Selective Reactions Using Allylic Metals

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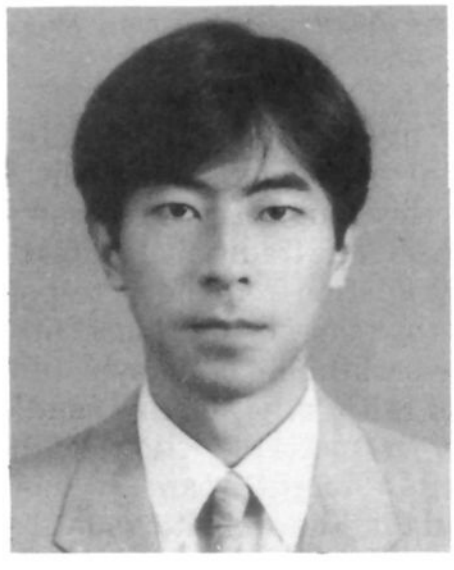
Received March 30, 1993 (Revised Manuscript Received June 23, 1993)

Contents

Yoshinori Yamamoto was born in Kobe, Japan, in 1942. He received his B.Sc. degree in 1965 and his Ph.D. degree in 1970 from Osaka University. He joined the faculty of Osaka University as an Instructor in 1970. He was a postdoctoral fellow at Purdue University with Herbert C. Brown from 1970 to 1972. He was appointed Associate Professor at Kyoto University in 1977 and moved to Tohoku University as Professor of Chemistry in 1986. Professor Yamamoto is the author of about 250 scientific publications, including a book entitled *Organometallic Chemistry* written in Japanese (Maruzen, Tokyo, 1983). In 1976, he received the Award of the Chemical Society of Japan for young scientists. His present research interests include the development of new synthetic methodologies *via* organometallic compounds, stereocontrol of acyclic systems, and asymmetric synthesis. Some reactions and reagents developed by his group include organocopper–Lewis acid reagents, allylic tin/boron trifluoride-based stereocontrol, and metal amide reagents. Since he moved to Sendai, he started the research on molecular design of ^{10}B carriers for boron neutron capture therapy (BNCT).



Naoki Asao was born in Sendai, Japan, in 1964. He obtained his B.Sc. (1987) and Ph.D. (1992) from Tohoku University working under the direction of Professor Y. Yamamoto. While studying for his Ph.D., he became a JSPS Fellow for Japanese Junior Scientists (1991). He is presently a research instructor at Tohoku University in Sendai (since 1992). His current research interests include development of new synthetic methods using organometallic compounds and metal amides, and of highly diastereo- and enantioselective reactions.

I. Introduction

Prior to the late 1970s, allylic organometallic compounds were studied primarily by a limited number of organometallic chemists[1] whose interests lay in the structural determination of allylmetals, e.g. 1,3-transposition of metals on the allyl system and stereochemistry of the double bond of the unit. Studies on the reactions of allylmetals with electrophiles were carried out which focused on the regioselectivity of the allylic unit (S_E2' or S_E2). Beginning in the late 1970s, a new emphasis appeared in this field. Significant synthetic interest began to emerge in the control of the stereochemistry of C–C-bond formation in the reactions of allylmetals with aldehydes and ketones. This widespread use of allylic organometallics in stereocontrolled organic synthesis appears to have been triggered by three papers: Heathcock's discovery that the Hiyama (*E*)-crotylchromium reagent[509a] undergoes highly antiselective addition to aldehydes;[2a] Hoffmann's finding that (*Z*)-crotylboronates produce syn-homoallylic alcohols stereoselectively,[2b] and Yamamoto's discovery that the Lewis acid mediated reaction of crotyltins with aldehydes produces syn-homoallylic alcohols regardless of the geometry of the double bond of the allylic tins.[2c]

Acyclic stereocontrol has been a pressing concern in modern organic chemistry and a number of useful methods have been developed for the stereoregulated synthesis of conformationally nonrigid complex molecules such as macrolide and polyether antibiotics. Special attention has been paid to aldol reactions, which constitute one of the fundamental bond constructions in biosynthesis. The reaction of allylic organometallic reagents with aldehydes is synthetically analogous to the aldol addition of metal enolates, since the resulting homoallyl alcohol can be easily converted to the aldol

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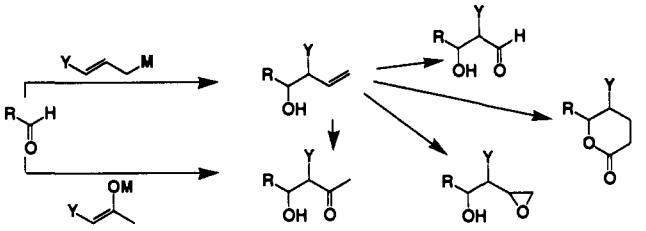
Scheme I. Allylmetal–Aldehyde Condensation and Aldol Reaction



(Scheme I).[3] Further, allymetal additions have significant advantages over aldol condensations since the alkenes may be readily transformed into aldehydes, may undergo a facile one-carbon homologation to δ-lactones via hydroformylation, or may be selectively epoxidized to introduce a third chiral center. Accordingly, the allylic organometallic reaction has attracted the attention of a wide range of organic chemists, and the allylic method has become one of the most useful procedures for controlling the stereochemistry in acyclic systems.

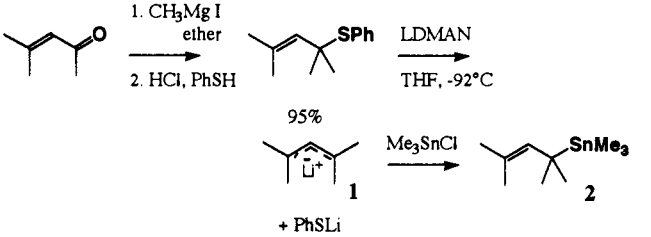
This review will survey some recent advances in allylation reactions of C=X electrophiles such as aldehydes, ketones, imines, Michael acceptors, and alkynes and alkenes (ene substrates). The allylation reactions in this review include nucleophilic (or radical) attack of allylic groups on electrophiles. However, electrophilic attack of nucleophiles, e.g. the reaction of π-allylpalladium complexes with nucleophiles, is not discussed here. The review will not attempt to provide comprehensive coverage of the literature, but will focus on the most recent developments since the literature before mid-1988 has been covered in recent articles.[4,5]

II. Group 1 (Li, Na, and K)

A. Allylic Lithium Reagents

1. Hydrocarbon Allyllithiums. A New Preparative Method

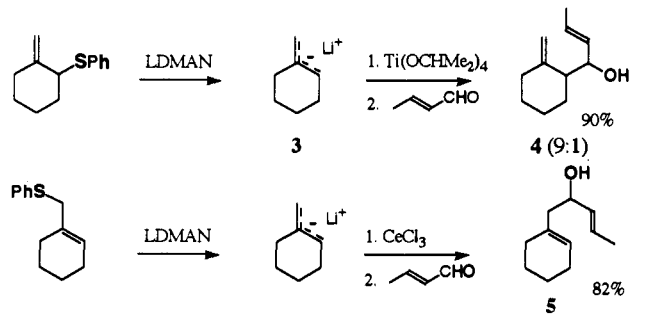
Alkyl and aryllithiums are usually prepared by halogen–metal exchange, but allyllithiums are not available by this route because of competing substitution reactions. The traditional routes to allyllithiums are (i) transmetalation from the corresponding allyltins and allylleads by using alkyllithiums,[6] (ii) ether cleavage with lithium or lithium biphenyl,[7] (iii) reactions of alkyllithiums with allyl methyl and allyl phenyl selenides,[8a] or (iv) metal reduction[8b] of the appropriate allyl halide. In recent years, it has been amply demonstrated that the aromatic radical anion induced reductive lithiation of allyl phenyl thioethers is a versatile and general method for generating of allyllithiums.[9] Two very attractive features of the reductive lithiation of phenyl thioethers are the great ease of preparation of the substrates and the fact that the more highly substituted, and thus less stable, organolithiums are more easily produced than the less highly substituted ones. Both of these features are demonstrated by the two-pot generation of (1,1,3,3-tetramethylallyl)-lithium (1) starting from inexpensive mesityl oxide.[10] Reductive lithiation with LDMAN resulted in a yellow solution containing 1. Quenching 1 with trimethyltin chloride yielded 2 in 88% yield.



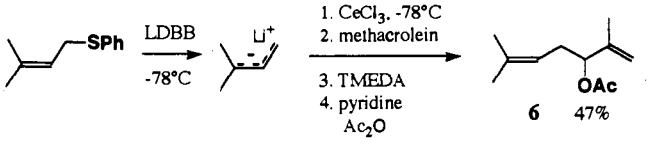
LDMAN : lithium 1-(dimethylamino)naphthalenide

While this radical anion induced reductive metalation has been used for allyllithiums that are substituted at one terminus with ether[11,12] or thioether[13] groups, the most important uses have been in the formation of hydrocarbon allyllithiums. The reason is that heteroatom substituted allyllithiums can often be prepared in other ways,[14] whereas reductive metalation is the only general method for preparing hydrocarbon allyllithiums,[15] except for the generation of allylic anions (Li and/or K as a gegen cation) via the allylic hydrogen abstraction of alkenes with Schlosser's base (n-BuLi/t-BuOK). Allyllithium itself may be prepared by the lithiation of allyl phenyl ether,[7] but more complex allylic phenyl ethers are not generally available.

In the case of unsymmetrical allyllithiums, regiochemical control in subsequent reactions with electrophiles is essential to their utility. However, unsymmetrical allyllithiums react with aldehydes nonselectively with a slight preference for attack at the most substituted allyl terminus.[15] Treatment of the allyllithium 3 with titanium tetraisopropoxide leads to reaction with enals only at the most substituted terminus;[15] the formation of 4 proceeded with substantial diastereoselectivity (9:1). On the other hand,

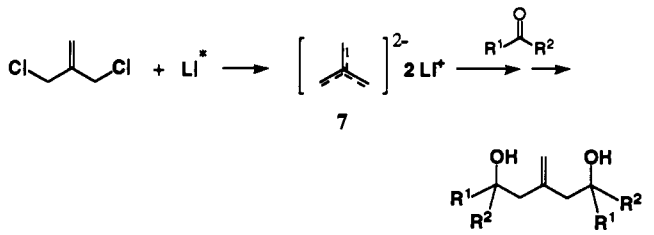


treatment of an unsymmetrical allyllithium with cerium(III) chloride, followed by an enal, results mainly in addition of the least substituted terminus to the carbonyl group;[16] the ratio of 5 to 4 was 18:1. This novel regioselectivity has made possible a highly efficient synthesis of the pheromone of the comstock mealybug 6, a very significant agricultural pest.[9]



LDBB : lithium p,p-di-tert-butylbiphenylide

Naphthalene acts as catalyst in the lithiation step of 3-chloro-2-(chloromethyl)propene.[17] The reaction of an equimolar amount of the chloride and a carbonyl compound with an excess of lithium powder and a catalytic amount (6%) of naphthalene in THF at −78 °C leads, after hydrolysis with water, to the corresponding diols in a Barbier-type process. Trimethylenemethane dianion **7** can be prepared by double deprotonation of isobutylene by using either butyllithium/tetramethylethylenediamine (TMEDA)[18] or a mixture of butyllithium and potassium *tert*-butoxide.[19] However, the preparation of **7** starting from halogenated precursors by halogen–lithium exchange fails due to decomposition reactions of the monolithiated intermediate initially formed.[19]



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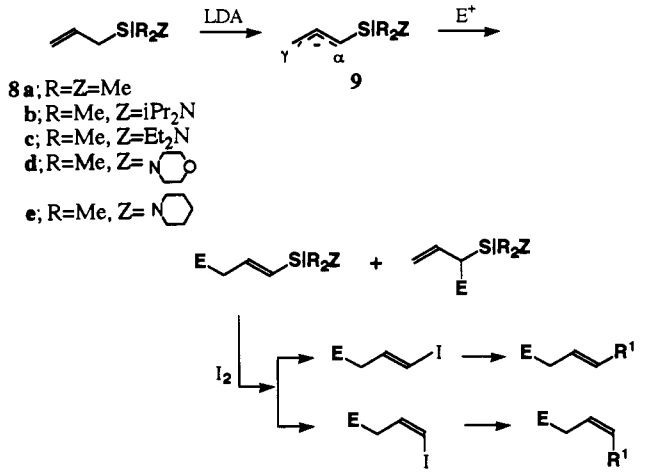
Li* = Li powder (1:6)/cat $C_{10}H_8$ (1:0.06)

2. Heteroatom-Substituted Allyllithiums

The review article entitled "Heteroatom-Stabilized Allylic Anions" covers papers in this field before late-1988.[20] An interesting area for the study of substituent effect is on the regiochemical control in substitution reactions of heteroatom-substituted allyl anion.[20,21] The [α-(trimethylsilyl)allyl]lithium (**9a**, R, Z = CH_3) can be generated from allyltrimethylsilane (**8a**, R, Z = CH_3) and reacted with electrophiles.[22] The regioselectivity

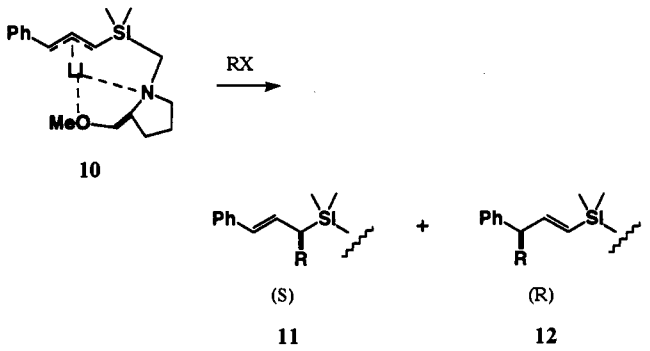


8a; R=Z=Me
b; R=Me, Z=iPr_2N
c; R=Me, Z=Et_2N
d; R=Me, Z=
e; R=Me, Z=

9

of the reaction depends on the nature of the electrophile. Carbonyl electrophiles gave regioselectively the γ-adducts,[23a] and if complexed with a Lewis acid, the reaction gave the α-adducts.[21a,23b-d] The γ-selectivity of the lithio anion of allyltrimethylsilane can be converted to the α-selectivity by adding $MgBr_2$[23b] or Et_3Al.[21a] The lithio anion of allyl(diisopropylamino)-dimethylsilane (**8b**, R = Me, Z = i-Pr_2N), upon treatment with dried $ZnCl_2$ in ether at 0 °C, reacts with aldehydes regio- and stereoselectively to form *syn*-3-silyl-1-alken-4-ols, which are further transformed into *syn*-1-alkene-3,4-diols by hydrogen peroxide oxidation of the carbon–silicon bond.[23c] The lithio anion of **8c** (R = Me, Z = Et_2N) is generated via hydrogen abstraction with n-BuLi/TMEDA in ether, and the reaction of cyclohexanecarboxaldehyde with the resulting **9c** produces the α-selectivity upon treatment with $MgBr_2$, $SnCl_2$, or $Ti(OiPr)_4$, whereas it affords the γ-selectivity upon treatment with CuI, CuSCN, or CuCN at −78 °C.[23d,538] Lithium anions **9d** and **9e** were generated from the reactions of **8d** and **8e**, respectively, with s-BuLi in toluene at −20 °C. The reaction of **9d** and **9e** with aldehydes and ketones at −78 °C gave the γ-adducts with *E* stereochemistry, whereas the γ-*Z* isomers were obtained predominantly upon treatment of the anions with the carbonyl compounds in the presence of dimethoxyethane at −90 °C.[23f]

Reactions with alkyl halides are more complicated. Regiocontrol of the alkylation is mentioned here, although this review is primarily concerned with the reactions of C=X. Alkylation of the α-silylallyl anion gave higher γ-regioselection by replacing the methyl groups on silicon by sterically larger groups (Et, Pr, or Ph).[24] This finding has provided a useful method to prepare regio- and stereoselectively (*E*)-vinylsilanes and, after appropriate transformations, disubstituted alkenes.[25] More demanding is a question whether the alkylation of the α-silylallyl anion can be controlled to give regioselectively the α-isomer. It was found that **10**, having metal ion complexing substituents on silicon, reacts with alkyl halides to give α-substituted allylsilanes regioselectively.[26] The extent of α-selection depends significantly on the nature of the ligand and solvent. The chelating ligands having two, or better, three appropriately positioned heteroatoms bind the lithium cation effectively enough to yield good α-selectivity in reactions with alkyl halides. γ-Alkylation was favored by dialkylamino group on silicon,[23g] whereas α-alkylation was favored by the alkoxy substituent on silicon.[27] Moreover, the reaction proceeds stereoselectively when the ligand is chiral.[28] Methylation of **10** in ether or toluene gave the (*S*)-α-adduct **11** with high diastereoselectivity, whereas isopropylation of **10** in ether or toluene afforded the (*R*)-γ-product **12** with good stereoselectivity. They are in fact derived from



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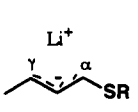
(S) **11** (R) **12**

electrophilic attack from the same face (upper face) of transoid allylic anion **10**. NMR data show that [1-(trimethylsilyl)allyl]lithium, although there is no substituent at the γ-terminus of the allylic unit, exists in a variety of media exclusively in the exo form,[29] supporting the geometry of **10**.

Sulfur-stabilized allyllithiums have been well documented and their regioselective reactions have been investigated.[20] Alkyl halides react with **13** predomi-

nantly at the α-position, whereas aldehydes generally produce the γ-adduct preferentially. Ketene dithioacetals are deprotonated with LDA-HMPA, and **14a** gives mostly α-alkylation product upon treatment with simple alkyl halides.[30] The reaction of **14b** with three to six-membered cyclic ethers takes place exclusively at the γ-carbon in the presence of BF_3·OEt_2.[31] The lithiated anion **15**, obtained by treatment of 2-(1-propenyl)-1,3-oxathiane with s-BuLi, reacts with alkyl halides yielding substitution products predominantly at the α-terminus; on the contrary, carbonyl compounds afford addition products at the γ-terminus.[32] Accordingly, the effect of the oxygen atom of **15** upon the regioselectivity is negligible, since oxygen-substituted allyllithium **16** generally directs alkyl halides to the γ-position.[20] Even when the γ-terminus is sterically crowded, as in the case of **14c**, an aldehyde reacts at the γ-position.[33] Although a sulfur atom attached to allyl anions at their terminus stabilizes them, as shown above, an oxygen atom attached the allylic terminus seems rather to destabilize the allylic anion. This is demonstrated in the deprotonation of **17**. Treatment of **17** with 2 equiv of s-BuLi complexed with potassium *tert*-butoxide in THF at −95 °C underwent a 1,4-eliminative ring fission with subsequent proton abstraction at the α-vinyl site of the enol ethers produced.[34] Accordingly, the first deprotonation takes place at the δ-position instead of the α-position. A deprotonation pathway at the α-site has been reported for acrolein acetal with s-BuLi at −95 °C.[35]



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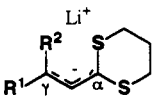
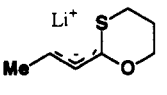


14a R^1=R^2=H
b R^1=Me, R^2=H
c R^1=R^2=Me



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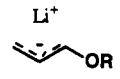

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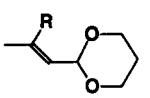
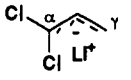


17a R=H
b R=Me

For *gem*-dichloroallyl anions, carbonyl compounds yield different products of attack depending on the substituents on the carbonyl carbon atom, presenting a whole spectrum of product distributions going from a complete α-attack to a complete γ-attack.[36] For example, aromatic aldehydes and diaryl ketones give γ-products, whereas aliphatic aldehydes and dialkyl ketones afford α-products. (Chloroallyl)lithium readily reacts with aliphatic and aromatic aldehydes and ketones to produce γ-chlorinated-β-ethylenic alcohols and bi- or trisubstituted epoxides.[36c] *gem*-Difluoroallyl anion **19** behaves quite differently: with every kind of carbonyl compounds studied perfect α-selectivity is observed.[37] A rationalization of this α-selectivity that stresses the role of the lithium counterion is offered and argues that it should preferentially engage the CH_2 terminus (γ), thus preventing the electrophilic attack on the γ-position. Substituted benzaldehydes and acetophenone preferentially attack the γ-position of **18**, but show a significantly increased α-selectivity if 12-crown-4 is present.[38] The role of 12-crown-4 could be 2-fold: (i) deaggregation of the oligomers (possibly dimers) present in THF solution or (ii) weakening of the ionic C–Li bond. In this case, perhaps the allylic part of the system would approximate the features of a free anion. (*gem*-Dichloroallyl)potassium (**20**), produced upon treatment of 3,3-dichloropropene with lithium diisopropylamide in the presence of potassium *tert*-butoxide, reacts with benzaldehyde and substituted benzaldehyde with perfect α-selectivity.[39]



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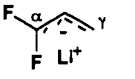

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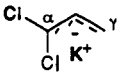

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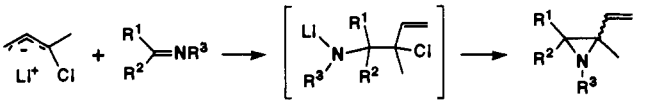
In general, reactions of linear α-alkylaldimines with allyllithiums are complicated by α-deprotonation of the aldimines owing to the basic property of the lithium reagents. The use of less basic magnesium and zinc reagents produces higher yields. The reaction of (*gem*-chloro(methyl)allyl)lithium with aldimines and ketimines is an efficient method for the synthesis of 2-vinylaziridines.[36d] The aziridine ring is formed by

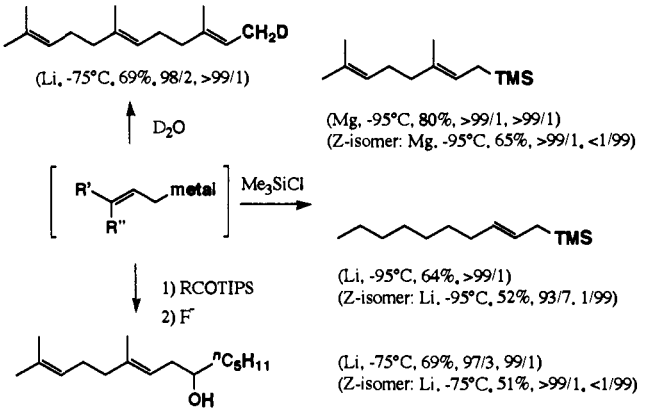


intramolecular S_N2 displacement of chloride via the intermediate lithium amide. The regioselectivity of additions of crotyllithium reagents to aldimines is discussed in the section of allylzinc compounds (see eq 15). Despite their versatility in organic synthesis, organolithium compounds are too basic to undergo appreciable addition to terminal alkynes. A few examples of such reactions are known, but these have more mechanistic than synthetic values. Accordingly, the ene-type reactions of allyllithiums are less important than those of the corresponding magnesium and zinc reagents.[61,62]

B. Allylic Sodium and Potassium Reagents

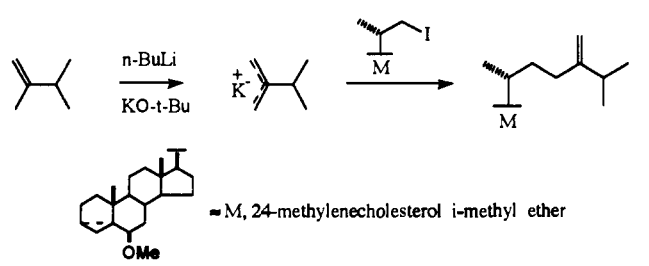
Geranyl or neryl chloride was transformed into the corresponding Grignard reagent at low temperature by using reactive magnesium powder,[40] and the corresponding lithium, sodium, and potassium derivatives were prepared via the aromatic radical anion method[9] (see section II.A). The isomer ratio of these allylmetal reagents was measured by analyzing protonated *E* and *Z* isomers.[41] There are five variables: the *E*/*Z* ratio of the olefin produced, the temperature of the system, the choice of metal, the yield (%), and the α/γ ratio of the protonation products. No remarkable *E*/*Z* selectivity is obtained by protonation of the magnesium reagents above −60 °C, but below −95 °C very high stereoselection is produced. In contrast, the double-bond geometry of the alkali allylmetals is stable at higher temperatures, and the allylpotassium reagents undergo isomerization only very slowly at 0 °C. The superiority of potassium metal for stereoselectivity is apparent, but the yields of the derived olefins are low because of the accompanying Wurtz coupling process. The versatility of stereochemically homogeneous mono- and disubstituted allylmetals in synthesis is shown in Scheme II. Stereochemically pure allylic silanes can be prepared from the corresponding lithium and magnesium derivatives. The reaction with acylsilanes

Scheme II. Stereochemically Homogeneous Allylmetals (Metal, Temperature, Yield, α,γ, E/Z)



selectively produces the stereochemically homogeneous linear homoallyl alcohols (see also section III.A and ref 44).

Allylpotassium derivatives are prepared from a variety of olefins by using Schlosser's base (BuLi/t-BuOK).[5] Reaction with (20*S*)-20-(iodomethyl)pregnane *i*-methyl ether followed by deprotection gave, in high yields, a wide variety of Δ^{24} and $\Delta^{24(28)}$ sterols, including the naturally occurring desmosterol, fucosterol, 24(*E*)-propylidenecholesterol, 24-methylenecholesterol, dehydroaplysterol, 25-methyl-24-methylenecholesterol, mutasterol, and 25-methylxestosterol.[42] The use of unsymmetrical olefins, which produce in turn unsymmetrical allyl potassiums, gives a regioisomeric mixture of C–C bond formation products: attack at both termini of the allyl system takes place with a preference for attack at the less substituted terminus. Perfect regiocontrol in favor of the less substituted terminus of the allyl system is accomplished by addition of Li_2CuCl_3. The potassium anion of allylsilane is generated by the reaction of **8b** with Schlosser's base (n-BuLi/t-BuOK) in ether–hexane at −78 °C, alkylation of which produces the γ-product with 95% γ-regioselectivity.[23g]

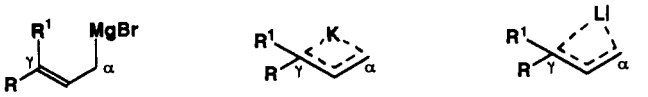


The thermodynamic *E*/*Z* ratio can be improved with use of potassium rather than lithium allyls.[5c] The treatment of an allyl phenyl sulfide with potassium 1-(dimethylamino)naphthalenide (KDMAN) results in the formation of an allylpotassium which is a powerful enough base to deprotonate the starting material, particularly if it is a primary phenyl thioether.[9] In the case of secondary thioethers, the yield of allylpotassium derived from **432** was decreased sharply by this phenomenon, but the anion from 3-(phenylthio)-1-octene was only marginally effected. The allylpotassiums generated in this way are mixtures of *Z* and *E* isomers, and the rate of equilibrium to the more stable *Z* isomer is very slow at low temperatures. However, a catalytic quantity of $MgBr_2$ causes rapid equilibration.[9] When butylpotassium is generated in the presence of commercial *cis*-2-pentene and the resulting allylpotassium is captured with $PhMe_2SiCl$, 1-(phenyldimethylsilyl)-2-pentene is produced in 65% yield with a 98.6:1.4 mixture of *Z* and *E* isomers. When the same deprotonation is performed on a mixture of (*Z*) and (*E*)-2-pentene, and the product is treated with catalytic $MgBr_2$ before silylation, the same product is formed with a ratio of 97:3.[9] Deprotonation of (*Z*)- or (*E*)-2-butene with Schlosser's base (t-BuLi/t-BuOK) followed by trapping with BX_3 is frequently used for the stereoselective synthesis of (*Z*)- or (*E*)-crotylboron compounds, respectively.

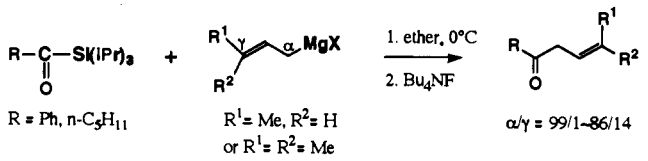
III. Group 2 and 12 (Mg, Ba, Zn, and Cd)

A. Allylic Grignard Reagents

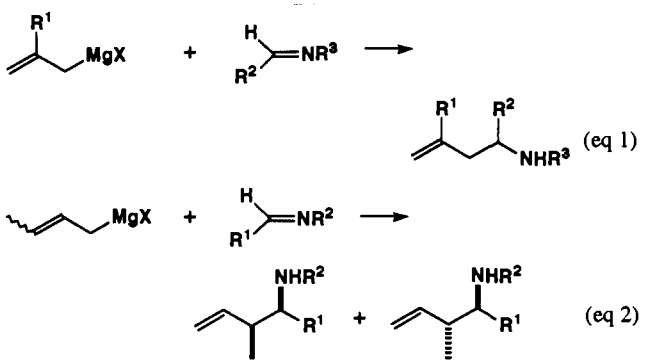
The isotopic perturbation technique has been used to distinguish between the σ- and π-bond structures of allyl- and crotylmagnesium, -potassium, and -lithium reagents.[43] The ^{13}C NMR spectra of the deuterated crotyl reagents demonstrate that: (i) crotylmagnesium reagents are σ-structures in which the metal is attached to the primary carbon; and (ii) crotylpotassium and crotyllithium reagents are π-structures in which the metals are bonded to carbon α and γ of the allylic system. The carbon–metal lengths in the crotylpotassium reagents are essentially equal, whereas those of the crotyllithium reagents are unequal.



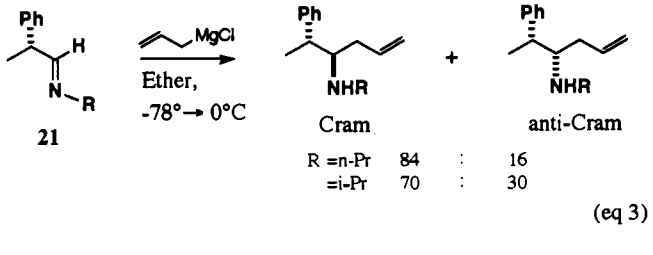
It is well known that crotyl and prenyl Grignard reagents react with aromatic and aliphatic aldehydes at the γ-position.[1] Regioselective α-allylation was accomplished by the reaction of triisopropylsilyl ketones with allyl Grignard reagents.[44] The corresponding trimethylsilyl ketones gave the γ-product predominantly (α/γ ≈ 2:98).



The reaction of allylmagnesium halides with a chiral aldimines produces homoallylamines containing one stereocenter in high yields (eq 1).[45] Examples involving the more reactive allyllithium, -magnesium, and -zinc reagents are limited to imines that are nonenolizable or contain branched α-alkyl substituents. Perhaps, reactions of linear α-alkylaldimines are complicated by α-deprotonation. Higher yields are reported using the less basic magnesium and zinc reagents rather than the corresponding lithium reagents. The reaction of crotylmagnesium bromide with aldimines affords a mixture of syn and anti homoallylamines with low diastereoselectivity (eq 2).[45] Examples involving crotylmagnesium reagents are limited to reactions with α-arylimines because α-alkylimines react to produce, primarily, linear products.

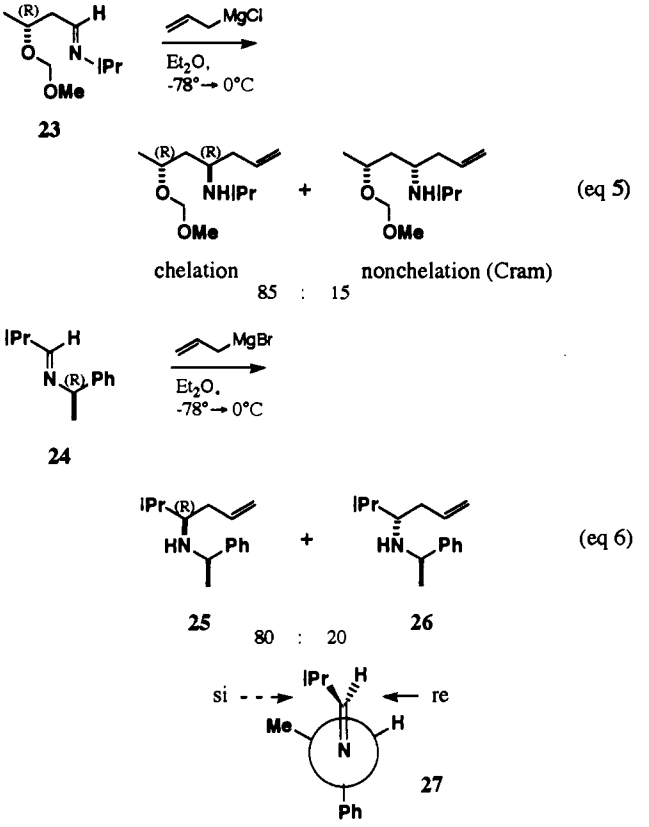


Imines containing one stereocenter at the α-position are treated with allylmagnesium chloride to evaluate the influence of either a nonchelating α-phenyl substituent (eq 3) or a chelating α-alkoxy substituent (eq 4) on reaction diastereofacial selectivity. The Cram product was obtained predominantly from **21**, and the Cram selectivity is consistent with Felkin–Ahn addition with the large phenyl substituent controlling the organometallic approach.[46] If there is an alkoxy substituent adjacent to the aldimine there is the opportunity for chelation control. Indeed, **22** gave the chelation product predominantly (eq 4).[47] If the oxygen-protecting group is (instead of methoxymethyl) *tert*-butyldimethylsilyl which is sterically bulky and thus prone to prevent chelation, nonchelation product is obtained with very high diastereoselectivity.[48]



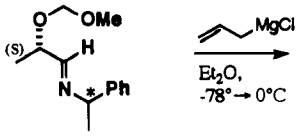
1,3-Asymmetric induction has been investigated by using an imine containing one stereocenter either at the β-position (**23**) or at the carbon attached to nitrogen atom (**24**).[50] Modest chelation control (chelation/nonchelation = 85:15), which is superior to that of the corresponding β-alkoxyaldehydes (chelation/nonchelation = 64:36),[49] can be obtained using **23** (eq 5).[49] The addition of organometallics to aldimines derived from chiral amines provides another option (unique to imines) for controlling reaction diastereofacial selectivity. The allylation of **24** gave a 80:20 mixture of **25** and **26** in high yield.[46] The origin of the *re* facial selectivity can be explained by the addition to a low-energy conformation of **24**, in which the largest (phenyl) substituent is antiperiplanar to the imine, which would render the *re* face of **24** more accessible to addition (see **27**).

The allylation of imines containing two stereocenters has been examined.[50] The chelation product was

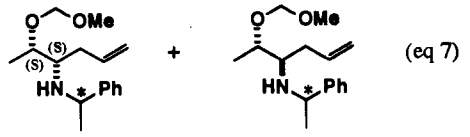


obtained predominantly from **28**; the imine derived from (*R*)-1-phenylethylamine gave higher chelation/nonchelation ratio than that from (*S*)-enantiomer (eq 7). However, the chirality of the α-alkoxy center (1,2-asymmetric induction) is the most important determinant of the stereochemical outcome of the reaction and essentially overrides the influence of the nitrogen chiral auxiliary (1,3-asymmetric induction). In the allylation of β-alkoxyaldimines **29** derived from (*R*)-3-(methoxymethoxy)butyraldehyde and (*R*)- and (S)-phenylethylamine, chelation and nonchelation products were produced, respectively. Of the two remote 1,3-centers of chirality, the chiral nitrogen auxiliary plays the major role in controlling diastereoselectivity as the (*R*,*S*) combination provides, predominantly, chelation product while the (*R*,*R*) combination provides nonchelation product (eq 8).

The addition of allylmagnesium chloride to the chiral α,β-epoxy imine **30** is highly diastereoselective, and the facial selectivity can be controlled by the use of $BF_3{\cdot}OEt_2$.[51] The allylation of **30** in the absence of a Lewis acid gave the chelation product in 62% yield, whereas if **30** was treated with $BF_3{\cdot}OEt_2$ prior to the addition of allyl Grignard reagent, a good yield of a diastereoisomerically pure nonchelation product was obtained. The stereochemistry of the group on nitrogen appears to have little influence on the stereochemical outcome of the reaction of allylmagnesium chloride, which was expected in view of the results summarized in eq 7. One rationalization for the effect of $BF_3{\cdot}OEt_2$ upon the diastereoselectivity is that boron trifluoride coordinates to the imine nitrogen, blocking chelation with magnesium ions. Trifluoromethyl ketone and oxime exhibit a different reactivity toward allyl Grignard reagents in comparison with ordinary ketones and oximes. Allylmagnesium bromide acts as a reducing



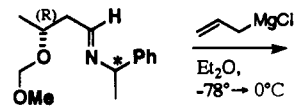
28



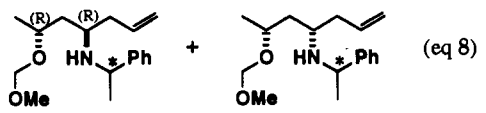
(eq 7)

chelation nonchelation

* = (S)	70	:	30
* = (R)	86	:	14



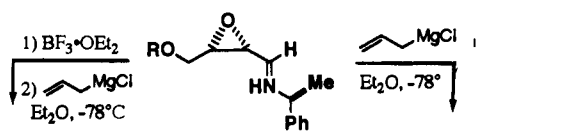
29



(eq 8)

chelation nonchelation

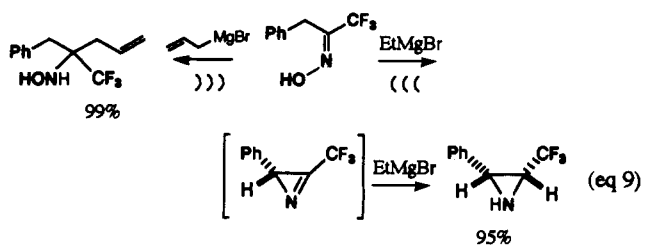
* = (S)	92	:	8
* = (R)	38	:	62



30 (R=p-bromobenzyl)

nonchelation chelation

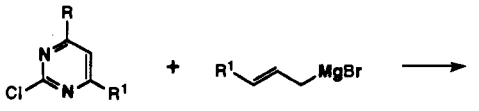
agent toward trifluoromethyl ketones; by using an excess of this Grignard reagent, an exclusive allylation is obtained.[52] Allylmagnesium bromide smoothly added to trifluoromethyl ketone oximes to produce the corresponding allylated hydroxylamines, whereas the reaction of ethylmagnesium bromide with benzyl trifluoromethyl ketone oxime gave aziridine by reduction of the 2*H*-azirine intermediate (eq 9). Regioselective



(eq 9)

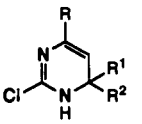
99% 95%

allylation of pyrimidines has been accomplished by reaction with allylic Grignard reagents;[53] reactions of **31a** and **31b** with **32a** and **32b** lead to allyldihydropyrimidines **33a–d** in very good yields. Grignard reagents have been reported to react with pyrimidines furnishing dihydropyrimidines or cross-coupled pyrimidines,[54] but this applies only to aryl and primary alkyl Grignards. No secondary or tertiary alkyl group had previously been introduced on the pyrimidine ring.



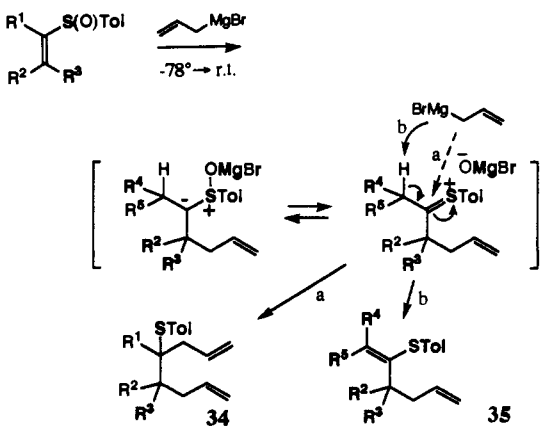
31a; R=R^1=H
b; R=Me. R^1=Cl

32a; R^1=H
b; R^1=Me



33a; R=R^1=H, R^2=$CH_2CH=CH_2$
b; R=R^1=H, R^2=$CH(CH_3)CH=CH_2$
c; R=Cl, R^1=Me, R^2=$CH_2CH=CH_2$
d; R=Cl, R^1=Me, R^2=$CH(CH_3)CH=CH_2$

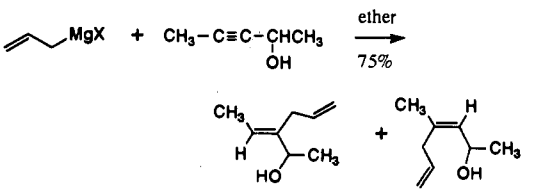
Vinylic sulfoxides underwent Pummerer-type reactions with allylmagnesium bromide to give diallylated sulfides together with monoallylated vinylic sulfides (eq 10).[55] The initially formed ylide gives the sulfonium cation by cleavage of the S–O bond. Attack of the Grignard reagent on the α-position affords the diallylated compound **34** (path a). Increasing the steric hindrance at the β-position prevents the second approach of the Grignard reagent; as a result, the Grignard reagent acts as a base and the product from pathway b predominates to give **35**. The latter process was applied to the synthesis of (−)-sibirine.[56]



(eq 10)

R^1	R^2	R^3	Yield (%) 34	35
H	Me	H	85	-
H	H	Ph	78	-
Me	Ph	H	43	18

Grignard reagents do not add easily to the triple bond of simple alkynes.[57] The enhanced reactivity of allylic Grignard reagents enables them to react with acetylenic alcohols by an antiaddition process (eq 11).[57,58] How-

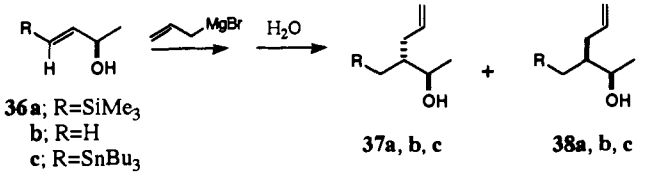


(eq 11)

ever, both regioisomers are obtained, making this

allylmetalation of limited synthetic utility. The reaction is clearly oxygen-assisted since the yield drops to 7% in the case of 4-hexyn-1-ol, and 0% in the case of 5-heptyn-1-ol,[59] where the heteroatom is too far removed for efficient assistance. Grignard reagents other than those of the allylic type do not add as well to alkynols. Propargylic alcohols react with vinylmagnesium chloride in THF and also with methyl, ethyl, isopropyl and phenyl Grignard reagents in benzene.[57] However, in the presence of 10% copper(I) iodide, most Grignard reagents (except vinyl) are able to undergo addition under much milder conditions and in an anti fashion. Propargylic amines also react with allyl Grignard reagents under reflux in THF.[60]

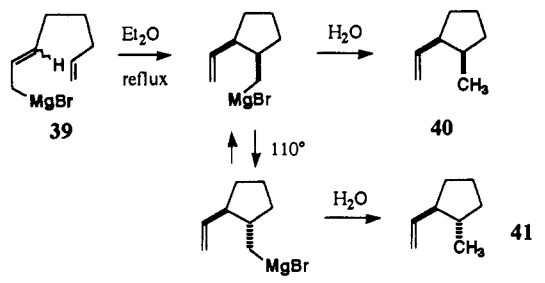
The addition of crotylmagnesium chloride to 1-octene in ether at 100 °C produced a mixture of 3,4-dimethyl-1-decene and 5-methyl-2-undecene in only 11% yield.[61] Thus, the magnesium–ene reaction to simple alkenes has received virtually no attention as a strategic tool in organic synthesis. However, the allylmagnesiation of (*E*)-1-(trimethylsilyl)but-1-en-3-ol (**36a**) proceeds very smoothly.[63] The reaction of **36a** with allylmagnesium bromide (2.1 equiv) in refluxing Et_2O was complete in 18 h to give, after hydrolysis, a mixture of alcohols **37a** and **38a** (81%) in a ratio of 20:1, respectively. By contrast **36b** required a large excess of allylmagnesium bromide in refluxing Et_2O for 170 h to achieve a 16% yield of alcohols **37b** and **38b** (8:1). The corresponding stannane derivative **36c** reacted in refluxing Et_2O (24 h) to give the alcohols **37c** and **38c** (10:1) in 61% yield. It is clear that the silicon (or stannane) substitution reinforces the substantial activation already provided by the proximate heteroatom.[63]



36a; R=$SiMe_3$
b; R=H
c; R=$SnBu_3$

37a, b, c **38a, b, c**

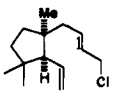
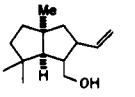
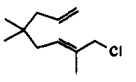
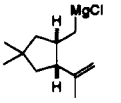
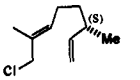
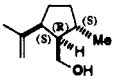
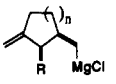
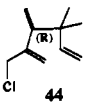
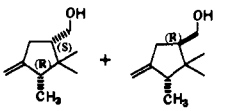
Problems of low regio- and stereoselectivity and low overall efficiency may limit the applicability of bimolecular reactions. In contrast, intramolecular versions of the metallo–ene process may be regio- and stereoselective, entropically favored, and thus more efficient.[62,64] The first encouraging example of an intramolecular magnesium–ene reaction dates back to 1972. 2,7-Octadienylmagnesium bromide (**39**) cyclized in boiling Et_2O to give, after aqueous workup, selectively *cis*-1-methyl-2-vinylcyclopentane (**40**) in 67% yield.[65]



39 **40** **41**

Heating the solution of the intermediate Grignard product to 110 °C (sealed tube, 24 h) furnished mainly

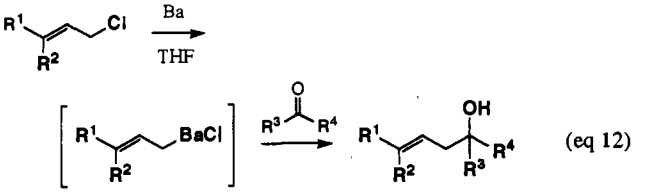
Table I. Intramolecular Allylmagnesium–Ene Reactions

				ref
	1) Mg powder, Et_2O 2) RT, 20 h 3) O_2		70%	66
	1) act. Mg -60°C 2) 65°C, 24 h		76%	67
 **42**	1) Mg, Et_2O 2) 40°C, 14 h 3) MoOPh, -78°C	 **43**	49%	68
	1) act. Mg -60°C 2) 80°C, 17 h (n=2) 130°C, 23 h (n=1) 130°C, 17 h (n=3) 80°C, 17 h (n=2)	 R=H, 71-72% $R=CH_3$, 86%		69
 **44**	1) act. Mg, -65°C, THF 2) 130°C, 23 h 3) O_2	 1 : 1 61%		70

the thermodynamically more stable trans product **41**, indicating the reversibility of the cyclization at higher temperatures. Some representative examples of metallo–ene reactions are summarized in Table I. The stereodirecting bias of a preexisting stereogenic center on the intramolecular magnesium–ene reaction is studied by using **42**. Metalation of **42** with commercial Mg powder yielded an 88.4:5.9:3.0:1.4 stereoisomer mixture of cyclized alcohols in 58% yield.[68] The major isomer has (4a*S*,7a*R*) configuration (**43**), being consistent with a favored six-membered cyclic transition state (with the C-7 methyl group oriented toward the convex face) assuming that 2,3-disubstituted 2-alkenylmagnesium chloride reacts in the (*E*) form. By contrast, no diastereoselectivity was observed in the cyclization/oxidation of **44**, which gave a 1:1 stereoisomeric mixture of five-membered carbocycles.[70] This is not surprising since transition states leading to both stereoisomers suffer similar steric crowding due to the *gem*-dimethyl substitution.

