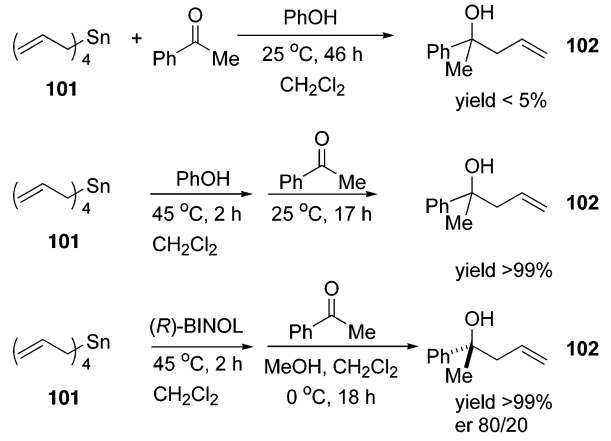
Chiral alcohols have been employed as promoters for the addition of allylic stannanes to ketones without the need for other Lewis acidic activators. The addition of **101** to acetophenone is significantly accelerated by premixing the **101** with alcohols such

**Scheme 54**




as phenol (Scheme 55).[148] It is proposed that an allylic aryloxystannane is formed, which is more reactive than the **101**, because of the enhanced Lewis acidity of the tin center. An enantioselective variant of this reaction has been developed using (*R*)-BINOL as the chiral promoter. Under optimized condition with a 3/1/2 ratio of 101/ketone/(*R*)-BINOL and 2 equiv of MeOH, the allylation product **102** is obtained in high yield albeit modest enantioselectivity.

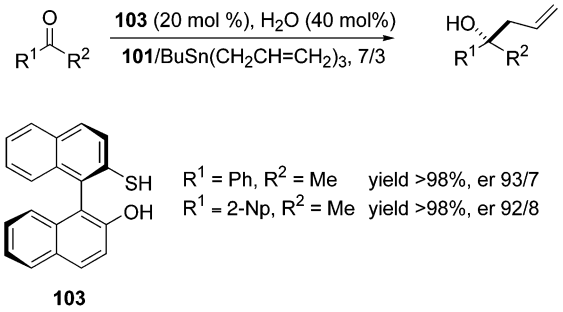
**Scheme 55**




Important improvements in enantioselectivity and chiral modifier loading are seen with the use of 1,1′-binaphthalen-2′-mercapto-2-ol **103**[149] (Scheme 56). With 20 mol % of **103** and 40 mol % of water, a number of aryl ketones are allylated with a mixture of **101** and (triallyl)butylstannane (optimized ratio 7/3), to provide the adducts in high yields and enantioselectivities. Interestingly, the reaction with either **101** or (triallyl)butylstannane alone is ineffective. In addition, a suitable amount of water is found to be important for consistent er values regardless of the reaction conversion. The role of water is proposed to be suppressing the competing nonselective addition of the allyloxystannane product. The allylation of aliphatic ketones is less selective.

Finally, a method for the allylation of ketones with **1** as well as (*E*)- and (*Z*)-**15** that employs stoichiometric modification of the ketone with a ephedrine derivative deserves mention because of the high selectivities obtained.[150]

**Scheme 56**

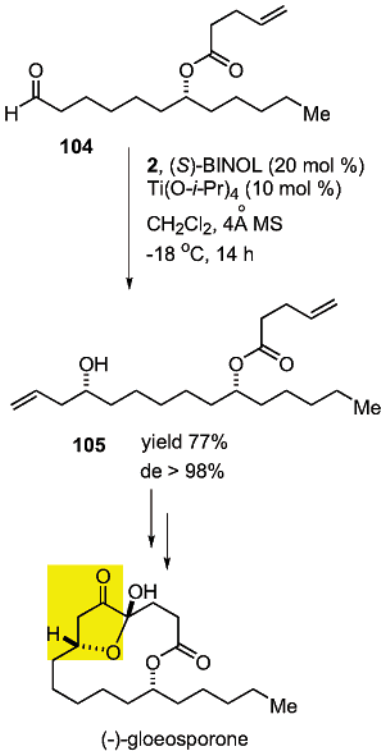



## 7. Applications in Synthesis

Although catalytic enantioselective allylation is a rather new reaction, it has already found applications in complex molecule synthesis in view of the efficiency, predictability and selectivity of the process. Among the methods developed for simple allylation, the addition of **2** catalyzed by the BINOL/Ti(IV) complexes has the broadest substrate scope. This method has been often employed in the allylation and crotylation of unsubstituted, unbranched aliphatic aldehydes[151−157] and unsaturated aldehydes.[158−162]