B. Allylic Barium Reagents

Allylbarium can be prepared directly by the reaction of in situ generated barium metal with various allylic chloride, and the regio- and stereoselective allylation of carbonyl compounds can be accomplished using these allylmetals (eq 12).[71a] Highly reactive barium was

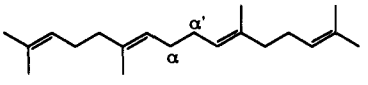


(eq 12)

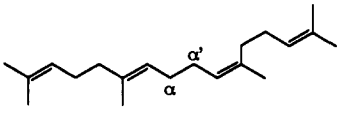
readily prepared by the reduction of barium iodide with

2 equiv of lithium biphenylide in dry THF at room temperature for 30 min. The resulting dark brown suspension was exposed to allylic chlorides at −78 °C, giving a reddish suspension of allylic barium. The allylic barium reagent reacted with a variety of aldehydes and ketones cleanly at −78 °C in a few minutes to produce the homoallylic alcohol with remarkably high α-selectivity and retention of stereochemistry of the starting halides. As mentioned above, it is well known that the corresponding magnesium, zinc, and calcium reagents give the γ-substituted product predominantly and the allylation with the lithium reagent is less selective. For example, α/γ ratios of the products obtained by the reaction of benzaldehyde with geranylmetals are following.[71a] M = Mg, α/γ = <1:99 (99% yield); M = Ca, α/γ = 8:92 (38% yield); M = Li, α/γ = 47:53 (36% yield); M = Ce, α/γ = 72:28 (52% yield); M = Ba, α/γ = 92:8 (90% yield, E/Z = 98:2).

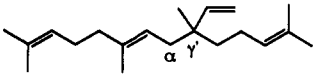
The highly α,α′-selective and stereocontrolled homocoupling reaction of allylic halides is achieved using allylic barium reagent.[71b] The double-bond geometry of the starting allylic chloride is completely retained. The effect of metals on the regio- and stereoselectivities of dimerization reaction of geranyl bromide was investigated; the metals, Li–Np, Na–Np, K–Np, Cs–Np, Mg, Ca, Ba, Cr, and Mn were used (Np = naphthalene). Among these metals, Ba is unique for α,α′-selective homocoupling reaction (α,α′/α,γ′ = 97:3, 47% yield).



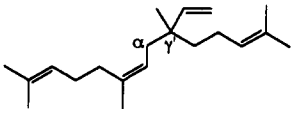
α-α′ (EE′)



α-α′ (EZ′)

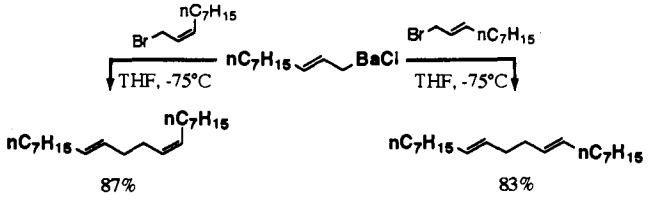


α-γ′ (E)



α-γ′ (Z)

Furthermore, the geometric purity of the α,α′ product is quite high; EE′/EZ′ = 96:1. Other metals provide the α,α′ product (60∼70%) along with the α,γ′ (22∼39%) and α,α′ product (1∼12%). α,α′ cross-coupling products are also prepared stereospecifically and regioselectively by this method. For example, treatment of (E)-2-decenylbarium reagent with (E)-2-decenyl bromide and (Z)-2-decenyl bromide affords (E,E)-diene and (E,Z)-diene in high yields, respectively.



87% 83%

C. Allylic Zinc Reagents

1. Reactions of Aldehydes and Ketones

The allylic zinc halides have generally been prepared in ether or THF and show a reactivity comparable with Grignard reagents. Alcohols can serve as solvent for the generation and addition of allylic zinc halides to aldehydes and ketones.[72] Thus slow addition (20–30 min) of allyl bromide (0.11 mol) to a stirred slurry of "activated" zinc dust (0.11 g atom), an aldehyde or ketone (0.1 mol) and 25 mL of 95% ethanol or *tert*-butyl alcohol at a bath temperature of 78–95 °C gave the products listed in Table II in yields comparable in some instances with those obtained in aprotic solvents (entries 1, 2, and 4–6). It is known that the use of ultrasonic waves promotes the formation of Grignard reagents even in the presence of unusually high concentration of water[73] and allylation of aldehydes and ketones can be easily effected in aqueous media in a Barbier-type reaction either by using ultrasonic waves and zinc as the metal or by stirring the mixture of a substrate, allyl halide, and zinc in saturated aqueous NH_4Cl/THF solvent without the use of ultrasonic waves (entries 3 and 8).[74] The allylation in the aqueous media was devised by the use of a solid organic support instead of the cosolvent THF.[75] Thus, the organic phase can be reused, and disposal of the reaction solvent after the reaction is uniquely environmentally safe. There are two applications where this process has special advantages. The formation of the Grignard reagent with dimethylallyl halides is plagued by coupling side products while the aqueous zinc cases react smoothly. Another advantage is that the reaction can be carried out without the protection of additional hydroxy functional groups (entry 13). The Zn-promoted transformation of carbonyl compounds to the homoallylic alcohols proceeds quite smoothly using DMF as a solvent.[76] For example, the reaction of crotonaldehyde gave the allylation product in 86% yield in Zn/DMF for 30 min (entry 14), whereas the aqueous Zn–silica method afforded the product in only 37% yield.[75] Further, it has been reported that the Zn-mediated reaction of hexanol with cinnamyl bromide carried out in THF did not give the allylation product,[74] whereas it proceeds very smoothly in DMF (entry 15). 2-Haloallylation of carbonyl compounds with 2,3-dihalopropene has been achieved only by using 2,3-dibromopropene with metallic tin as a promoter.[78] From an industrial viewpoint, the use of 2,3-dichloropropene is more desirable than the use of the bromide. With metallic tin, however, no effective 2-chloroallylation of carbonyl groups by the chloride takes place. The zinc-promoted 2-chloroallylation of aldehydes and ketones has been achieved in a two-phase system of water and toluene containing a small amount of acetic acid (entries 16–18).[77] Normally, allylic zinc reagents are prepared by the insertion of zinc dust into the corresponding allylic halides as shown above. The use of mesylates or the more stable allylic phosphates allows the generation of the corresponding allylic zinc reagent under Barbier conditions in the presence of zinc (ca. 2 equiv), a catalytic amount of LiI, and the carbonyl compound in DMA or MDPU, leading to homoallylic alcohols in excellent yields (79–95%) (entries 19–21).[79a] No homocoupling products were produced under these conditions

Table II. Allylation of Aldehydes and Ketones with Allylic Zinc Reagents

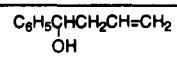
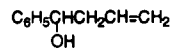
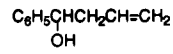
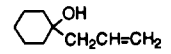
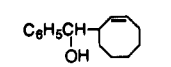
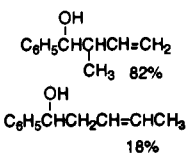
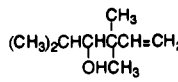
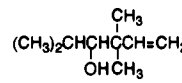
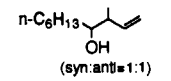
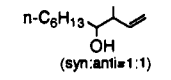
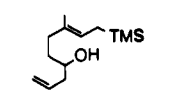
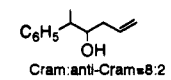
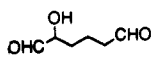
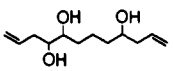
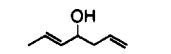
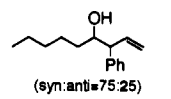
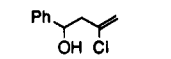
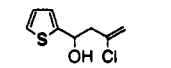
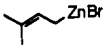
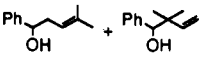
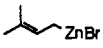
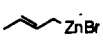
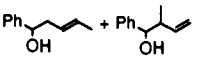
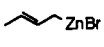
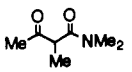
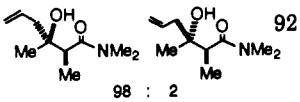
entry	reactant	allyl halide	conditions[a]	product	yield, %	ref(s)
1	C_6H_5CHO		activated Zn, 95% EtOH, 78 °C		66	72
2	C_6H_5CHO		activated Zn, t-BuOH, 95 °C		71	72
3	C_6H_5CHO		Zn, saturated aqueous NH_4Cl/ THF, rt, ST		100	73, 74
4			activated Zn, t-BuOH, 95 °C		63	72
5	C_6H_5CHO		activated Zn, 95% EtOH, 90 °C		48	72
6	C_6H_5CHO	$CH_3CH{=}CHCH_2Br$	activated Zn, 95% EtOH, 90 °C		60	72
7	$(CH_3)_2CHCHO$		Zn, H_2O/THF, rt, US		90	73
8	$(CH_3)_2CHCHO$		Zn, saturated aqueous NH_4Cl/ THF, rt, ST		95	73, 74
9	$n\text{-}C_6H_{13}CHO$		Zn, saturated aqueous NH_4Cl, rt, C-18 silica		85	75
10	$n\text{-}C_6H_{13}CHO$		Zn, saturated aqueous NH_4Cl, rt, C-18 silica		100	75
11			Zn, saturated aqueous NH_4Cl, rt, C-18 silica		68	75
12			Zn, H_2O, C-18 silica pyridinium tosylate		90	75
13			Zn, saturated aqueous NH_4Cl, rt, C-18 silica		60	75
14			Zn, DMF, rt		86	76
15			Zn, DMF, rt		87	76
16	PhCHO		Zn, H_2O/toluene HOAc, 45 °C, 1 h		95	77
17			Zn, H_2O/toluene HOAc, 45 °C, 1 h		92	77
18			Zn, H_2O/toluene HOAc, 45 °C, 1 h		81	77
19			Zn, Li(I) (0.2 equiv) DMPU, 35 °C, 24 h (or DMA)		80	79
20	PhCHO		Zn, Li(I) (0.2 equiv) DMPU, 25 °C, 12 h		95	79
21			Zn, Li(I) (0.2 equiv) DMPU, 25 °C, 12 h		78	79

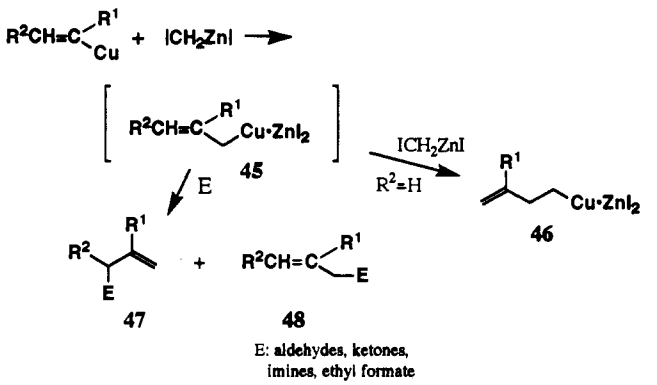
Table II. (Continued)

entry	reactant	allyl halide	conditions[a]	product	yield, %	ref(s)
22			(1) THF, 0 °C, 20–60 min; (2) Bu_4NF	 90 : 10	>80	44
23			(1) THF, 0 °C, 20–60 min; (2) Bu_4NF	>99 : 1	>80	44
24			(1) THF, 0 °C, 20–60 min; (2) Bu_4NF	 3 : 97	>80	44
25			(1) THF, 0 °C, 20–60 min; (2) Bu_4NF	>99 : 1	>80	44
26			THF, 25 °C	 98 : 2	92	247b
27	RCHO R=Ph, C_6H_{11}		Pd(0)/Zn, dioxane		51∼99	79b

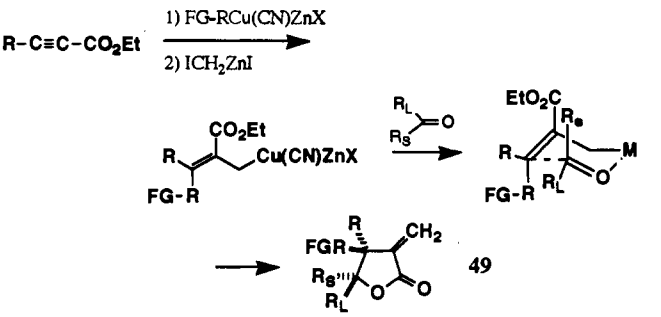
[a] Abbreviations are as follows: ST, stirring; US, sonication; rt, room temperature; DMPU, *N,N'*-dimethylpropyleneurea; DMA, *N,N*-dimethylacetamide.

even in the first case of disubstituted allylic precursors. The preparation of the allylic organometallic in a first step followed in a second step by the addition of an electrophile is also possible. Not only allylic substrate but also benzylic phosphates and sulfonates, primary alkyl chlorides, bromides, phosphates, and sulfonates can be converted to the corresponding zinc reagents under the same reaction conditions. Regioselective α-allylation has been accomplished by using (triisopropylsilyl) ketones and allylic zinc bromides.[44] The reaction of benzaldehyde with crotyl and prenylzinc bromides gives the γ-allylation products exclusively, whereas the use of the silylated ketone as an electrophile followed by desilylation affords only the α-products (entries 23 and 25). Benzoyltrimethylsilane gave the α-adduct predominantly upon treatment with prenylzinc bromide, whereas it afforded the γ-adduct with crotylzinc bromide (entries 22 and 24). Regioselective α-propargylation is also realized by the reaction of triisopropylsilyl ketones with propargyl zinc and Grignard reagents.[44] Allylation of 2-methyl-3-oxo amides with allylzinc bromide provides syn 3-allyl-3-hydroxy-2-methyl amides with very high diastereoselectivity (entry 26). The allylzinc addition to the corresponding 3-oxo esters results in lower syn selectivity (∼7:3). Allylic acetates are reduced by zinc in the presence of a catalytic amount of $Pd(PPh_3)_4$ to serve as nucleophilic allylating agents, which react with aldehydes to afford the corresponding homoallyl alcohols (entry 27).[79b] The diastereoselectivity is in most cases syn, but it is low (see also **312** and Table VI). Aldehydes and ketones react with allylic bromides in the presence of Cp_2TiCl_2 (cat)/Zn system at room temperature to give homoallyl alcohols in high yields, but with low diastereoselectivity in the case of crotyl and cinnamyl bromide.[79c]

The addition of (iodomethyl)zinc iodide (1.7 equiv) to an alkenylcopper in THF at −30 °C leads to a methylene homologated allylic zinc and copper reagent (**45**), which readily inserts a further methylene unit in the absence of any electrophile to give a homoallylic copper reagent (**46**).[80] However, if the allylic reagent **45** is generated in the presence of an electrophile (0.6–



0.7 equiv), such as an aldehyde, ketone, ethyl formate, or imine, then its trapping by the electrophile is faster than further methylene homologation to **46**; excellent yields (71–96%) of allylated products of type **47** and **48** can be obtained. The reaction of the substituted allylic reagent **45** ($R^2 = C_6H_{13}$, R^1 = H) with hexanal gave mostly the branched allylated product **47** (47/48 = 94:6). The alkenylcopper is generally prepared from the corresponding Grignard reagent and CuI·LiI in THF at −50 °C.[80] The carbocupration of acetylenic esters with (FG-R)Cu(CN)ZnX (FG = functional group) provides the alkenylcopper stereoselectively which is then treated with a mixture of a carbonyl compound and ICH_2ZnI to afford the α-methylene-γ-butyrolactone **49**.[81a] The groups R of the alkyne, FG-R of the zinc–



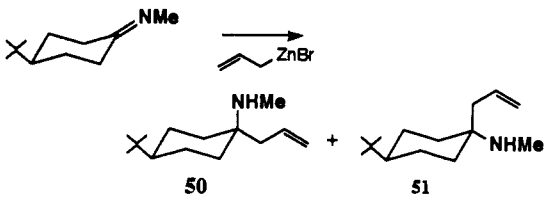
copper organometallic, and R_L of the aldehyde can bear

a wide range of functionalities (ester, nitrile, halide, triple bond), allowing a unique approach to the synthesis of α-methylene-γ-butyrolactones.

2. Reactions of Imines

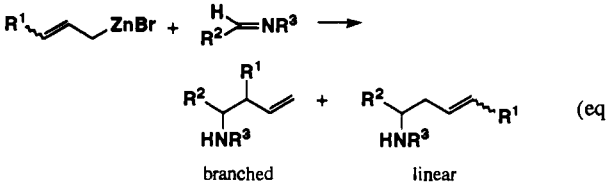
As observed in the case of allyllithium and magnesium reagents, the allylation of imines with allylzinc reagents is limited to those which are nonenolizable or contain branched α-alkyl substituents (eq 13).[82] Both allylzinc bromide and allylmagnesium bromide favor axial attack in ether or in THF, giving mainly diastereoisomer **51**. In THF/DMSO, allylzinc bromide gives predominantly **50** via equatorial attack (85:15) (eq 14).[83] The reason

(eq 13)



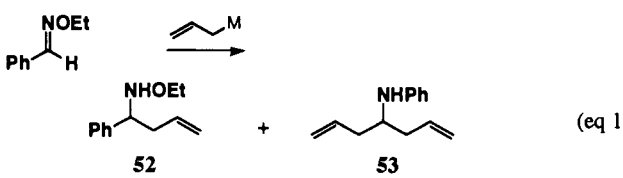
(eq 14)

for this difference is not clear. In the 1,2- and 1,3-asymmetric inductions shown previously (eqs 3–8), allylzinc bromide exhibited diastereoselectivities similar to allylmagnesium chloride.[46–50] The regioselectivity of additions of crotylzinc (and magnesium and lithium) reagents to aldimines has been studied (eq 15),[64] and the following two trends are observed: (i) metals favor branched products in the order MgBr > ZnBr > Li for a given imine and (ii) linear products predominate using α-alkylimines while branched products predominate using formaldehyde imines and α-arylimines. The



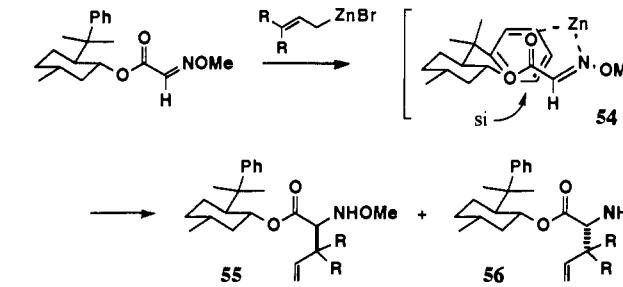
(eq 15)

levels of syn–anti diastereoselectivity in the reaction of crotylzinc reagents are not synthetically useful, as also observed in the reaction of crotylmagnesium and lithium reagents (eq 2). Among these reagents, crotyllithium is the most selective, favoring anti product.[45,85] The course of the addition to an aldoxime is reagent and solvent dependent; allylzinc bromide affords predominantly 1,2-adduct **52** in 60% yield while allylmagnesium bromide provides amine **53**, a Beckmann rearrangement product, in 93% yield (eq 16).[86] Both allyl- and prenylzinc bromide provide good stereocontrol in the



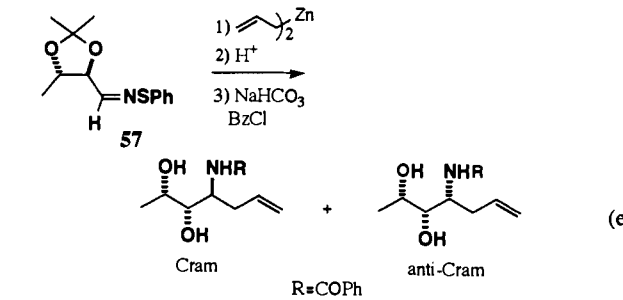
(eq 16)

addition to 8-(−)-phenylmenthyl (*N*-methoxyimino)-acetate (eq 17); the allyl reagent gives a 87:13 mixture of **55** and **56** (R = H), and the ratio increases to >99:1 in the case of the prenyl reagent (R = Me).[87] Pre-

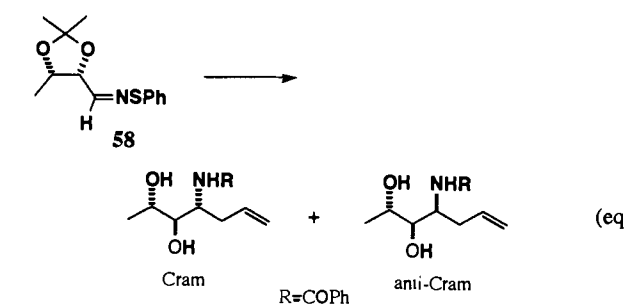


(eq 17)

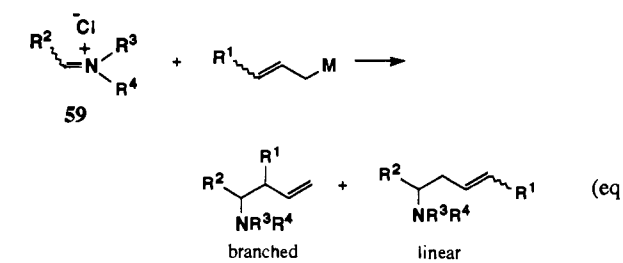
dominant formation of **55** (R = H) is consistent with a chelation-controlled allyl addition as shown in **54**, with attack occurring from the more accessible *si* face. The addition of diallylzinc and allylmagnesium bromide to sulfenimine **57** and isomeric sulfenimine **58** was carried out to clarify the influence of the α- and β-alkoxy substituents on reaction diastereoselectivity. Treatment of **57** with diallylzinc provides exclusively the Cram product in 60% yield (eq 18).[88] Allylmagnesium bromide affords nearly 1:1 mixture of the products. The Cram product is also obtained as the sole product in the reaction of **58** with diallylzinc (eq 19). The



(eq 18)



(eq 19)



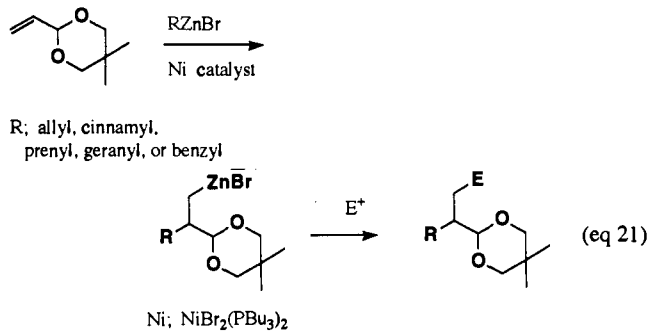
(eq 20)

diallylzinc-induced Cram diastereofacial selectivity closely parallels that of the corresponding aldehyde precursors[89] and is consistent with Felkin–Ahn addition; the aldehyde precursors give a 95:5 ratio of Cram and anti-Cram products in the diallylzinc addition. In the

case of preformed iminium salts **59**, α-deprotonation is not a serious problem since yields are generally good even though the iminium salts are enolizable.[90] The preference for branched homoallylamines follows the trend $Al_{2/3}X > ZnX > MgX > Li$, paralleling the covalent character of the carbon–metal bond (eq 20).

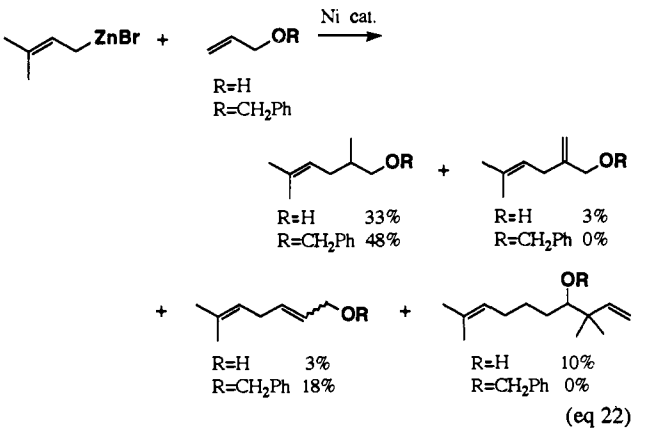
3. Reactions of Alkenes and Alkynes

An α,β-unsaturated acetal undergoes rapid metalation upon treatment with allylzinc bromides in the presence of nickel catalyst.[91] Allylzinc reagent, as a nucleophile, attacks the α-carbon of the acetal, and then the resulting carbanion at β-position reacts with a variety of electrophiles, such as I_2, allyl iodide, and propargyl bromide, to give α,β-dialkylated acetal (eq 21). Regioselective allylmetalation of allylic alcohol



(eq 21)

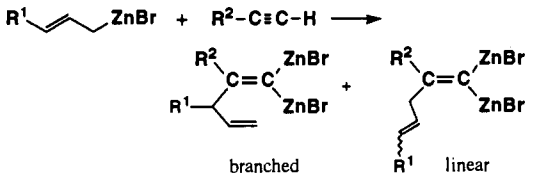
has been accomplished by treatment with allylzinc in the presence of a nickel catalyst, $NiBr_2(PBu_3)_2$ (eq 22).[92] Allyl alcohols were less reactive toward allyl metal reagents than α,β-unsaturated acetal, probably due to its higher basicity. The benzyl allyl ether reacted rapidly with allylzinc reagent, giving a higher C2/C-3 regioselectivity (eq 22). Allylic Grignard reagents or



(eq 22)

alkyllithium reagents are known to readily add to allylic alcohols.[93] The importance of intramolecular coordination is demonstrated in those reactions. Copper[94]- or nickel[95]-catalyzed reaction of the Grignard reagent with α,β-unsaturated acetals produces only the corresponding Michael type addition (β-alkylation) products. The more reactive allylic Grignard reagent reacts with nonactivated double bonds in some cases as shown previously (eq 11 and **36**). Allylic zinc reagents, in contrast, are relatively unreactive toward simple alkenic bonds.[96] Needless to say, Michael addition of allylic zinc reagents to an activated double bond takes place very readily.[97]

Organozinc reagents are able to add to a wide variety of alkynes.[57] Allylic-, propargylic-, di-*tert*-butyl-, and malonic-type organozinc derivatives undergo carbometalation reactions. Other organometallic reagents of the same type (lithium, magnesium, boron, aluminum, or copper) do not react intermolecularly with simple alkynes. Representative examples are summarized in Table III. Acetylene itself reacts with allylic zinc halides in THF (entry 1).[98] Monosubstituted alkynes and enynes react with all the zinc reagents mentioned above. These alkynes are metalated by allylic and propargylic reagents prior to the addition, giving a bismetalated vinylic species (entry 2),[100] but the reactions with di-*tert*-butylzinc and malonic zinc reagents proceed without the metalation of acetylenic hydrogen atom (entry 3).[99] The addition of allylic zinc halides to alkynes is a reversible process, and thus allylic rearrangement occurs widely, and often exclusively, when the allylic zinc halide is substituted (eq 23).[101]



(eq 23)

Since the addition is reversible, the amount of the minor thermodynamic linear isomer can be increased by prolonged contact of the reactants. The regiochemistry of the addition is always of the Markovnikov type, whatever the R group of the alkyne. Disubstituted, nonfunctionalized alkynes do not react with either type of organozinc derivative. There is only one example of intramolecular cyclization (entry 4).[102]

Functionalized alkynes and enynes react with all of the organozinc derivatives mentioned above. Among them, allylic zinc halides are the most studied. They react with propargylic alcohols, ethers, acetals, amines, halides, and with enyne systems.[57] Generally, the reaction affords the Markovnikov type regioisomer (entries 5 and 6).[103,104] Bisaddition is sometimes observed and this becomes the main reaction if the alkyne is metalated with an organomagnesium or lithium reagent prior to the addition of allylic zinc halides (entry 7). A similar cyclopropane derivative is the only product obtained from the reaction of 2-(methyl-2-propen-1-yl)zinc bromide with propargyl bromide and phenyl-2-propynyl ether (entry 8).[104] The addition of allylic zinc bromide to silylated alkynes proceeds regioselectively to produce 1,4-pentadienylzinc halides in high yields, although the reaction is only about 85% stereoselective (syn addition) (entry 9).[105] This preferential syn addition (85:15) becomes an anti addition when an ether function is located at the propargylic position on the substrate (entry 10).[106] The zinc–ene cyclization shows interesting possibilities (entries 11–12);[107] the allylic zinc bromides were prepared in situ from the corresponding chlorides via the transmetalation of the Grignard intermediates with $ZnBr_2$ (1.5 equiv). Analogous attempts to cyclize the allylmagnesium chloride failed in most cases: the less nucleophilic zinc derivatives cyclized readily at 80 °C. Oxygen and nitrogen heterocycles are prepared by this intramolecular cyclization.

Table III. Allyliczincation of Triple and Double Bonds

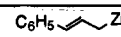
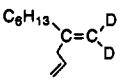
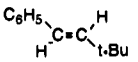
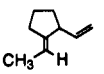
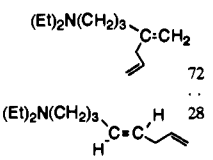
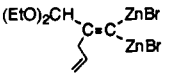
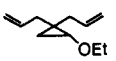
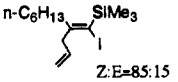
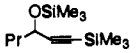
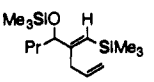
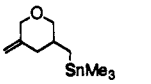
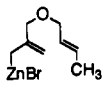
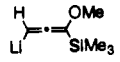
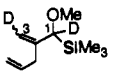
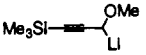
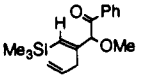
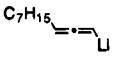
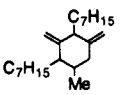
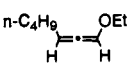
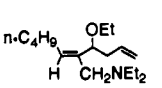
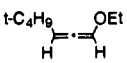
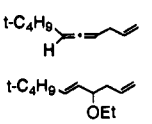
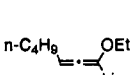
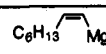
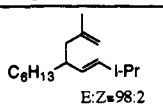
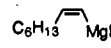
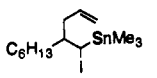
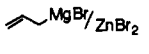
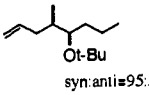
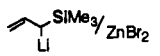
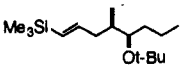
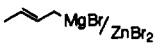
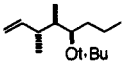
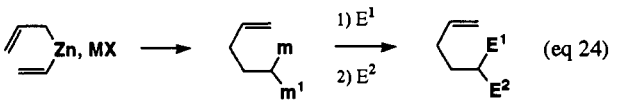
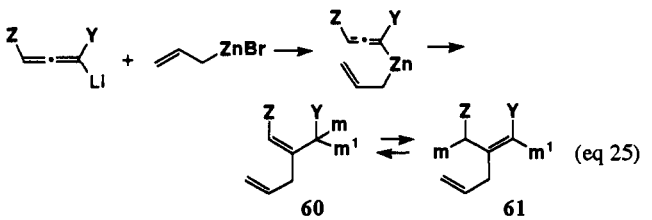
entry	zinc reagent	substrate	conditions	product	yield, %	ref(s)
1		HC≡CH (excess)	(1) THF, 25 °C, 15 h; (2) H_3O^+		66	98
2		$C_6H_{13}C{\equiv}CH$	(1) THF, 30 °C, 24 h; (2) D_2O		70	100
3	$(t\text{-}C_4H_9)_2Zn$	$C_6H_5C{\equiv}CH$	(1) ether, reflux, 48 h; (2) H_3O^+		70	99
4	$H_3CC{\equiv}C(CH_2)_3CH{=}CHCH_2Br$		(1) Zn/THF, reflux, 24 h; (2) H_3O^+		50	102
5		$(Et)_2N(CH_2)_3C{\equiv}CH$	(1) THF, reflux, 23 h; (2) H_3O^+		16	103
6		$(EtO)_2CHC{\equiv}CH$	THF, reflux		37	104
7		$(EtO)_2CHC{\equiv}CMgBr$	THF		37	104
8		$PhOCH_2C{\equiv}CH$	THF		75	104
9		$C_6H_{13}C{\equiv}CSiMe_3$	(1) THF, 60 °C, 18–24 h; (2) I_2		83	105
10			(1) THF, 60 °C, 18–24 h; (2) saturated aqueous NH_4Cl		52	106
11			(1) THF; 80 °C, 23 h; (2) $ClSnMe_3$		57	107
12			(1) THF, 80 °C, 45 h; (2) H_2O		80	107
13			(1) THF, 65 °C, 12 h; (2) NH_4Cl, MeOD		60	109
14			(1) THF, 65 °C, 0.5 h; (2) $PhCO_2Et$; (3) H_2O		55	109
15			(1) THF 60 °C, 2 h; (2) H_2O		70	110
16			(1) THF, CuBr; (2) $PhSCH_2NEt_2$		60	111
17			(1) THF; (2) H_2O		70	111
18			(1) THF; (2) i-PrCHO; (3) H_2O		75	111
19			(1) THF, 0 °C, 1 h, >95%; (2) THF, 120°C, 0.5h	100% Z	80	112

Table III. (Continued)

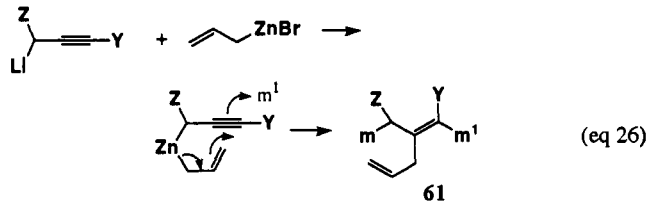
entry	zinc reagent	substrate	conditions	product	yield, %	ref(s)
20			(1) THF, 35 °C, 0.75 h, 92%; (2) i-PrCHO/BF_3·OEt_2, THF, −90 °C → −50 °C	 E:Z=98:2	79	113a
21			(1) THF, 35 °C, 0.75 h, 92%; (2) Me_3SnCl, −25 °C → −5 °C; (3) I_2		75	113b
22			(1) THF; (2) H_3O^+	 syn:anti=95:5	81	114
23			(1) THF; (2) H_3O^+	 syn:anti=73:27 E:Z=98:2	78	114
24			(1) THF; (2) H_3O^+	 d.r. >95:5	75	115

A "metalla Claisen" rearrangement or, alternatively, internal deliverly of allyl–vinyl zinc reagents leads to bismetallic derivatives, which can react, once or twice, with a variety of electrophiles (eq 24).[108] The real nature of m and m′ is unknown, and the corresponding organometallics are probably a nonmonomeric cluster. The rearrangement of allyl–allenylzinc reagents may produce a mixture of two equilibrating allylic species **60** and **61** (eq 25).[109] As shown in entry 13, the (1-(trimethylsilyl)-1-methoxyallenyl–allyl)zinc system undergoes deuterolysis on carbons 1 and 3 almost exclusively, indicating an intervention of intermediate **61**. There is an equilibrium between an allenic and a propargylic structure. If the internal delivery of the allyl moiety takes place with the mixed propargylic–allylic reagent, we obtain an intermediate **61** (eq 26) (entry 14).


(eq 24)

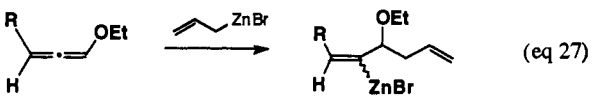

(eq 25)

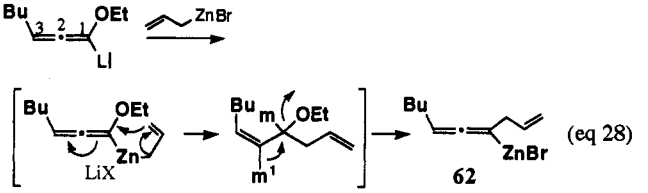
60 **61**


(eq 26)

61

The addition of allyl zinc bromide to allenic ethers in THF gives 1:1 mixtures of (*Z*)- and (*E*)-vinyl organozinc compounds in high yields (eq 27).[111] However, treatment of allylzinc bromide with 1 equiv of CuBr prior to the addition to the allenic ether leads to a predominant syn addition (*Z*/*E* = 91:9). The syn addition occurs from the less hindered side of the C=C bond (entry 16). If a bulky substituent is present in the allenic ether, β-elimination of zinc alkoxide competes with the ordinary allylic zincation (entry 17). When the starting alkoxyallene is metalated on carbon atom 1, further addition of allylzinc bromide leads to a metalated skipped allene–ene **62**, presumably via the internal delivery of the allyl group on carbon atom 1 (eq 28). The intermediate bismetalated species is highly

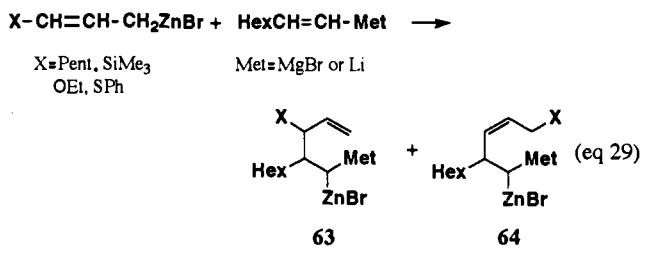

(eq 27)


(eq 28)

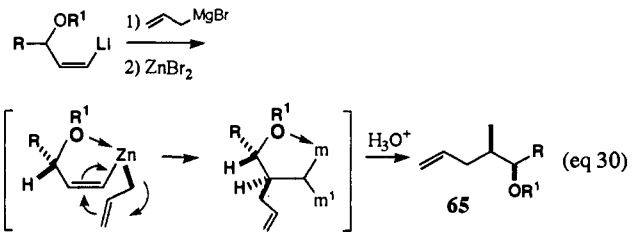
62

unstable since this allylic carbenoid has some carbocationic character and is prone to β-elimination of a metal alkoxide, in contrast to the vinylic zinc derivative shown in eq 25 (entry 18). The addition of vinylmagnesium bromide to allylzinc bromide gives the dimetallic reagent in quantitative yield, as shown in eq 24, which reacts with diethyl (7-acetoxyheptylidene)malonate to afford the stereochemically pure (*Z*)-1-acetoxy-7,11-dodecadiene (entry 19).[112] A number of geminal dimetallic compounds have been prepared by carbometalation of an alkenyl organometallic derivative of Mg, Li, or Al by an allylic zinc bromide. The 1-magnesia-1-zincaalkanes react smoothly with various aldehydes in the presence of BF_3·OEt_2 to furnish (*E*)-1,5-dienes in high yields and high isomeric purity (for example, entry 20).[113a] The 1-magnesia- or 1-lithia-1-zincaalkanes are able to react successively with two different electrophiles to give good yields of various geminal difunctionalized compounds (entry 21).[113b] Transmetalation of the Mg– or Li–Zn reagents to the corresponding 1-zincacyanocuprate is accomplished by the reaction with copper cyanide. These new Cu–Zn reagents react efficiently with various alkylating or allylating agents to give *gem*-bisalkylated or *gem*-

bisallylated compounds in good to excellent yields.[113c] The reactivities of 1-lithia-1-zincaalkanes,[113d] 1-zinca-1-stannaalkanes,[113e] and 1-lithia-1-stannaalkanes[113f] have been studied. The addition of the substituted or functionalized allylic zinc bromides to octenylmagnesium bromide or octenyllithium is always regiospecific and leads, depending on the substituent X, specifically to products of type **63** or **64** (eq 29).[113g]



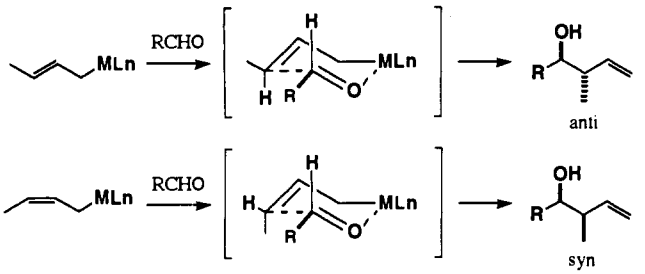
(*Z*)-γ-Lithiovinylic ethers can be added in a stereoselective way to allylic zinc bromide, leading to 1,1-dimetallic species with two asymmetric carbon atoms and, after acidic hydrolysis, to compound **65** (eq 30).[114] The high diastereoselectivity observed in this rearrangement is expected by the well-established preference for a chairlike transition state: the allyl part approaches the vinyl moiety anti to the R group. The use of allylic Grignard reagents or lithium reagents can be utilized in the presence of $ZnBr_2$ (entries 22 and 23), but no rearrangement takes place between the vinyllithium and the Grignard or lithium reagents in the absence of $ZnBr_2$. Even three asymmetric centers can be obtained with good diastereoselectivity via this metalla Claisen rearrangement (entry 24).[115]



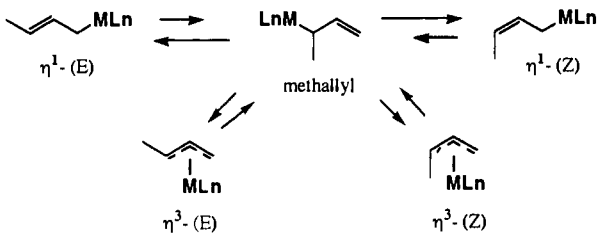
D. Allylic Cadmium Reagents

A commercially available cadmium powder is effective for Barbier-type allylation of carbonyl compounds with allylic halides.[116] The reaction is regioselective, giving homoallylic alcohols coupled at the γ-position of allylic halides as observed in the case of allylic magnesium and zinc reagents. α,β-Unsaturated carbonyl compounds undergo only 1,2-addition. Electrochemical allylation of aldehydes or ketones with allylic halides by the use of a cadmium-modified platinum anode and by alternating the cathode and anode at constant intervals gives high yields of the corresponding homoallylic alcohols.[117] Here also, the allylation at the γ-position predominates. Cadmium-mediated allylation of a variety of carbonyl compounds and imines in a $Cd/Bu_4NBr/THF$ system affords excellent yields of the corresponding homoallylic alcohols and amines under very mild reaction conditions.[118]

Scheme III. Six-Membered Cyclic Transition State



Scheme IV. Metallotropic Rearrangement of Crotyl Metals



IV. Group 13 (B, Al, and In)

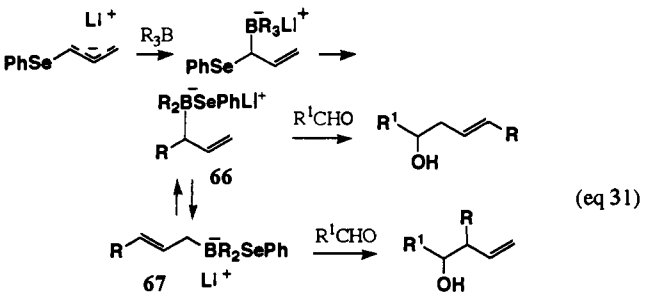
A. Allylic Boron Reagents

1. Reactions of Aldehydes and Ketones

It was shown in 1964 that triallylborane adds to aldehydes and ketones with the formation of the borane esters which are hydrolyzed to yield the corresponding homoallyl alcohols.[119] Crotylboron reagents react with aldehydes presumably via chairlike transition states: from (*E*)-crotyl boron compound an anti homoallyl alcohol is produced, whereas a syn homoallyl alcohol is afforded from (*Z*)-crotyl boron derivative. The stereochemical information present in the reagent is transmitted to an anti or a syn relationship about the new C–C bond of product (Scheme III).[2,3,120] This stereoselectivity has been observed for crotyl organometals incorporating boron, aluminum, pentavalent silicon, and tin (thermal and high-pressure reactions). Configurational stability of crotyl organometallics plays an important role in the stereoselective C–C-bond formation shown in Scheme III. Allylmetals can exist in either the monohapto (η^1) or trihapto (η^3)-forms. Crotylmetal compounds that exist in η^1-form are generally sensitive to metallotropic rearrangements which affect *E* to *Z* isomerization via the intermediacy of the methallyl isomer (Scheme IV).[3] If any *E* to *Z* isomerization of crotylboron takes place prior to the reaction with aldehydes, the stereochemical information of the reagent cannot be transmitted to the product stereochemistry and a detrimental effect on the ratio of anti/syn product diastereomers will ensue.

Reactions of nonchiral allylboranes with nonchiral aldehydes and ketones are summarized in Table IV. The dialkylcrotylboranes are the most reactive but also the least configurationally stable among the allylboron reagents.[121] The reaction of crotyl-9-BBN with glyoxylate esters provides the anti diastereomer with up to 3:1 selectivity (entry 1),[122] and the stereoselectivity in the reaction with pyruvate esters depends on the steric bulk of the ester group (entry 2).[123] The stereochemistry of the major product suggests that CO_2R substituent adopts an equatorial position in the six-

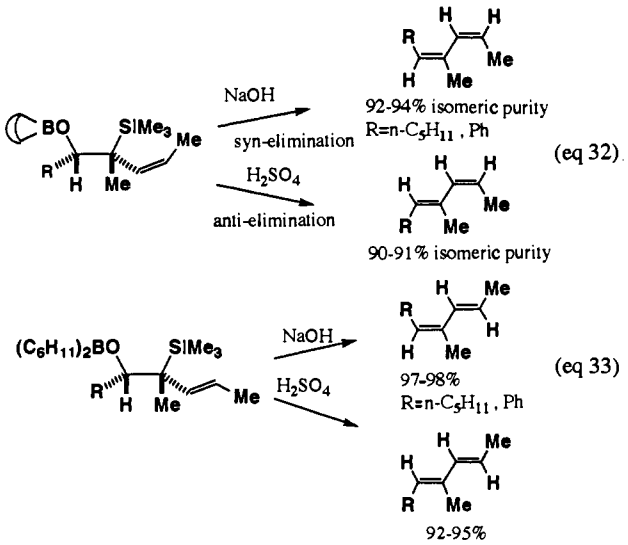
membered cyclic transition state (Scheme III). Crotylboronate complex, generated by the addition of Et_3B to crotyllithium, exists mainly as the *E*-isomer and displays moderate anti selectivity (entry 4).[125] Either branched or linear homoallyl alcohols can be prepared independently, by choosing the reaction conditions, through the reaction of (phenylselenyl)allyl carbanion with trialkylboranes (entries 5 and 6).[126] The reaction presumably proceeds as shown in eq 31. A facile



(eq 31)

migration of R group from boron to the α-carbon produces **66** (or the uncomplexed borane instead of the PhSe–boronate complex[3]). The reactions of **66** with aldehydes give linear homoallyl alcohols (entry 5). The allylic rearrangement of the boron atom of **66** takes place after a prolonged period of time, affording **67** which produces branched alcohols upon treatment with aldehydes. Diastereoselectivity is very high in reactions in which the α-silylsubstituted crotyl-9-BBN is first treated with *n*-butyllithium (entry 7).[127] This enhancement of the anti selectivity is due to formation of the ate complex from the 9-BBN and *n*-butyllithium. Similarly, pyridine may coordinate with the boron atom, leading to the high regio- and stereoselectivity (entry 8). The γ-trimethylsilyl-substituted allyl-9-BBN reacts smoothly with aldehydes to afford the condensation product with high diastereoselectivity (entry 9), which gives a variety of internal 1,3-butadienes after elimination of hydroxytrimethylsilane by either basic or acidic workup (the Peterson olefination reaction). The geometry of the double bond can also be controlled by selecting either 9-BBN (entry 9) or dicyclohexylboron (entry 10). Although the intermediate boronate products are shown in entry 9 and 10, treatment of these intermediates with NaOH or H_2SO_4 provided 1,3-butadienes with high stereoselectivity (eqs 32 and 33). Lithium *n*-butyltriallylborate allylates a range of acetals activated by TMSOTf.[132] Not only acyclic acetals but also cyclic acetal of benzaldehyde undergo allylation in good yield (entry 14).

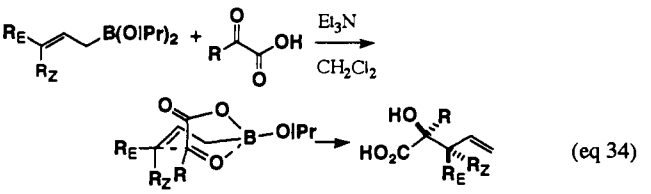
In contrast to the crotyldialkylboranes, crotylboronates are configurationally stable and the reactions with aldehydes proceed in general with high diastereoselectivity. In general, (*E*)-allylic boronates are more reactive than their *Z*-isomers (entries 15 and 16). Therefore, it is possible to accomplish a kinetic enhancement of the reaction diastereoselectivity by using excess (*E*)-allylic boronates. For example, as shown in entries 23 and 25, reagents of ca. 90% isomeric purity were treated with 0.9 equiv of aldehyde and the *anti*-homoallyl alcohols were produced with 95% or 98% stereoselectivity. Diastereoselectivity in the case of (*Z*)-crotylboronates deviates markedly from the reagent isomeric purity (entries 24, 26, and 27). Especially, the deviation becomes remarkable when a sterically de-



(eq 32)

(eq 33)

manding aldehyde or a bulky protecting group is used. Allylboronates and crotylboronates react with α-hydroxy ketones (entries 19 and 20) or α-oxocarboxylic acids (entries 21 and 22) to yield tertiary homoallylic alcohols in a highly stereocontrolled manner. The reaction presumably proceeds via a rigid bicyclic transition state as shown in eq 34.[137] A possible



(eq 34)

mechanism for the highly stereoselective triethylamine-initiated allylation involves the formation of an α-oxocarboxylic triethylammonium salt, followed by a ligand exchange between an isopropyl and the carboxylate group, to form a mixed boronate which then reacts via the bicyclic transition state (eq 34). The reaction of ethyl pyruvate takes place under 6 kbar at 45 °C for 80 h to give a 9:1 mixture of diastereoisomers (entry 30).[141] The stereochemistry of this reaction parallels that of the reaction of crotyl-9-BBN (entry 2), where the CO_2-Et group adopts an equatorial position in the six-membered chair transition state. The α-substituted allylboronates add to aldehydes giving the homoallyl alcohols with high *Z*-preference (entry 31),[142] as observed in entries 7 and 8 in the case of crotyltrialkylboranes.

The stereochemistry of the reactions of chiral aldehydes with nucleophiles can be understood by the Felkin–Anh or Cram model if a chelation mechanism does not operate in the reactions. Analyses of the transition-state geometries in the reactions of crotylboranes with a chiral aldehyde are shown in Scheme V, and the reactions are listed in Table V. In the reaction of (*E*)-crotylboranes, the Felkin–Anh or Cram model predicts either **68** or **69** as a stable transition-state geometry. However, **69** is unfavorable due to the steric repulsion between R and Me, and between R and H. Accordingly, the 3,4-anti-4,5-syn diastereomer should be favored over the 3,4-anti-4,5-anti isomer (entry 2).[143,144] The extent of relative diastereoselection must depend on the difference in size of the R substituent

Table IV. Reactions of Achiral Allylboranes with Achiral Aldehydes and Ketones

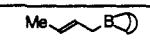
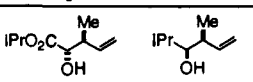
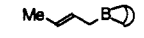
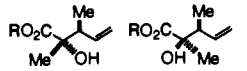
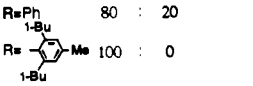
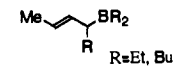
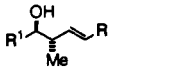
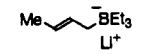
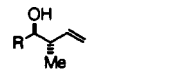
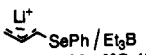
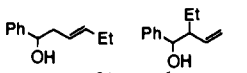
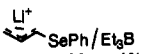
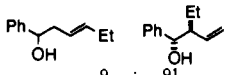
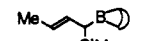
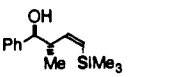
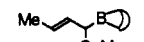
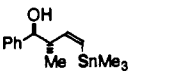
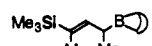
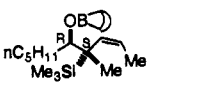
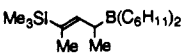
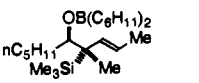
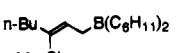
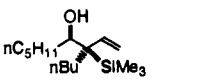
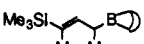
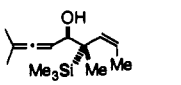
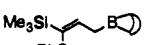
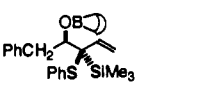
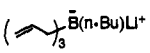
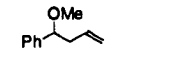
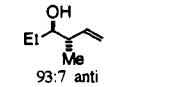
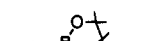
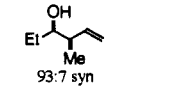
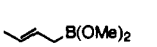
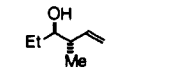
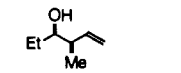
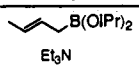
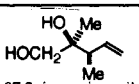
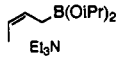
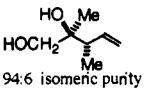
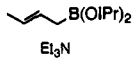
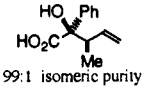
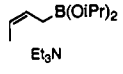
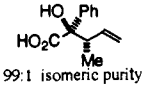
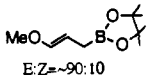
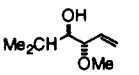
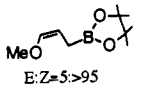
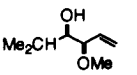
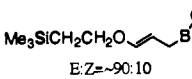
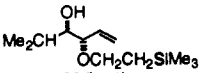
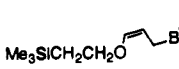
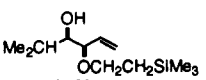
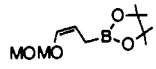
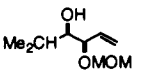
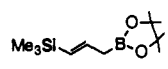
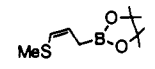
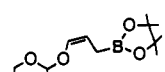
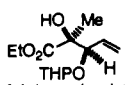
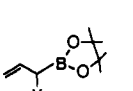
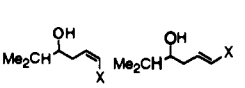
entry	allylboron	aldehyde	product ratio	yield, %	ref(s)
1		$HCOCO_2i$-Pr	 75 : 25	80	122
2		CH_3COCO_2R			123
			 R=Ph 80 : 20	89	
			R= 100 : 0	90	
3	 R=Et, Bu	R^1CHO	 >95% anti	52–84	124
4		RCHO (R=Me, Ph, i-Pr)	 68–85% anti	78–91	125
5	 -78°C→0°C, 1h	PhCHO	 94 : 6 (E:Z=86:14)	88	126
6	 -78°C→rt, 12h	PhCHO	 9 : 91 (syn:anti=24:76)	89	126
7	 (n-BuLi as an additive)	PhCHO	 >98:2 anti	50	127
8	 (pyridine as an additive)	PhCHO		90	127
9		n-$C_5H_{11}CHO$		77	128
10		n-$C_5H_{11}CHO$		78	128
11		n-$C_5H_{11}CHO$		90	129
12				93	130
13		$PhCH_2CHO$		68	131
14		$PhCH(OMe)_2$/TMSOTf		94	132
15	 E:Z=93:7	EtCHO	 93:7 anti	62	2b, 133
16	 E:Z=5:>95	EtCHO	 93:7 syn	26	2b, 133
17		EtCHO	 97:3 anti	61	134
18		EtCHO	 96–98:2–4 syn	62	134, 135

Table IV. (Continued)

entry	allylboron	aldehyde	product ratio	yield, %	ref(s)
19		CH_3COCH_2OH	 97:3 isomeric purity	72	136
20		CH_3COCH_2OH	 94:6 isomeric purity	65	136
21		$PhCOCO_2H$	 99:1 isomeric purity	97	137
22		$PhCOCO_2H$	 99:1 isomeric purity	96	137
23	 E:Z=~90:10	Me_2CHCHO	 >98:2 anti	77	138
24	 E:Z=5:>95	Me_2CHCHO	 11:89 syn	94	138
25	 E:Z=~90:10	Me_2CHCHO	 >95:5 anti	86	138
26	 E:Z=5:>95	Me_2CHCHO	 11:89 syn	76	138
27	 E:Z=5:>95	Me_2CHCHO	 20:80 syn	90	138
28		PhCHO	 >98:2 anti	89	139
29	 E:Z=5:>95	PhCHO	 98:2 syn	95	140
30		CH_3COCO_2Et	 9:1 isomeric mixture	85	141
31		Me_2CHCHO	 X=Cl 96 : 4 X=Br 96 : 4 X=SC_2H_5 85 : 15 X=OCH_3 >95 : 5	83 83 85 55	142

relative to Me: aldehydes bearing more bulky R group exhibit higher diastereoselectivities (entry 2 vs 4 and 5). In the case of (*Z*)-crotylboronates, the transition state **70** is destabilized by the nonbonded interaction between methyl groups, and **71** still suffers from a significant interaction between Me and R group which becomes serious especially with a sterically bulky R substituent. Accordingly, the transition state **72** is the most favored geometry, although it corresponds to an arrangement leading to an anti-Cram stereoisomer. Thus, 3,4-syn-4,5 anti homoallyl alcohols are produced predominantly from (*Z*)-crotylboronates (entry 3, 6, and 7).[143] As shown in entries 4–7, the diastereoselectivity also depends on the stereochemistry at C-3 of aldehydes. The effect of C-3 substituent stereochemistry upon the diastereoselectivity is remarkable in reactions of (*Z*)-crotylboronate (entries 6 and 7), and this difference has been reasonably explained by inspecting their transition states corresponding to **72**.[3] The diastereofacial preference switches from syn to anti preference upon moving from an α-methyl chiral aldehyde (entry 1) to an oxygenated aldehyde (entries 10 and 11). Electronic arguments have been presented to rationalize the low diastereoselectivity of the reaction shown in entry 8.[145] The transition state **75** corresponds to **68**, and **76** has greater nonbonded interaction than **75**. In

Table V. Reactions of Chiral Aldehydes and/or Chiral Allylboranes

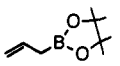
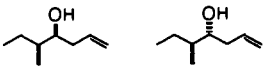
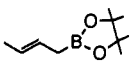
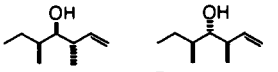
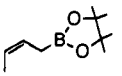
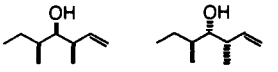
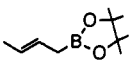
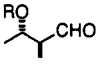
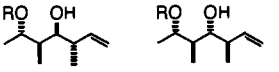
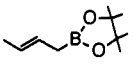
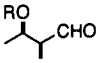
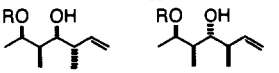
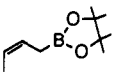
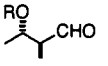
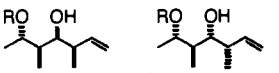
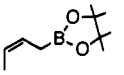
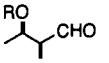
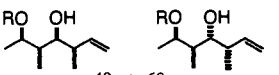
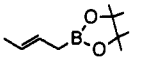
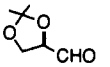
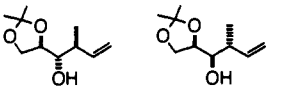
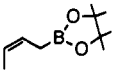
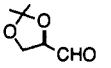
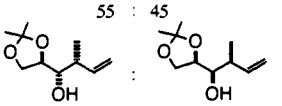
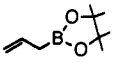
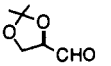
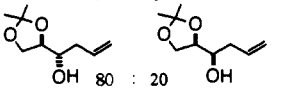
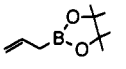
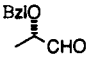
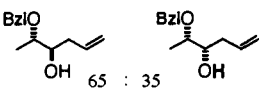
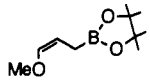
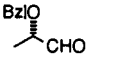
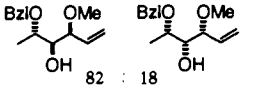
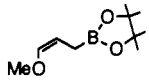
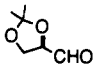
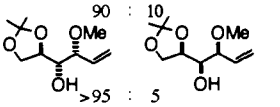
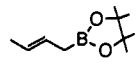
entry	allylborane	substrate	isomer ratio	yield, %	ref(s)
1			 (62 : 38) structural assignment uncertain		143
2			 83 : 17		143
3			 30 : 70		143
4		 R=TBDMS R=MOM	 95 : 5 89 : 11		143
5			 98 : 2 94 : 6		143
6			 9 : 91 22 : 78		143
7			 40 : 60 41 : 59		143
8			 55 : 45	75-85	145
9			 97 3	75-85	145
10			 80 : 20	75-85	145,146
11			 65 : 35	97	145,147
12			 82 : 18 90 : 10	87 84	147 148
13			 >95 : 5		148 145 188
14			>99 : 1	68	150
15			87 : 13	61	151
16			77% ee	91	152
17			92% ee	92	153

Table V. (Continued)

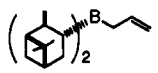
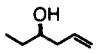
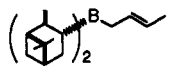
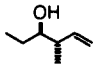
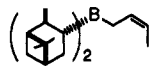
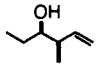
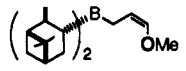
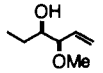
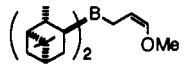
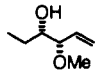
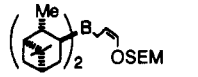
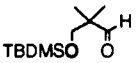
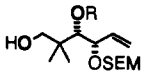
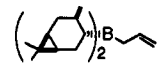
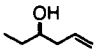
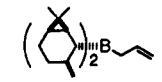
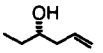
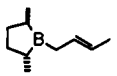
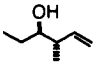
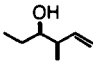
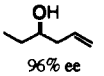
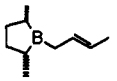
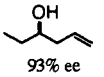
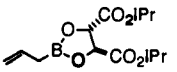
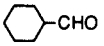
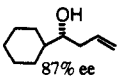
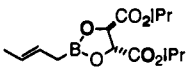
entry	allylborane	substrate	isomer ratio	yield, %	ref(s)
18			 86% ee	71	154
19			 90% ee		155 160 161
20			 90% ee		155 162
21			 88% ee, >99% syn	65	156
22			 90% ee, >99% syn	88	156
23	 SEM=$Me_3SiCH_2CH_2OCH_2$		 R=4-$MeOC_6H_4CH_2$ >95% ee, >95% syn	49	162
24			 91% ee	76	157
25			 94% ee	~74	158
26			 96% ee, 93% anti	81	163
27			 86% ee, 93% syn	73	163
28			 96% ee	80	164
29			 93% ee	86	164
30			 87% ee	72	165
31		$nC_9H_{19}CHO$	88% ee, >99% anti	87	167
32		$nC_9H_{19}CHO$	82% ee, 97% syn	80	167
33			96% ee, 97% anti	85	188

Table V. (Continued)

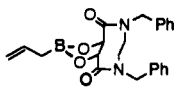
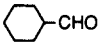
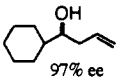
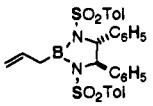
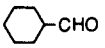
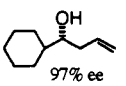
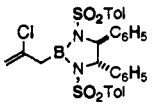
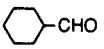
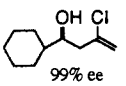
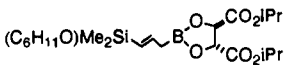
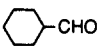
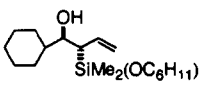
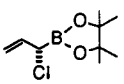
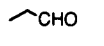
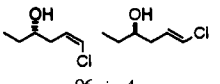
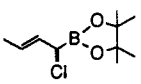
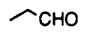
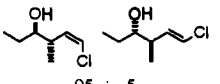
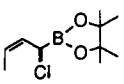
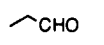
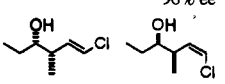
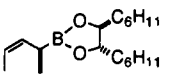
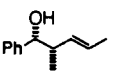
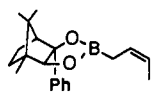
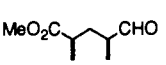
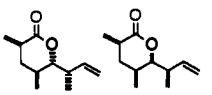
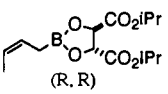
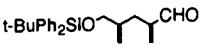
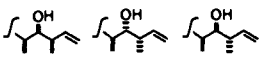
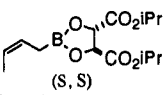
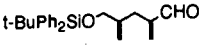
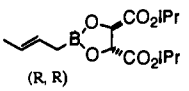
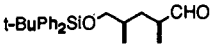
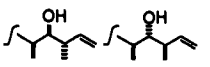
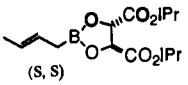
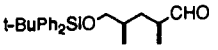
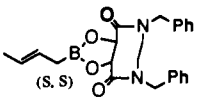
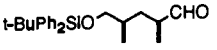
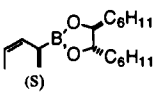
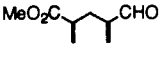
entry	allylborane	substrate	isomer ratio	yield, %	ref(s)
34			 97% ee	40 (conversion 80%)	169
35			 97% ee	>90	170
36			 99% ee	81	170
37			 72% ee	93	173
38			 96 : 4 89% ee	86	174
39			 95 : 5 96% ee	47-65	176
40	 (racemic)		 91 : 6	81	176
41		PhCHO	 99% ee	68	178
42	 (-)		 32 : 68 81 : 19 (from (+)-reagent)		143b, 152c
43	 (R, R)		 78 : 16 : 6	52	182
44	 (S, S)		6 : 94 : -	51	182
45	 (R, R)		 >98 : <2	56	182
46	 (S, S)		16 : 84	55	182
47	 (S, S)		12 : 88	44	182
48	 (S)		selectivity >95%		178 187

Table V. (Continued)

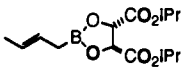
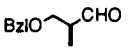
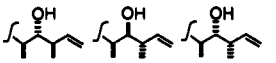
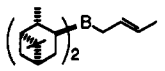
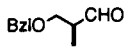
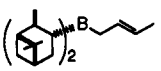
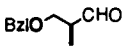
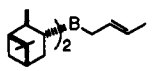
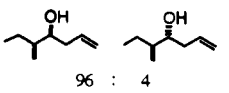
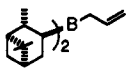
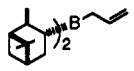
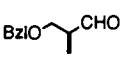
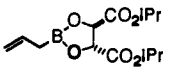
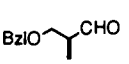
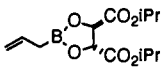
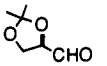
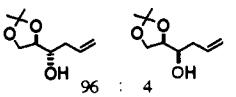
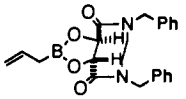
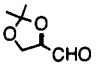
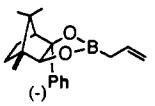
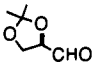
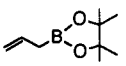
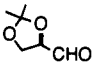
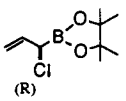
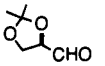
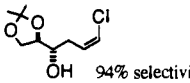
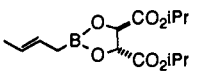
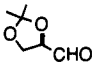
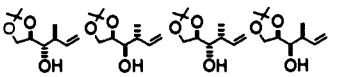
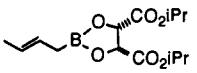
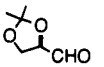
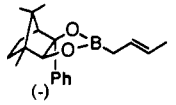
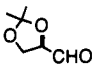
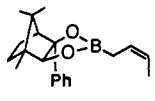
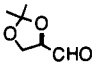
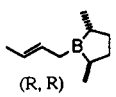
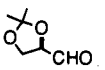
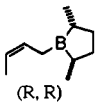
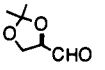
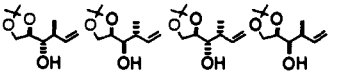
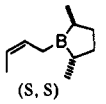
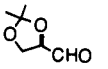
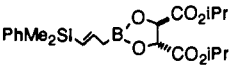
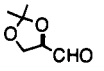
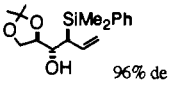
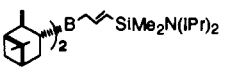
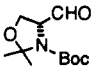
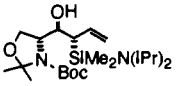
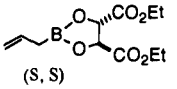
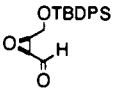
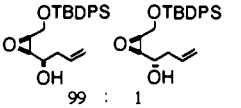
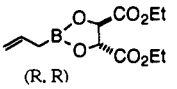
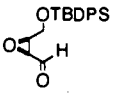
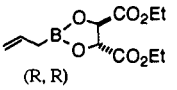
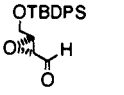
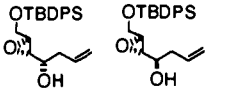
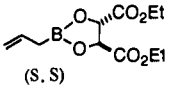
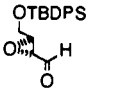
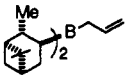
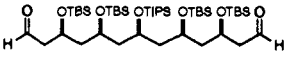
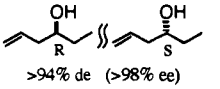
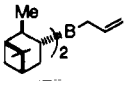
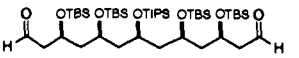
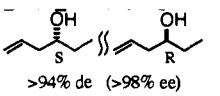
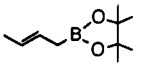
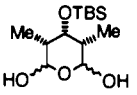
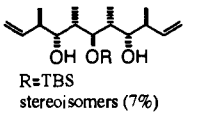
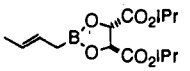
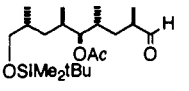
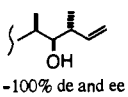
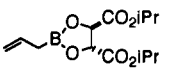
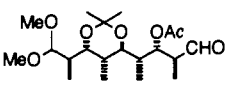
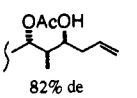
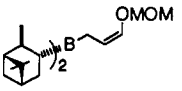
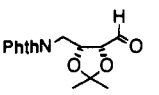
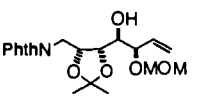
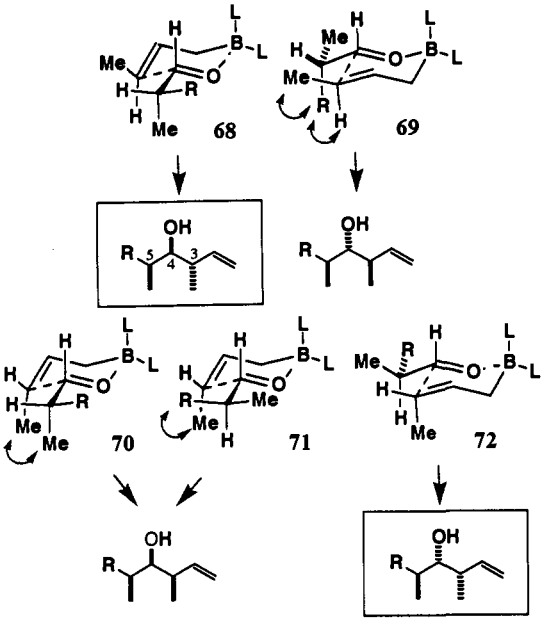
entry	allylborane	substrate	isomer ratio	yield, %	ref(s)
49			 85 : 14 : 1	-	144
50			95 : 5 : 0	-	183 197
51			2 : 98 : 0	-	183, 197
52			 96 : 4	81	184
53			5 : 95	81	184
54			 95 : 5	-	
55			83 : 17	-	171
56			 96 : 4	90	165
57			99.7 : 0.3	81	169
58			96 : 4	87	146
59			80 : 20	75	145, 146
60			 94% selectivity	45	174
61			 87 : 9 : 4 : -	87	185 193
62			2 : 96 : 2 : -	85	185 193
63			72 : 28 : - : -	85	146
64			- : - : >98 : <2	86	146
65			96 : 3 : 1 : -	71	163, 164
66			12 : 86 : - : 2	74	163, 164

Table V. (Continued)

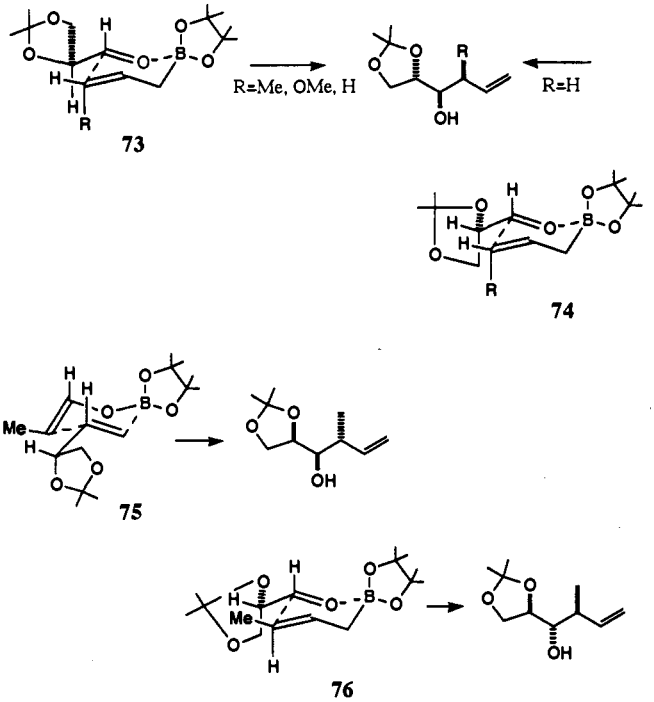
entry	allylborane	substrate	isomer ratio	yield, %	ref(s)
67	 (R, R)		 4 : 2 : 92 : 2	66	163, 164
68	 (S, S)		- : 2 : 16 : 82	65	163, 164
69			 96% de	90	173
70				57	198
71	 (S, S)		 99 : 1 (>98% ee) (58% ee)	96	186
72	 (R, R)		25 : 75 (53% ee) (>97% ee)	82	186
73	 (R, R)		 97 : 3 (>96% ee) (46% ee)	95	186
74	 (S, S)		23 : 77 (49% ee) (>97% ee)	86	186
75			 >94% de (>98% ee)	80	189
76			 >94% de (>98% ee)	80	189
77			 R=TBS stereoisomers (7%)	53	190
78			 -100% de and ee	77	191 194
79			 82% de	70	192
80		 PhthN : phthalimide		60	195 196

the reactions with α-methyl chiral aldehyde, the major pathway was via **68**. In the case of α-oxygenated aldehydes, the electronic effect (Felkin-type transition state) is sufficient to lower the energy of **76** so that it is slightly more accessible than **75**. However, the acetonide-protected aldehyde may be a special case, since C-3 of the aldehyde is not very sterically demanding owing to the acetonide protection which minimizes interaction of the C-3 alkoxy group with the crotyl unit. In fact, very high syn selectivity was obtained in the reaction of the aldehyde protected by the sterically bulky group which may proceed through a transition state corresponding to **75** (entry 14).[150] In the case of entries 9–13, good to high anti selectivities are obtained, and this selectivity can be accounted for by either **73** or **74**. The reactions of β-alkoxy-α-

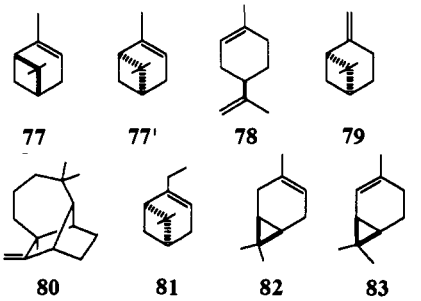
Scheme V. Transition-State Geometries of the Allylboration Reaction of a Chiral Aldehyde



unsubstituted aldehydes are generally not highly diastereoselective, except in cases where the allyl metal addition takes place via a chelated transition state. The reactions of 1,3,2-dioxaborinanes with allylboron compounds presumably proceed through the intramoleculer delivery of the allyl unit (entry 15).[151]

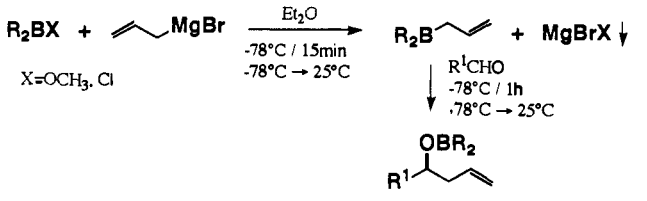


A number of highly enantioselective chiral allylboron reagents have been developed. There are two kind of chiral allylboron reagents: those with conventional, easily introduced chiral auxiliaries as the boron ligands (BLn), and ones in which the chiral center is a structural component of the allylic unit. As shown in entry 16, the bornanediol-derived allylboronate gives 77% ee in the reaction with propanal; it gives 86% ee with acetaldehyde at −90 °C, but for most other aldehydes the selectivity is in the range of 36% ee (PhCHO) to 72% ee (PrCHO) for reactions at −40 °C. The 3-amino-2-borneol derived allyl reagent gives 88–96% ee with a range of aldehydes at −78 °C.[153] It should be noted that the absolute configurations of the product alcohols in entries 16 and 17 are opposite. Allyldiisopinocampheylborane ($Ipc_2Ballyl$) gives consistently excellent results (83–96% ee) in reactions with aldehydes at −78 °C: CH_3CHO (93% ee), C_2H_5CHO (entry 18), C_3H_7CHO (87% ee), PhCHO (96% ee), $(CH_3)_2CHCHO$ (90% ee), $(CH_3)_3CCHO$ (83% ee).[154] Use of isomerically pure (*E*)- or (*Z*)-crotyldiisopinocampheylborane reagent ($Ipc_2Bcrotyl$) makes possible the stereocontrolled formation of two asymmetric centers at one time (entries 19 and 20).[155] In entries 19 and 20, the Ipc_2B group is prepared by hydroboration of (+)-α-pinene ($^dIpc_2B$). The use of (−)-α-pinene gives $^lIpc_2B$ which has an absolute configuration opposite to $^dIpc_2B$. Indeed, by judicious use of (*E*)- and (*Z*)-crotylborane reagents with Ipc groups from (+)- or (−)-α-pinene, it is possible to synthesize all four possible isomers of 3-methyl-4-penten-2-ol. The enantiomeric [(*Z*)-γ-methoxyallyl]-diisopinocampheylboranes are successfully condensed with various aldehydes, such as acetaldehyde, propionaldehyde (entries 21 and 22), and benzaldehyde in a regioselective and stereoselective manner to yield the corresponding *syn*-β-methoxyhomoallyl alcohols in ≥99% diastereoselectivities and ≥95% enantioselectivities.[156] *B*-Allyldialkylboranes can be prepared from (+)-α-pinene (**77**) (or (−)-α-pinene (**77′**), as mentioned above), (+)-limonene (**78**), (−)-β-pinene (**79**), (+)-longifolene (**80**), (−)-10-methyl-α-pinene (**81**), and (+)-3-carene (**82**). In the case of allylboranes derived from



78–80, less satisfactory results were obtained on the enantioselectivities in reactions with aldehydes. *B*-Allyldiisocaranylborane, 4-$^dIcr_2Ballyl$, derived from **82** shows exceptionally high enantiomeric purity of the product alcohol, >99% ee in the reaction with acetaldehyde (72% chemical yield).[157] *B*-Allylbis(10-methylisopinocampheyl)borane derived from **81** and $Ipc_2Ballyl$ from **77** (or **77′**) give 93% ee in the reactions with acetaldehyde. The boron atom is directly attached to the chiral center in the allylboranes derived from **77**, **81**, and **82**, and presumably this is a reason for the very high enantioselectivity. Hydroboration of (+)-2-carene (**83**), commercially available, provides bis(2-isocaranyl)-borane, which can be readily transformed into *B*-allylbis(2-isocaranyl)borane, 2-$^dIcr_2Ballyl$. This new reagent undergoes asymmetric allylation with a variety of aldehydes and affords the corresponding homoallyl alcohols in 94–99% ee (for example, entry 25).[158] The enantioselectivities realized with this reagent are significantly higher than those realized with $^dIpc_2Ball$ (entry 18) and 4-$^dIcr_2Ball$ (entry 24). Generally, the allylborane reagents in entries 18, 24, and 25 were

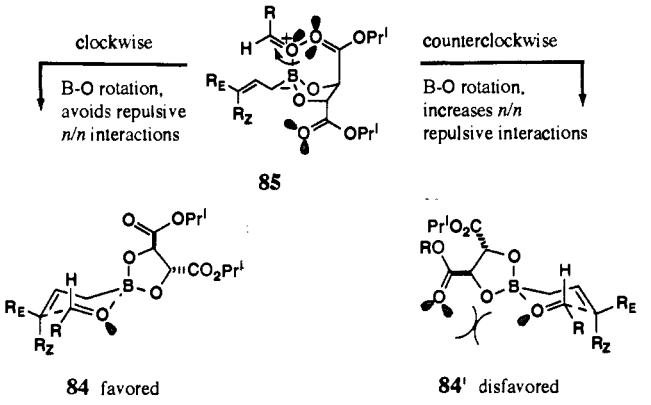
prepared from allylmagnesium bromide (eq 35) and condensed in situ with aldehydes at −78 °C. Under

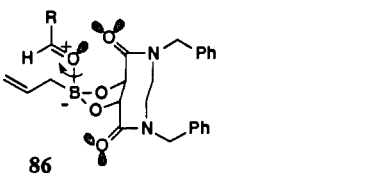


(eq 35)

these conditions, magnesium salts are present in the reaction mixture. In the absence of magnesium salts, the chiral allylborane reagents react with aldehydes practically instantaneously at −100 °C to give homoallyl alcohols with optically purities approaching 100% ee.[159a] The short reaction time adopted (<0.5 h) facilitates maintaining the reaction temperature at −100 °C. In this way, $^{d}Ipc_2Ballyl$ gives homoallylic alcohols of >96–99% ee, 4-$^{d}Icr_2Ballyl$ affords alcohols of ≥98% ee, and 2-$^{d}Icr_2Ballyl$ provides alcohols of ≥99% ee. Reactions of chiral (*E*)- and (*Z*)-crotyl-*trans*-2,5-dimethylborolanes with aldehydes proceed to provide homoallyl alcohols with excellent diastereo- and enantioselectivity (entries 26 and 27).[163] The ee's of the major product range from 95% to 97% for the (*E*)-crotyl reagent and from 86% to 97% for the *Z*-reagent, and the diastereoselectivity is greater than 20:1.[163] (*R*/*S*)-*B*-Allyl-2-(trimethylsilyl)borolanes react with aldehydes at −100 °C to produce homoallyl alcohols in 92–97% ee (entry 28).[164] Normally, the isolation of homoallyl alcohols is accomplished via oxidation of the borinate intermediate (eq 35), but oxidative workup destroys the chiral auxiliary and produces a large amount of nonrecyclable byproduct, terpenol. Simple procedures for efficient recycling of the terpenyl chiral auxiliaries have been developed;[159b] these include treatment of the borinates with isobutyraldehyde and 1% $BF{\cdot}OEt_2$, ethanolamine workup, or 8-hydroquinoline workup.

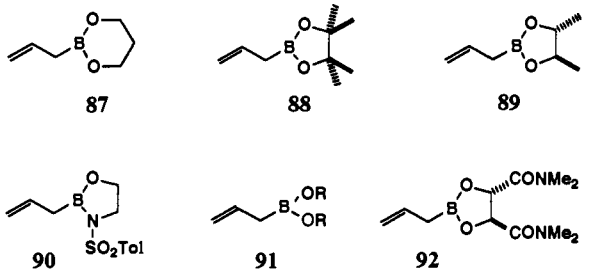
The tartrate ester modified allylboronates are attractive alternatives to the allyltrialkylborane reagents owing to their ease of preparation and stability of storage. In the best cases, the tartrate allylboronates are about as enantioselective as the allylborane reagents (82–88% ee with unhindered aliphatic aldehydes) but with hindered aliphatic, aromatic, α,β-unsaturated and most α- and β-alkoxy aldehydes the enantioselectivity falls to a level of 55–75% ee. The allylboronate prepared from diisopropyl tartrate reacts with aldehydes to produce good chemical yields and high enantioselectivities (71–87% ee) (entry 30).[165] Several other C_2 symmetric diol auxiliaries were investigated, but the use of diisopropyl tartrate ester as an auxiliary gave the highest ee and chemical yield in the reaction with cyclohexanecarboxaldehyde.[166] Diisopropyl tartrate modified (*E*)- and (*Z*)-crotylboronates are easily prepared in high isomeric purity (≥98% *E* and >99% *Z*) via the metallation of (*E*)- and (*Z*)-2-butene with n-BuLi and KOt-Bu in THF followed by treatment of the (*E*)- and (*Z*)-crotylpotassiums with $(i\text{-}PrO)_3B$, aqueous hydrolysis, and esterification with diisopropyl tartrate. The crotylboronates undergo highly diastereo- and enantioselective reactions with aliphatic (linear or α-monobranched; 72–91% ee), aromatic, and α,β-unsaturated aldehydes (55–74% ee) (entries 31 and 32).[167] Assuming that R of RCHO has priority over the crotyl group that is transferred, the crotylboronate reagents derived from (*R*,*R*)-diisopropyl tartrate produce homoallyl alcohols with *S* configuration at the carbinol center. The enantioselectivity is best in toluene for all substrates except benzaldehyde in which best results are obtained in THF. This stereochemical course is consistent with the allylation occurring preferentially through transition state **84**. Although the enantioselectivity of the allyl- and crotylboration of α,β-unsaturated and aromatic aldehydes is poor (62–74% ee for (*E*)-decenal),[165] the use of their metal carbonyl derivatives enhances the enantioselectivity (entry 33):[168] the crotylation was carried out in toluene at −78 °C followed by oxidative decomplexation with $Fe(NO_3)_3$ in EtOH to give the desired product. An electronic origin of asymmetry has been proposed (**84** and **84′**) since the origin of asymmetry in entries 30–33 cannot be explained by simple steric interactions. Electronic repulsive interaction (n/n) between the nonbonding lone pair on the aldehyde oxygen and an ester carbonyl presumably destabilizes transition state **84′** relative to **84**.[165] For this mechanism to be correct, the dioxaborolane system must exist in conformation **85**. As long as the tartrate unit is held within an eight-membered ring (cf., **86**), the critical conformational features shown in **85** become structural constants, and intermediate aldehyde complexes have no choice but exist in conformations analogous to **86**.[169] In fact, this



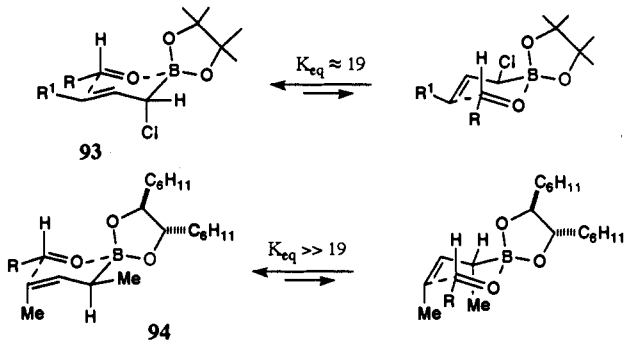


new reagent, derived from *N*,*N′*-dibenzyl-*N*,*N′*-ethylenetartramide, was found to be significantly more enantioselective than the corresponding tartrate ester derivative (entry 34 vs 30).[169] However, the tartramide reagent is less reactive and less soluble than the tartrate ester reagent and, consequently, is less attractive for large-scale work. The stereoselectivity of the tartrate allylboranes is sensitive to variables such as reaction temperature (best results invariably are obtained at −78 °C), solvent (toluene is best for aliphatic aldehydes, THF is preferred for aromatic aldehydes), and moisture (use of molecular sieves is recommended to maintain an anhydrous reaction environment), but not on the

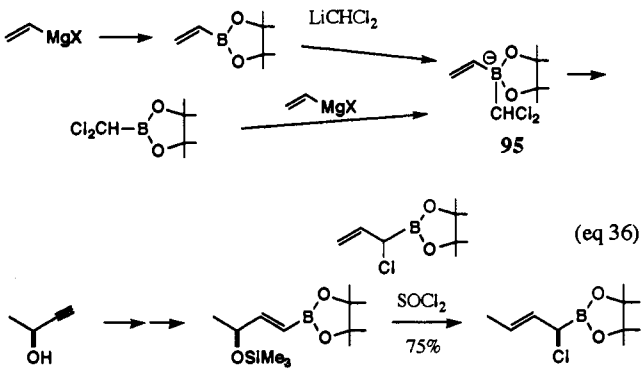
structure of the tartrate ester.[171] The allylborane derived from the bis-*p*-toluenesulfonyl derivative of (*R*,*R*)-stien reacts with a variety of aldehydes in toluene or CH_2Cl_2 at −78 °C to give the corresponding homoallyl alcohols in high yields with very high ee (entry 35).[179] Chiral 2-haloallylboranes derived from the (*S*,*S*)-stien also produce very high ee and chemical yields (entry 36). In order to evaluate the importance of solvent, temperature, and structural effects on the rates of allylborations, the reactions of benzaldehyde with structurally representative allylboranes were examined under a variety of conditions.[172] Polar solvents, such as $HCCl_3$, CH_2Cl_2, CS_2, and Et_2O, which are either poorly coordinating or noncoordinating, enhance the rate of allylboration, while solvents capable of stronger coordination with boron, such as THF, retard the rate. α-Trisubstituted aldehydes, such as pivalaldehyde, undergo allylboration significantly slower than less substituted aldehydes. While allylboration is extremely difficult at −78 °C with cyclic allylboronates such as **87**–**89**, the *B*-allyl-3-(*p*-tolylsulfonyl)-1,3,2-oxazaborolidine (**90**) undergoes very rapid (<10 min) allylboration under identical conditions. In general, acyclic allylboronates **91** are significantly more reactive compared to the cyclic allylboronate analogues. The *N*,*N*,*N*′,*N*′-tetraalkyltartramide **92** undergoes allylboration very sluggishly at −78 °C. On the contrary, the tartrate ester reagent (entry 30) undergoes remarkably facile allylboration under the same conditions. The allyldialkylboranes (entries 18 and 24) have proven themselves to be two of the most reactive among reagents presently known.