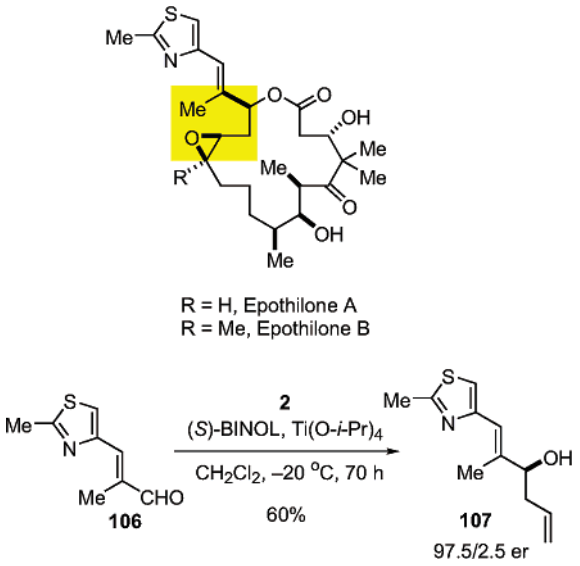
For example, in the synthesis of (−)-gloeosporone reported by Fürstner,[152] the linear aldehyde **104** is converted to the homoallylic alcohol **105** in good yield and high enantioselectivity using the allylation procedure developed by Keck (Scheme 57).

**Scheme 57**



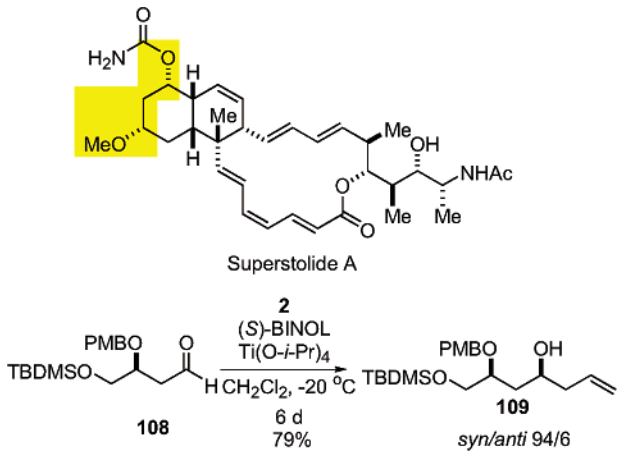

In the synthesis of epothilones reported by Danishefsky, the addition of **2** to unsaturated aldehyde **106** is achieved with high enantioselectivity with BINOL/Ti(IV) as the catalyst (Scheme 58).[158,160] The reaction however is quite slow, requiring 70 h to obtain a 60% yield.

**Scheme 58**




The high stereocontrol observed with BINOL/Ti(IV) catalysts is very useful for the synthesis of 1,3-*syn*-diol subunits, as demonstrated by Roush in the synthesis of superstolide A (Scheme 59).[155] The conversion of chiral aldehyde **108** to diol **109** is achieved with high diastereoselectivity (94/6, syn/anti) using the Keck allylation procedure. In this case, the reaction under substrate control favors the 1,3-anti-product. In a direct comparison, the reaction with a chiral allylborane reagent such as the (*R*,*R*)-tartrate-modified allylboronate provides only a 3/1, syn/anti selectivity.

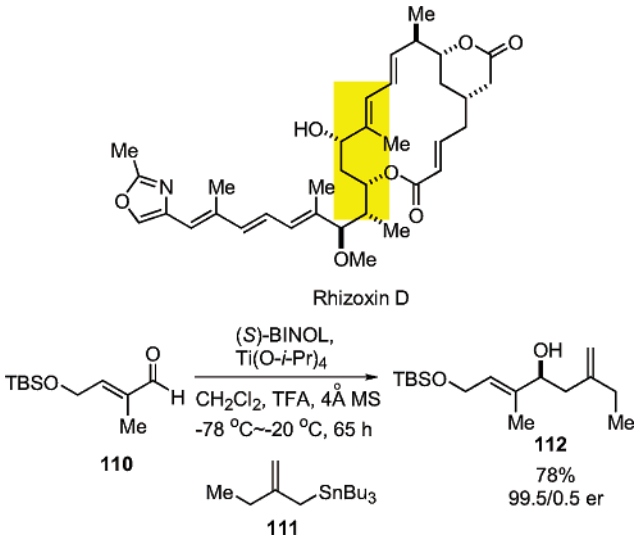
**Scheme 59**




The highly selective addition of $\beta$-substituted allylic stannanes catalyzed by BINOL/Ti(IV) complexes has served as a ketone equivalent in synthesis.[162] In the total synthesis of rhizoxin D reported by Keck, the stereocenter at C(12) is set with high selectivity by the addition of **111** to unsaturated aldehyde **110** using the BINOL/Ti(IV) catalyst (Scheme 60). The resulting double bond is then oxidized to provide the necessary carbonyl group for continuation of the synthesis.