Allylboron compounds with stereocenters at either C-1 or C-4 of the allyl/crotyl unit are frequently less convenient to synthesize than those with conventional auxiliaries as the boron ligand, but the reactions with aldehydes often occur with nearly 100% asymmetric induction. (α-Chloroallyl)boronate of 92% ee adds cleanly to representative achiral aldehydes at 0–20 °C to give predominantly (*Z*)-homoallyl alcohols with 82–92% ee (entry 38).[174] Other α-heterosubstituted allylboronates, such as OCH_3, Br, SR, and $SiMe_3$ substituted ones, react similarly with aldehydes to form (*Z*)-alcohols preferentially.[175] (*Z*)-(α-Chlorocrotyl)boronate adds to nonchiral aldehydes to give the *syn*-(*E*)-homoallyl alcohols predominantly rather than the *syn*-(*Z*)-derivatives (entry 40).[176] The corresponding (*E*)-(α-chlorocrotyl)boronate produces *anti*-(*Z*)-homoallyl alcohols with diastereoselectivity greater than 95% and with 96% ee (entry 39).[176] The α-chlorosubstituted allyl and (*E*)-crotylboronate reagents react preferentially via transition state **93** with an axial orientation of the chloro substituent that is favored for steric and/or stereoelectronic reasons.[175,176] (see also Table V, entries 7 and 8).[127] (*Z*)-α-Methylcrotylboronate undergoes an exceptionally enantioselective reaction with benzaldehyde to give the *syn*-(*E*)-homoallyl alcohol (entry 41).[172] Predominant formation of the (*E*)-alkenes in the case of (*Z*)-crotylboronates (entries 40 and 41) is due to the reason that the α-substituents prefer an equatorial position as indicated in **94** in order to avoid 1,3-interaction with the (*Z*)-Me group. The synthetic



method of a chiral 1-chlorocrotylboronic ester deserves comments. Homologation of vinylboronates with dichloromethyllithium via the ate complex **95** gives (α-chloroallyl)boronate (eq 36).[179] The addition of vinylmagnesium chloride to (dichloromethano)boronate generates **95**, which rearranges to give the same allylboronate (eq 36).[175] The attempted synthesis of the 1-chloro-(*E*)-crotyl derivative (entry 39) starting from (*R*,*R*)-2,3-butanediyl (dichloromethyl)methylboronate and (*E*)-1-propenyllithium failed.[180] Instead, silylation and hydroboration of (*S*)-1-butyn-3-ol led to the alkenylboronic ester which was converted by thionyl chloride to 1-chloro-2-alkenylboronic ester (eq 37).[180]

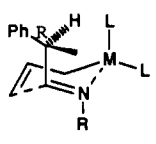


Significant improvement in diastereoselectivity is possible by using double asymmetric synthesis.[181] Two types of double asymmetric reactions are known: (1) (matched double asymmetric synthesis) the intrinsic diastereofacial preferences of the carbonyl (or other C=X) electrophile and the chiral allyl metal reagent are cooperative, each favoring the production of the same diastereomer and (2) (mismatched double asymmetric synthesis) the intrinsic diastereofacial preferences of the reagent and electrophile are inharmonious, each favoring different stereochemical outcomes. It is generally more difficult to realize high diastereoselection in mismatched than in matched double asymmetric reactions. The reaction of chiral (−)-crotylboronate and the chiral aldehyde produces a 32:68 mixture of product

diastereomers (entry 42), whereas the corresponding (+)-crotylboronate gives the ratio of 81:19.[143b,152c] The reaction of this chiral aldehyde with nonchiral (*Z*)-crotylboronate (shown in entry 3) affords the ratio of 60:40. Accordingly, the use of the chiral crotyl reagents leads to modest changes in the stereoselectivity of the reactions of the chiral aldehyde. The tartrate crotylboranes show excellent stereoselectivity in entries 44 and 45, but are much less selective in entries 43 and 46. Substantial improvements in selectivity is seen in entry 47, in which the tartramide reagent is utilized. It is clear that the reactions of $(Ipc)_2B$(crotyl) with chiral α-methylaldehydes consistently give excellent results (entries 50 and 51, vs 49). It is surprising that even a simple chiral aldehyde such as 2-methylbutanal produces very high diastereoselectivity (entries 52 and 53). Tartrate allylboronate is also less selective than $(Ipc)_2B$allyl for the reactions shown in entries 54 and 55. Asymmetric allylation of chiral α-alkoxyaldehydes has been also studied extensively. D-Glyceraldehyde acetonide shows an 80:20 preference in reactions with the achiral pinacol allylboronate (entry 59), and the selectivity improves to 96–99.7% with chiral boronate reagents (entries 56–58). The reaction of (*s*)-α-(benzyloxy)propanal with $(Ipc)_2B$(allyl) reagents provides excellent diastereoselectivity: the (+)-allylborane gives a 94:6 mixture of syn and anti diastereomers, whereas the corresponding (−)-allylborane affords a 4:96 mixture of syn and anti isomers.[183,184] Matched double asymmetric induction is also observed with chiral (*R*)-α-chloroallylboronate (94% selectivity, entry 60), but the reaction with *S*-reagent results in mismatched induction, giving only 77% diastereoselectivity. High selectivity is obtained in the reaction of D-glyceraldehyde with the tartrate crotylboronates (entries 61 and 62). The (*Z*)-crotylboronate derived from pinacol derivative produces very high diastereoselectivity (entry 64), whereas the corresponding (*E*)-boronate gives low selectivity (entry 63). The 2,5-dimethylborolane reagents provide the greatest selectivity for the crotylation of D-glyceraldehyde (entries 65–68). The γ-silyl-substituted allylboronate bearing tartrate auxiliary also provides very high selectivity (entry 69). The serine aldehyde reacts with the γ-silyl-substituted allylborane to give the homologated alcohol with very high de (entry 70). The α-silylated alcohols in entries 69 and 70 can be easily converted to the corresponding diols with high chemical yields upon treatment with $H_2O_2/KF/KHCO_3$/MeOH–THF;[73,198] the conversion of the C–Si bond to C–OH bond proceeds through complete retention. The matched double asymmetric allylborations of chiral 2,3-epoxyaldehydes using tartrate allylboronates provide erythro epoxy alcohols with excellent diastereoselectivity (>97%) and enantioselectivity (>96% ee) (entries 71 and 73), whereas the mismatched double asymmetric reactions give the diastereoisomeric threo epoxy alcohols with lower (ca. 75:25) selectivity (entries 72 and 74). The double asymmetric method or the simple allylboration procedure is utilized for the synthesis of some complicated compounds, including natural products, having many chiral centers. For example, it is remarkable that a single enantiomeric reagent [(+)- or (−)-Ipc_2Ballyl] introduces two new stereocenters with high de and ee and determines the absolute stereochemistry at five preexisting stereocenters (entries 75 and 76). Double crotylboration of the dialdehyde with achiral pinacol (*E*)-crotylboronate gives bisadduct in 53% yield together with its stereoisomers (7%) and monoadduct (8%) (entry 77).[190] Other examples are shown in entries 78–80.

2. Reactions of Imines

The addition of allyl-9-BBN to aldimines shown in eq 3 provides predominantly Cram products; the aldimine (R = i-Pr) affords exclusively the Cram isomer, whereas the n-propyl derivative (R = n-Pr) gives a 96:4 mixture of the Cram and anti-Cram diastereomers.[46] The allyl-9-BBN addition to imines generally provides higher diastereoselectivity than the addition of other allylorganometallics, and further, the allylboration of imines produce much higher selectivity than that of the corresponding aldehyde (2-phenylpropanal).[46] These observations can be explained by considering the geometry of imines coordinated by metal. As shown in **96** and **97**, the additional steric demands created by the axial metal ligand (ML) via a 1,3-diaxial interaction are responsible for the difference in energy between the Cram (**96**) and anti-Cram (**97**) transition states; **97** is strongly destabilized by 1,3-diaxial interactions. On



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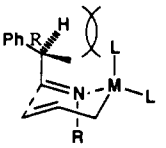

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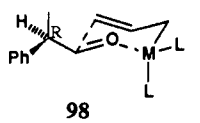
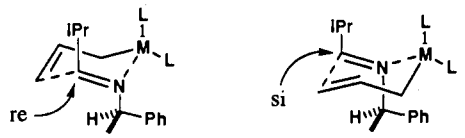


98

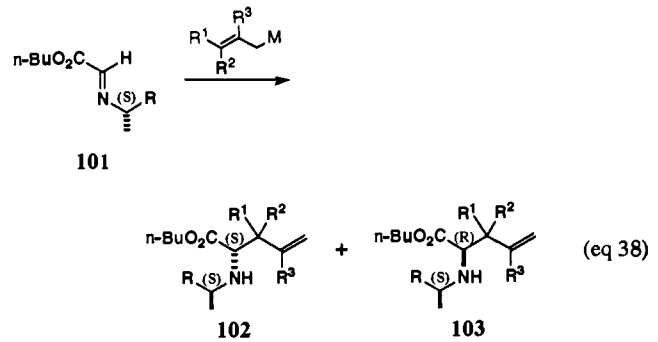
the other hand, the α-chiral carbon occupies the equatorial position (as shown in **98**) in the case of aldehyde addition and avoids the nonbonded interactions, providing low diastereoselectivities. Even in the case of α-alkoxy-substituted aldimines (i.e. **22** in eq 4),[47] which provide the opportunity for chelation control in reactions with allylmagnesium, -zinc, and -aluminum ate complexes and produce the chelation product, allyl-9-BBN provides excellent Cram diastereocontrol (>99:1 in the case of **22**). Allylboration is the method of choice for preparing the anti homoallylamine;[50] the ratio of the Cram/anti-Cram (chelation) becomes 93:7 with allyl-$B(OMe)_2$. This observation is consistent with the proposed transition state **96**. Little or no diastereoselectivity is obtained in the reaction of chiral β-alkoxy aldimine **23** (eq 5) with reagents incapable of internal chelation such as allyl-9-BBN or allyl $Ti(OiPr)_3$.[50] Since the chiral center of **23** is at the β-position of imine, the steric effect of the chiral center upon the 1,3-diaxial interaction in **96** is diminished significantly in comparison with that of the α-alkoxy imine, leading to low diastereoselection. Allylorganometallic reagents such as (allyl)$AlEt_3MgCl$ and (allyl)MgCl, which provides chelation-controlled reactions, produce significant diastereoselectivity; the former reagents affords a 90:10 ratio and the latter a 85:15 ratio (see eq 5). As illustrated in eq 6, the allylmagnesium addition to **24**, in which a chiral center is attached to the nitrogen atom, provides an 80:20 ratio. Again, allyl-9-BBN provides the best diastereoselectivity (**25**/**26** = 92:8).[46,50] In the case of allyl-9-BBN, cyclic chair transition states **99** and **100** can be used to explain this selectivity. Similar to **96** and **97**, nonbonded 1,3-diaxial interactions exist be-

tween the chiral center and the two hydrogen atoms at the axial positions of **99** and **100**, and **99** is more stable than **100**. Actually, the addition mode of **99** is *re*-facial



99 **100**

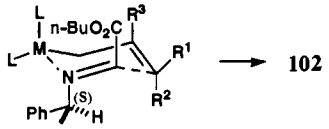
attack, which is consistent with **27**. An enantioselective synthesis of amino acids has been examined by the reactions of allyl-, methallyl-, and prenyl-9-BBN with chiral nonracemic α-imino esters **101** derived from (*S*)-1-phenylethylamine and (−)-1-cyclohexylethylamine (eq 38).[199] The high 1,3-asymmetric induction (96:4) ob-



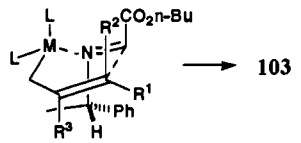
101

102 **103** (eq 38)

tained in allyl-9-BBN addition to **101** (R = Ph) is in agreement with the cyclic chair transition state shown in **104**. The addition of allylzinc reagents to **101** results in low diastereoselection in all cases. The allyl-9-BBN addition to the α-imino ester derived from (−)-1-cyclohexylethylamine (**101**, R = C_6H_{11}) provides much higher diastereoselection (98:2). Diastereofacial selectivity is reversed in methallyl-9-BBN ($R^1 = R^2 = H$, $R^3 = CH_3$) addition to **101** (R = Ph). As a result of additional 1,3-diaxial interactions arising from the methallyl methyl group ($R^3 = CH_3$) in the chair transition state **104**, a boat transition state **105** is presumably more stable than **104**, leading to amine **103**.



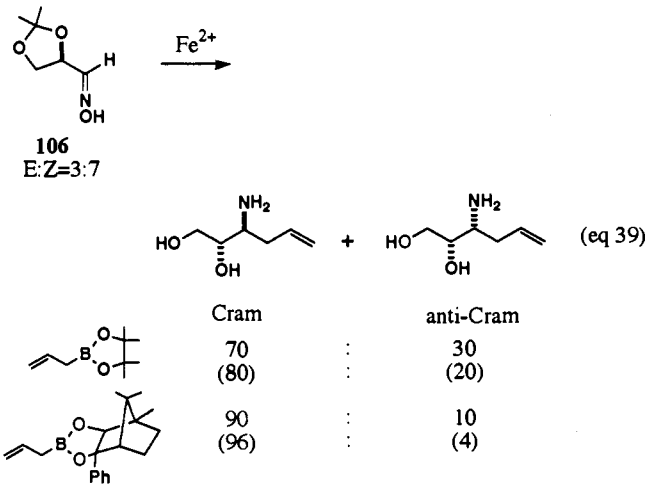
104 → **102**



105 → **103**

The addition of prenyl-9-BBN resulted in low yield and selectivity. The addition of allyl-9-BBN to the imines (**28**) containing two stereocenters produces the Cram (nonchelation) product with very high diastereoselectivity; the ratio of chelation to nonchelation was 3:97 with *S*-chirality, and <1:99> with *R*-chirality (see eq 7).[50] The chirality of the α-alkoxy center of **28** dictates the asymmetric induction, and the influence of the nitrogen chiral auxiliary is negligible (compare the 9-BBN allylation of **22**). The allylation of β-alkoxyaldimines (**29**) with allyl-9-BBN produces the nonchelation product predominantly (90:10) in the case of *R*-chirality of the nitrogen auxiliary, whereas it affords the chelation product preferentially (63:37) in the case of *S*-chirality. The chiral nitrogen auxiliary plays the major role in controlling diastereoselectivity.

Reactions of allylboronates (shown in entry 1 of Table V, entry 30 of Table IV) with aldoximes,[200] imines,[200a] and sulfenimides[201] are considerably slower than those of aldehyde, and also slower than those of allyltrialkylboranes with imines. The reactions of imines and (allyl)$B(OMe)_2$ proceed at room temperature, while those of the allylboronates having cyclic boronate structure (such as pinacolboronate) generally require heating in refluxing CCl_4 or toluene. The addition of allylboronates to 2,3-isopropylidene-D-glyceraldehyde oximes (**106**) provides the Cram product predominantly (eq 39).[200a] [The ratios in the addition of the allylbo-



106
E:Z=3:7

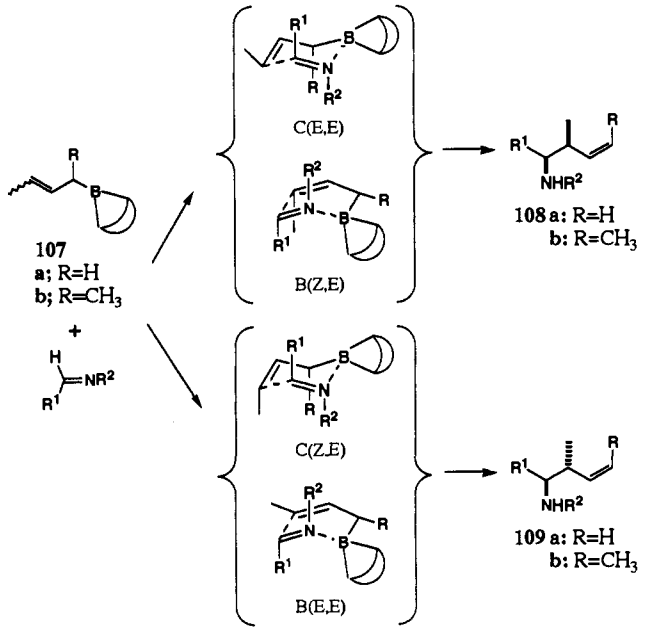
	Cram		anti-Cram
	70 (80)	:	30 (20)
	90 (96)	:	10 (4)

(eq 39)

ronates to the corresponding aldehydes are shown in parentheses.] The chiral boronate gives better selectivity than the achiral pinacolboronate.

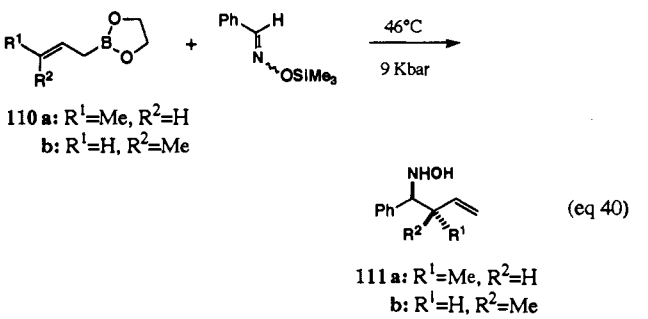
The diastereoselectivity in the addition of crotyl-9-BBN to imines is very sensitive to the structural feature of the imines (Scheme VI). For example, the anti product **109a** is produced exclusively with benzylideneaniline ($R^1 = R^2 = Ph$) in 93% yield, whereas the syn product **108a** is formed exclusively with the aliphatic imine (R^1 = n-Pr, R^2 = i-Pr) in 97% yield. α-Alkylimines (R^1 = n-Pr, R^2 = i-Pr, and $R^1 = R^2$ = n-Pr) exhibit syn selectivity when the α-alkyl group is linear, whereas α-arylimines ($R^1 = R^2$ = Ph and R^1 = Ph, R^2 = n-Pr) show anti selectivity when the N-substituent is aryl or linear alkyl. The formation of syn products presumably arises via a C (*E*,*E*) transition state (six-membered cyclic transition state involving (*E*)-crotyl and (*E*)-imine). The decreased syn selectivity, which is observed in the case of bulky α-substituents (syn/anti = ~30:70 in the case of R^1 = i-Pr and R^2 = n-Pr, or $R^1 = R^2$ = i-Pr) is attributed to destabilizing nonbonded 1,3-diaxial interactions between the R^1 substituent and the 9-BBN ring, and to 1,2-axial–equatorial interactions between R^1 and the crotyl methyl group. Accordingly, the B (*E*,*E*) transition state (boat form) leading to anti products may dominate in these cases. These transition-state hypotheses are supported by the diastereoselectivity observed in the

Scheme VI. Transition States in the Crotylboronation of Imines



addition of pent-3-en-2-yl-9-BBN (**107b**) to imines. Syn selectivity is more dominant in these reactions than with crotyl-9-BBN; a small amount of syn product is produced in the reaction of benzylideneaniline (syn/anti = 8:92) which gives 100% anti product using crotyl-9-BBN. The syn product is produced exclusively by the pentenylation of the imine (R^1 = Ph, R^2 = n-Pr), which provides the anti product predominantly (85:15) by the crotylboration. The increase in syn selectivity over the crotylboration is explained by destabilizing interactions of the α-methyl group in the alternative cyclic transition states; in the C (*Z*,*E*) transition state, the α-methyl group produces an additional 1,3-diaxial interaction, whereas in both boat transition states there are 1,2-interactions between the α-methyl group and the 9-BBN ring. Both syn and anti products contain the *cis*-alkene geometry (**108b** and **109b**), which is consistent with a dominant C (*E*,*E*) transition state.

The stereoselectivities of the reactions of crotylboronates with two isomers of oxime silyl ether are independent of the geometry of the oxime, both isomers are configurationally stable under the reaction conditions (eq 40).[203] From (*E*)-crotylboronate **110a**, the *anti*-homoallylamine derivative **111a** is produced in 95% de regardless of the geometry of the oxime, and the syn product **111b** is provided from *Z*-isomer **110b** in 85–87% diastereoselectivity. Since the oxime stereochemistry defines the site of coordination to the boron atom,

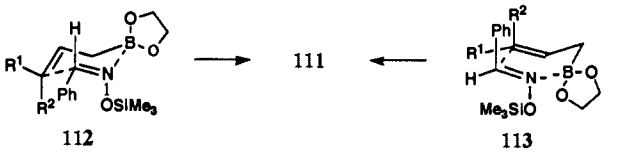


110 a: R^1=Me, R^2=H
b: R^1=H, R^2=Me

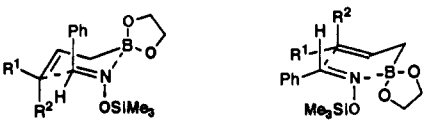
111 a: R^1=Me, R^2=H
b: R^1=H, R^2=Me

(eq 40)

presumably the (*Z*)-oxime reacts predominantly through the chair transition state **112**, while the (*E*)-oxime reactions proceed preferentially through the boat transition state **113**. The chair transition state **114** or

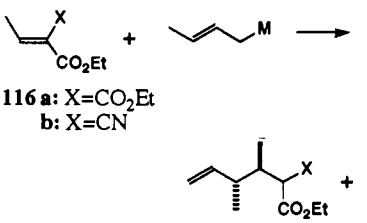


the boat analog **115** is destabilized in these cases. However, the differences in product diastereoselectivities and favorable transition state geometries between this case and the crotyl-9-BBN addition to imines shown in Scheme VI are not clear. The crotylboronate reactions were carried out at 46 °C under 9 kbar, whereas the crotyl-9-BBN additions at −78 °C under 1 bar.

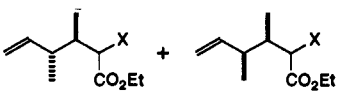


3. Reactions of Alkenes and Alkynes

The Michael addition of crotyl-9-BBN to α,β-unsaturated carbonyl compounds **116a** produces the anti adduct **117** predominantly in a ratio of 9:1 (eq 41).[204,205]



116 a: X=CO_2Et
b: X=CN



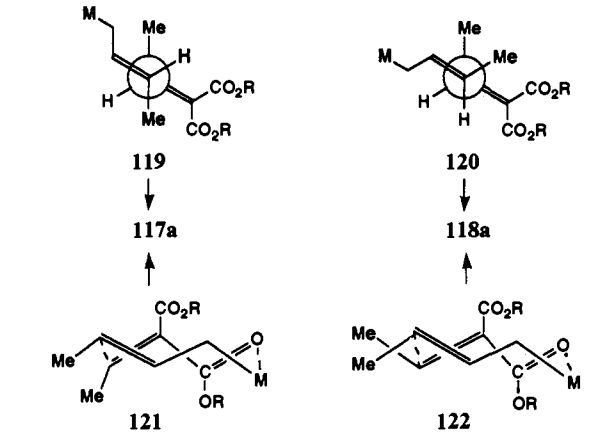
(eq 41)

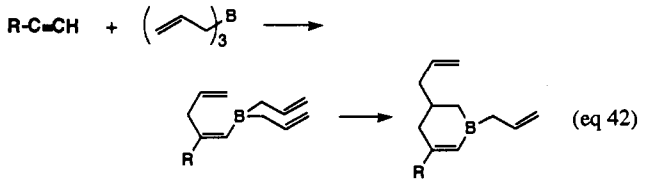
117 a: X=CO_2Et
b: X=CN

118 a: X=CO_2Et
b: X=CN

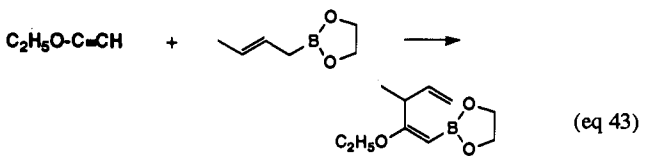
The steric bulk of the ester group does not exert a strong influence upon the selectivity. Reaction of **116b** with crotyl-9-BBN does not take place, but it reacts with crotylmagnesium, -titanium, and -zirconium reagents to produce the anti adduct **117b** preferentially in a ratio of 8:2. The anti selectivity can be explained by either an acyclic or an eight-membered cyclic transition state. Although two possible conformations, crown and boat–chair, are conceivable in the eight-membered transition state, the former is generally more stable than the latter. In the crown conformation, it seems that **121** is destabilized in comparison with **122** owing to the pseudoaxial Me group. Further, the comparative stabilities of **121** and **122** should be sensitive to variations of size in the alkoxycarbonyl groups, which is not observed. Therefore, the reaction must proceed through the acyclic transition state, in which it is clear that **119** is more stable than **120** for steric reasons.

Although trialkylboranes generally do not add to alkynes even under forcing conditions, the exceptionally reactive triallylborane is able to react with alkynes by a syn-addition process.[206,207] However, the monoaddition product reacts further, intramolecularly (eq 42). Only in the cases of (trimethylsilyl)acetylene[206] and of ethoxyacetylene[208] does allylation stop at the first step



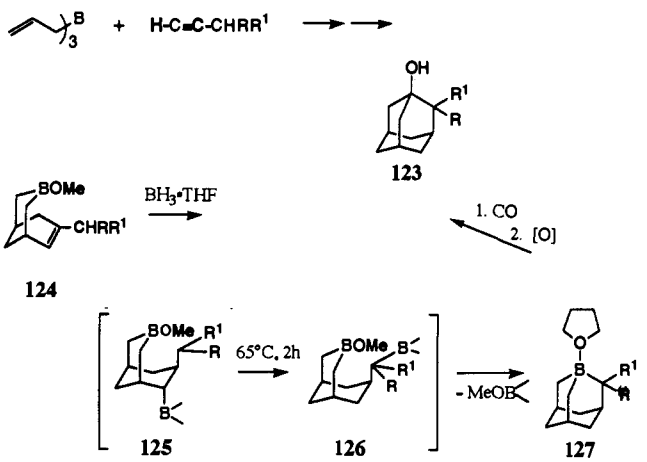


(eq 42)



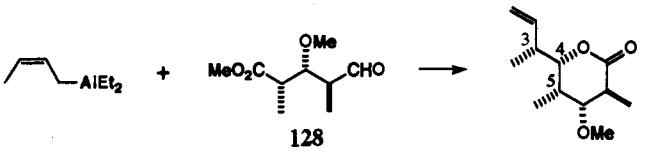
(eq 43)

to give the monoallylated product. The reaction occurs with complete allylic rearrangement with crotylborane. The triallylborane–acetylene condensation gives a hardly accessible cage compound **123**.[120c] Heating triallylborane with monosubstituted acetylenes at 130 °C for 2–3 h affords high yields (75–98%) of 7-substituted 3-allyl-3-borabicyclo[3.3.1]non-6-enes, which are converted to **124** in 90% yield upon treatment with MeOH. Hydroboration of **124** gives **125**, which isomerizes to **126** upon heating at 65 °C. Subsequent closure to 1-boraadamantane proceeds smoothly to give **127**. Carbonylation–oxidation reactions of **127** produces **123**.



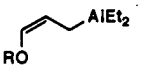
B. Allylic Aluminum Reagents

(*Z*)-Crotyldiethylaluminum, generated by the reaction of (*Z*)-crotylpotassium with diethylaluminum chloride, reacts with chiral aldehyde **128** to give good 3,4-syn selectivity (3,4-syn/3,4-anti = 3:1) (eq 44).[209] The stereoselectivity not only on C-3 and C-4, but also on C-4 and C-5, which is 3,4-syn-4,5-syn in eq 44, is



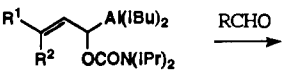
(eq 44)

opposite to that of the (*Z*)-crotylboronate reactions with α-methyl chiral aldehydes which produce 3,4-anti-4,5-anti selectivity predominantly (Table VI, entries 3, 6, and 7). γ-Alkoxysubstituted allyldiethylaluminum reagents **129** are prepared by treatment of the corresponding alkoxylithiums with Et_2AlCl in THF at −78 °C.[210,211] The aluminum reagents **129b** provide syn-

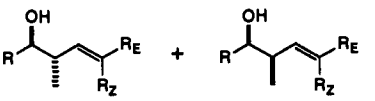


129a; R=Me
b; R=CH_3OCH_2

isomers with 9-11:1 diastereoselectivity in reactions of aldehydes at −78 °C, whereas **129a** gives 4:1 syn selectivity in the reaction with acetophenone.[210] (*E*)- and (*Z*)-Crotylaluminum reagents **130a** and **130b** have been prepared at low temperature by treating the corresponding crotyllithium reagents with either i-Bu_2-AlCl or i-Bu_2AlOMe.[212] The (*E*)-crotyl reagent **130a** gives the anti homoallyl alcohols **131a** with reasonable level of stereoselectivity in reactions with aliphatic aldehydes. The (*Z*)-crotyl reagent **130b** provides the syn alcohols **132a** with good selectivity. These dia-

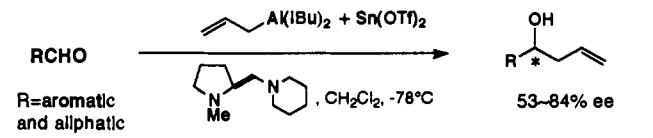


130a; R^1=Me, R^2=H
b; R^1=H, R^2=Me



131a; R_E=OCONiPr$_2$, R_Z=H **132a**
131b; R_E=H, R_Z=OCONiPr$_2$ **132b**

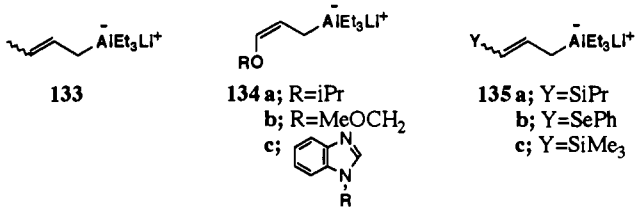
stereoselectivities are consistent with cyclic transition states with preferential equatorial placement of the allylic OCON(i-Pr)$_2$ group. The equatorial placement is opposite to the axial placement of the α-substituents of allylic boranes (cf. **93** and **94**), in which (*Z*)-alkenes are produced stereoselectively. A new enantioselective allylating agent, prepared by treatment of a mixture of stannous trifluoromethanesulfonate and a chiral diamine with allyldialkylaluminum, reacts with prochiral aldehydes to give homoallyl alcohols in good optical yield (eq 45).[213a] The crotylaluminum ate complex **133**,



(eq 45)

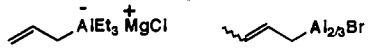
generated from crotyllithium and triethylaluminum, reacts with benzaldehyde with poor diastereoselectivity (56:44, anti/syn).[125] However, γ-oxygen-substituted allylic aluminum ate complexes **134** exhibit high regio-

and stereoselectivities in reaction with aldehydes; reagents **134a** and **134b** are quite regioselective in reactions with aliphatic aldehydes to give the γ-adduct exclusively and show >99% syn selectivity, but in reactions with benzaldehyde the syn/anti selectivity is somewhat lower (92:8).[21a] The reactions of **134c** with aldehydes at −100 °C give the syn-diol derivative with >95% diastereoselectivity and >80% γ-regioselectivity.[213b] The heteroatom-substituted aluminum ate complexes **135** react regioselectively with aldehydes at the γ-position to give the syn adducts predominantly: the syn selectivity is not as high as that of alkoxy-substituted reagents **134**. The (trimethylsilyl)allylaluminum reagent, generated from (trimethylsilyl)-allyllithium and $EtAlCl_2$, shows excellent selectivity for the anti diastereomer (86–100%).[214]



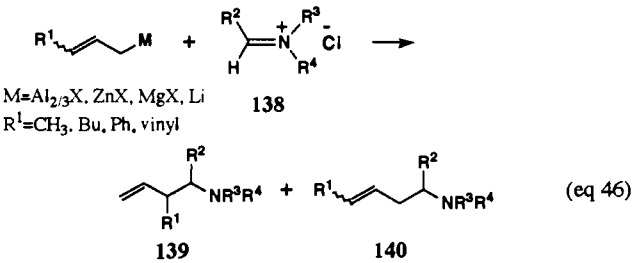
133 **134a**; R=iPr **135a**; Y=SiPr
b; R=MeOCH$_2$ **b**; Y=SePh
c; **c**; Y=SiMe$_3$

The allylaluminum ate complex **136**, prepared in situ from allylmagnesium chloride and Et_3Al, reacts with α-chiral imine **22** to give the chelation product in a ratio of 93:7, whereas the corresponding allylmagnesium chloride provides the chelation adduct in a 79:21 ratio (see eq 4).[50] The chelation selectivity in the reaction of **23** with **136** (90:10) is higher than that of allylmagnesium chloride with **30** (85:15) (eq 5).[50] Further, the use of **136** in the allylation of **28** provides higher selectivity than the use of allylmagnesium chloride; 89:11 in the case of *S*-chirality (cf. 70:30 of the magnesium reagent) and 95:5 in the case of *R*-chirality (cf. 86:14) (eq 7).[50] Accordingly, the aluminum ate complex **136** provides better diastereoselectivity in reactions of chiral imines than the magnesium reagent. The reaction of



136 **137**

the crotylaluminum reagent **137** with imines results in low chemical yields and low syn/anti diastereoselectivities (eq 2),[85] and therefore is not synthetically useful. The iminium salts **138** can be prepared by treatment of the corresponding enamines with hydrogen chloride. The reactions of crotylzinc, -magnesium, and -lithium reagents with **138** produce a mixture of the branched **139** and linear tertiary amines **140**, but the reaction of the crotylaluminum reagent **137** provides exclusively **139** in good yields (eq 46).[90] The syn/anti ratio was not

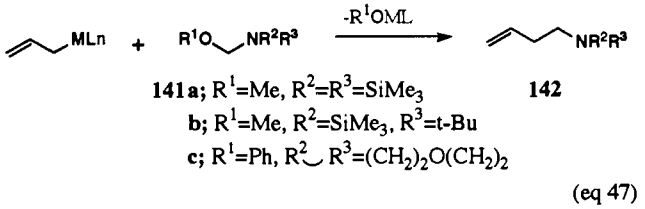


M=$Al_{2/3}X$, ZnX, MgX, Li
R^1=CH_3, Bu, Ph, vinyl

138

139 **140** (eq 46)

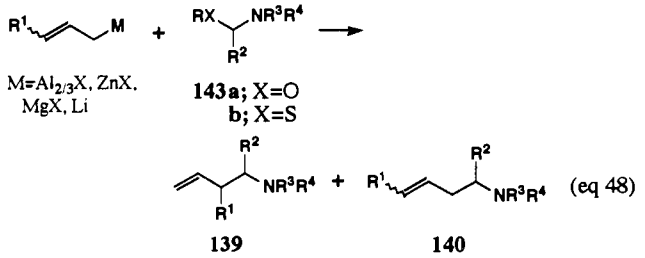
determined. The preference of the branched homoallylamines **139**, with the exception of vinyl crotyl reagents, follows the trend $Al_{2/3}X > ZnX > MgX > Li$, paralleling the covalent character of the carbon–metal bond. With vinyl crotyl reagents (R^1 = vinyl), the linear amines **140** are produced predominantly and the aluminum reagent gives exclusively **140**. It seems that α-deprotonation, which causes low yields in reactions of certain imines with allyllithium and -magnesium reagents, is not a serious problem in the iminium salts since yields are generally good even though they are enolizable. There is little similarity between the regiochemistry of reactions of iminium salts and that observed in the imine reactions, the latter of which are strongly influenced by imine substituent. The iminium salts do not contain an available lone pair of electrons which is necessary for the involvement of cyclic transition states. *gem*-Amino ethers **141** behave as masked iminium salts and react with allylic organometallic reagents to afford N,N-disubstituted homoallylamines (eq 47). The use of *gem*-amino ethers is more convenient than that of iminium salts, because they are more easily handled and can be purified by distillation. The reaction of allylmagnesium bromide with **141a**[215,216] or **141c**[218] produces the homoallylamine **142** in 70–88% yields, although that of the allylaluminum reagent (CH_2=$CHCH_2Al_{2/3}Br$) with **141a** or **141b** provides **142** in 40–45% yields.[217] The additions of crotylorgano-



141a; R^1=Me, R^2=R^3=SiMe$_3$ **142**
b; R^1=Me, R^2=SiMe$_3$, R^3=t-Bu
c; R^1=Ph, R^2⌣R^3=$(CH_2)_2O(CH_2)_2$

(eq 47)

metallics to *gem*-amino ethers **143a** and sulfides **143b** provide the branched adducts **139** predominantly over linear products **140** as in the reactions of preformed iminium salts (eq 48).[217,219,220] It seems that the reactions



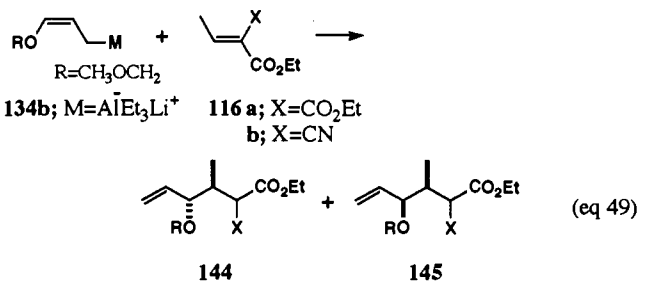
M=$Al_{2/3}X$, ZnX, MgX, Li

143a; X=O
b; X=S

139 **140** (eq 48)

of **143** are somewhat more regioselective than those of **138**. Little difference in regioselectivity is observed between the *gem*-amino ethers **143a** and *gem*-amino sulfides **143b**. As observed in reactions of **138**, the decrease of γ-regioselectivity in reactions of **143** takes place with more ionic crotyl reagents; the preference of **139** again follows the trend $Al_{2/3}X \geq ZnX > MgX > Li$. The syn/anti diastereoselectivity of **139** was not investigated.

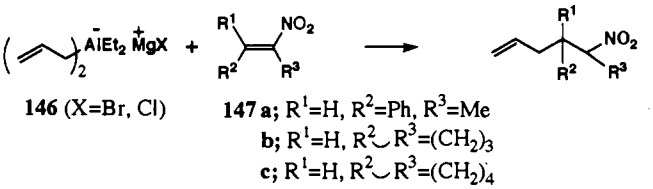
The Michael addition of the γ-oxygen substituted allylic aluminum ate complex **134b** to diesters **116a** produces a 1:1 mixture of anti and syn adducts (**144** and **145**).[205] As mentioned later, the titanium reagent provides significantly higher anti selectivity (87:13).



134b; M=AlEt$_3$Li$^+$ 116a; X=CO$_2$Et
b; X=CN

144 145 (eq 49)

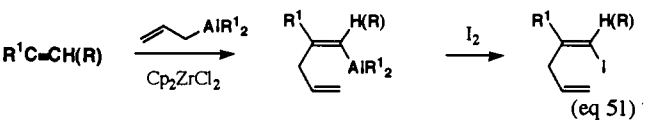
The allylaluminum ate complex **146**, prepared in situ from Et_2AlCl and 2 equiv of allylmagnesium halides, reacts with nitroolefins **147** to give the conjugate adducts in high yield (eq 50).[221] Although a 1:1 mixture of the diastereomers is obtained in the acyclic nitroolefin **147a**, the five- and six-membered derivatives **147b** and **147c** provide very high transselectivity (>93:7).



146 (X=Br, Cl) **147a**; R^1=H, R^2=Ph, R^3=Me
b; R^1=H, R^2⌣R^3=(CH$_2$)$_3$
c; R^1=H, R^2⌣R^3=(CH$_2$)$_4$

(eq 50)

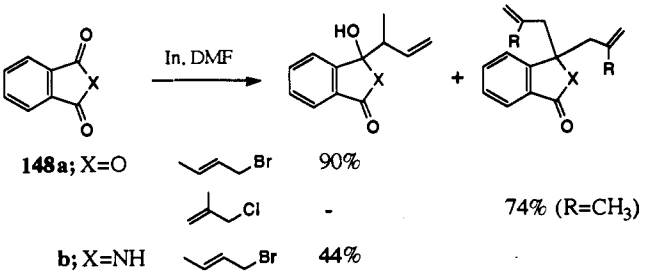
Organoaluminum compounds add in a syn manner to many alkynes, but these reactions are synthetically not useful owing to the poor reactivity of triorganoalanes. The carboaluminum is accelerated remarkably in the presence of catalytic or even stoichiometric amounts of transition metal salts. As shown in entries 9 and 10 of Table III, the allylzincation of alkynylsilanes produces 1,4-pentadienylzinc halides in high yields, but the corresponding reaction of terminal alkynes is generally complicated by competitive zincation of alkynes and double allylzincation.[98,101] Further, internal alkynes fail to react with allylzinc halides. Both terminal and internal alkynes undergo Zr-catalyzed allylalumination (eq 51).[222] The reaction is >98% stereoselective but only ca. 75% regioselective. The use of a deficient amount of an electrophile, e.g. I_2, can produce isomerically pure alkene derivatives. Internal alkynes also undergo a similar Zr-promoted allylzincation with diallylzinc reagents in the presence of I_2-$ZrCp_2$.[105a]



(eq 51)

C. Allylic Indium Reagents

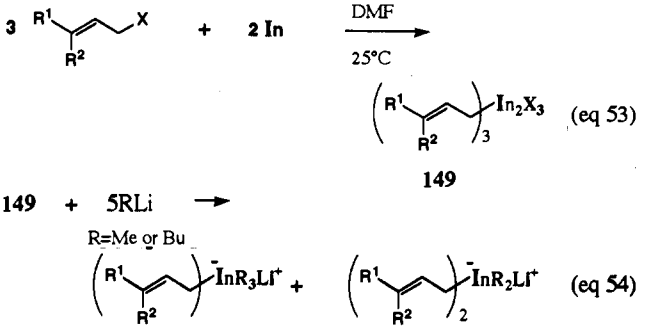
Indium powder mediated Barbier-type allylations of a variety of ketones and aldehydes afford excellent yields of the corresponding homoallyl alcohols.[223] Crotyl bromide gives the branched homoallyl alcohol regioselectively, but the diastereoselectivity is low; syn/anti = 66:34. Cinnamyl and prenyl bromides also provide the corresponding branched alcohol exclusively. Not only allylic halides but also allylic phosphates can be utilized as starting materials. The indium-mediated allylations of cyclic acid anhydrides (**148a**) or cyclic imides (**148b**) give the corresponding mono- or diallylated products depending on the degree of substitution of the allylic indium reagents used (eq 52).[224] A short



148a; X=O 90%
74% (R=CH$_3$)
b; X=NH 44%

(eq 52)

synthesis of (±)-bakuchiol has been accomplished by using geranylindium reagent and 2-(4-methoxyphenyl)-acetaldehyde.[224c] In contrast to allylic magnesium and lithium reagents, the allylic indium reagents **149**, prepared from the corresponding allylic chloride, bromide, and iodide, do not react with allylic halides; the Wurtz-type side products that are often formed in the preparation of allylmagnesium and lithium reagents are not formed in this case (eq 53).[224b] The allylic indium ate complexes can be prepared by the addition of 5 equiv of RLi to **149** (eq 54).[224d] The allylic indates



(eq 53)

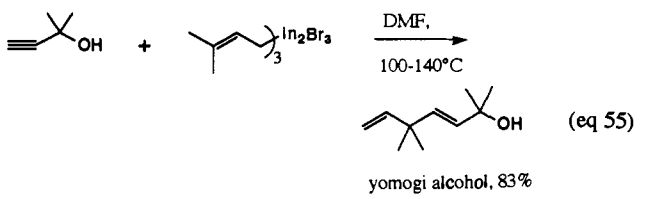
149

(eq 54)

thus prepared are presumably 1:1 mixtures of allyltrialkyl- and diallyldialkylindates. Regio- and stereospecific allylic–allylic coupling has been accomplished using these indates and allylic bromides; only the products coupled at the α-position of allylic bromides and γ-position of allylic indates are obtained in good yields (for the regioselective allylic borates–allyl halides coupling, see ref 125). Allylation reactions of aldehydes and ketones occur smoothly with indium metal in aqueous media (in powder, H_2O, at room temperature).[225] Compared to similar reactions with zinc and tin where acid catalysts, heat, or sonication are often required, the reaction with indium proceeds without the need for any promoter. Carboindation of alkynols by allylic indium sesquihalides **149** proceeds in DMF at 100–140 °C via a syn addition (eq 55).[226] Synthesis of yomogi alcohol is shown in eq 55. The allylic unit of **149** adds predominantly to the terminal carbon of alkynes (anti-Markovnikov addition), but the cinnamyl indium reagent adds to propargyl alcohol preferentially in a Markovnikov manner.

V. Group 14 (Si, Ge, Sn, and Pb)

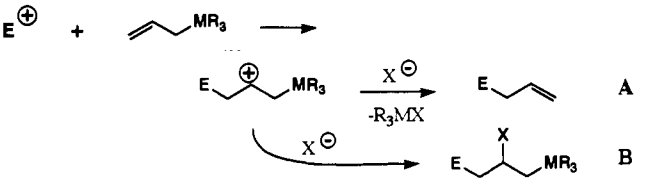
Allylsilanes[227] and allylstannanes[451] have been used as extensively allyl anion equivalents during the last two decades. Their regioselective reactions with elec-



(eq 55)

yomogi alcohol, 83%

trophiles have been explained by the intermediate formation of carbenium ions, which are hyperconjugatively stabilized by the carbon–silicon or carbon–tin bond in the β-position.[228] The quantitative determination of the nucleophilicity of allylsilicon, -germanium, and -tin compounds has been accomplished.[229] Second-order rate constants for the reactions of para-substituted diarylcarbenium ions ($ArAr'CH^+$) with allylsilanes, allylgermanes, and allylstannanes have been determined in CH_2Cl_2 solution at −70 to −30 °C. Generally, the attack of $ArAr'CH^+$ at the C–C double bond of the allylorganometallics is rate determining and leads to the formation of the β-element (MR_3) stabilized carbenium ions, which subsequently react with the negative counterions to give the substitution product (A) or the addition products (B). For compounds with the formula



$H_2C{=}CHCH_2MPh_3$, the relative reactivities are 1 (M = Si), 5.6 (M = Ge), and 1600 (M = Sn). From the relative reactivities of compounds with the formula $H_2C{=}CHCH_2X$ (X = H, $SiBu_3$, $SnBu_3$), the activating effect of an allyl trialkylsilyl (5×10^5) and trialkylstannyl group (3×10^9) is derived. This effect is strongly reduced, when the alkyl groups at Si or Sn are replaced by inductively withdrawing substituents, and an allylic $SiCl_3$ group deactivates by a factor of 300. Relative nucleophilicities of the allylorganometallics with respect to propene (left) and isobutene (right) are shown in Figure 1. The reactivity of these compounds covers a wide range, and a single reference electrophile is not sufficient for kinetic comparison. Therefore $AnPhCH^+$ and An_2CH^+ are selected to qualify the nucleophilicity of these compounds (An = $CH_3OC_6H_4$). The reactivity of allyltriphenylmetal series increases by 1 order of magnitude from Si to Ge and by 2 orders of magnitude from Ge to Sn. An analogous reactivity pattern is found in the methallyl series in the right column of Figure 1, but the methallyltriphenyl metals differ less in reactivity than their lower homologs (allyl series) due to the saturation effect. The $SnBu_3$ group is found to be a considerably stronger electron donor than the $SnPh_3$ group.

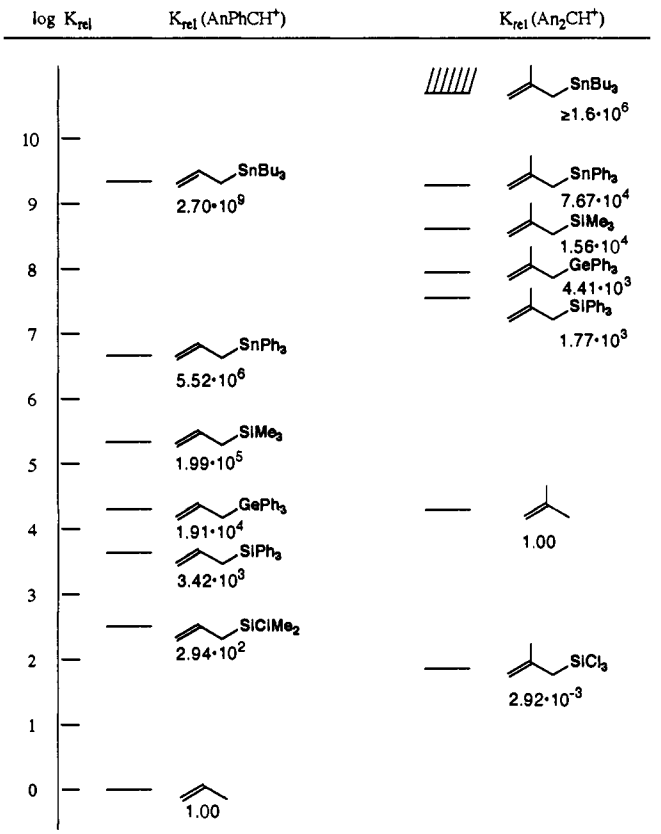
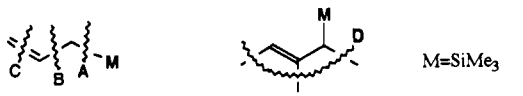


Figure 1. Relative nucleophilicities of allylsilanes, -germanes, and -stannanes with respect to propene (left) and isobutene (right). The graphic representation allows a direct comparison of all compounds; i.e., the nucleophilicities of allyltriphenylgermane and isobutene are almost identical.

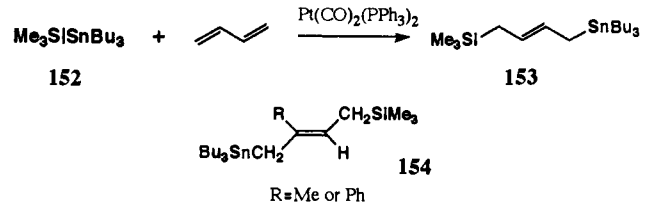


150 **151**

A. Allylsilane Reagents

1. New Synthetic Methods

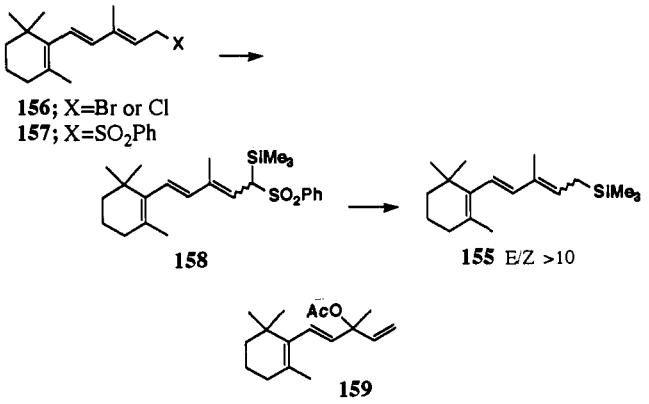
According to Fleming's classification,[227c] the synthetic methods can divided into four categories depending upon which bond (A–D) in the general structures (**150** and **151**) is made in the key step. Since the late 1980s, some new synthetic methods have been reported, most of which involve transition metal catalyzed (or mediated) reactions. Syntheses based on disconnection A are mentioned first. The reaction of $(Me_3Si)SnBu_3$ **152** with 3 equiv of 1,3-butadiene in the presence of catalytic amount (5 mol %) of $Pt(CO)_2(PPh_3)_2$ gives (*E*)-1,4-silyl-stannylation product **153** in 93% yield as a single stereoisomer.[230] Isoprene and 2-phenyl-1,3-butadiene



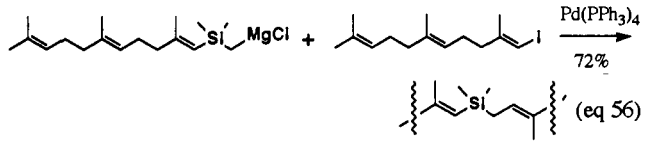
152 **153** **154**

also react with **152** to afford **154** in high yields, in which Me_3Si group bonded to the sterically less bulky carbon. The most direct route for the synthesis of allylsilanes is the silylation of an allylmetal reagent such as a Grignard or lithium reagent.[227] However, the reported general methodologies proved to be unsatisfactory for the synthesis of polyenylsilane;[155] the bromide or chloride **156**, on reaction with Mg and $(CH_3)_3SiCl$ according to the procedure of Calas,[231a] did not give **155**. An alternative approach using the "counterattacking principles", that is, the reaction of $(Me_3Si)_2CuLi$

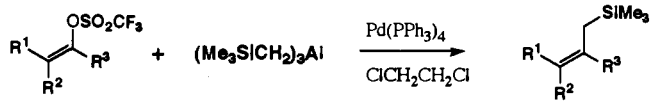
with **159**, gives **155** only in 10% yield. The use of sulfone chemistry is effective for the synthesis of **155**. Treatment of **157** with t-BuLi generated the anion which reacted with Me_3SiCl to give **158** in 80% yield. Sodium amalgam reduction (Na/DMAN/Et_2NH) of **158** in MeOH gives **155** in 84% yield (for DMAN, see 1).[231b]



Syntheses based on disconnection B use primarily palladium catalysts. The catalyzed reaction of (trimethylsilyl)methyl Grignard reagent with various substrates, such as esters, enol derivatives, or vinyl halides provides allylsilanes in good yields.[227] The synthesis of silanes bearing both an allylic and a vinylic moiety is accomplished with Pd(0)-catalyzed coupling reaction (eq 56).[232a] Allyltrimethylsilanes are obtained in good

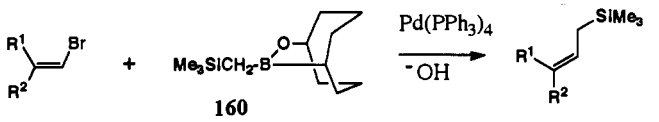


to excellent yields by the Pd(0)-catalyzed cross-coupling of vinyl triflates with $(Me_3SiCH_2)_3Al$, generated in situ from commercially available Me_3SiCH_2Li and $AlCl_3$ (eq 57).[232b] The palladium-catalyzed coupling of vinyl

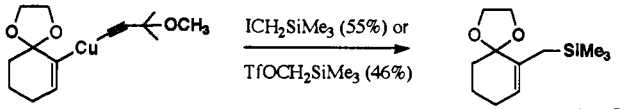


(eq 57)

bromides with borinate ester **160**, obtained by the trimethylamine *N*-oxide oxidation of the corresponding Me_3SiCH_2-9-BBN, gives allylsilanes in excellent yields.[233]

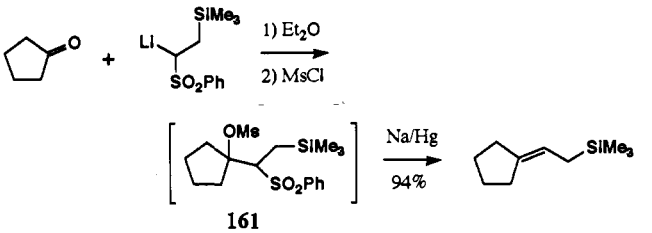


Gilman reagents derived from vinylic nucleophiles react with (iodomethyl)trimethylsilane or (trimethylsilyl)-methyl trifluoromethane sulfonate to afford allylsilanes not readily accessible by other procedures (eq 58).[234]

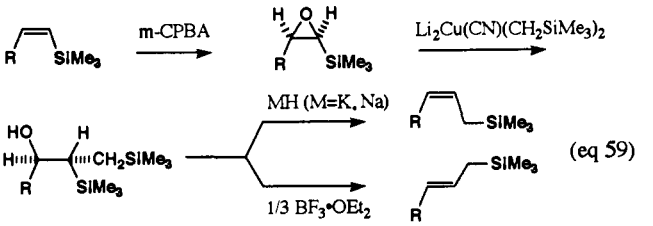


(eq 58)

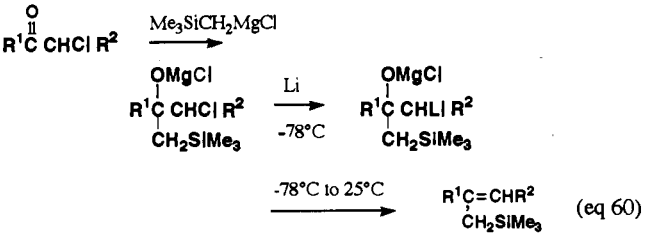
The most simple of the category (disconnection C) is the synthesis based on the Wittig reaction.[227] An alternative approach is reductive desulfonylation of the γ-[(methanesulfonyl)oxy]-β-sulfonyl derivative **161**.[231b,235] Pure *cis*-vinylsilanes, available from the



hydroboration–protonolysis of silylacetylenes, are efficiently converted to *cis*-epoxysilanes which react smoothly with $Li_2Cu(CN)(CH_2SiMe_3)_2$ to provide the erythro-disilylated alcohol in excellent yield and isomeric purity. The Hudrlik elimination of Me_3SiOH affords either the pure cis- or trans-γ-substituted allylsilanes, under basic or acidic conditions, respectively (eq 59).[236] The reaction of α-chlorocarbonyl compounds with (trimethylsilyl)methylmagnesium chloride followed by the treatment with lithium powder leads to allylsilanes in good yields (eq 60).[237] However, this method provides ca. 1:1 mixture of the *E*/*Z* stereoisomers.

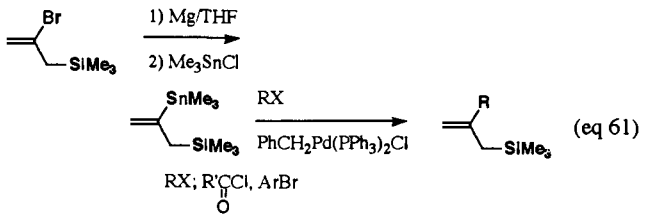


(eq 59)



(eq 60)

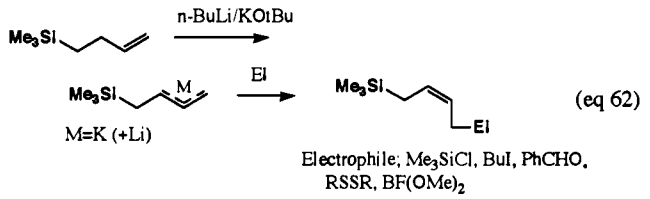
The commonly used procedure of disconnection D is to add substituents to or manipulate substituents on an existing allylsilane system, or alternatively to move the double bond into the allylic position from somewhere else in the molecule.[227] Allylsilanes bearing the various functionalities are prepared from the palladium-catalyzed cross-coupling reactions of 2-(trimethylstannyl)-3-(trimethylsilyl)propene with acid chlorides and with aryl halides (eq 61).[238] The metalation of homo-



(eq 61)

allylsilane, easily prepared by the coupling reaction of allyl bromide and Me_3SiCH_2MgCl, with butyllithium/

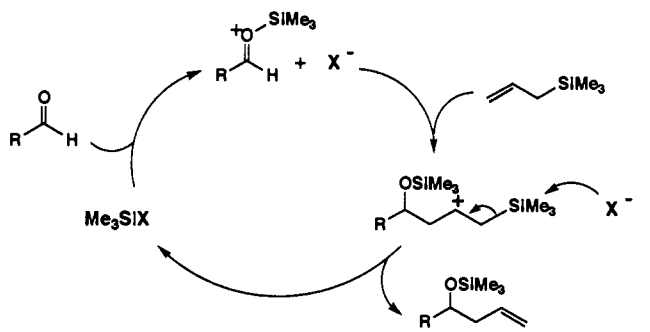
potassium *tert*-butoxide followed by quenching with electrophiles leads to a series of 3-substituted allylsilanes under mild conditions and with satisfactory yield (eq 62).[239] Although trapping with Me_3SiCl and $BF(OMe)_2$ gives exclusively *Z*-isomers, other electrophiles produce ca. 70:30–80:20 mixture of *Z*/*E* isomers; trapping with $BF(OMe)_2$ gives the hydroxy derivative (E = OH) upon oxidation with $NaOH/H_2O_2$.



(eq 62)

2. Intermolecular Reactions of Aldehydes and Ketones

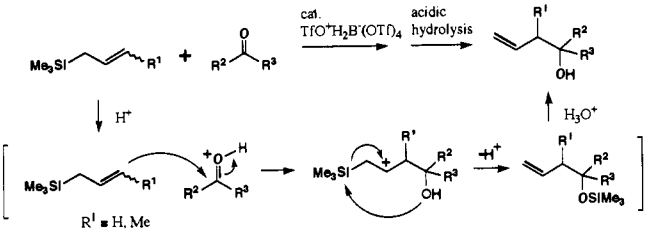
The addition of trialkylallylsilanes to aldehydes and ketones, widely appreciated as a mild method for C–C-bond formation, is induced either by stoichiometric amounts of Lewis acids or by catalytic quantities of fluoride ions.[227,240-242] Allylsilanes are known to be decomposed rapidly by strong protic acids.[243] Therefore, catalysis of the allylation reaction by Brönsted acids has not previously been reported. The superacid $TfOH_2^+B(OTf)_4$, prepared from BBr_3 and TfOH,[244] is found to catalyze the addition of trialkylallylsilanes to aldehydes and ketones at levels of ca. 0.5 mol %; the reactions are clean, high yielding, and regioselective with respect to allylic inversion (eqs 63 and 64).[245]



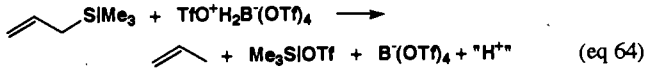
It is proposed that the protonated aldehydes and ketones initiate the catalytic cycle shown in eq 63. The proton is presumably produced by the reaction of allylsilanes with the superacid (eq 64). The allylsilane is presumably unable to quench this proton because its counterion is the highly nonnucleophilic $B(OTf)_4^-$, which cannot be used to remove the Me_3Si group. The new "supersilylating reagent" $Me_3SiB(OTf)_4$, prepared from $B(OTf)_3$ and Me_3SiOTf, is an excellent catalyst for allylation of aldehydes: the reaction is very rapid when 1 mol % of the catalyst is used at room temperature and gives the corresponding allylic alcohols in yields greater than 80%.[246] The use of Me_3SiOTf or Me_3SiI as a catalyst gives less satisfactory results. The most reasonable mechanism is shown in Scheme VII.

Dramatic changes in diastereoselectivity, depending upon the quantity of $TiCl_4$ used in the Lewis acid mediated reactions of allylsilane with chiral α-*N*-(carbobenzyloxy)amino aldehydes are observed (eq 65).[247a] A high anti stereoselectivity (20:1) is observed using 1 equiv of $TiCl_4$, whereas the use of 0.5 equiv of $TiCl_4$ produces a good syn selectivity (8:1). The anti

Scheme VII. Catalytic Cycle by $Me_3SiB(OTf)_4$

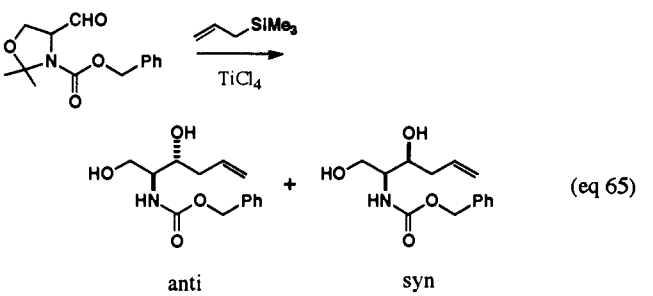


(eq 63)



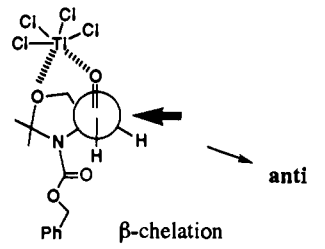
(eq 64)

selectivity rapidly decreases as the quantity of $TiCl_4$ is increased over 1.0 equiv. This trend is interpreted in



(eq 65)

terms of two differently derived species: aldehyde–$TiCl_4$, 1:1 (**162**) and 2:1 complexes (**163**), which can proceed to their respective transition states. The anti



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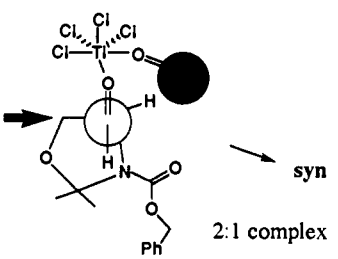
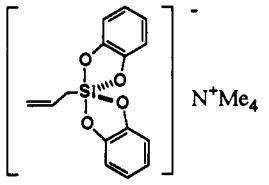


163

selectivity observed with 1.0 equiv is consistent with β-chelation. The disturbance of β-chelation, with excess $TiCl_4$ over 1.0 equiv, results in lower anti selectivity. The syn selectivity observed at 0.5 equiv of $TiCl_4$ is explained by the 2:1 complex shown in **163**. Allylation of 2-methyl-3-oxo amides with allylsilanes in the presence of $TiCl_4$ gives *syn*-3-allyl-3-hydroxy-2-methyl amides with very high diastereoselectivity (see also Table II, entry 26);[247b] the Bu_4NF-mediated reaction provides opposite stereoisomers, anti diastereomers, predominantly. The $SnCl_4$-mediated addition of allylsilane to α-aminoaldehydes[247d] proceeds in a chelation-controlled manner to provide *syn*-amino alcohols with

excellent diastereoselectivity.[247c] The addition of allyltributyltin gives lower syn selectivity.

Silicon can expand its coordination number from the normal value of 4 to 5 or 6 to form penta- or hexacoordinated compounds, if the silicon atom carries highly electronegative and sterically compact ligands such as fluorine. The pentacoordinated silicon species bears a unit negative charge, which is delocalized into the electronegative ligands. As a result, the silicon atom becomes rather electron deficient with a significant Lewis acid character.[246] Two allylsilicates **164** and **165** exhibit quite different reactivity in the allylation of carbonyl compounds under nucleophilic conditions (Bu_4NF, KF, or NaOMe) and electrophilic conditions ($TiCl_4$, $AlCl_3$, or BF_3).[249] The allylation via **164** takes place under nucleophilic conditions in DMSO, whereas it results in decomposition of **164** under electrophilic conditions. On the other hand, **165** provides the allylation product under Lewis acid conditions but it does not react with aldehydes under the nucleophilic conditions. The completely different reactivity of silicates **164** and **165** is explained by different arrangement of the allyl group, which is in an equatorial position in **164** and in an apical position in **165**. Pentacoordinate triethylammonium bis(catecholato)allylsiliconates **166** are synthesized by reaction of allyltrialkoxysilanes, catechol, and triethylamine.[250] The lithium salts **167** are prepared via the reactions of the corresponding allylic trichlorosilanes with dilithium catecholate.[251] Addition of a CH_2Cl_2 solution of bis(triphenylphosphoranylidene)ammonium chloride [(PPN)Cl] to **167**, followed by filtration of LiCl under argon gives the PPN salt of allylic silicates **168**.[251] The reaction of allyltrifluorosilanes in the presence of CsF is believed to proceed through the allylsilicates, having Cs^+ as a gegen cation (**169**).[252]



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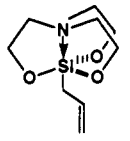
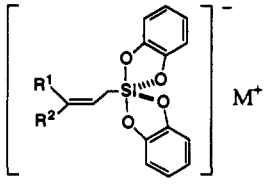
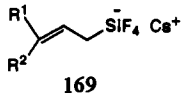


165



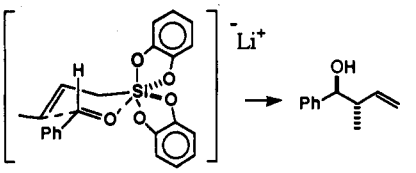


169

166; $M^+=Et_3N^+H$
167; $M^+=Li^+$
168; $M^+=PPN^+$
$(Ph_3P{=}N^+{=}PPh_3)$

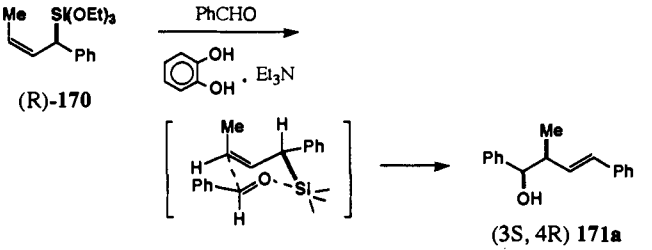
These pentacoordinate allylsilicates (**166**–**169**) react with aldehydes via a six-membered cyclic transition state (eq 66). The allylation does not need the assistance of a Lewis acid or a fluoride anion. Since the silicon atom of the pentacoordinate species possesses sufficient Lewis acidity, it can coordinate to the aldehyde oxygen. Accordingly, (*E*)-allylic siliconates give *anti*-homoallyl alcohols, whereas *Z*-isomers afford *syn*-homoallyl alcohols. The stereochemical outcome of pentacoordinate

167 (R^1=H, R^2=Me) + PhCHO →



(eq 66)

allylic silicates is completely different from that of tetracoordinate allylsilanes in the presence of Lewis acids (this will be mentioned later; see Scheme X). Without isolation of the pentacoordinate species, the allylation of aldehydes can be carried out through the in situ generation of the allylsiliconate. The homoallyl alcohols are prepared by mixing aldehydes with an allyltrialkoxysilane, catechol, and triethylamine.[250a] Reaction of (*R*)-(*Z*)-1-phenyl-1-(triethoxysilyl)-2-butene (**170**) with benzaldehyde in the presence of catechol and triethylamine gives (3*S*,4*R*)-(*E*)-1,4-diphenyl-3-methyl-4-hydroxy-1-butene (**171a**) and 3*S*,4*S*-isomer **171b** in a ratio of 90:10, indicating that the allylation proceeds via a six-membered cyclic transition state. The

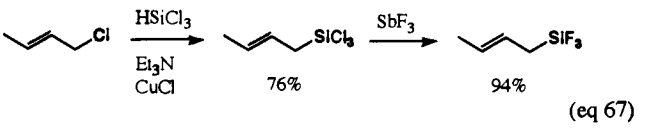


(R)-**170**

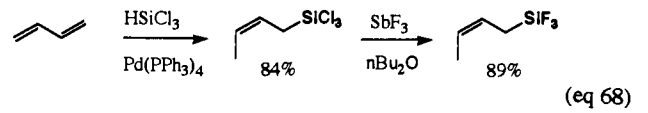
(3S, 4R) **171a**

syn stereochemistry of S_E' reaction of allylic organometals has been observed only when the reaction is forced to proceed via a cyclic transition state. This is also the case with the allylic siliconate reaction. Allylation with (*R*)-(*Z*)-1-phenyl-1-(trifluorosilyl)-2-butene in the presence of cesium fluoride also proceeds via six-membered transition state.[252]

(*E*)- and (*Z*)-crotyltrifluorosilanes are prepared with more than 99% purity as shown in eqs 67 and 68. These



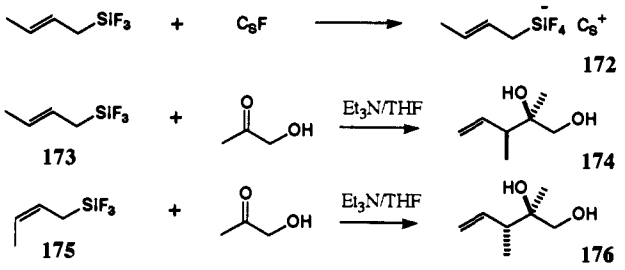
(eq 67)



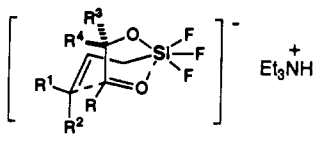
(eq 68)

trifluorosilanes are configurationally stable and may be stored for a few months at 0 °C.[252] The allylation of aldehydes in the presence of CsF proceeds in high yields with high stereoselectivity. Here also, the pentacoordinate silicate **172** is produced in situ, which reacts with aldehydes to give the homoallyl alcohol with high diastereoselectivity. The diastereoselectivity can be explained by a six-membered chair cyclic transition state (for example, eq 66). Instead of CsF, a combination of triethylamine and a hydroxy compound such as catecol, can be utilized as an activator.[253] This reagent system can discriminate linear from α-branched alkanals; prenylation of primary aldehydes proceeds very smoothly, while no reaction takes place with secondary and tertiary aldehydes.

Crotyltrifluorosilanes react with α-hydroxy ketones in the presence of Et_3N without protection of the hydroxy group, producing the tertiary homoallyl alcohols with very high regio- and stereoselectivity; for example, the (*E*)-crotyltrifluorosilane (**173**) gives **174** in 83% yield with a syn/anti ratio of 97:3, whereas the *Z*-isomer **175** affords **176** in 87% yield with a syn/anti ratio of 5:95.[254] It is suggested that the reaction proceeds

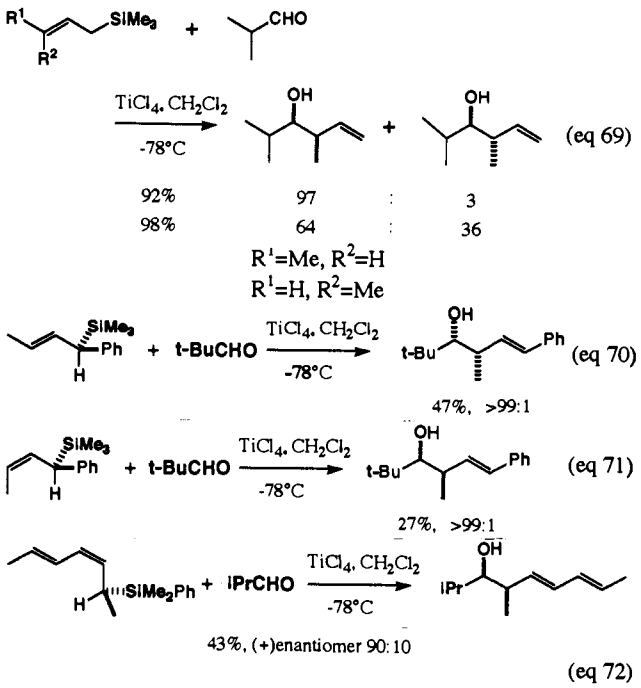


via the 1,3-bridged cyclohexane-like transition state **177**, where coordination of the silicon atom by both the internal alkoxy and carbonyl oxygens is involved. Similarly, α-keto carboxylic acids react with **173** and **175** under the similar conditions to give the corresponding 2-hydroxy-4-alkenoic acids with high diastereoselectivity.[255]



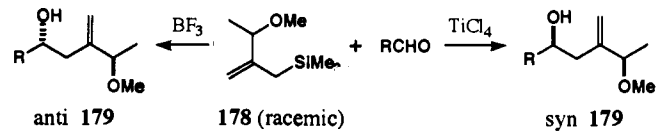
177

In contrast to the allylic silicate additions, the Lewis acid mediated reaction of allylic silanes (tetravalent silicon) with aldehydes proceeds through an acyclic transition state; *syn*-homoallyl alcohols are obtained predominantly regardless of the geometry of the double bond of crotylsilanes. For example, (*E*)-crotyltrimethylsilane produces the *syn*-alcohol in 97% diastereoselectivity upon treatment with isobutyraldehyde–$TiCl_4$

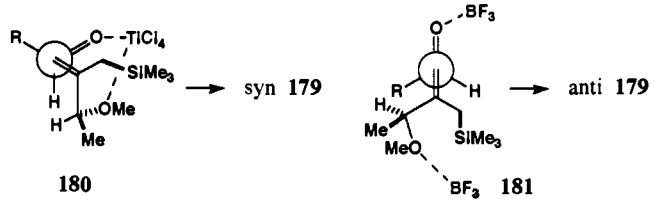


complex, and (*Z*)-crotyltrimethylsilane also affords the *syn*-alcohol predominantly (64% selectivity) (eq 69).[256] Mechanisms involving acyclic transition states are discussed in detail in the allylic stannane section. Chiral crotylsilanes react antarafacially; the incoming electrophile attacks the double bond on the surface opposite to the silyl group, leading to the *syn*-(*E*) product from the (*E*)-crotylsilane (eq 70) and to the enantiomeric *syn*-(*E*) product from the (*Z*)-crotylsilane (eq 71).[257] Chiral (*Z*,*E*)-dienylsilane reacts with isobutyraldehyde in an anti-S_E2'' manner to produce the *syn*-(*E*) adduct predominantly (syn/anti = 80:20) (anti-S_E2''/syn-S_E2'' = 90:10) (eq 72).[258] It should be noted that the overall anti-S_E2' type displacement of silicon atom is operative even though the new stereocenters are five and six atoms from the original stereocenter.

The effect of a substituent at the β-position of allylsilanes upon the diastereoselectivity has been investigated. The $TiCl_4$-mediated reaction of **178** gives the *syn*-**179** either exclusively or with very high stereoselectivity, whereas the BF_3-induced reaction produced the *anti*-**179** predominantly.[259] The diastereo-



selectivity difference is explained by the different mode of chelation of these two Lewis acids; a bidentate Lewis acid, $TiCl_4$, can coordinate the two oxygen atoms and thus the reaction proceeds via **180** to give *syn*-**179**, whereas the reaction with a monodentate BF_3·OEt_2 proceeds via **181** to afford *anti*-**179**. The substituent

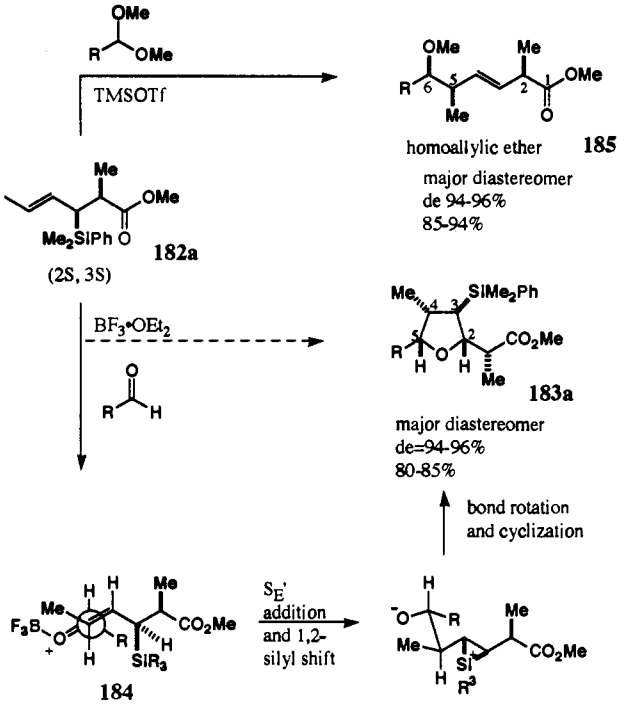


180 **181**

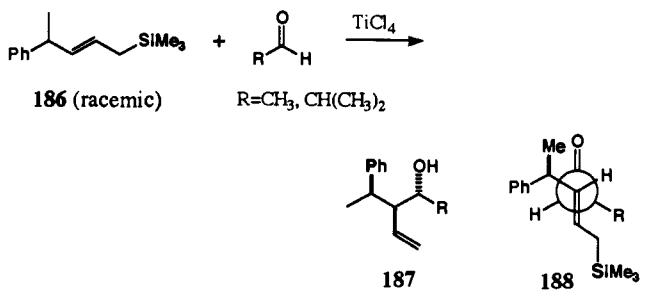
effect at the α-position of allylsilanes upon the diastereoselectivity has also been investigated.[260] The asymmetric addition of chiral (*E*)-crotylsilanes to α- and β-benzyloxy aldehydes in the presence of BF_3·OEt_2 constitutes a remarkably simple procedure for the construction of optically pure 2,5-*cis*-tetrahydrofurans (Scheme VIII).[260] The (2S,3S)-diastereomer **182a** produces **183a** with 96% de in 85% yield (the ratio of 4,5-syn/anti is 30:1). The reaction proceeds through an acyclic transition state **184**, in which the aldehyde attacks the double bond of **182a** in an anti S_E2' manner, followed by the 1,2-silyl migration and subsequent heterocyclization. The diastereomers of **182a**, (2*S*,3*R*)-**182b**, (2*R*,3*S*)-**182c**, and (2*R*,3*R*)-**182d**, also provide the corresponding chiral tetrahydrofurans in high yields with high de. The preparation of **182** is accomplished by the Ireland–Claisen rearrangement from nearly enantiomerically pure (*R*)- and (*S*)-(*E*)-vinylsilanes.[261] Trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalyzed asymmetric addition reactions of achiral acetals to **182a** gives the homoallylic ether **185** with excellent levels of 1,4- and 1,5-asymmetric induction.

The reaction of allylsilanes, containing a stereogenic center in the δ-position with several electrophiles shows

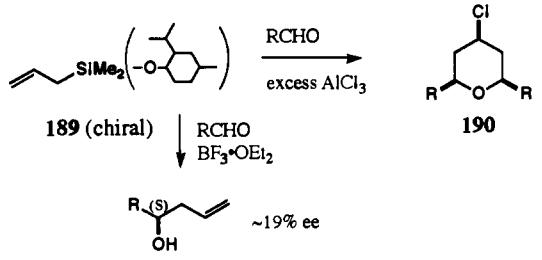
Scheme VIII. Asymmetric Synthesis of Tetrahydrofurans



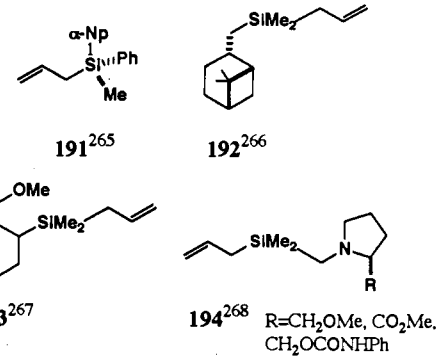
that the influence of this stereocenter on the stereoselectivity of the reaction can be rationalized using the model of approach of nucleophiles to double bonds (Houk model).[262] The reaction of **186** with aldehydes in the presence of $TiCl_4$ gives **187** as the major product (among four diastereomers **187** is obtained with the stereoselectivity of 70–75%).[263] This diastereoselectivity can be explained by the antiperiplanar transition state **188**. The reaction of **186** with other electrophiles, such as PhSCl and chlorosulfonyl isocyanate is also studied.



The effect of a stereocenter present on one ligand of the silicon atom, or a stereocenter on the silicon atom (chiral silicon), upon the diastereoselectivity has been studied. The reaction of **189** with aldehydes in the

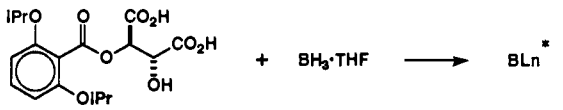


presence of excess (>1 mol) $AlCl_3$ gives the tetrahydropyran **190** exclusively, whereas the reaction in the presence of BF_3•OEt_2 (<1 mol) afforded the homoallyl alcohol with 19% ee.[264] Chiral auxiliaries other than (−)-menthoxy were also examined, but the enantiomeric excess in the allylation was in the range of 18–23%. Allylsilanes bearing an optically active silicon atom were prepared (**191**–**194**). Their allylation reactions with

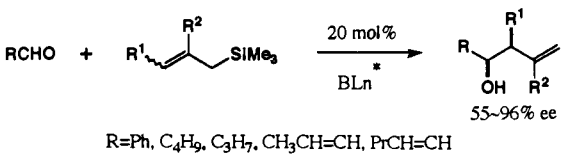


aldehydes produced enantiomeric excess in the range of 5–50%.[265-268] However, the low asymmetric induction seems to be reasonable, since the Lewis acid mediated reaction proceeds through an acyclic transition state and therefore the chiral silicon center is located away from the carbon where a new C–C-bond formation takes place. If the reaction proceeds through a rigid six-membered cyclic transition state, high asymmetric induction could be obtained. In this respect, it would be interesting to test asymmetric addition via a chiral pentavalent silicate. There is room to improve the ee of these asymmetric reactions.

Significantly high ee can be accomplished by the chiral (acyloxy)borane-catalyzed allylation of aldehydes.[269a] Reaction of borane THF complex with mono-(2,6-diisopropoxy)benzoyltartaric acid **195** in dry propionitrile at 0 °C affords the catalyst solution BLn*.

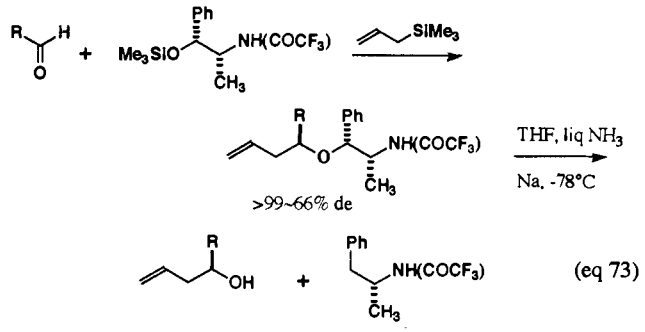


Condensation of aldehydes with allylsilanes is promoted by this catalyst at −78 °C to produce homoallyl alcohols in good to reasonable yields with ee of 55–96%. Simple



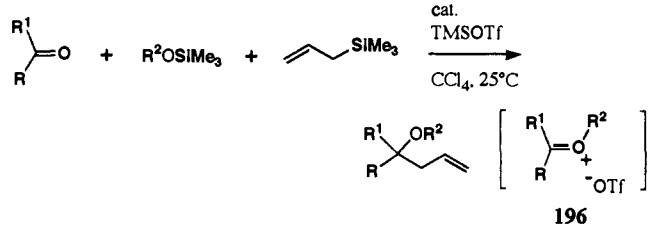
allyltrimethylsilane ($R^1 = R^2 = H$) is not reactive enough to give adducts efficiently, but alkyl substituents on the olefin moiety of allylsilanes increases the reactivity, permitting a lower reaction temperature and improved asymmetric induction. γ-Alkylated allylsilanes produce high syn diastereoselectivities (94–97%) and excellent enantioselectivities (85–96%). Direct and simple preparation of homoallylic alcohols with excellent ee values from aliphatic aldehydes and trimethylsilyl ether derivatives of chiral 1,2-amino alcohols have been developed.[269b] Two equivalents of the aldehydes are stirred at −78 °C with 1 equiv of the TMS ether of (1*R*,2*R*)-*N*-(trifluoroacetyl)norpseudoephedrine in CH_2-

Cl_2 in the presence of 0.1 equiv of TMSOTf, and then the mixture is treated with 2 equiv of allylsilane and 0.1 equiv of TMSOTf at −78 °C (eq 73). The homoallylic ethers are obtained in 49–81% yields.