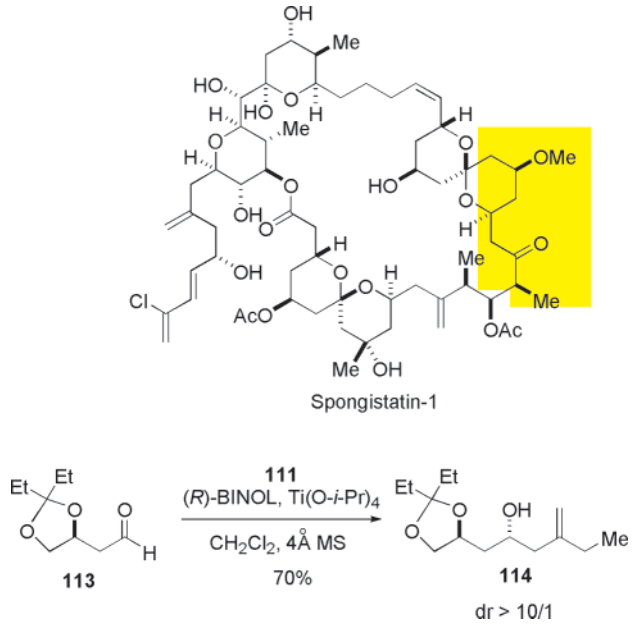
Smith applied this approach in the synthesis of spongistatin-1 (Scheme 61).[156] A high 1,3-anti

**Scheme 60**



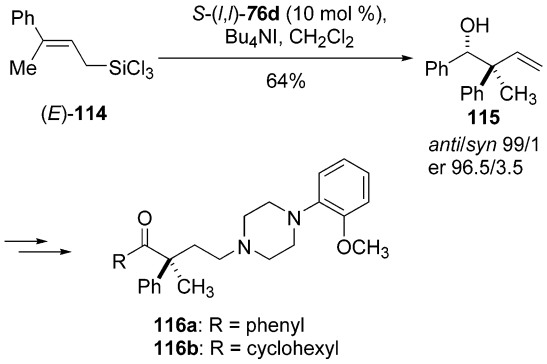

diastereoselectivity is obtained in the addition of reagent **111** to aldehyde **113** catalyzed by the (*R*)-BINOL/Ti(IV) complex. Again, in this case, the allylation is an equivalent of an ethyl ketone group as the olefin is eventually oxidized to a carbonyl group for the synthesis plan.

**Scheme 61**




The chiral Lewis base-catalyzed allylation provides a method for the highly diastereo- and enantioselective allylation of aldehydes. In particular, the addition of $\gamma$-disubstituted allyltrichlorosilanes provides a very versatile method for the construction of quaternary centers. The power of this approach is demonstrated in the enantioselective synthesis of serotonin antagonists **116** (Scheme 62).[137] The key intermediate **115** is prepared with excellent diastereo- and enantioselectivity by the addition of trichlorosilane (*E*)-**114** to benzaldehyde catalyzed by *S*-(*l*,*l*)-**76d**.

**Scheme 62**




## 8. Compilation of Examples

The following table was compiled to give the reader a comparison of the most common reagent/chiral Lewis acid combinations for the allylation of aldehydes. This is the most widely developed class of allylations for which many options are available. The overview provides comparison of three major classes of aldehyde substrate, aromatic (benzaldehyde) olefinic (cinnamaldehyde), and aliphatic (hydrocinnamaldehyde and cyclohexanecarboxaldehyde). This should facilitate selection of the preferred catalyst for a given method on the basis of rate, yield, enantioselectivity, and availability of catalyst.

## 9. Conclusion and Outlook

Excellent progress has been made over past decade in the development, understanding, and application of catalytic, enantioselective allylation reactions. For simple allylation, good methods are available, but they require the use of toxic tin reagents and high loadings of the catalyst. For addition of substituted allylic residues, the problem of predictable and selective diastereocontrol has not been solved in general. With Lewis acid-catalyzed reactions and in situ generation of allylic organometallic species, there are selective cases (usually stereoconvergent type II and III reactions) but also wide variability. Only in the newly developed additions of allylic trichlorosilanes under chiral Lewis base catalysis is there predicable and high stereoselectivity. However, these reactions are limited to aromatic and unsaturated aldehydes.