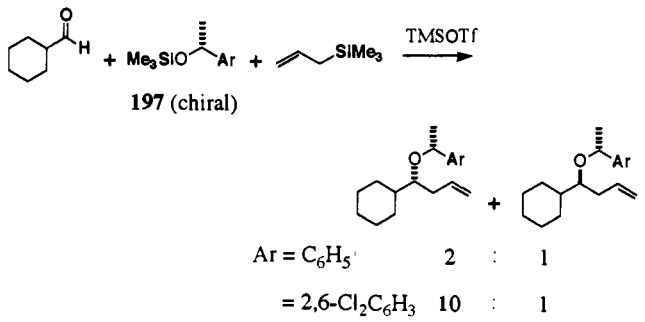
(eq 73)

An efficient and versatile preparation of homoallyl ethers from trimethylsilyl ethers, allyltrimethylsilane, and carbonyl compounds has been accomplished.[270] It is proposed that the three-component condensation involves the in situ generation of the oxonium cation **196**. The diastereoselectivity of this one-step synthesis

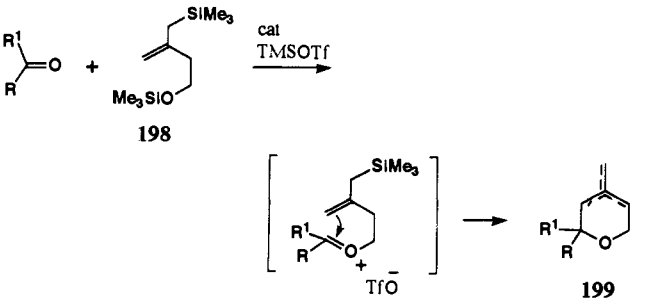


196

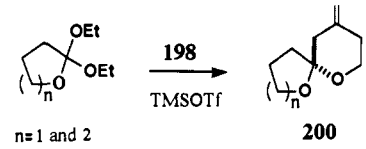
of homoallyl ethers was investigated using the chiral silyl ether **197**. The diastereoisomer ratio depended upon the nature of the aromatic group in **197**. When



the phenyl-substituted silyl ether was used, a 2:1 ratio of the diastereomers was obtained. Replacement of the phenyl group by a 2,6-dichlorophenyl group lead to a substantially increased ratio of 10:1. By employing the intramolecular version **198** of the reaction shown above, oxocenes including spiroethers and spiroketals

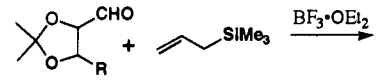


can be prepared in a highly convergent, one-step operation.[271] However, a mixture of regioisomeric olefins **199** are obtained; the exocyclic isomer predominates when the reaction is performed at −15 °C, and only the endo isomers are produced at room temperature. With ortho esters, instead of ketones, the spiroketals **200** are obtained in good yields. Although

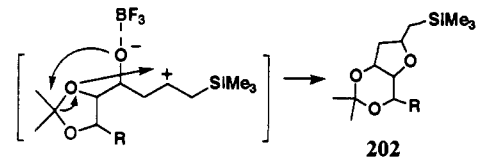


n = 1 and 2 **200**

the procedure gives a mixture of regioisomeric olefins **199**, the addition of a simple trimethylsilyl ether such as $C_6H_{13}OSiMe_3$ or $C_2H_5OSiMe_3$ to the reaction mixture containing the carbonyl compound, **198**, and TMSOTf, dramatically modifies the product ratio, leading to the almost exclusive formation of the exocyclic isomer.[272] The reaction of allylsilanes with aldehydes in the presence of Lewis acids not always affords homoallyl alcohols. The following example is an exceptional case. The reaction of 2,3-isopropylidene derivatives of aldehydoaldose **201** with allylsilane in the presence of BF_3·OEt_2 gives **202**, presumably through the migration of the isopropylidene group to the cationic center.[273a] Fluoride ion promoted reactions of allylsilanes with thioketones affording compounds deriving from a direct thiophilic addition and providing a new entry to a wide range of allyl sulfides.[273b]



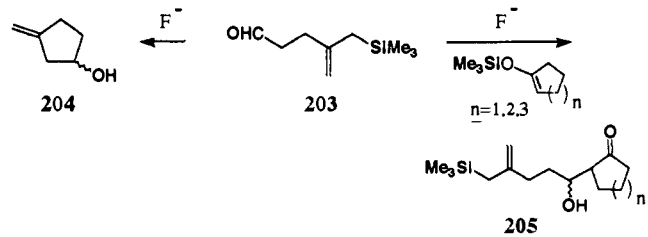
201



202

3. Intramolecular Reactions of Aldehydes and Ketones

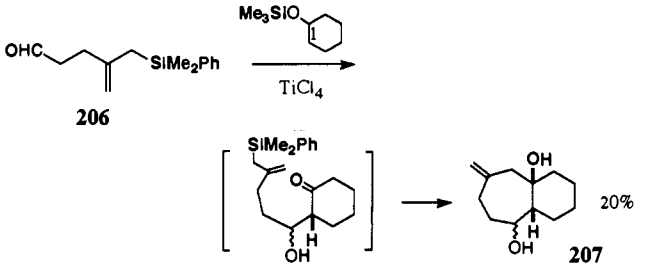
An excellent review of intramolecular reactions of allylsilanes has recently been published.[274] Treating **203** with fluoride results in a high yield of the cyclized product **204**, whereas the reaction gives a different outcome in the presence of a trimethylsilyl enol ether, resulting in no trace of **204** but giving the ketone **205** as a mixture of diastereomers.[275] This shows that the



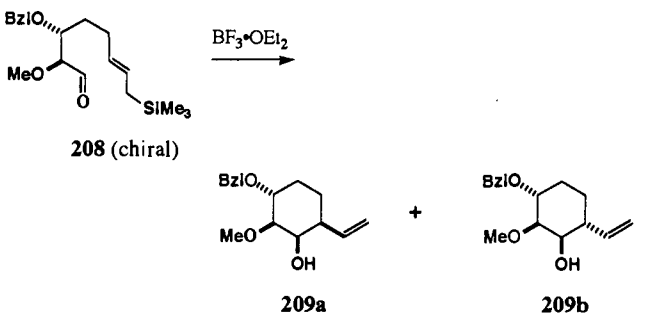
205

intermolecular attack of the enol silane predominates over the kinetically slower (disfavored) intramolecular cyclization. Further cyclization of **205** is not successful under the influence of F^-, instead the desilylated ketone is isolated. However, the aldehyde allylsilane **206** reacts with the enol trimethylsilyl ether in the presence of $TiCl_4$, giving the bicyclic[6.7] system **207**; the inter-

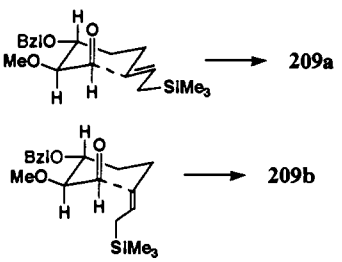
molecular attack by the enol silane takes place, followed by subsequent intramolecular attack upon the initially formed ketone. The BF_3·OEt_2 mediated cyclization of



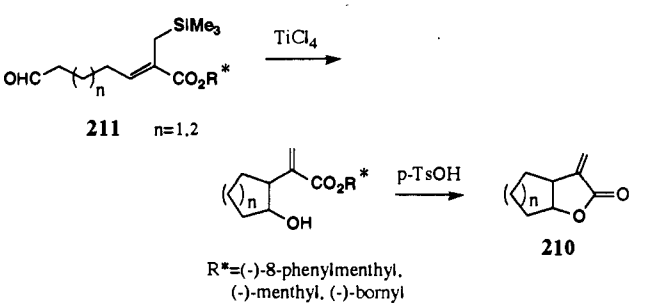
208 gives a mixture of two diastereomers **209a** and **209b** in a ratio of 47:53 in 82% total yield.[276] The stereo-



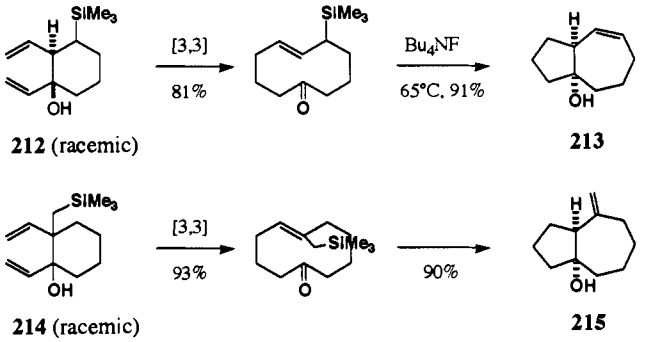
chemical result of the cyclization may be explained by assuming a transition structure with a chair-like conformation where the two alkoxy groups occupy equatorial positions. The carbonyl group must point in the axial direction, since this corresponds to a Cram–Felkin-type transition structure. Thus, the synclinal orientation of the double bond of allylsilane would give **209a**, while the antiperiplanar transition structure would lead to **209b**.



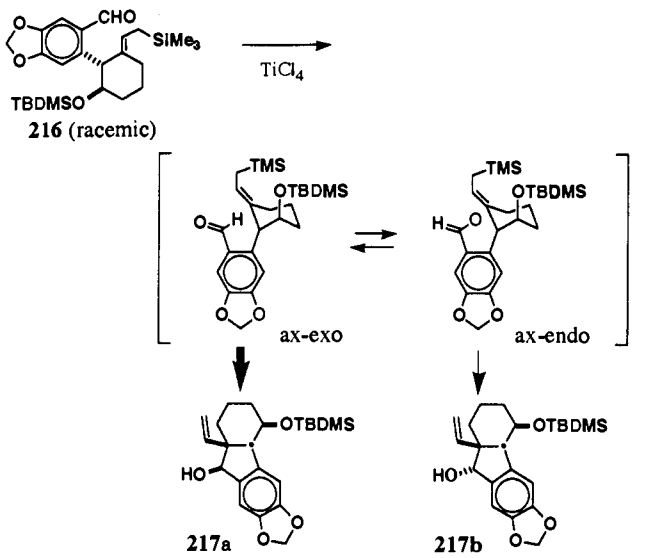
Optically active α-methylene-γ-butyrolactones **210** fused to five- or six-membered carbocyclic ring are synthesized in 62–92% enantiomeric excess using the intramolecular reaction of ω-formylated β-(chiral)-(alkoxycarbonyl)allylsilanes **211**.[277] Intramolecular cyclization of the allylsilanes produced from anionic oxy-



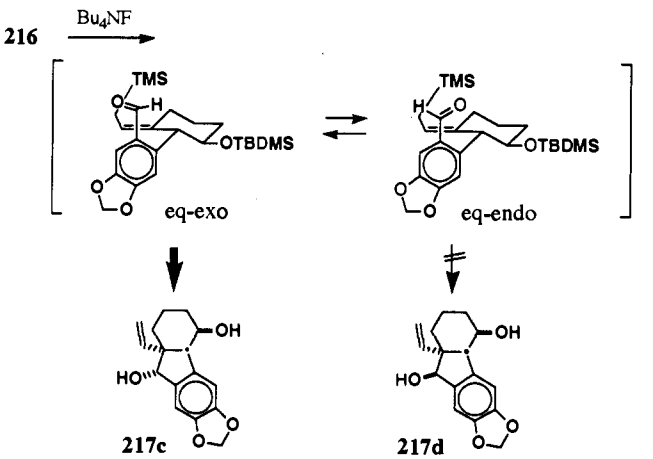
Cope rearrangements of 1,2-divinylcyclohexanols led to hydroazulenols with the cis ring fusion.[278] The reaction of **212** with 5 equiv of KH and 0.4 equiv of I_2 in THF at 60 °C gives cyclodecenone with the trans double bond, which is converted to **213** upon treatment with Bu_4NF at 65 °C. Similarly, **214** is converted to **215**. Treatment of **216** with $TiCl_4$ in CH_2Cl_2 at −78 °C



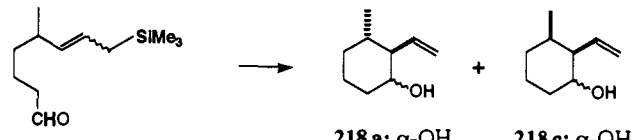
affords a 4:1 mixture of cis-fused alcohols **217a** and **217b** in 70% yield.[279] No trans-fused products are obtained. This diastereoselectivity can be reasonably explained by the transition-state geometries (ax-exo and ax-endo). However, the reaction of **216** with excess



Bu_4NF in THF provides a ca. 10:1 mixture of diols **217c** and **217d** in 86% yield. The selectivity for the F^--induced trans fusion process is between 5–7:1.

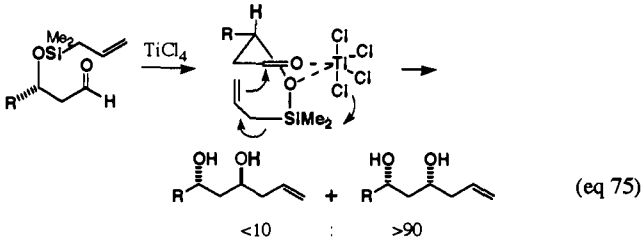


Generally speaking, all annulation reactions which generate small rings (≤7) are expected to form cis ring fusions. Accordingly, the fluoride-induced annulation seems to be a rare case. The cyclization of (*E*)-5-methyl-8-(trimethylsilyl)-6-octenal in the presence of $SnCl_4$ or CF_3CO_2H provides *trans*-hydroxy product **218a** preferentially; **218a/218b** = >5:1 in reactions of CF_3CO_2H and >3:1 in $SnCl_4$ (eq 74). On the other hand the (*Z*)-allylsilane isomer affords *cis*-product **218b** predominantly; **218b/218a** = >100:1 in CF_3CO_2H and >3:1 in $SnCl_4$.[280]



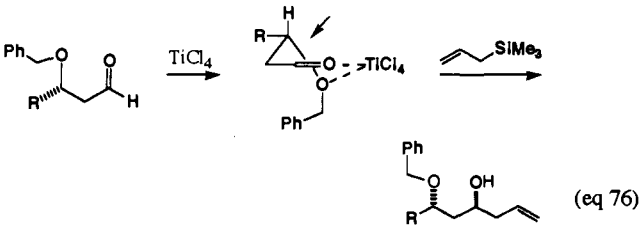
218a; α-OH **218c**; α-OH
b; β-OH **d**; β-OH
(eq 74)

The $TiCl_4$-mediated allylsilane additions to α- and β-alkoxyaldehydes proceed in a chelation-controlled manner to produce excellent diastereoselectivity, whereas activation of such aldehydes by a monodentate Lewis acid such as $BF_3{\cdot}OEt_2$ affords nonchelation-controlled adducts predominantly. The reagent control for stereoselection using chelation or non-chelation procedure can be applied not only to allylsilanes but also to other organometallic compounds. The intramolecular allylsilane additions to chiral siloxy aldehydes in the presence of $TiCl_4$ provide yet another approach. As shown in eq 75, the *syn*-isomer is produced in a diastereoselectivity greater than 90%.[281]



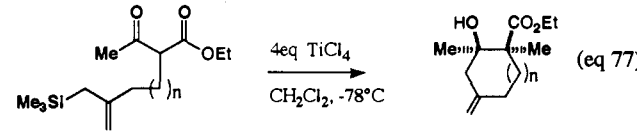
(eq 75)

This selectivity (syn) is opposite to that observed in intermolecular allylsilane additions to the related chelates (anti preference) (eq 76). The switch from



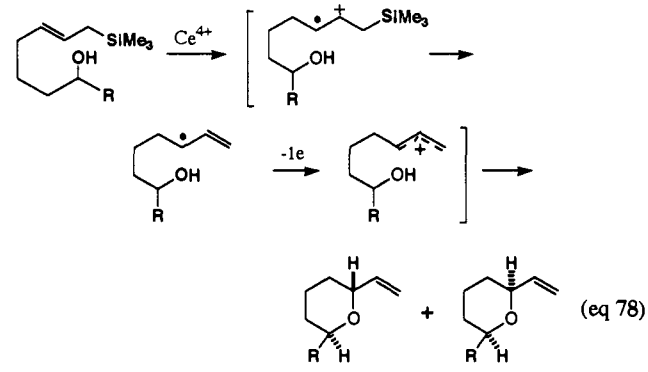
(eq 76)

$TiCl_4$ to $SnCl_4$ in the intramolecular reaction (eq 75) results in the reversal of diastereofacial selectivity and an intermolecular allyl transfer which gives the anti-product.[283] Although the mechanistic picture of the intermolecular $SnCl_4$ induced allylation is less clear, the formation of 2:1 complex (2 equiv of RCHO/1 equiv of $SnCl_4$) seems to provide a possible reason for the anti selectivity in the reaction shown in eq 75. Excellent diastereoselectivity is achieved by the $TiCl_4$-promoted intramolecular additions of allylsilanes to β-dicarbonyl compounds.[264] Cyclizations occur under mild conditions and are highly chemoselective, providing direct routes to highly functionalized five-, six-, and seven-membered carbocycles (eq 77). Allylsilanes containing



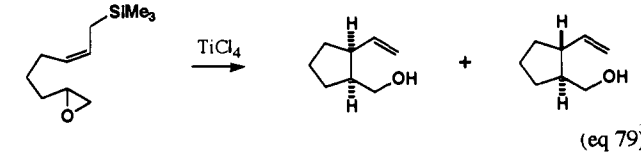
(eq 77)

heteroatom nucleophiles yield cyclic products when treated with $(NH_4)_2Ce(NO_3)_6$ (eq 78).[282] The cyclization



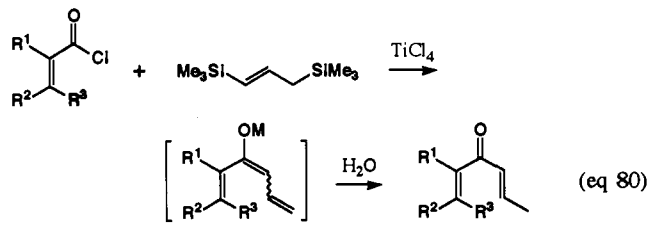
(eq 78)

presumably proceeds through direct oxidation of the double bond of the allylsilane unit rather than formation of an oxy radical intermediate due to the hydrogen abstraction from the hydroxy group. The resulting radical cation is converted to the allyl radical via removal of trimethylsilyl cation. Further oxidation provides the allyl cation which undergoes cyclization to give the tetrahydropyranyl derivatives in ca. 1:1 ratio of the trans- and cis-isomers. Instead of a hydroxy group, the use of an amide group for oxidative cyclization produces the corresponding nitrogen heterocycles. The cyclization of epoxide allylsilane occurs on treatment with titanium tetrachloride in CH_2Cl_2 at low temperature (−95 °C) and produces a mixture of *cis*- and *trans*-cyclopentane derivatives with the cis-isomer predominating (4:1) (eq 79).[285] The intermolecular version of



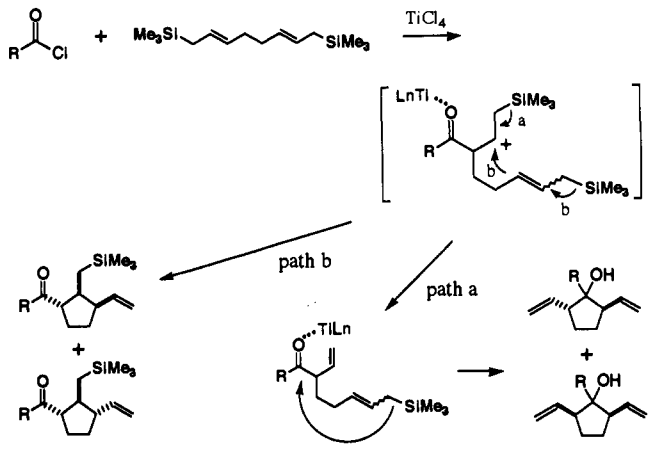
(eq 79)

this type of epoxide–allylsilane reactions has been carried out previously.[286] Lewis acid directed intramolecular additions of allylstannanes to epoxides also provide excellent regiocontrol and diastereoselectivity.[285b] The addition of α,β-ethylenic acyl chlorides to 1,3-bis(trimethylsilyl)propene in the presence of $TiCl_4$ leads to propenyl alkenyl ketones presumably via the titanium or silyl dienolates (eq 80). On the other hand, the addition of acyl chlorides with 1,8-bis(trimethylsilyl)-1,7-octadiene gives 1-alkyl-2,5-divinylcyclopentanols and 1-acyl-2-[(trimethylsilyl)methyl]-3-vinylcyclopentanes (eq 81). The cyclo-



(eq 80)

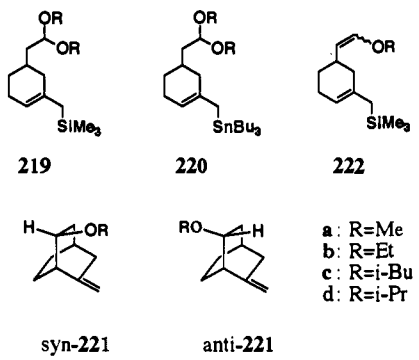
pentanol derivatives, in which the trans-isomer predominates, are formed via path a, whereas the cyclopentane derivatives are produced via path b where the trans–cis isomer is, in general, a major isomer.[287]



(eq 81)

4. Reactions of (O,O)-, (O,S)-, and (N,O)-Acetals

The mechanism and stereochemical outcome of allylsilane–acetal addition reaction have been investigated, but it seems to be difficult to draw clear-cut and firm conclusions. The first series of experiments addresses the Lewis acid dependence of cyclization stereochemistry with **219** and **220**. The wide range of

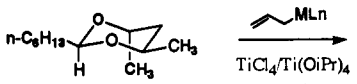


219 220 222

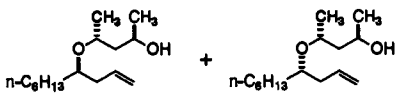
syn-221 anti-221

selectivities from highly syn selective (**221**, in the presence of TMSOTf) to unselective ($TiCl_4$) strongly suggested the involvement of the Lewis acid in the stereochemistry-determining step and argues against a common oxocarbenium ion intermediate.[288] The effect of the acetal structure on the stereochemical course of reaction with **219** and **220** was examined by using TMSOTf as the Lewis acid. The methyl, ethyl, and isobutyl series are generally syn selective, but the isopropyl cases exhibit a slightly anti preference. These observations suggest that these may be a stereochemical manifestation of the changes in mechanism: S_N2 via a complex and S_N1 via an oxocarbenium ion.[289] To test this hypothesis by establishing the stereochemical outcome of cyclizations with the putative oxocarbenium ion, protonation of **222** with TfOH was examined. The stereochemical outcome for the isopropyl cases (**222d** vs **219d**) is similar, suggesting the reaction proceeds via a common intermediate. However, for the methyl and ethyl cases (**222a** vs **219a**, **222b** vs **219b**), a dramatic difference was observed, suggesting the operation of two different mechanism of cyclization. Not only the acetal systems, but also the corresponding aldehydes have been used for mechanistic studies of the intramolecular 1,2-addition process; in these cases, the Lewis acid mediated reactions produce, in general, the *syn*-alcohol (*syn*-**221**, R = H) through the synclinal transition state over the antiperiplanar.[290] Detailed discussions on this aldehyde cases have been presented in recent reviews.[227c,e,291]

The stereoselectivity of chiral dioxane acetals with allylmetals in the presence of Lewis acids depends upon the metal, and it was found that the reaction of allyltributylstannane with steroidal acetals proceeds through a S_N2-like mechanism, whereas that of allyltrimethylsilane proceeds via a S_N1-like mechanism.[289] Similar conclusions were reached in the study of the stereoselective opening of **223** with allylmetals. Here

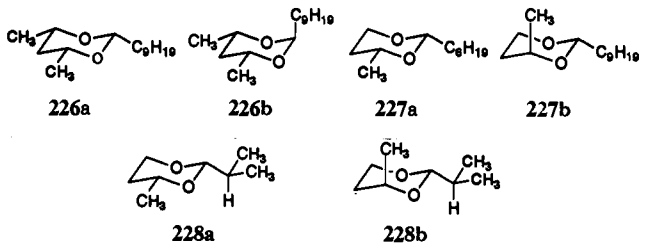


223 (racemic)



224 **225**

also, the stereoselectivity (**224**/**225**) is highly dependent on the nature of the allylmetal reagent: L_nM = Ph_3Si (19:1), Me_3Si (58:1), Ph_3Sn (90:1), Me_3Ge (100:1), n-Bu_3-Sn (>300:1).[292] The $TiCl_4$-promoted reactions of allyltrimethylsilane with **226**–**228** were investigated to clarify the mechanism of the acetal cleavage. Seemingly minor

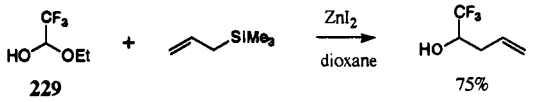


226a **226b** **227a** **227b**

228a **228b**

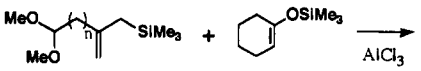
perturbations in the structure of the acetal can substantially change the outcome and mechanism of the reaction. It is difficult to draw firm conclusions regarding the mechanism, but it is clear that an oxocarbenium ion mechanism displays lower selectivity than a direct displacement mechanism (S_N2 like).[293a] More recently, it was demonstrated by the experiments using deuterated chiral acetals that the Lewis acid ($TiCl_n(OiPr)_{4-n}$, n = 4, 3, 2) mediated reaction does not proceed through the direct displacement mechanism, the diastereoselectivity is not due to selective complexation to one of the two acetal oxygens, and the reaction proceeds predominantly by way of an oxocarbenium ion mechanism.[293b]

Although there remain some ambiguity regarding the mechanism, the acetal–allylsilane condensation is synthetically very useful. Trifluoroacetaldehyde ethyl hemiacetal (**229**) reacts with allyltrimethylsilane in the presence of ZnI_2 to afford α-trifluoromethylated allyl alcohol in 75% yield.[294] Related to **203** (aldehyde-

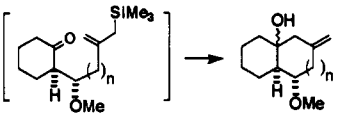


229

allylsilane system), the acetal–allylsilane system **230a** is useful for the synthesis of fused bicyclic compounds. The process involves the chemoselective intermolecular reaction of the acetal function of an allylsilanes **230a** with an enolsilane to form stereoselectively the ketone **231**, which is not isolated, but reacts under the same conditions, to form the annulated product. By using



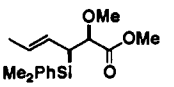
230 a; n=0, 1, 2
b; n=3, 4



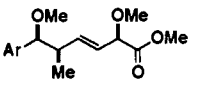
231

this procedure, a one-pot synthesis of fused five-,[295] six-,[296] eight-,[297] and nine-membered[297] rings, and spirocyclic systems[298a] was accomplished. However, the reaction of the next higher homologs **230b** (n = 3, 4) with TMSOTf in the presence of enol silane gave only the products derived from intramolecular cyclization of the allylsilanes. This difference is explained on the basis of the transition-state topology—(allyl-endo)-Exo-Trig ring closure. The reaction of α-bromo-substituted allylsilane with acetal produces the corresponding alkenyl bromide.[298b]

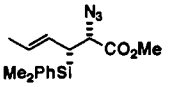
The TMSOTf-mediated reactions of α-methoxy- and α-methyl-β-(dimethylphenylsilyl)-(*E*)-hexenoates (**232** and **182a,b**, respectively) with aryl acetals proceed in a diastereo- and enantioselective manner to produce homoallylic ethers (for example **185** from **182a**) in high yields;[299] **233a** is obtained from **232a**. Three stereocenters and an *E*-double bond are perfectly controlled. The two new stereocenters (5,6-syn) emerged with excellent levels of absolute stereochemical control with ee's reaching 95%. This high asymmetric induction is explained by anti-S_E2' mechanism via an acyclic antiperiplanar transition state as shown in **184**. The TMSOTf-mediated addition of **232** to α-alkoxy and β-alkoxy acetals also results in the highly diastereo- and enantioselective construction of homoallylic ethers with excellent 1,4- and 1,5-asymmetric induction.[300] *syn*- and *anti*-methyl α-azido-β-(dimethylphenylsilyl)-(*E*)-hex-4-enoates (2*R*,3*R*)-**234a** and (2*S*,3*R*)-**234b** undergo highly diastereo- and enantioselective addition reactions with oxonium ions, generated from acetals $RCH(OR^1)_2$ and TMSOTf, to give the α-azido-β,γ-unsaturated esters **235** with well-defined 1,4- and 1,5-stereochemical relationships, and a subsequent stereospecific allylic azide isomerization produces 1,3-azido ethers **236**, synthetic equivalents of γ-hydroxy-α-amino acids.[301]



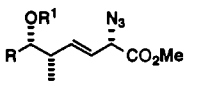
232a: (2S, 3S)
b: (2R, 3R)



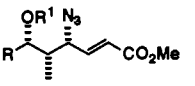
233a: (2S, 5S, 6R)
b: (2R, 5R, 6S)



234a: (2R, 3R)
b: (2S, 3R)

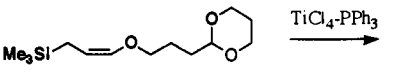


235a
b

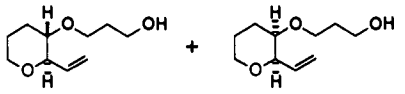


236a
b

The intramolecular cyclization of the acetal–(γ-oxoallyl)silane **237** produces β-alkoxycyclic ethers **238**. The use of $TiCl_4/PPh_3$ as the Lewis acid produces a 98:2 mixture of **238a** and **238b** in 95% combined yield.[302]

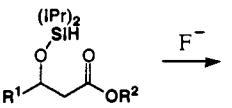


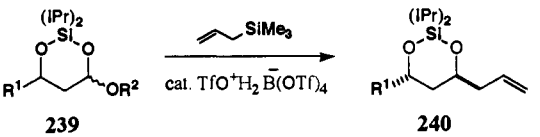
237



238a **238b**

The use of the Lewis acids such as $TiCl_4$ and $TiCl_3(OiPr)$ results in lower yields and diastereoselectivities. The $TfOH_2^+B(OTf)_4^-$ catalyzed reaction of allylsilane with the acetal **239** gives the trans product **240** with very high diastereoselectivity.[303] The sense of the



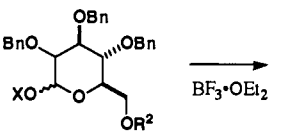


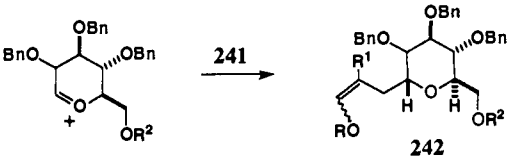
239 **240**

stereoselectivity is consistent with axial attack by the allylsilane on oxonium ion. The α-oxo-substituted allylsilanes **241** are prepared.[304] It is thought that the

241a: R=OAc, R^1=H
b: R=OCO_2Et, R^1=H
c: R=OAc, R^1=CH_3

inductive effect of an oxygen atom may reduce the nucleophilic reactivity of allylsilanes. However, the allylsilanes undergo a stereoelectronically controlled axial addition to pyranoside oxonium ions to give **242**.[304]

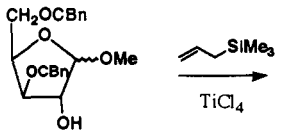




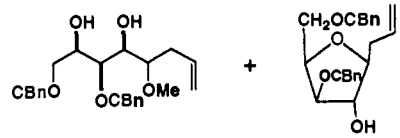
242

2-Azido *C*-glycosyl sugars can be prepared by the BF_3·OEt_2-mediated reaction of allylsilanes to the nitrate glycosides of 2-azido sugars.[305]

As noted above, most of the reactions of glycosides have promoted the substitution of the exocyclic C–O bond, thereby leading to cyclic products (*C*-glycosides). By contrast, the formation of chain-extended acyclic products, that is the regiocontrolled substitution of the endocyclic C–O bond in glycosides by a C–C bond, has been rarely observed. The C-allylation of glycosides and of the corresponding hemiacetals mediated by a bidentate Lewis acid, $TiCl_4$, provides access to open-chain products with a high degree of regio- and stereoselectivity (eq 82).[306] The reaction of partially

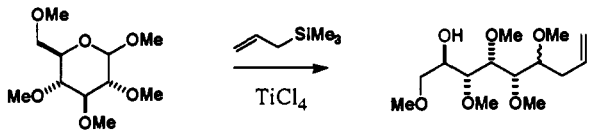


CBn=p-chlorobenzyl



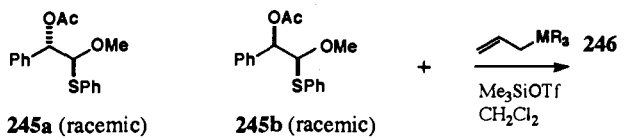
52% 45% (eq 82)

protected xylofuranoside with allylsilane in the presence of $TiCl_4$ gives the open-chain alditol derivative as the major product (eq 82). Although per-O-alkylated glucopyranosides are known to undergo C-allylation with exocyclic C–O-bond cleavage only on reaction with allyltrimethylsilane and Me_3SiOTf, the $TiCl_4$-mediated allylation of **243** gives open-chain products **244** exclusively.

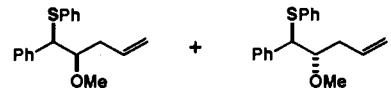


243 **244**

The mechanism of allylmetal–thioacetal reactions has been investigated by using 2-acetoxy-2-phenylacetaldehyde thioacetals in the presence of TMSOTf.[307] Upon treatment with the monothioacetal **245**, allyltrimethylsilane **246a** and allyltrimethylgermane **246b** provide allylation products **247** in ca. 80:20 syn (**247a**)/anti (**247b**) ratio irrespective of the stereochemistry of **245**.

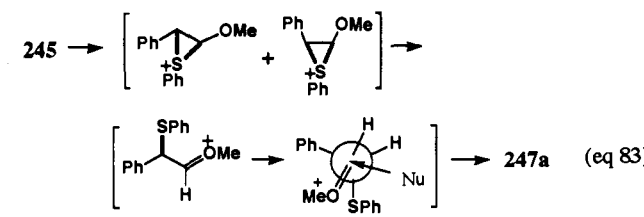


245a (racemic) **245b** (racemic)

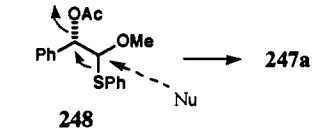


247a, syn **247b**, anti

With trimethyl- and tributylallyltin (**246c** and **246d**), the syn-product **247a** is obtained from **245a** and the anti-product **247b** is afforded from **245b**. These results



indicate that reactions of the less nucleophilic silicon and germanium compounds proceed through a S_N1 mechanism while the allyltins react through a S_N2-type mechanism.[289] Apparently, the reactions with the silyl and germyl reagents produce an oxonium intermediate (S_N1 mechanism), which undergoes a nucleophilic attack through a charge attraction induced model leading to predominantly **247a** (eq 83). Direct attack of the allyltins on **245** in a concerted manner (as depicted in **248**) is proposed as a S_N2-type mechanism. Reaction of the dithioacetal **249** furnishes predominantly the syn product **250** with both allylsilane and -stannanes, indicative of an S_N2-type mechanism. These results

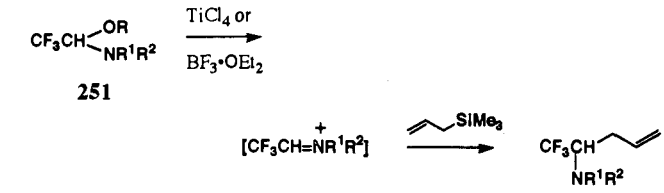


248

249 **250**

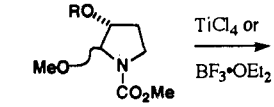
reflect the inferior ability of a sulfenyl group to stabilize an α-carbocation, relative to a methoxy group. The reaction of anodically prepared β-trifluoromethylated *O,S*-acetals with allyltrimethylsilane produces the corresponding allylated sulfides in good yield.[308a]

The reaction of *N,O*-acetals with allylsilanes in the presence of Lewis acids produces C-allylated amine derivatives via an iminium ion-intermediate. This procedure is applied to the α-trifluoromethylated *N,O*-acetals **251**.[308b] The allylation of **252** in the presence

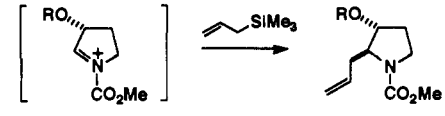


251

of Lewis acids gives **253** in high yields.[309a] It was established from low-temperature NMR experiments that *N*-acyliminium ion intermediates are produced



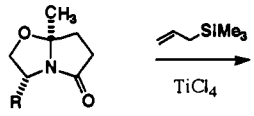
252a: R=Ac
b: R=TBDMS



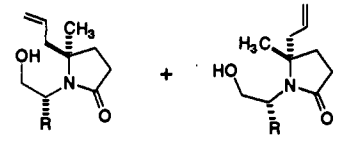
253a: trans, **253b**: cis

from α-methoxylated carbamates.[310] The trans isomer **253a** is obtained predominantly from **252a**, while the cis isomer **253b** is formed preferentially from **252b**.

The stereochemistry of the allylation reaction of **254** is highly dependent upon the substituent R.[311] With Me and Ph substituents, the retention product **255a** is produced predominantly, whereas the inversion product **255b** is afforded preferentially with sterically bulky i-Pr and t-Bu groups. When R is a large group, entry by

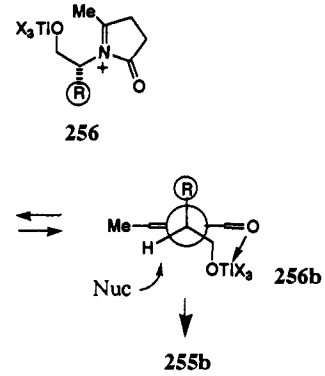


254 (chiral)

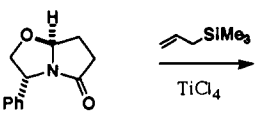


R	**255a** (retention)		**255b** (inversion)
Me	8	:	1
Ph	5	:	1
i-Pr	1	:	2
t-Bu	1	:	11

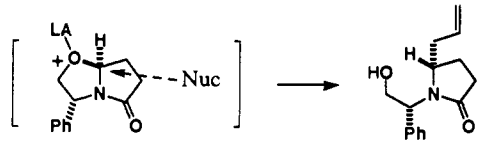
silane occurs from the face opposite this large group (**256b**) to generate the product of inversion **255b**. When R is the smaller group, the alkoxytitanium assumes the role of the large group and occupies the antiperiplanar position (**256a**), thus directing the entry from the β-face to provide **255a**. In contrast to the disubstituted lactam



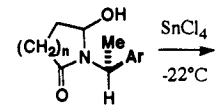
254, the allylation of the angular hydrogen lactam **257** gives the product with inversion at the angular position (S_N2-like product).



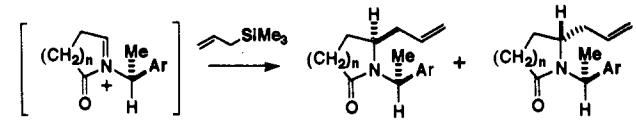
257



(*S*)-(−)-α-Phenylethylamine (Ar = C_6H_5), (*S*)-(−)-1-(2-Cl-C_6H_4), (*S*)-(−)-1-(2,6-dichlorophenyl)ethylamine (Ar = 2,6-$Cl_2C_6H_3$), and (*S*)-(−)-1-(2,3,4,5,6-pentachlorophenyl)ethylamine (Ar = Cl_5C_6) have been incorporated into acyliminium ions of structural type **258** and **259**. The chlorinated derivatives of **258** provide **260** predominantly, whereas the nonchlorinated five-membered iminium ion of **258** affords **261** preferentially.



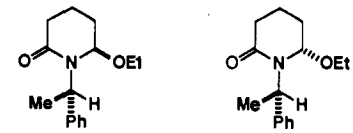
(chiral)



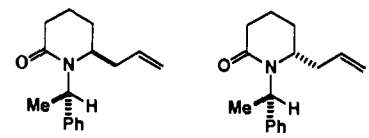
258: n=1
259: n=2

260 **261**

The similar trend is observed also in the case of the six-membered iminium ions **259**.[312] This interesting reversal of diastereoselection is rationalized by application of molecular orbital theory and selection of locally preferred substrate conformational preferences. This allylation procedure was applied to the enantioselective total synthesis of indolizine alkaloids.[313] Chiral ethoxy lactams **262a** and **262b** were respectively treated with allyltrimethylsilane in the presence of $TiCl_4$ in CH_2Cl_2 at temperatures ranging from −30 °C to room temperature to give 69–93% yield of a mixture of two allylated products **263a** and **263b** in identical ratios (83:17), suggesting that the allylation proceeds through a common intermediate, an acyl iminium ion.[314] The Me_3-



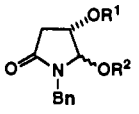
262a (chiral) **262b** (chiral)



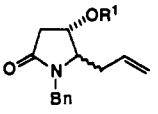
263a **263b**

SiOTf-mediated reactions of **264a** and **264b** with allyltrimethylsilane provide amide **265** with moderate trans selectivity, the stereoselectivity of which can be explained by the known ability of acetoxy groups to bridge to adjacent cationic centers, thus favoring trans addition.[315] This interpretation is also supported by the fact that no selectivity is observed upon the Me_3-SiOTf-mediated allylation to benzylether **264d**. Prevalent formation of the cis isomer of **265** is possible by using **264c** and $MgBr_2$ as a Lewis acid. The best cis selectivity (4:1) is achieved by the $MgBr_2$-mediated reaction of **264c** with allyltributyltin in toluene.[315] These procedures were applied to the chiral synthesis of statine analogs. Treatment of **266** with methallyltrimethylsilane in the presence of BF_3·OEt_2 yielded an 11:1 mixture of **267** and its cis-isomer.[316a] The use of $TiCl_4$ as Lewis acid provided a 9:1 trans/cis ratio, and lower selectivity was obtained for less sterically demanding allyltrimethylsilane which provided a 7:3 trans/cis ratio in the presence of BF_3·OEt_2. Several 2-(phenylsulfonyl)piperidines and -pyrrolidines **268** react with allyltrimethylsilane in the presence of Lewis acids such as

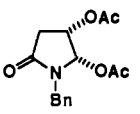
$AlCl_3$ and $MgBr_2$ to give the corresponding allylated products **269** in good to high yields.[317] Not only allylsilane but also allylmagnesium bromide in the presence of $ZnCl_2$ produces **269** in high yield. The BF_3·OEt_2-mediated reaction of allylsilanes with *N*-(alkoxycarbonyl)-α-methoxyglycinamides leads to the corresponding α,δ-unsaturated α-amino carboxamides.[316b] The S_N1 character of this process was proven in the case of α-methoxyglycine methyl ester.



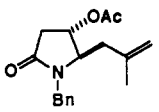
264 a: R^1=Ac, R^2=Et
b: R^1=Ac, R^2=Ac
c: R^1=Bn, R^2=Ac
d: R^1=Bn, R^2=Et



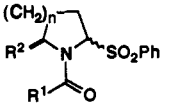
265; R^1=Ac



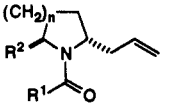
266 (chiral)



267 (chiral)

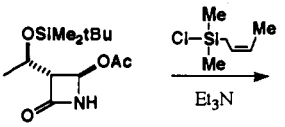


268

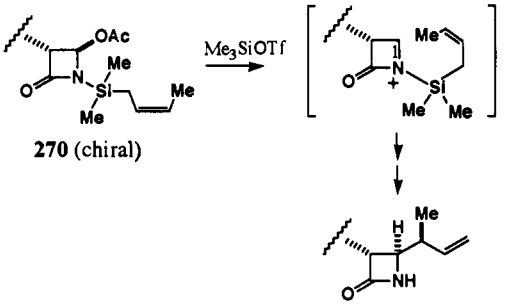


269

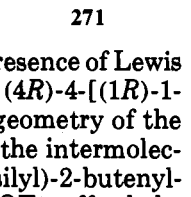
The intramolecular allylation of the α-acetoxyazetidinone **270** proved very useful for the stereoselective synthesis of (4*R*)-4-[(1*S*)-1-methylallyl]-2-azetidinone **271**. (For the intermolecular reactions, see ref 456.) The commercially available **272** was converted to **270** in quantitative yield, which was treated with 0.4 equiv of TMSOTf followed by the N–Si bond cleavage with MeOH/Et_3N gives **271** in 84% yield.[318] Reaction of



272

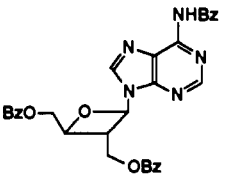


270 (chiral)

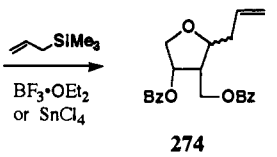


271

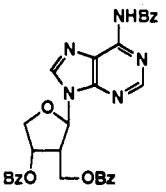
272 with crotyltrimethylsilane in the presence of Lewis acids gave a 1:1 mixture of **271** and (4*R*)-4-[(1*R*)-1-methylallyl]-isomer regardless of the geometry of the double bond of crotylsilane. Further, the intermolecular reaction of **272** with 2-(trimethylsilyl)-2-butenyltrimethylsilane in the presence of BF_3·OEt_2 afforded a 3:1 mixture of the α-Me and β-Me stereoisomers of 4-[1-methylallyl] derivative.[319] The oxetanosyl *N*-glycoside could be converted to furanosyl *C*-allylglycosides with allyltrimethylsilane. When **273** was treated with allyltrimethylsilane in the presence of BF_3·OEt_2 or $SnCl_4$, a 1:5–1:6 mixture of α- and β-**274** is obtained in moderate yields.[320] In the absence of allyltrimethylsilane, **275** was isolated as the sole product. The allylation of **275** under the similar conditions used for **273** gave **274**. Generally the C–O bond cleavage of *N*,*O*-acetals is observed in the Lewis acid mediated allylation, but this example clearly indicates that the C–N-bond cleavage



273

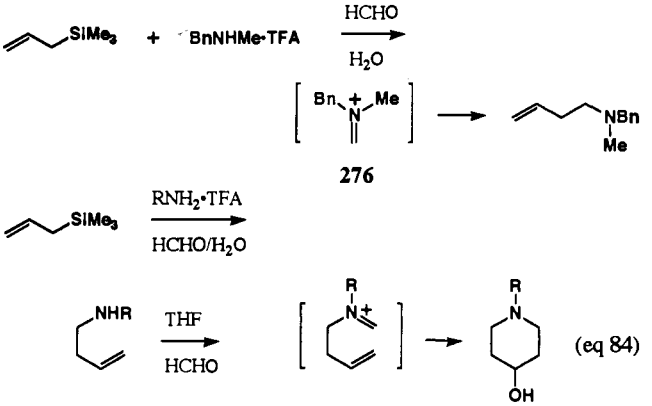


274



275

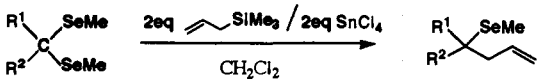
may take place in certain cases. Most of the above examples of iminium ions contain an electron-withdrawing group attached to the nitrogen atom of the iminium intermediates; acyliminium ions are generated in situ in the presence of Lewis acids. This is reasonable, since such acyliminium ions are relatively stabilized by the electron-withdrawing substituent. *N*,*N*-Dialkyl-substituted iminium ion, generated from ethyl 3-ethoxy-2,2-difluoro-3-(dimethylamino)propionate, was detected by NMR spectroscopic experiments at −78 °C.[321] The reaction of allyltrimethylsilane with *N*-benzyl-*N*-methylammonium trifluoroacetate and formaldehyde afforded allylated tertiary amine, via dialkyliminium salt **276**, in 50% yield.[322] When primary amines/TFA salts were used, the corresponding secondary homoallylamine products were difficult to isolate because *N*-homoallyliminium salts, formed by further condensation with formaldehyde, cyclized to produce 4-hydroxypiperidines (eq 84).



276

(eq 84)

Lewis acid activation of bis(methylseleno)alkanes causes them to react with allylsilane to produce the corresponding homoallyl selenides in moderate to good yields, depending on the structure of the starting selenoacetals (eq 85).[323]

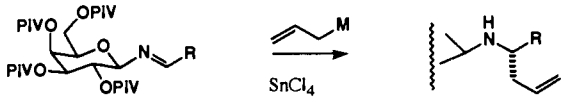


(eq 85)

5. Reactions of Imines

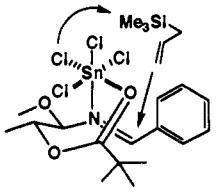
The reaction of imines with allylsilanes is sluggish even in the presence of Lewis acids, compared to the

reaction of aldehydes. As mentioned above, the reaction of iminium salts (particularly acyliminium ions) proceeds smoothly in contrast to that of uncharged imines. Aromatic *N*-galactosyl imines **277** (R = Ar) react with 1 equiv of allyltrimethylsilane in THF in the presence of 2.2 equiv of $SnCl_4$ to give **278** in moderate to good yields with high diastereoselectivity.[324] Aliphatic imines



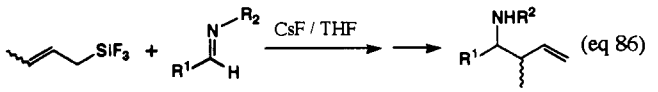
277 (chiral) **278**

(R = alkyl) do not react with allyltrimethylsilane under the same conditions, but more the nucleophilic allyltributyltin reacts with those imines in allowable yields. The high diastereoselectivity observed in the allylsilane reaction is explained by the transition state shown in **279**. Two coordination sites of the tin(IV) chloride are



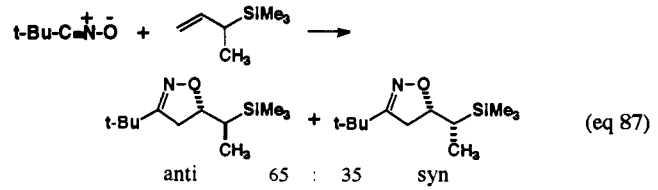
279

occupied by the imine nitrogen and the carbonyl oxygen of the (C-2) pivaloyloxy group, respectively. The S_N2'-type attack of the allylic compound from the back side of the imine is initiated by the interaction of one chlorine with the silyl group, giving **278** with high diastereoselectivity. It seems that pentacoordinate silicates react with imines more readily than the corresponding tetracoordinated analogs. The reaction of crotyltrifluorosilanes with aldimines in the presence of cesium fluoride affords the corresponding homoallylamines in good to high yields (except for a hindered imine such as n-PrCH=N-i-Pr) in a regiospecific manner, but the diastereoselectivity is not high (eq 86).[325] The cycload-

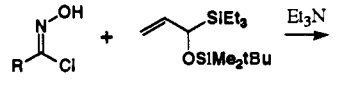


(eq 86)

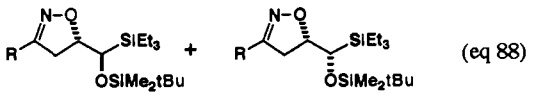
dition reactions of nitride oxides with α-chiral butenylsilanes provide Δ^2-isoxazolines with low diastereoselectivity (eq 87).[326] However, (α-siloxyallyl)silane



anti 65 : 35 syn (eq 87)



R=t-Bu, Ph

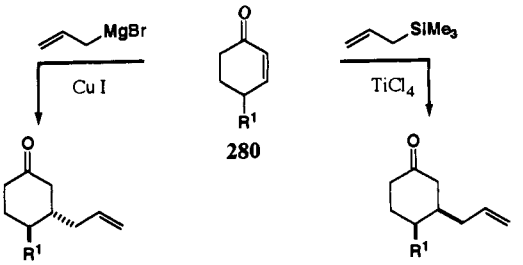


92~94 : 6~8 (eq 88)

produces high anti selectivity (eq 88).[327] 2,2-Dimethylpropane- and -benzonitrile oxide are generated in situ from the corresponding oxime chloride and Et_3N. The use of [α-[(acyloxy)- or -(alkoxy)carbonyl]oxy]allyl]-silanes results in low diastereoselectivity. The high anti selectivity in reactions of (α-siloxyallyl)silane is best understood in terms of the Houk steric model, which places the (large) trialkylsilyl group anti, the (medium) alkyl or oxy group inside, and the (small) hydrogen outside.

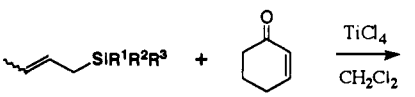
6. Michael Addition

In 1977, Hosomi and Sakurai reported the intermolecular Michael addition of allylic silanes to α,β-unsaturated ketones in the presence of titanium tetrachloride.[328] Since then, a number of inter- and intramolecular Michael additions of allylsilanes has been reported and are reviewed in recent excellent articles. We consider only the most recent advances in this field (since 1989). In a study of the stereochemistry of this process, the allylsilanes and the copper-catalyzed allylmagnesium reactions are compared.[329] The allylsilane addition to 4-substituted cyclohexenone **280** provides preferentially the *cis*-allylated cyclohexanone, whereas the copper-catalyzed allylation affords predominantly the trans-isomer. However, both add to

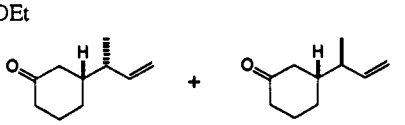


280

the 5-substituted cyclohexenone give the *trans*-3-allyl-5-substituted product predominantly irrespective of the reagent types. It is proposed that the major products formed in the allylsilane additions are those favored for stereoelectronic reasons, whereas the copper-catalyzed addition affords less of the stereoelectronically controlled product, probably as a result of steric hindrance to approach of the more bulky cluster to the enone coordinated by Lewis acids. The $TiCl_4$-mediated additions of (*E*)- and (*Z*)-crotylsilanes **281** to cyclohexenone provide a mixture of the syn- and anti-isomers **282** and **283**,[330] the anti-isomer **283** is formed from (*E*)-



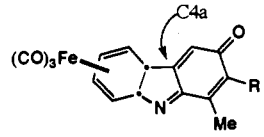
281 **a**; $R^1=R^2=R^3$=Me
b; R^1=Me, $R^2=R^3$=Ph
c; $R^1=R^2$=Me, R^3=OEt



syn **282** anti **283**

281 predominantly (11:1 from **281a**, 15.6:1 from **281b**, and 6:1 from **281c**), while the syn-isomer **282** is produced from (*Z*)-**281** with lower diastereoselectivites (3:1 from

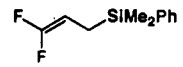
281a, 2.7:1 from **281b** and 4:1 from **281c**). These selectivities have been explained using an eight-membered synclinal transition state (see the related geometries **121** and **122**). The $TiCl_4$-mediated allylation of the iron complexed **284** allows the complete chemo-, regio-, and stereoselective introduction of an allyl group at C4a of the carbazole nucleus (with up-stereochemistry).[331]



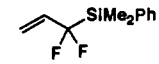
284

Previously it was reported that the allylation of aldehydes with allylsilanes in the presence of catalytic amounts of Bu_4NF would proceed through the intermediacy of an allyl anion.[332] However it was later proposed that there was no allylic anion but a nucleophilic intermediate of hypervalent silicon resulting from the addition of F^- to the silicon atom.[333a] It is reported that in the presence of fluoride anions, β-substituted allylsilanes **285** behave as nucleophiles and not as anionic 1,3-dipoles.[334] The addition of **285** to aldehydes in the presence of CsF in DMF gives the corresponding homoallyl alcohols, and the CsF-mediated conjugate addition to Michael acceptors provides the allylation products in good yields. If an allyl anion intermediate is formed as suggested previously, **285a** should add to *trans*-stilbene in the presence of 1 equiv of CsF to give triphenylcyclopentane as was shown in the reaction of α-methylstyrene anion with *trans*-stilbene. However, this is not the case. On the other hand, the following observation suggests an intermediate of a free allyl anion. (γ,γ- and α,α-difluoroallyl)dimethylphenylsilanes (**285d** and **285e**) react with benzaldehyde to afford 2,2-difluoro-1-phenyl-3-buten-1-ol under TASF catalysis ($(Et_2N)_3S^+Me_3SiF_2^-$) at room temperature in DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone) and an equilibrium between **285d** and **285e** is not observed under the reaction conditions. Accord-

285a: R=Ph
b: R=$SiMe_3$
c: R=CO_2Me



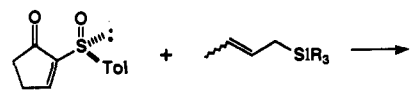
285d



285e

ingly, a metal-free *gem*-difluoroallyl anion as the common intermediate, although *gem*-difluoroallyllithium **19** exists only at low temperature of −95 °C,[37] is involved in this TASF-catalyzed (6 mol %) reaction.[333b]

The Lewis acid mediated addition of crotylsilanes to 2-cyclopentenone derivatives (**286** and **289**) having chiral auxiliaries at 2-position was investigated.[335] As observed previously in the case of simple cycloalkenones (see the additions of **281**), the anti diastereoselectivity is obtained from the reaction of **286** with (*E*)-crotylsilanes and the syn selectivity from (*Z*)-crotylsilanes, but the latter selectivity is much higher in comparison with the previous cases; from (*E*)-crotylsilanes the anti/syn ratio (**287a** + **288a**/**287b** + **288b**) ranges from 5:1 to 12:1, whereas the best syn selectivity from *Z*-isomers is 14:1. The diastereofacial selectivity arising from the enantioselection at the chiral auxiliary is excellent in



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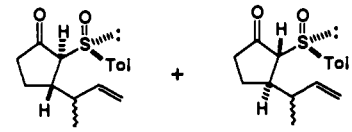
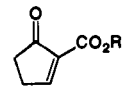


287a (anti)
287b (syn)

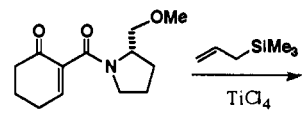
288a (anti)
288b (syn)

the reactions with (*E*)- and (*Z*)-crotylsilanes, and the 3*S*-enantiomers (**287a** and **287b**) are obtained as high as 99% de. Although the diastereofacial selectivities (leading to 3*S*-isomers) observed in the reaction of **289a** are moderate for both (*E*)- and (*Z*)-crotylsilanes, those (leading to 3*R*-isomers) in reactions of **289b** are perfect; 3*R*/3*S* ratio is found to be 100:0. In contrast to the

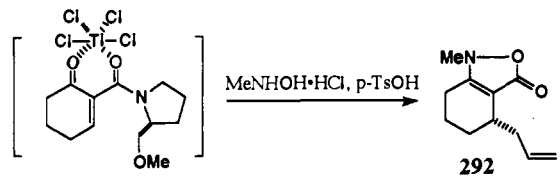


289 a: R=(+)-menthyl
b: R=(-)-8-phenylmenthyl

previous explanation,[330] the direct Si–O interaction is not counted although the silyl group is thought to be located in vicinity of the carbonyl group. Conjugate addition of allylsilane to chiral 2-amidocyclohexenone **290** takes place in excellent yield with high diastereoselectivity.[336] The addition presumably proceeds through a six-membered chelated complex **291** to give **292** with 94–96% ee.

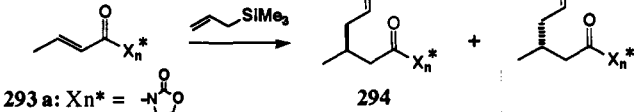


290



291 **292**

The 1,4-addition reaction of allyltrimethylsilane to α,β-unsaturated *N*-acyloxazolidinones or *N*-enoyl sultams in the presence of Lewis acids proceeds in good chemical yield with high diastereomeric excess.[337] The $TiCl_4$-mediated addition to **293a** at −78 °C provides a



293 a: Xn* =

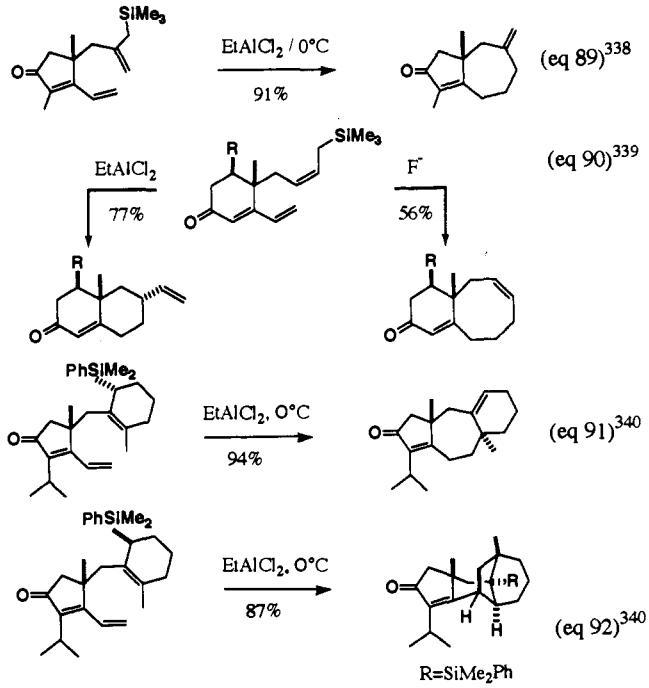
294

b: Xn* = 

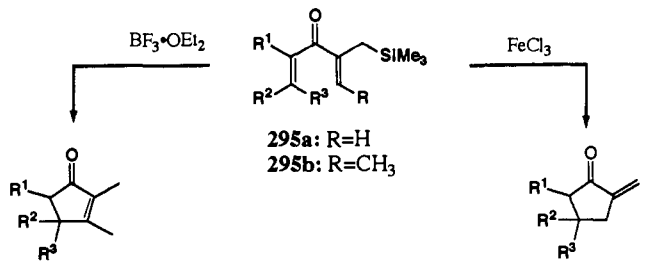
c: Xn* = 

89:11 mixture of **294** and its diastereomer in 88% yield. The diastereoselectivity decreases in the reactions of **293b** (70:30) and **293c** (78:22).

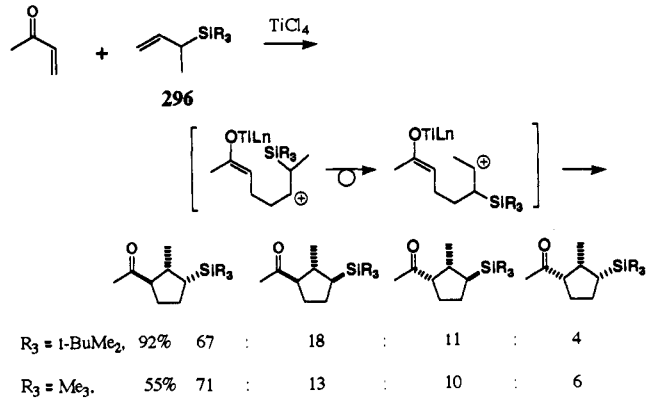
The intramolecular version of the Lewis acid of F-mediated conjugate addition of allylsilanes to α,β-unsaturated carbonyl systems has been studied extensively primarily for the synthesis of carbocyclic compounds including natural products. Excellent reviews have appeared recently,[274] and they cover most of papers published before 1988. Some representative examples are shown in eqs 89–92,[338-340] and they demonstrate that the intramolecular allylsilane additions are extremely powerful means for synthesizing seven- and eight-membered rings.



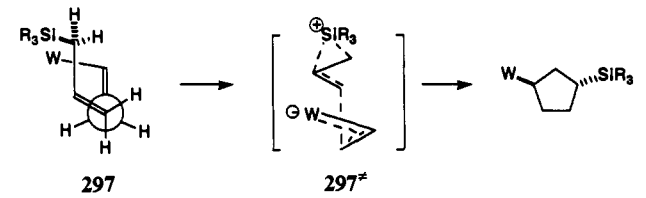
The reaction of **295a** with anhydrous $FeCl_3$ in dichloromethane gives the corresponding α-methylenecyclopentanones.[341] A completely different regioselectivity on the double-bond formation is found in the reaction of **295b** with $BF_3{\cdot}OEt_2$.[342] Allylsilanes can serve



as three-carbon components in a [3 + 2] annulation strategy for the synthesis of five-membered carbocycles and heterocycles.[343] Butenylsilanes **296** can function as three carbon units in the [3 + 2] annulation; in the case of less bulky SiR_3 group such as Me_3Si small amounts (~15%) of the ordinary conjugate adduct is also obtained. The major product has the electron-withdrawing carbonyl group and trialkylsilyl group substituted trans about the new five-membered ring. This stereoselectivity presumably arises from a preference for a synclinal transition state (**297**$^{\neq}$). As



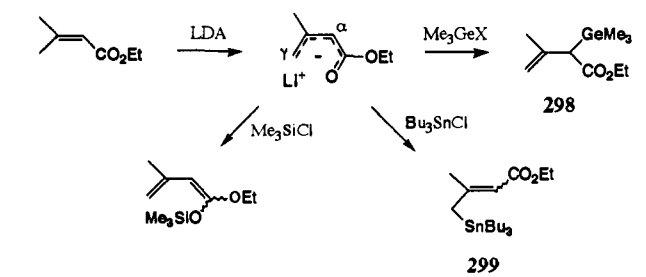
mentioned above, allylsilanes bearing large R_3Si group are essential for the desired [3 + 2] annulation. For example, even the reaction of methyl vinyl ketone with allyltriisopropylsilane produces the desired cyclopentane derivatives in 77% yield along with small amounts of the ordinary conjugate adduct. Aryldiazonium



tetrafluoroborates react with allylsilanes to yield allylazo compounds.[344a] A zwitterionic equivalent of trimethylenemethane is generated by formation of a palladium(0) complex from β-acetoxymethyl-substituted allyltrimethylsilane. This undergoes a facile reaction with a range of electron deficient alkenes to give [3 + 2] annulation products.[344b]

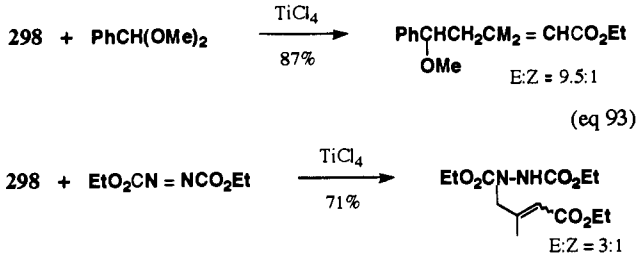
B. Allylgermanium Reagents

There are very few synthetic reactions via allylgermanium compounds compared to those via allylsilyl reagents. Trapping of the lithium dienolate, derived from 3-methyl-2-butenoate, with Me_3GeX (X = Br or Cl) gives the α-germylated derivative **298**, which reacts with various electrophiles at the γ-position of the allylic germanium compound.[345] On the other hand, trapping with Bu_3SnCl provides the γ-stannylated derivative **299** and trapping with Me_3SiCl affords the O-silylated compound as expected from the reactivity of Me_3SiCl.



Alkylation of the lithium dienolate produces the α-alkylated product due to higher electron density at the α-position than that at the γ-position. Accordingly, the regioselective formation of **298** is reasonable and the formation of **299** is presumably due to the fact that the γ-regioisomer is thermodynamically more stable than the α-isomer; in general the C–Sn bond is weaker

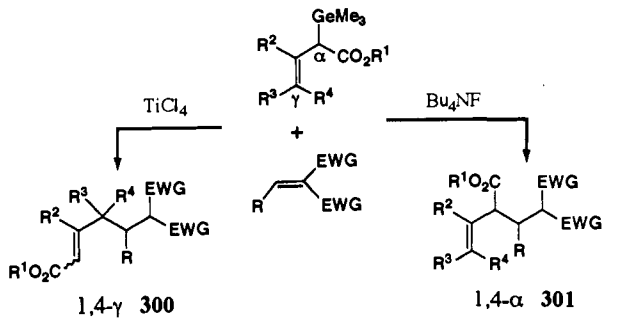
than the C–Ge bond. In fact, heating **298** gives the corresponding γ-trimethylgermyl derivative. The Lewis acid mediated reactions of **298** with electrophiles such as acetals, aldehydes, and reactive halides provide the coupling products at the γ-position of **298**, in turn, at the γ-position of the lithium enolate (for example eq 93). This is synthetically important since the C–C-



(eq 93)

(eq 94)

bond formation of the lithium dienolate always takes place at the α-position. The reaction of **298** with diethyl azodicarboxylate provides the γ-adduct in a regio- and stereoselective manner (eq 94).[346] Not only the lithium dienolate derived from 3-methyl-2-butenoate but also several other alkenoates including cyclic systems afford the corresponding α-germylated compounds regioselectively.[347] The conjugate addition of α-germylated β,γ-unsaturated esters to Michael acceptors having two electron-withdrawing groups provides the 1,4-γ adduct **300** in the presence of $TiCl_4$, while it affords the 1,4-α adduct **301** in the presence of Bu_4NF (eq 95).[348] The



(eq 95)

regiocontrol of the reactions between the ambident nucleophiles and ambident electrophiles, such as allylic halides and α,β-unsaturated carbonyl compounds, has not been studied widely. In the latter case we encounter the potential difficulties associated with controlling the 4-fold regioselection in comparison with the 2-fold regioselection in the former case. For example, the reaction of dienolates with enones could give four possible adducts. The use of the Ge-masked dienolates for controlling the regioselectivity in the coupling between ambident nucleophiles and electrophiles provides a new approach as shown in eq 95. The $TiCl_4$/PPh_3-mediated intramolecular cyclization of γ-oxo-substituted allylic silane **237** and germane having an acetal group at the terminus of the carbon chain produces the six-membered trans-isomer **238a** with very high diastereoselectivity in high yield.[349] The use of $TiCl_4$ as a Lewis acid in reactions of **237** and the germane derivative results in the formation of **238** in very low yields with lower diastereoselectivities. However, the reactions via the combined Lewis acids system, PPh_3·$TiCl_4$, provide **238a** in 98:2 selectivity with **237** and in 87:13 diastereoselectivity with the trimethylgermane derivative.

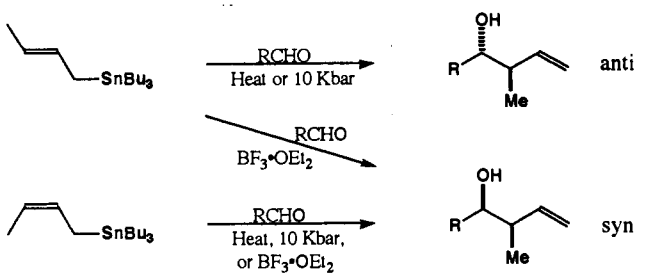
C. Allylic Stannane Reagents

1. Reactions of Aldehydes and Ketones

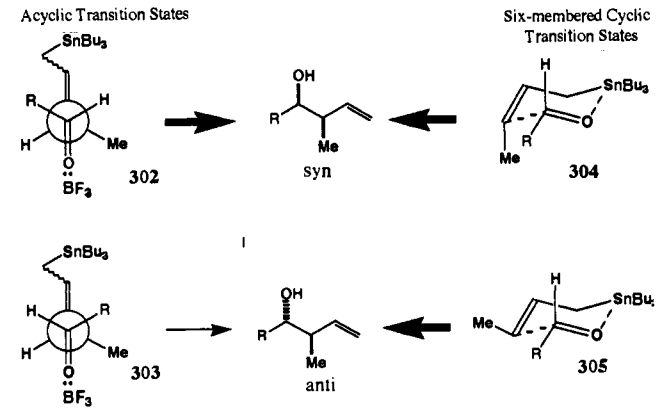
The stereochemical outcomes of allylic tin–aldehyde condensation reactions are summarized in Scheme IX. The Lewis acid mediated reaction of allylic tins and silanes (cf. the silicate case eq 66) produces *syn*-homoallyl alcohols predominantly regardless of the geometry of the but-2-enyl unit.[2c] (In contrast to the reactions of silicates, the aldehyde condensation of seemingly pentavalent allylic stannates was reported quite recently; see Scheme XI.) In marked contrast, however, the stereochemistry in thermal reactions of allylic tin derivatives generally depends upon the geometry of the but-2-enyl unit[350,351] as observed in ordinary allylic organometallic reactions; the *E*-isomer produces *anti*-alcohols while the *Z*-isomer affords *syn*-alcohols. The reaction of allylic trialkyltins with aldehydes takes place at room temperature under neutral conditions by using a high-pressure technique (10 kbar in CH_2Cl_2 or Et_2O), and the stereochemical outcome is same as that of the thermal reaction.[352]

The syn diastereoselectivity of the BF_3-mediated reaction can be explained by the acyclic transition state shown in Scheme X. Boron trifluoride coordinates to the carbonyl oxygen, preventing the coordination of the metal to the oxygen atom. Consequently, among several possible transition-state geometries, the conformation **302** leading to the syn isomer must be more favorable for steric reasons than **303** which produces the anti isomer. It is easily understood that the

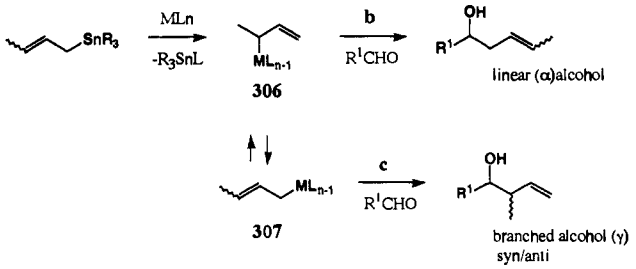
Scheme IX. Stereochemical Outcome of Allylic Tin–Aldehyde Condensation



Scheme X. Acyclic and Cyclic Transition-State Geometries



Scheme XI



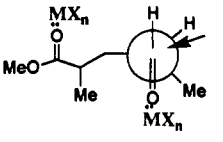
geometry of the 2-butenyl unit does not exert an important role in stabilizing the transition states. On the other hand, the thermal or high-pressure reaction proceeds through the six-membered cyclic transition states **304** and **305**. It is widely accepted that the *Z*-isomer produces the *syn*-homoallyl alcohol, while the *E*-isomer affords the *anti*-alcohol in reactions via the cyclic transition states.[3]

The early studies of the mechanism and the stereochemistry are summarized in the reviews of Yamamoto,[3a,c,d] Hoffmann,[3b] and Roush.[4] Since then a number of new findings have appeared, and we emphasize the most recent progresses on the stereochemistry, mechanism, and application to natural product synthesis. The Lewis acid mediated reaction may proceed via addition of a Lewis acid–aldehyde complex as shown in Scheme X or via transmetalation to yield a reactive allylmetal halide which then reacts with the aldehyde. The reaction pathway depends on the Lewis acid, the aldehyde, the stoichiometry of reactants, the order of addition and the reaction conditions; these will determine the regio- (linear or branched) and stereochemistry (syn or anti) of the product (Scheme XI). If transmetalation is involved, the product may consist of a mixture of regioisomers due to allylic rearrangement of the allylmetal halide intermediate. The following is a representative example for the allyltin reaction which involves such a transmetalation step. The reaction of crotyltributyltin with aldehydes such as benzaldehyde, propanal, butanal, pentanal, and decanal in the presence of $AlCl_3$/i-PrOH produces the linear adduct either predominantly or exclusively, while the reaction in the presence of ordinary Lewis acids, such as $TiCl_4$, $SnCl_4$, $AlCl_3$, and BF_3·OEt_2, affords the branched product exclusively.[353] On the other hand, less reactive aldehydes (or ketones) such as crotonaldehyde, isobutyraldehyde, and acetophenone give the branched alcohol exclusively even in the case of $AlCl_3$/i-PrOH. Transmetalation from crotyltin with the acid of $AlCl_3$/i-PrOH, presumably $AlCl_2$(Oi-Pr), would proceed via an S_E2' process to produce the α-methallyl aluminum intermediate **306** (M = Al), which reacts with aldehydes to give the α-adduct (path b). At higher temperatures and/or over a prolonged period of time, further rearrangement to crotylaluminum reagent **307** (M = Al) takes place, which reacts with aldehydes to give the γ-adduct (path c). Needless to say, crotyltin itself reacts with aldehydes in the presence of $AlCl_3$/i-PrOH to give the γ-adduct (path a; the Lewis acid mediated process of Scheme IX). The reaction system would consist of the following pathways. $AlCl_3$ and other Lewis acids induce the aldehyde condensation via path a. The relatively soft and weak Lewis acid, $AlCl_3$/i-PrOH, causes transmetalation, and the reactive aldehydes react immediately via path b. Relatively unreactive aldehydes and ketones permit further rearrangement to crotylaluminum compound, resulting in the reaction via path c. Accordingly, the sequence of addition is important; the addition of aldehydes to Lewis acids prior to the addition of crotyltin makes path a favorable.

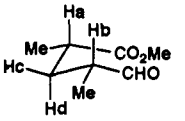
The effect of addition modes upon product distribution was investigated in the reaction of (*E*)- and (*Z*)-crotyltributyltins with benzaldehyde and aliphatic aldehydes in the presence of Bu_2SnCl_2, BF_3·OEt_2, or $TiCl_4$.[354] The detailed experimental results indicate that the allylic trialkyltin–aldehyde condensation primarily proceeds through the RCHO·Lewis acid complex as shown in the acyclic mechanism **302** of Scheme X. However, in some cases, the reaction between the allylic tin and Lewis acid itself takes place, and the resulting new allylic species may participate in the condensation reaction (like the allylic aluminum species in Scheme XI). The balance between the former and latter mechanism depends upon the mode of mixing, Lewis acid, and reactivity of aldehydes. In conclusion, most of (γ-alkylallyl)trialkyltins in the presence of Lewis acids produce syn adducts via an acyclic transition state if the addition of the three components of reactions is carried out in the following manner (*normal addition*): (i) RCHO, (ii) Lewis acid, and the RCHO·Lewis acid complexation is accomplished at this stage, and (iii) allyltins.[357]

Reactions of achiral allyltins with achiral aldehydes and ketones are summarized in Table VI. The BF_3·OEt_2-mediated reaction of pyruvates provides the anti-adduct predominantly in the case of a small ester group such as methyl, whereas it gives the syn-adduct preferentially with a sterically bulky ester group such as 2,6-dimethylphenyl (entries 2 and 3).[356] This difference can be explained reasonably on the basis of acyclic transition-state geometries.[123] The BF_3·OEt_2-mediated reaction of glyoxylate esters affords the syn-product predominantly as expected (entry 1),[122] and the syn selectivity is decreased from 90:10 (with i-Pr ester) to 75:25 (in the case of Me ester). For additions of crotyltributyltin to simple aldehydes mediated by BF_3·OEt_2, syn selectivity is increased considerably by simply using 2 equiv of stannane (entry 4);[357] syn/anti ratio is 25:1 as shown in entry 4, whereas it decreases to 9:1 in the use of 1 equiv of allylic tin. By using 2 equiv of mixtures of (*E*)- and (*Z*)-crotyltin, it has been shown that the *E*-isomer reacts somewhat faster than the *Z*-isomer and also gives higher syn selectivity, although a slower, but still competing, *Z*/*E* isomerization complicates precise analysis of relative rates and selectivities. Using normal addition [(i) RCHO, (ii) Lewis acid, (iii) crotyltin], very good syn selectivity (93:7) is also obtained by the use of $TiCl_4$, instead of BF_3·OEt_2, in entry 4. On the other hand, dropwise addition of crotyltin to a solution of $TiCl_4$ in CH_2Cl_2 at −78 °C, stirring at that temperature for 8–10 min, and dropwise addition of aldehyde affords the anti adduct with excellent selectivity (21:1). Clearly, the *inverse addition* produces crotyltitanium intermediate via transmetalation from tin to titanium [see Scheme XI and **307** (M = Ti)], which reacts with aldehyde through a six-membered cyclic transition state (**305**). By proper choice of Lewis acid and protecting group, the Lewis acid mediated addition of allyltributyltin to the α-hy-

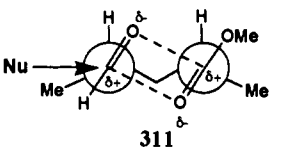
droxyaldehyde derivatives can be controlled to give excellent stereoselectivity for the formation of either syn- or anti-products (entries 5 and 6); the syn adduct can be obtained with 95:5 selectivity using the *tert*-butyldimethylsiloxy substrate (sterically demanding protective group) with 2 equiv of BF_3·OEt_2 (nonchelation product) while the anti-adduct is obtained with >250:1 stereoselectivity using the benzyloxy substrate (sterically less bulky group) with $TiCl_4$ or $MgBr_2$ (chelation-controlled product).[359] The use of THF as solvent in the $MgBr_2$-mediated reaction results in stereochemical reversal, and the "chelation-controlled" product becomes the minor component of an 80:20 mixture. The inverse addition of $SnCl_4$ to allyltributyltin provides excellent diastereofacil selectivity (60:1) favoring a chelation product (anti-adduct) (entry 7) in comparison with the normal addition of $SnCl_4$ (which affords a selectivity of 9:1).[360] The actual organotin species in this instance is allyltrichlorotin, which is formed very rapidly by redistribution between allyltributyltin and $SnCl_4$.[354,361] The BF_3·OEt_2-mediated reaction of crotyltin with the *tert*-butyldimethylsiloxy aldehyde provides very high syn–syn selectivity (entry 8); the syn–syn corresponds to nonchelation-controlled Cram (or Felkin–Anh) selectivity and the anti–syn corresponds to chelation-controlled Cram selectivity. The use of $TiCl_4$, instead of BF_3·OEt_2, results in lower syn–syn selectivity (67:33). The use of $MgBr_2$ provides very high preference for "chelation control" over "Felkin–Anh or Cram control" (entries 9 and 10);[362] both syn–syn and syn–anti adducts correspond the chelation-controlled products, and the anti selectivity for the bond construction is presumably due to reaction via a cyclic transition state. Unusual anti diastereoselectivity is obtained predominantly in the reactions of β-substituted crotylsilane or stannane with 2-(benzyloxy)propanal under chelation conditions (entries 11 and 12;[363] again, both the syn–anti and syn–syn adducts correspond to chelation-controlled products and the anti selectivity is a reflection of either the synclinal acyclic transition state (over the usual antiperiplanar one) or the usual 6-membered chair transition state which may be involved after transmetalation of the tin reagent (or silicon analog) to the corresponding magnesium reagent (or tin reagent in entry 12). Cobalt(II) chloride can promote the regioreversed addition of crotyltributyltin to a variety of aldehydes in good yields (entry 13, see Scheme XI). Irradiation of benzil in acetonitrile in the presence of (*E*)- and (*Z*)-but-2-enyl-, -pent-2-enyl-, and -hex-2-enyltributyltins affords the corresponding (*E*)- and (*Z*)-homoallylic alcohols, respectively, with complete retention of the original double-bond configuration in good yields (entries 14 and 15).[365] Butyltin trichloride mediated reaction of (*Z*)-crotyltin with aldehydes provides the corresponding *Z*-linear homoallyl alcohols in good yields with high stereoselectivity (entries 16 and 17)[366] (see also ref 354 for the use of Bu_2SnCl_2). The Lewis acids, CH_3SiCl_3 and $(CH_3O)_2SiCH_3Cl$, promote the addition of aldehydes to allyltins to yield the homoallyl silyl ethers in high yields (entry 18).[370] These reactions do not proceed via an initial transmetalation, although $BuSnCl_3$ (or Bu_2SnCl_2) induces the transmetalation step (entries 16 and 17). The addition of CH_3SnCl_3 to crotylstannane in CD_2Cl_2 at −78 °C indicates initial γ-attack of the Lewis acid to produce the corresponding α-methallyl derivative **306** as shown in Scheme XI.[371] Addition of CH_3SnCl_3 to allyltributyltin ($CDCl_3$, room temperature) followed by benzaldehyde and water hydrolysis yields the expected homoallyl alcohol quantitatively.[371] α-Methyl-(*E*)-crotyltins react stereoselectively on heating with aldehydes to form *anti*-(*Z*)-adduct in high yields with high diastereoselectivity (entry 19),[367] whereas in the presence of BF_3·OEt_2 the major products are the corresponding *syn*-*E*-products (entry 20).[367] The former reaction proceeds through a six-membered cyclic transition state in which the α-methyl group occupies an axial position of the six-membered chair form, giving the (*Z*)-olefin stereoselectively. The BF_3·OEt_2-mediated reaction of the *meso*-dimethylglutaric hemialdehyde with pent-3-en-2yltributyltin gives the anti–syn adduct (anti-Felkin–Anh mode for the 1,2-asymmetric induction and syn manner for the C–C-bond formation) predominantly (entry 21), while the reaction of the (±)-dimethylglutaric hemialdehyde produces the syn–syn isomer (Felkin–Anh mode) preferentially (entry 24).[368] The inverse addition, addition of aldehyde to a solution prepared from the allyltin and $TiCl_4$, provides the anti–anti-isomer predominantly (entry 22), whereas the normal addition using $TiCl_4$ again affords the anti–syn-isomer preferentially (entry 23).[368] The inverse addition to the (±)-isomer using $TiCl_4$ produces high anti selectivity for the C–C-bond-forming process, but resulted in low Felkin–Anh/anti-Felkin–Anh selectivity (entry 25). The dramatic stereochemical difference exhibited between the *meso*- and (±)-dimethylglutaric hemialdehyde is explained as follows. The fact that the Felkin–Anh syn selectivity in the reaction of the (±)-isomer (entry 24) does not depend upon the amount of BF_3·OEt_2 suggests a nonchelation transition-state model **308**, which is an ordinary model for nucleophilic addition to chiral aldehydes. The anti-Felkin–Anh selectivity in the reactions of the *meso*-isomer is due to an intrinsic conformational characteristic of this particular acyclic molecule.[369] The *meso*-isomer adopts a rigid conformation **309** in solution without any assistance of chelating reagents, while in the (±)-isomer a rapid equilibrium between **310a** and **310b** exists as an



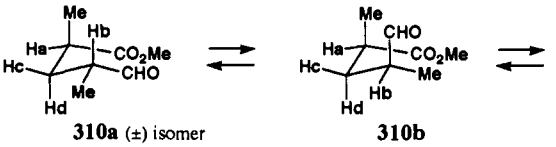
308



309 meso isomer



311



310a (±) isomer **310b**

ordinary acyclic molecule.[369] The nucleophilic attack to the aldehyde carbon of **309** presumably takes place at a stable conformation **311**, giving the anti-Felkin–Anh product. In fact, not only the BF_3·OEt_2-mediated

Table VI. Reactions of Achiral Allyltins with Achiral Aldehydes and Ketones

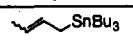
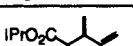
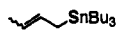
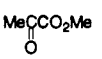
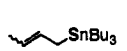
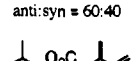
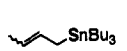
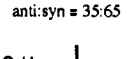
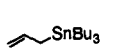
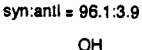
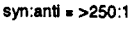
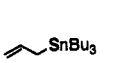
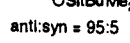
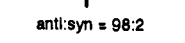
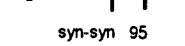
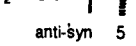
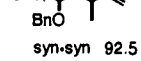
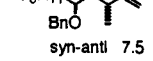
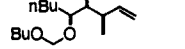
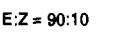
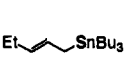
entry	allyltin	aldehyde	conditions	product	yield, %	ref(s)
1		$HCOCO_2iPr$	$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 syn:anti = 90:10	80	122
2			$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 anti:syn = 60:40	84	356, 123
3			$EtAlCl_2$, CH_2Cl_2, −78 °C	 anti:syn = 35:65	84	123, 356
4	 Z:E = 43:57		$BF_3{\cdot}OEt_2$, CH_2Cl_2, 2 equiv of crotyltin, −78 °C	 syn:anti = 96.1:3.9	94	357
5			$MgBr_2$, CH_2Cl_2, −78 °C	 syn:anti = >250:1	85	358
6			$BF_3{\cdot}OEt_2$ (2 equiv), CH_2Cl_2, −78 °C	 anti:syn = 95:5	83	358
7			$SnCl_4$ (inverse addn)	 anti:syn = 98:2	88	360
8			$BF_3{\cdot}OEt_2$ (2 equiv)	 syn-syn 95  anti-syn 5	92	360
9			$MgBr_2$	 syn-syn 92.5  syn-anti 7.5	85	363
10			$MgBr_2$	 syn-syn:syn-anti=90.5:9.5  syn-anti syn-syn	85	362
11	E:Z = 90:10		$MgBr_2$, CH_2Cl_2, −78 °C	76 : 24	85	363
12			$SnCl_4$, CH_2Cl_2	93 : 7	85	363
13		PhCHO	$Co^{II}Cl_2$, CH_3CN, rt, 12 h	linear only	54	364
14	 E:Z = 95:5		$h\nu$, CH_3CN, 20 °C, 5 h	linear:branch=77:23 E:Z = 92:8	94	365
15	E:Z = 7:93		$h\nu$, CH_3CN, −30 °C, 5 h	linear:branch=63:37 E:Z = 9:91	81	365

Table VI. (Continued)