Clearly, the level of understanding of the origin of stereoselectivity is rudimentary at this stage. Only in very few cases has the structure of the catalyst been elucidated and in still fewer have the kinetic details of the reaction been investigated. These critical features must be studied for there to be more than an empirical optimization of reaction attributes. At this juncture there is no shortage of catalyst types and allylmetal nucleophiles that have been conscripted into useful service for this transformation. Nevertheless, for applications in complex molecule synthesis, only the BINOL/Ti(IV) system has been

**Table 22. Allylation of Aldehydes Catalyzed by Chiral Lewis Acids[a]**

| R | cat. | additive | solvent | temp, time | yield, % | er[ref] |
|---|---|---|---|---|---|---|
| Ph | (*S*)-BINOL/$TiCl_2$(O-*i*-Pr)$_2$ (20 mol %) | 4 Å MS | $CH_2Cl_2$ | 25 °C, 48 h | 96 | 91/9[56] |
| Ph | (*S*)-BINOL/Ti(O-*i*-Pr)$_4$ (2/1) (10 mol %) | | $CH_2Cl_2$ | 23 °C, 3 h | 85 | 94.5/5.5[57] |
| Ph | (*S*)-BINOL/Ti(O-*i*-Pr)$_4$ (2/1) (10 mol %) | *i*-PrSSiMe$_3$ | $CH_2Cl_2$ | −20 °C, 5−8 h | 91 | 98.5/1.5[19] |
| Ph | bidentate Ti complex **28** (10 mol %) | | $CH_2Cl_2$ | 0 °C 2.5 h | 94 | 99/1[74a] |
| Ph[b] | (*S*)-BINOL/$TiF_4$ (2/1) (10 mol %) | | $CH_2Cl_2$/$CH_3CN$ | 0 °C, 4 h | 85 | 90/10[75] |
| Ph | (*S*)-BINOL/Zr(O-*i*-Pr)$_4$ (20 mol %) | 4 Å MS | $CH_2Cl_2$ | −40 °C, 6 h | 79 | 96.4/3.6[78] |
| Ph | (*S*)-BINOL/Zr(O-*t*-Bu)$_4$ (10 mol %) | 4 Å MS | toluene/pivalonitrile | −20 °C, 1.5 h | 90 | 95/5[80] |
| Ph | bidentate Zr complex **34** (10 mol %) | | $CH_2Cl_2$ | 0 °C, 4∼6 h | 91 | 97/3[81] |
| Ph | (*S*)-BINAP/AgOTf (5 mol %) | | THF | −20 °C, 8 h | 88 | 98/2[82] |
| Ph[c] | (*R*)-BINAP/AgF (3 mol %) | | MeOH | −20 °C, 4 h | 84 | 96.5/3.5[85] |
| Ph | bisphosphoramide **44** (5 mol %)/$SiCl_4$ | | $CH_2Cl_2$ | −78 °C, 6 h | 91 | 97/3[93] |
| PhCH=CH | (*S*)-BINOL/$TiCl_2$(O-*i*-Pr)$_2$ (20 mol %) | 4 Å MS | $CH_2Cl_2$ | 25 °C, 24 h | 85 | 94.4/5.6[56] |
| PhCH=CH | (*S*)-BINOL/Ti(O-*i*-Pr)$_4$ (2/1) (10 mol %) | 4 Å MS | $CH_2Cl_2$ | 23 °C, 43 h | 77 | 92.5/7.5[57] |
| PhCH=CH | bidentate Ti complex **28** (10 mol %) | | $CH_2Cl_2$ | 0 °C, 10 h | 83 | 98/2[74a] |
| PhCH=CH | (*S*)-BINOL/Zr(O-*i*-Pr)$_4$ (20 mol %) | 4 Å MS | $CH_2Cl_2$ | −20 °C, 3 h | 81 | 95.5/4.5[78] |
| PhCH=CH | (*S*)-BINOL/Zr(O-*t*-Bu)$_4$ (10 mol %) | 4 Å MS | toluene/pivalonitrile | −20 °C, 2.5 h | 85 | 96.5/3.5[80] |
| PhCH=CH | (*S*)-BINAP/AgOTf (15 mol %) | | THF | −20 °C, 8 h | 83 | 94/6[82] |
| PhCH=CH[c] | (*R*)-*p*-Tol-BINAP/AgF (5 mol %) | | MeOH | −20 °C, 4 h | 93 | 89/11[85] |
| PhCH=CH | bisphosphoramide **44** (5 mol %)/$SiCl_4$ | $SiCl_4$ | $CH_2Cl_2$ | −78 °C, 6 h | 91 | 82.5/17.5[93] |
| $C_7H_{15}$ | (*S*)-BINOL/$TiCl_2$(O-*i*-Pr)$_2$ (20 mol %) | 4 Å MS | $CH_2Cl_2$ | −20 °C, 24 h | 83 | 98.7/1.3[56] |
| $PhCH_2CH_2$ | (*S*)-BINOL/Ti(O-*i*-Pr)$_4$ (2/1) (10 mol %) | | $CH_2Cl_2$ | 23 °C, 4 h | 86 | 94/6[57] |
| $PhCH_2CH_2$ | (*S*)-BINOL/Ti(O-*i*-Pr)$_4$ (2/1) (5 mol %) | *i*-PrSSiMe$_3$ | $CH_2Cl_2$ | −20 °C, 5∼8 h | 82 | 96.5/3.5[19] |
| $PhCH_2CH_2$ | bidentate Ti complex **28** (10 mol %) | | $CH_2Cl_2$ | 0 °C, 3 h | 90 | 98.5/1.5[74a] |
| $PhCH_2CH_2$[b] | (*S*)-BINOL/$TiF_4$ (2/1) (10 mol %) | | $CH_2Cl_2$/$CH_3CN$ | 0 °C, 4 h | 69 | 80.5/19.5[75] |
| *n*-$C_7H_{15}$ | (*S*)-BINOL/Zr(O-*i*-Pr)$_4$ (20 mol %) | 4 Å MS | $CH_2Cl_2$ | 0 °C, 6 h | 58 | 93.6/6.4[78] |
| $PhCH_2CH_2$ | (*S*)-BINOL/Zr(O-*t*-Bu)$_4$ (10 mol %) | 4 Å MS | $CH_2Cl_2$ | −20 °C, 2.5 h | 85 | 96.5/3.5[80] |
| $PhCH_2CH_2$ | bidentate Zr complex **34** (10 mol %) | | $CH_2Cl_2$ | 0 °C, 4∼6 h | 82 | 97/3[81] |
| $PhCH_2CH_2$ | (*S*)-BINAP/AgOTf (20 mol %) | | THF | −20 °C, 8 h | 47 | 94/6[82] |
| *c*-$C_6H_{11}$ | (*S*)-BINOL/$TiCl_2$(O-*i*-Pr)$_2$ (20 mol %) | 4 Å MS | $CH_2Cl_2$ | 25 °C, 24 h | 75 | 96.3/3.7[56] |
| *c*-$C_6H_{11}$ | (*S*)-BINOL/Ti(O-*i*-Pr)$_4$ (2/1) (10 mol %) | 4 Å MS | $CH_2Cl_2$ | 0 °C, 46 h | 59 | 91.5/8.5[57] |
| *c*-$C_6H_{11}$ | (*S*)-BINOL/Ti(O-*i*-Pr)$_4$ (2/1) (10 mol %) | *i*-PrSSiMe$_3$ | $CH_2Cl_2$ | −20 °C, 5∼8 h | 75 | 92.5/7.5[19] |
| *c*-$C_6H_{11}$[b] | (*S*)-BINOL/$TiF_4$ (2/1) (10 mol %) | | $CH_2Cl_2$/$CH_3CN$ | 0 °C, 4 h | 72 | 80/20[75] |
| *c*-$C_6H_{11}$ | (*S*)-BINOL/Zr(O-*i*-Pr)$_4$ (20 mol %) | 4 Å MS | $CH_2Cl_2$ | −20 °C, 6 h | 34 | 95.2/4.8[78] |
| *t*-Bu[b] | (*S*)-BINOL/$TiF_4$ (2/1) (10 mol %) | | $CH_2Cl_2$/$CH_3CN$ | 0 °C, 4 h | 91 | 97/3[75] |

[a] Allyltributylstannane was used unless noted. [b] Allyltrimethylsilane was used. [c] Allyltrimethoxysilane was used.

reliably implemented for allylation or methallylation processes. What is most clearly needed for the process in general are the kind of insights that will elevate these reactions to "strategy level status" and make them the methods of preference for controlled introduction of decorated homoallylic alcohol units.

## 10. Acknowledgements

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