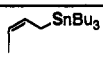
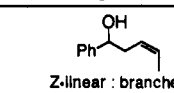
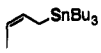
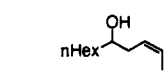
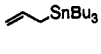
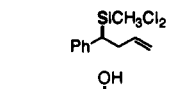
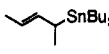
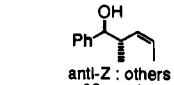
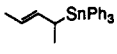
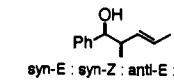
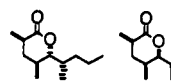
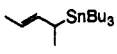
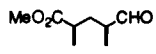
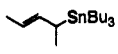
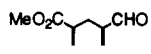
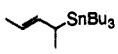
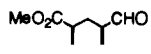
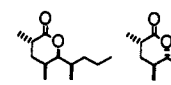
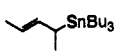
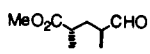
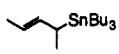
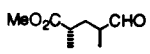
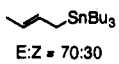
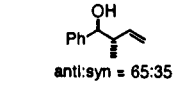
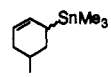
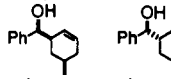
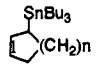
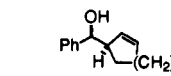
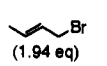
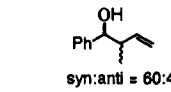
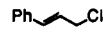
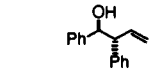
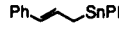
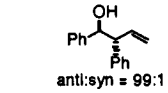
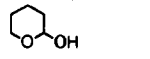
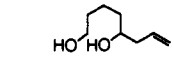
entry	allyltin	aldehyde	conditions	product	yield, %	ref(s)
16		PhCHO	$BuSnCl_3$, CH_2Cl_2, −78 °C	 Z-linear : branched 96 : 4	96	366
17		n-HexCHO	$BuSnCl_3$, CH_2Cl_2, −78 °C	 Z-linear : branched 95 : 5	94	366
18		PhCHO	CH_3SiCl_3, CH_2Cl_2, rt, 22 h		~100	370
19		PhCHO	150 °C, neat, 18 h	 anti-Z : others >99 : 1	72	367
20		PhCHO	$BF_3{\cdot}OEt_2$, −78 °C, CH_2Cl_2, 4 h	 syn-E : syn-Z : anti-E : anti-Z 73 : 15 : 6 : 6  anti-syn : syn-syn : anti-anti : syn-anti	62	367
21			(1) $BF_3{\cdot}OEt_2$; (2) H_2/Pd-C	63 : 10 : 7 : -	80	368,369
22			(1) 2 equiv of $TiCl_4$ (inverse addn); (2) H_2/Pd-C	12 : - : 88 : -		368,369
23			(1) 1 equiv of $TiCl_4$; (2) H_2/Pd-C	89 : - : 11 : .  syn-syn : anti-syn : anti-anti : syn-anti		368,369
24			(1) 1 equiv of $TiCl_4$; (2) H_2, Pd-C	86 : 7 : - : 7	70	368
25			(1) 2 equiv of $TiCl_4$; (2) H_2, Pd-C	5 : . : 53 : 42	70	368
26	 E:Z = 70:30	PhCHO	(1) 10 kbar, Et_2O, 3 days; (2) H_2O	 anti:syn = 65:35	41	372
27	 cis:trans 67:33	PhCHO	(1) 9 kbar, neat, 30 °C; (2) H_2O	 cis-syn : cis-anti : trans-syn : trans-anti 64 : 4 : 30 : 4	85	373
28		PhCHO	$BuSnCl_3$, CH_2Cl_2, rt, 0.5 h	 syn:anti = ~100:0	75	376
29	 (1.94 eq)	PhCHO (1.42 eq)	Sn (0.81 equiv), Al (0.85 equiv), Et_2O (2 mL) H_2O (1 mL)	 syn:anti = 60:40	87	377
30		PhCHO	Sn-Al, ether/H_2O, (HBr)	 anti:syn = 100: -	72	378
31		PhCHO	$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 anti:syn = 99:1	76	379
32			Sn/THF-H_2O (1:4), rt,))), 30–60 min		79	380

Table VI. (Continued)

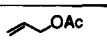
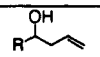
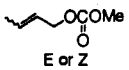
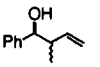
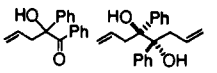
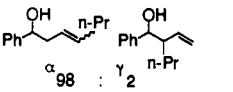
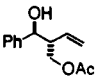
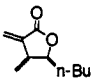
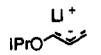
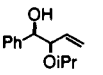
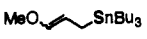
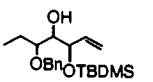
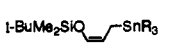
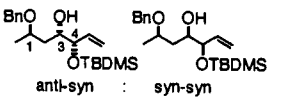
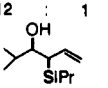
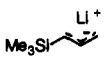
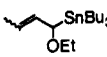
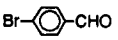
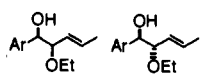
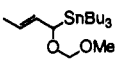
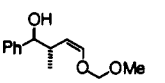
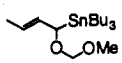
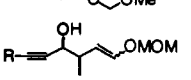
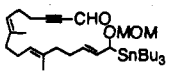
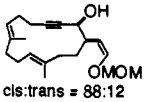
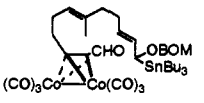
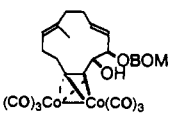
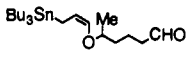
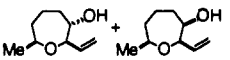
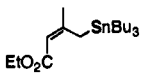
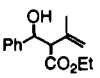
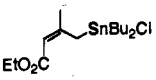
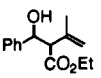
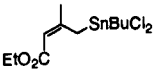
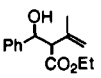
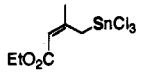
entry	allyltin	aldehyde	conditions	product	yield, %	ref(s)
33		RCHO R=Ph, n-C_5H_{11}, PhCH=CH	cat. $PdCl_2(PhCN)_2$, $SnCl_2$, DMI*, 25–60 °C		52~82	381
34	 E or Z	PhCHO	cat. $PdCl_2(PhCN)_2$, $SnCl_2$, DMI, 25 °C	 from E carbonate syn:anti=33:67 from Z carbonate syn:anti=48:52	80 42	382
35			cat. $PdCl_2(PhCN)_2$, $SnCl_2$, DMI, 50 °C	 22% 61% (anti 100%)	83	384
36		PhCHO	cat. $PdCl_2(PhCN)_2$, $SnCl_2$, Et_2O, 10–15 °C Ultrasound	 α 98 : γ 2 (E/Z=67/33) (syn/anti=70/30)	57	385
37		PhCHO	cat. $PdCl_2(PhCN)_2$, $SnCl_2$, DMI, 25 °C	 anti:syn = 69:31	56	386
38		n-BuCHO	cat. $PdCl_2(PhCN)_2$, $SnCl_2$, DMI/H_2O, 80 °C	 syn:anti = 96:4	40	387
39		PhCHO	$Bu_3SnCl/BF_3{\cdot}OEt_2$, −78 °C, THF	 syn 100%	89	211
40	 (E) or (Z)	PhCHO	$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 syn:anti = 14:1 from (E), syn:anti = 10:1 from (Z),	87 86	388a
41			$MgBr_2{\cdot}OEt_2$	 syn-syn ~100%	67	389
42			$MgBr_2{\cdot}OEt_2$	 anti-syn : syn-syn R=Bu 4 : 1 R=Ph 12 : 1	75 72	359
43			$Bu_3SnCl/BF_3{\cdot}OEt_2$, −78 °C, THF	 syn 100%	89	211
44		$n\text{-}C_9H_{19}CHO$	$Bu_3SnCl/BF_3{\cdot}OEt_2$, −78 °C, THF	 Z olefin 100%	85	211,214
45	 E:Z = 80:20		$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C → 0 °C	 syn-E:anti-E = 93:7	95	391,392
46		PhCHO	115 °C, neat, 90 h		79	393
47		R-≡-CHO (R= $(CH_2)_3OTBS$)	$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 syn:anti = 70:30 E:Z = 1:1	–	394,395
48			$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 cis:trans = 88:12	88	394,395
49	 (BOM = $PhCH_2OCH_2$)		$BF_3{\cdot}OEt_2$, −78 °C, CH_2Cl_2		70	396

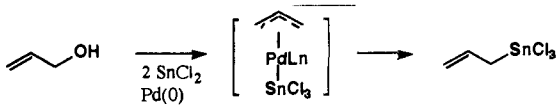
Table VI. (Continued)

entry	allyltin	aldehyde	conditions	product	yield, %	ref(s)
50			BF_3·OEt_2, −78 °C, CH_2Cl_2	 93 : 7	95	397
51		PhCHO		 syn 100% anti:syn = 72:28	~100	398
			BF_3·OEt_2, CH_2Cl_2, −78 °C Bu_4NF, THF			
52		PhCHO	Bu_4NF, THF or BF_3·OEt_2, CH_2Cl_2, −78 °C	 syn 100%	65	398
53		PhCHO	room temp	 syn 100%	70	398
54		PhCHO	Bu_4NF room temp	syn:anti = 78:22 syn:anti:linear adduct =48:16:37	100 100	398

reaction (entry 21) but also the thermal reaction (at 150 °C) and the high-pressure reaction (at 10 kbar) of the *meso*-isomer, both of which are known to proceed through a six-membered cyclic transition state, provide the anti-Felkin–Anh products predominantly.

Allylation of aldehydes with allylic tins takes place at room temperature under neutral conditions by using a high-pressure technique (entry 26).[372] The high-pressure-induced reaction proceeds via a six-membered cyclic transition state owing to the affinity of the Sn atom for the carbonyl oxygen atom, as observed in the thermal reaction (entry 19). The high-pressure-mediated addition of benzaldehyde to (5-methylcyclohex-2-enyl)trimethyltin occurs stereospecifically with syn approach of the electrophile to the tin atom (entry 27).[373] This syn-S_E2-type stereoselectivity (that is, cis preference in the products) is in good agreement with the intervention of the six-membered cyclic transition state. The syn selectivity between the OH group and the γ-substituent of the allylic tin unit is also consistent with intervention of the cyclic transition-state geometry. The volume data of the octanal–crotyltin condensation were obtained from the pressure dependence of the rate coefficient and of diastereoselectivity.[374] Analysis of the activation volumes ($\Delta V^{\ddagger}$) leading to the syn and anti adducts, the difference of the activation volumes ($\Delta\Delta V^{\ddagger} = \Delta V^{\ddagger}_{anti} - \Delta V^{\ddagger}_{syn}$), and volume data ($V^{\ddagger}$) of substituted cyclohexanes indicate the intervention of the boat transition state under very-high-pressure condensation.[374] The activation volume for the addition of chloral to allyltributyltin was found to be -33.4 ± 0.6 cm^3 mol^{-1}, which is consistent with a concerted cyclic transition state.[375] This volume lies within the range established for many examples of the Diels–Alder reaction (-35 ± 5 cm^3 mol^{-1}) and is consistent with a single-step metallo–ene mechanism involving a tight transition state and well-developed bonding. 3-(Butyldichlorostannyl)cyclopentene and 3-(butyldichlorostannyl)cyclohexene, which are prepared by the transmetalation of the corresponding 3-(tributylstannyl)cycloalkenes with $BuSnCl_3$, react with aromatic aldehydes to give 2-cycloalkenylated products with excellent syn selectivity (entry 28).[376] The reaction proceeds through a six-membered cyclic transition state, and the diastereoselectivity is consistent with that of the high-pressure-induced reaction (entry 27). Allylation of aldehydes and ketones to give the homoallyl alcohol can be carried out by allyl bromide and metallic tin in the presence of water, and also the allylation by various allylic bromides is realized in the presence of water by using metallic tin and aluminum (entry 29).[377] Unfortunately the diastereoselectivity of the crotyl bromide–aldehyde condensation is not high; the syn isomers are obtained predominantly (entry 29). However, the reaction of cinnamyl chloride with a series of aryl and alkyl aldehydes mediated by tin and aluminum provides regio- and stereoselectively the corresponding anti-isomers (entry 30).[378] The anti selectivity is also observed in the reaction of (*E*)-cinnamyltriphenyltin with benzaldehyde in the presence of BF_3·OEt_2 (entry 31).[379] The BF_3·OEt_2-mediated reaction of (*E*)-cinnamyltributyltin with benzaldehyde produces a 90:10 mixture of the anti- and syn-isomers, indicating that the ligands on tin (phenyl or *n*-butyl) have an influence on the stereospecificity of the reaction. The inductive effect of the phenyl ligands relative to *n*-butyl ligands is considered to increase the relative positive charge on the tin center thereby increasing coordination to carbonyl and biasing the reaction toward a cyclic mechanism (even in the presence of BF_3·OEt_2) and anti formation. Sonication accelerates the allylation of aldehydes and ketones with allylic bromides or chlorides in the presence of Sn powder in a THF/H_2O, 4:1 mixture (entry 32).[380] This allylation method exhibits a satisfactory degree of selectivity, as aldehydes react much faster than ketones and bifunctional molecules undergo a clean monoallylation. The method appears to be of special value for substrates which are either highly soluble in water and insoluble in the common solvents for organometallic synthesis, or commercially available as aqueous solutions. Carbonyl allylation by allylic acetates with Pd(0)/$SnCl_2$ occurs regio- and chemoselectively to afford the corresponding homoallyl alcohols (entry 33).[381] The allylation of an aldehyde is chemoselectively performed in the presence of a ketone group

or an ester group; for example, the allylation of 10-oxo-undecanal provides 13-oxotetradec-1-en-4-ol in 68% yield.[381] In the case of crotyl, 1-methylallyl, cinnamyl, and 1-phenylallyl acetates, benzaldehyde regioselectively attacks the more substituted allylic position to give a single regioisomer (branched homoallyl alcohol). Anti selectivity is obtained in the case of (*E*)-cinnamyl acetate; the ratio of syn/anti is 28:72 from (*E*)-cinnamyl acetate and 5:95 from 1-phenyl-1-acetoxy-2-propene (cf. entries 30 and 31). For (*E*)-crotyl acetate, syn preference is obtained as usual, although the stereoselectivity is low; the ratio of syn/anti is 61:39 from (*E*)-crotyl acetate, and 69:31 from 2-acetoxy-3-butene. Allylic carbonates are more active than the corresponding acetates in carbonyl allylation using $PdCl_2(PhCN)_2/SnCl_2$, and the crotylation of benzaldehyde at 10 °C exhibits slight anti selectivity (entry 34),[382] which is the opposite diastereoselectivity in comparison with that generated by (*E*)-crotyl acetate. Even allylic alcohols can be used for the $PdCl_2(PhCN)_2/SnCl_2$-mediated allylation.[383] Diastereoselectivity in the allylation of benzaldehyde with (*E*)-but-2-en-1-ol is controlled by the choice of polar solvents although the selectivity achieved is not high; use of DMSO at 25 °C leads to syn preference (at most 86:14), whereas anti preference is observed in THF at −10 °C (90:10).[383] The addition of 3–10 equiv of H_2O in any solvent enhances the selectivities, and the control of the amount of H_2O in DMSO permits both syn selection (a small amount of H_2O) and anti selection (a large amount of H_2O). Palladium-catalyzed diallylation of 1,2-diketones and 1,2-ketoaldehyde by allyl alcohol with $SnCl_2$ in DMI proceeds diastereoselectively, owing to a Sn(IV)-mediated chelation of two oxygen atoms (carbonyl oxygen and oxygen of the tin alkoxide of monoallylated intermediate) (entry 35).[384] Heterogeneous carbonyl allylation by γ-substituted allylic alcohols with $PdCl_2(PhCN)_2/SnCl_2$ in a nonpolar solvent such as diethyl ether is promoted by ultrasound to produce α-addition, with a regioselectivity which is the reverse of that in homogeneous carbonyl allylation reactions in polar solvents such as DMF, DMI, and THF/H_2O (entry 36).[385] Allylic alcohols with a more bulky substituent than methyl at the γ-position show high α-selectivity; in the case of crotyl alcohol the ratio of α/γ is 75:25. The addition of benzaldehyde to allylic alcohols bearing one or two substituents in the α-position, such as but-3-en-2-ol and linalool, affords products (>96% regioselectivity) analogous to the α-adducts shown in entry 36. The reactivity order of allylating agents is allylic carbonate > allylic alcohol > allylic acetate (entry 37).[386] An NMR spectroscopic investigation demonstrates that the actual allylating agent in dry media is allyltrichlorotin: ^1H, ^{13}C, and ^{119}Sn NHR spectra of the reaction of allyl alcohol with $PdCl_2(PhCN)_2/SnCl_2$ in DMF-d_7 correspond to those of the reaction of allyl chloride with $PhCl_2(PhCN)_2/SnCl_2$ in DMF-d_7.[386] The allylation with allyl alcohol may proceed through an initial formation of π-allylpalladium intermediate **312**, which gives allyltrichlorotin (eq 96). The allylation with allyl

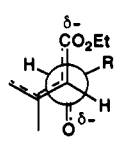


312 (eq 96)

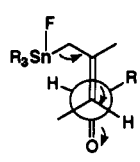
carbonates and acetates also proceeds, presumably via π-allylpalladium complexes, analogous to **312**. Ethyl 2-(hydroxymethyl)acrylate derivatives serve as reagents for 2-ethoxycarbonylallylation of carbonyl compounds using the $PdCl_2(PhCN)_2/SnCl_2$ system to produce α-methylene-γ-butyrolactones diastereoselectively (entry 38).[387a] α-Selective coupling reactions of allylic alcohols with aldehydes are efficiently mediated by the $Me_3SiCl/NaI/H_2O$–Sn system, giving linear homoallyl alcohols in good yields.[387b]

The [(isopropyloxy)allyl]lithium is once trapped with tributyltin chloride, and subsequent treatment with aldehydes in the presence of $BF_3·OEt_2$ provides the *syn*-1,2-diol derivatives with very high diastereoselectivity (entry 39). Presumably, (*Z*)-[γ-(isopropyloxy)allyl]-tributyltin is formed as an intermediate which reacts with aldehydes via an acyclic transition state. Both (*E*)- and (*Z*)-(γ-methoxyallyl)tins stereoselectively add to aldehydes in the presence of $BF_3·OEt_2$ to produce the syn vicinal diol monomethyl ether unit (entry 40).[388] The key intermediate to *exo*-brevicomin is conveniently synthesized in three steps from the *syn*-diol derivative of this type. [γ-(*tert*-Butyldimethylsiloxy)allyl]tin also exhibits syn diastereoselectivity in the presence of $MgBr_2·OEt_2$ as Lewis acid.[389] α-(Benzyloxy)butanal is converted to the syn–syn-isomer exclusively via a chelation-controlled addition (entry 41).[389] The reaction of 3-(benzyloxy)-1-butanal produces the anti–syn-isomer (chelation-controlled product) predominantly over the syn–syn-isomer (entry 42), but not exclusively as in the case of entry 41. The triphenyltin reagent provides higher diastereoselectivity than the tributyl derivative (entry 42). [(Methoxymethoxy)allyl]tributyltin ($CH_3OCH_2OCH{=}CHCH_2SnBu_3$) also exhibits diastereoselectivities similar to those of entries 41 and 42.[390] The in situ trapping of [(isopropylthio)allyl]- or [(trimethylsilyl)allyl]lithium with tributyltin chloride also produces the corresponding γ-heteroatom-substituted allyltributyltins, which provide the syn-isomers exclusively upon treatment with aldehydes in the presence of $BF_3·OEt_2$ (entries 43 and 44). In the case of the silyl-substituted case, the Peterson elimination of the resulting *syn*-α-silyl alcohol takes place to give the *Z*-olefin stereoselectively (entry 44).[211] The reaction of (α-ethoxycrotyl)tin with *p*-bromobenzaldehyde in the presence of $BF_3·OEt_2$ produces the *syn*-1,2-diol monoether with high diastereoselectivity, while the thermal reaction gives the ordinary adduct at the γ-position of the allylic tin (vinyl ether derivative) (entry 45). Isomerization of (α-ethoxyallyl)tributyltin to (γ-ethoxyallyl)tributyltin is promoted by the presence of $BF_3·OEt_2$,[391] and a similar methathesis process is mentioned in Scheme XI. Accordingly, the formation of the diol derivatives in entry 45 in the presence of $BF_3·OEt_2$ can be rationalized by an initial isomerization of the α-ethoxy to γ-ethoxyallylic tin. Both (*Z*)- and (*E*)-allylic tins give syn selectivity, which is in agreement with an intervention of acyclic transition state. (*E*)-[1-(Methoxymethoxy)but-2-enyl]tributyltin, readily available by the addition of tributyltin lithium to crotonaldehyde and alkylation of the adduct using chloromethyl methyl ether, reacts on heating with aldehydes to give the *anti*-(*Z*)-adduct exclusively (entry 46).[393] The *anti*-(*Z*) stereochemistry is consistent with these reactions proceeding via a chairlike six-membered

cyclic transition state in which the anti stereochemistry is a consequence of the *E*-geometry of the tin, and the (*Z*)-enol ether geometry is due to a preference of the α-methoxymethoxy substituent to adopt an axial position (see also entry 19). The [α-(methoxymethoxy)-crotyl]tin reacts with the acetylenic aldehyde in the presence of BF_3·OEt_2 to give the syn-adduct predominantly (entry 47); unfortunately the syn selectivity is low and the *E*/*Z* selectivity of the double bond is 1:1.[394] Heating at 140 °C for 5 min affords a 1:1.3 mixture of the syn- and anti-adducts. The intramolecular version of entry 47, the BF_3·OEt_2-mediated cyclization of the MOM-protected (α-hydroxyallyl)stannane propargylic aldehyde, gives a 7:1 mixture of cis- and trans-isomers of the 14-membered cembranolide derivative (entry 48).[394,395] The cis preference in this cyclization is consistent with reactions proceeding through Lewis acid mediated C–C-bond formation which provides syn diastereoselectivity. The [α-(alkoxy)allyl]stannane dicobalt hexacarbonyl alkynal complex affords the cyclization product (cis) as a single diastereoisomer upon treatment with BF_3·OEt_2 at −78 °C (entry 49).[396] The cis (or syn) selectivity is enhanced in the dicobalt hexacarbonyl complex (entry 49) in comparison with the ynal derivative (entry 48). The BF_3·OEt_2-mediated intramolecular cyclization of the γ-oxo-substituted allylic stannane having an aldehyde group at the terminus of the carbon chain proceeds in a stereocontrolled manner to give the seven-membered β-hydroxy cyclic ether with high diastereoselectivity (entry 50).[397] The reactions of the lithium dienolate, generated from ethyl 3-methyl-2-butenoate, with Bu_3SnCl, Bu_2SnCl_2, $BuSnCl_3$, and $SnCl_4$ provide the allylic tin derivatives of entries 51–54, respectively.[398] As expected, the BF_3·OEt_2-mediated reaction of the Bu_3Sn derivative with aldehydes gives the syn-adducts exclusively (entry 51), whereas the Bu_4NF induced reaction with benzaldehyde affords a 72:28 mixture of the anti- and syn-adducts. On the other hand, the reaction of the $SnBu_2Cl$ derivative with benzaldehyde produces the syn-adduct exclusively upon treatment with either BF_3·OEt_2 or Bu_4NF (entry 52). Similarly, the $SnBuCl_2$ derivative gives the syn-adduct exclusively in the presence of BF_3·OEt_2 or Bu_4NF and affords the same isomer even without assistance of any additives (entry 53). The $SnCl_3$ derivative produces the syn-adduct predominantly upon treatment with Bu_4NF (entry 54). The syn preference in the BF_3·OEt_2-mediated reactions of entries 51–53 is reasonable since the reactions proceed via an acyclic transition state. The syn preference in the Bu_4NF-mediated reactions (entries 52–54) is understood by considering the intervention of the ate complex **313** owing to the strong electron-withdrawing effect of the Cl atom. The reaction of Bu_4NF with the $SnBu_3$



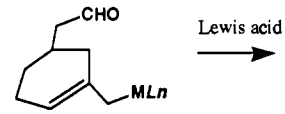
314



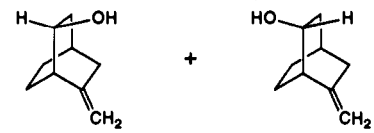
313

derivative (entry 51) may give the naked dienolate, in which the negative charge will be localized at the ester function. Accordingly the reaction proceeds through **314** which is the most stable intermediate from both steric and electronic points of view, resulting in the predominant formation of the anti isomer.

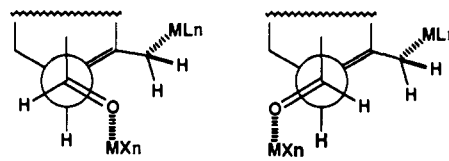
To clarify the origins of stereoselectivity in the intramolecular reactions of allylic tins and silanes, the model **315** was designed which allowed an unambiguous correlation between product stereochemistry and transition-state geometry. Thus, *syn*-**316** and *anti*-**316** arise from synclinal and antiperiplanar transition states, respectively.[399] All of the cyclizations via **315a** are very



315 **a:** MLn=$SnBu_3$
b: MLn=$SiMe_3$



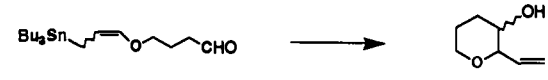
syn-316 **anti-316**



synclinal antiperiplanar

syn selective and relatively insensitive to the nature of the Lewis acid (BF_3·OEt_2, $AlCl_3$, Et_2AlCl, $ZrCl_4$, $SnCl_4$, $FeCl_3$, 87–98% syn[399,400]), indicating a significant preference for the synclinal orientation. On the other hand, variable syn selectivity (47–99%) with a strong dependence on the nature of the Lewis acid is obtained for **315b**; the bulk of the Lewis acid–aldehyde complex must be important in these reactions. Further, the reactivity of **315a** is greater than that of **315b** as expected. The insensitivity of Lewis acid size in **315a**, together with the facility of reaction, argue for an early transition state. For **315b**, the effects of experimental variables (concentration, stoichiometry, and dummy ligand) on the stereoselectivity are investigated with $SnCl_4$ as the Lewis acids.[401]

For the intramolecular condensation of ω-stannyl ether aldehydes **317a,b**, the third mechanism is proposed,[402] the first one is for reactions via six-membered cyclic transition state (thermal and high-pressure reactions), and the second one is for reactions via an acyclic transition state (Lewis acid and Bu_4NF mediated reactions). The stereochemical outcome of the protic acid induced cyclization depends strongly upon the double-bond geometry; the cyclization of **317a** in the presence of the protic acids predominantly gives **318a**, whereas that of **317b** produces **318b** exclusively; as

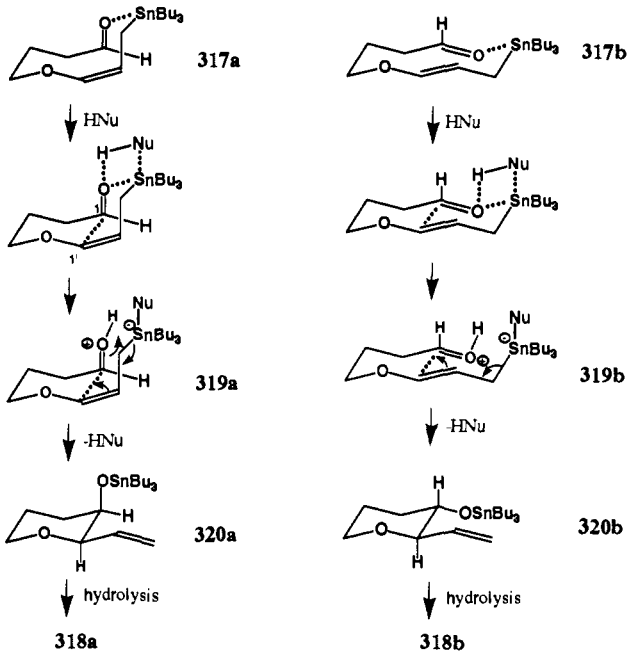


317a: (Z)
b: (E)

318a: syn
b: anti

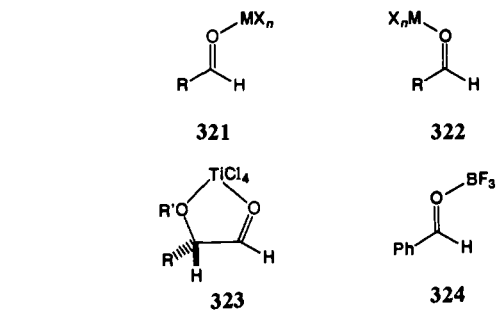
protic acids TfOH, CF_3CO_2H, CCl_3CO_2H, $ClCH_2CO_2H$, CH_3CO_2H, and HCl can be used, and even a catalytic amount of TfOH can induce the cyclization of **317**. As

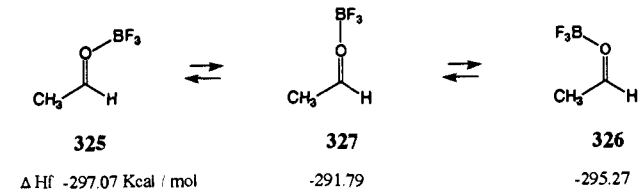
Scheme XII. "Push-Pull" Mechanism



expected, the Lewis acid induced cyclization using $TiCl_4$ or BF_3·OEt_2 affords **318b** predominantly regardless of the double-bond geometry. The observed stereochemical results can be explained by a new "push–pull" mechanism via cyclic transition state (Scheme XII). In the presence of protic acid (HNu), the proton pulls electrons from the oxygen to produce positively charged carbonyl oxygen, and the nucleophilic part pushes electrons into the tin atom to afford hypervalent tin species (**319a** or **319b**). There is an attractive interaction between the positively charged oxygen and negative tin atom. Accordingly, the new C–C-bond formation takes place between C-1 and C-1′, to give the alkoxystannane **320a** or **320b** with concomitant elimination of protic acid (HNu). It is well known that the Lewis acid mediated reaction needs stoichiometric amounts of Lewis acids. In the case of protic acid induced reactions, a catalytic amount of TfOH is sufficient for the conversion of **317a** to **318a**, supporting the push–pull mechanism since HNu is regenerated in the step from **319** to **320**. Further, the cyclization occurs smoothly with $Bu_4NF/TiCl_4$ system (push–pull system) and the diastereoselectivity is also dependent upon the double-bond geometry. Cyclization of **315a** was also studied in the presence of CF_3CO_2H.[399,400] However, the invariability of the double-bond geometry (cis/double bond in **315a**) leads to the same stereochemical outcome as in the case of Lewis acids, which does not allow the authors to find an essential difference between protic and Lewis acid mediated reactions.

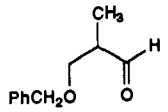
Is the structure of aldehyde–Lewis acid complexes *anti*-**321** or *syn*-**322**? At the outset of the BF_3-mediated reaction of allylic tins, this question was not taken into consideration.[2c] Later on, the anti complexation **321** has been usually assumed rather than the stereoisomeric *syn*-**322**. In contrast, the chelation-controlled addition in the presence of bidentate Lewis acids such as $TiCl_4$, $SnCl_4$, and $MgBr_2$ to α- and β-alkoxyaldehydes has been thought to involve syn complexation **323**.[359,403] X-ray crystallography of the benzaldehyde–BF_3 adduct clearly shows anti complexation **324**.[404] The B–O–C–C fragment lies essentially in a common place. Anti complexation also pertains in solution, as shown by a heteronuclear Overhauser experiment.[404] MNDO calculations of the acetaldehyde–BF_3 adduct show that anti complexation **325** does indeed lead to the lowest energy species.[404] However, the syn-adduct **326** lies only 1.8 kcal/mol higher in energy. On the other hand, the difference between anti and syn PhCHO·BF_3 is 2.5 kcal/mol. The linear form **327** is not a minimum on the energy surface but it represents the least-energy transition state for possible internal anti–syn isomerization.





BF_3 complexation lowers the energy of the π^*_{CO} orbital, rendering the molecule more susceptible to nucleophilic attack. The extent of LUMO lowering is a little greater in the anti complex than in the syn isomer. The coefficient of the orbital at the carbonyl C atom in π^*_{CO} increases in magnitude upon complexation, a phenomenon which also enhances the ease of nucleophilic addition.[404] Ab initio MO computations also show that the difference in energy between syn and anti complexation is much larger for benzaldehyde–BF_3 than for acetaldehyde–BF_3.[405] The other obvious difference between PhCHO·BF_3 and CH_3CHO·BF_3 is their B–O bond lengths. The B–O bond distances have the following order: *anti*-PhCHO·BF_3 (1.62 Å) < *syn*-PhCHO·BF_3 (1.63 Å) < *anti*-CH_3CHO·BF_3 ≈ *syn*-CH_3CHO·BF_3 (1.65 Å). The BF_3 complexes have the following order of stability: *anti*-PhCHO·BF_3 > *anti*-CH_3CHO·BF_3 > *syn*-CH_3CHO·BF_3 > *syn*-PhCHO·BF_3.[406] The strong anti complexation of PhCHO is rationalized by considering the ability of the phenyl ring to stabilize the developing positive charge by resonance. Steric effect is accountable for the instability of the *syn*-PhCHO·BF_3 complex (steric repulsion between ortho phenyl H and the BF_3 group).

The structure of Lewis acid complexed intermediates derived from alkoxy carbonyl compounds in solution was studied by variable-temperature NMR spectroscopy.[407] The $TiCl_4$ complex of **328** adopts the bidentate chelate conformation **329** in which the CH_3 group occupies a pseudoequatorial position, and the $SnCl_4$ and $MgBr_2$ complexes also adopt similar bidentate chelated structures. With the isomeric β-benzyloxy aldehyde **330**, the formation of a discrete $TiCl_4$ bidentate complex **331** is again observed in which the CH_3 group occupies the axial position. The choice of O-substituent



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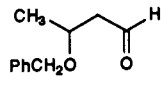

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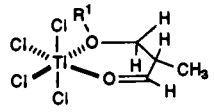

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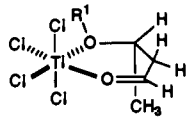
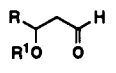
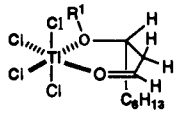


331

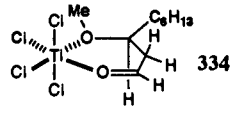
plays a critical role in determining the conformation of chelates derived from β-alkoxyaldehydes in solution.[408] With **332a**, where the methyl substituent of **330** is replaced by *n*-hexyl, the $TiCl_4$ or $MgBr_2$ complex takes a bidentate chelated structure **333** similar to **331**. However, simply changing the O-substituent to methyl (**332b**) results in a dramatic change: the *n*-hexyl group at C_3 occupies an equatorial position **334** in the chelates formed by reaction with $TiCl_4$ or $MgBr_2$. With **332c**, the *n*-hexyl substituent returns to an essentially axial position **333**. With **332d**, a bidentate complex with any





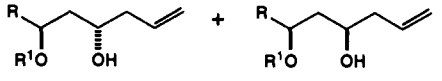
333 R^1=Et, CH_2Ph

330 R=CH_3, R^1=CH_2Ph
332a R=n-C_6H_{13}, R^1=CH_2Ph
332b R=n-C_6H_{13}, R^1=CH_3
332c R=n-C_6H_{13}, R^1=CH_2CH_3
332d R=n-C_6H_{13}, R^1=Si(t-Bu)Me_2



334

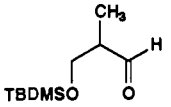
of the Lewis acids ($TiCl_4$, $MgBr_2$, and $SnCl_4$) is not formed.[469] The nonchelating ability of sterically demanding siloxy group was utilized for the stereocontrolled allylation of diprotected bis(hydroxymethyl)-acetaldehyde.[358,360,410] The diastereoselectivity in additions of allyltriphenyltin to β-alkoxyaldehydes correlates very well with the solution structures of the Lewis acid complexes formed from such aldehydes.[408] The predictions based upon NMR spectroscopy are the following: (1) High stereoselectivity for the formation of anti-products **335** should be realized for additions to **330** and **332a,c** using $TiCl_4$ or $MgBr_2$, since the axial substituent at C_3 effectively blocks one face of the aldehyde (**333**). (2) Low levels of stereoselectivity are



anti **335**

syn **336**

expected for **330** and **332a** with $SnCl_4$, in which chelation is much less complete. (3) Low levels of stereoselectivity are expected for **332b** with any Lewis acid, since the *n*-hexyl group occupies the equatorial position (**334**). (4) Low levels of stereoselectivity are expected with **332d** which does not form a bidentate complex. (5) With the monodentate Lewis acid BF_3·OEt_2, high levels of stereoselectivity are not expected. Most of the results agree with the predictions. H^1 and ^{13}C NMR spectroscopy also support the postulation that chelation with siloxy oxygen is not involved in nucleophilic additions to α- or β-siloxy aldehydes.[409] A bidentate chelate complex is formed with **328** and $SnCl_4$, but such a chelation as not observed with **337** and $SnCl_4$. It is suggested that with **337** a 2:1 complex **338** is formed, in which the stereochemistry of complexation is presumably *E* (or anti).



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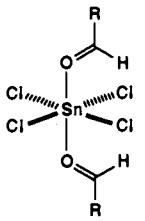


338

The possibility of a metathesis process was studied by Tagliavini,[354] Keck,[408] Yamamoto[353] (Scheme XII), and Pereyre[392] based on product analysis. Denmark and co-workers presented, using ^{13}C NMR spectroscopy, direct evidence for interaction between a Lewis acid and allyltin in the presence of a substrate aldehyde.[411] A ligand metathesis in the presence of BF_3·OEt_2 may occur depending upon the amount of trimeric aldehyde present under the reaction conditions, and the degree of trimerization at ~80 °C is acetaldehyde > pivalaldehyde > 4-*tert*-butylbenzaldehyde. The metathesis of the allyl group of allyltrimethyltin takes place more readily in the acetaldehyde condensation, since it exists as the trimer in the presence of BF_3·OEt_2 at −80 °C and the metathesis occurs before the trimer begins to dissociate to the monomeric aldehyde. The results with $SnCl_4$-complexed aldehydes fundamentally differ from those with BF_3·OEt_2. Allyltrimethyltin is not involved in aldehyde additions when free $SnCl_4$ is present, and metathesis with fully complexed $SnCl_4$ is demonstrably faster than addition in most if not all cases. Keck also investigated a dynamic process, the reaction of allyltributyltin with the complexes formed from three aldehydes (**328**, **330**, and **337**) with $SnCl_4$, via variable-temperature ^{119}Sn NMR spectroscopy.[412] The 2:1 complexes [(**382**)$_2$·$SnCl_4$, (**330**)$_2$·$SnCl_4$, and (**337**)$_2$·$SnCl_4$] and the chelate complexes do not promote metathesis, and this Keck's observation is in conflict with Denmark's results; Denmark concludes that with (RCHO)$_2$·$SnCl_4$ complex metathesis with allylSnMe_3 or allylSnBu_3 is instantaneous at low (−90 °C) temperature and that addition products are formed only via the intermediary of the metathesis products (e.g., allyl$SnCl_3$ or (allyl)$_2SnCl_2$). Accordingly, Keck's group reinvestigated a mechanistic and spectroscopic study reported by Denmark using ^{119}Sn NMR spectroscopy and using pivalaldehyde and 4-*tert*-butylbenzaldehyde. Keck's reinvestigation demonstrates that metathesis is only important under conditions where free $SnCl_4$ is present or where fast ligand exchange opens up vacant coordination sites on the metal. It seems that potential presence of free $SnCl_4$ cannot be addressed in the Denmark experiments which utilized ^{13}C NMR, although the reason for the discrepancy between Keck's and Denmark's results is not yet clarified.

Reactions of chiral aldehydes and/or chiral allyltins are summarized in Table VII. The reaction of a steroidal aldehyde with allyltributyltin and allyltrimethyltin in the presence of $TiCl_4$ produces significantly

Table VII. Reactions of Chiral Aldehydes and/or Chiral Allyltins or in the Presence of a Chiral Catalyst

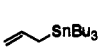
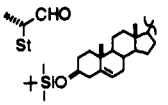
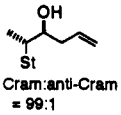
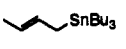
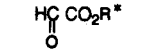
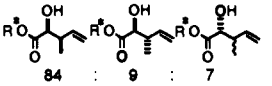
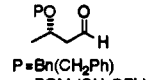
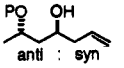
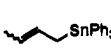
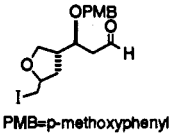
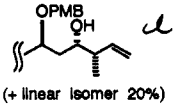
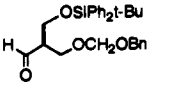
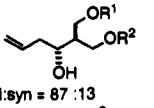
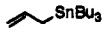
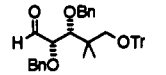
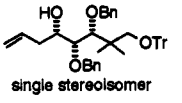
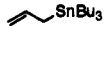
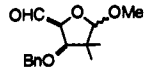
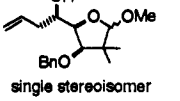
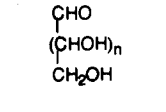
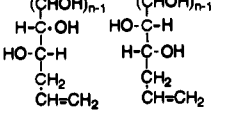
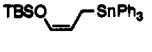
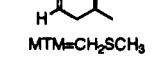
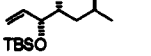
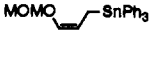
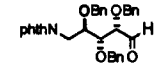
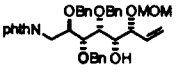
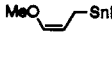
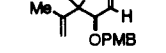
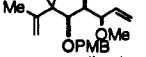
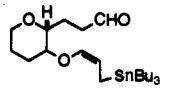
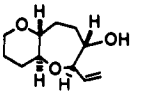
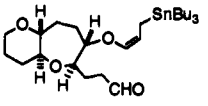
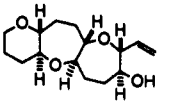
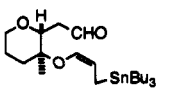
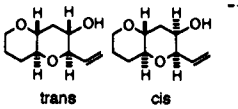
entry	reagent	aldehyde	conditions	product	yield, %	ref
1			$TiCl_4$, CH_2Cl_2, −78 °C	 Cram:anti-Cram = 99:1	85	413
2		 R^* = 8-phenylmenthyl	$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 84 : 9 : 7	80	122
3		 P=Bn(CH_2Ph) =BOM (CH_2OPh) =MTM (CH_2SCH_3)	$TiCl_4$, CH_2Cl_2, −78 °C	 anti : syn 29 : 1 9 : 1 2 : 1	75 – –	415
4		 PMB=p-methoxyphenyl	$SnCl_4$, −78 °C	 (+ linear isomer 20%)	60	416
5			$MgBr_2$, CH_2Cl_2, −78 °C → 0 °C	 anti:syn = 87 :13 (R^1=$SiPh_2tBu$, R^2=CH_2OBn)	92	410
6			$MgBr_2$, CH_2Cl_2	 single stereoisomer	92	417
7			$MgBr_2$, CH_2Cl_2, −25 °C	 single stereoisomer	95	418
8			Sn powder, 9:1 EtOH/H_2O, ultrasonification	 3.5~6.5 : 1	52~90	419
9		 MTM=CH_2SCH_3	$MgBr_2{\cdot}OEt_2$, CH_2Cl_2, −23 °C	 4.1:1 mixture	46	420
10		 phthN=phthalimido	$MgBr_2{\cdot}OEt_2$, CH_2Cl_2, −78 °C → 0 °C		87	196
11		 PMB=p-$MeOC_6H_5$	$MgBr_2{\cdot}OEt_2$, CH_2Cl_2, −40 °C	 syn-syn : another isomer =7.5 : 1	71	421
12			$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 ~100% de	99	397
13			$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 ~100% de	97	397
14			$BF_3{\cdot}OEt_2$ 120 °C	 trans : cis 33 : 67 3 : 97		397

Table VII. (Continued)

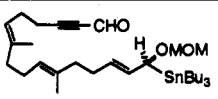
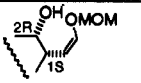
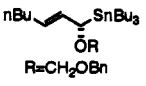
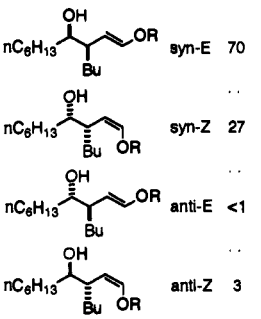
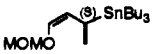
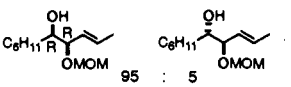
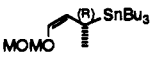
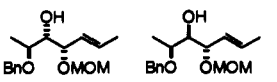
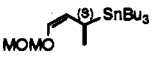
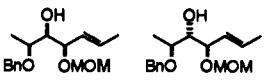
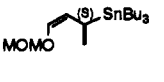
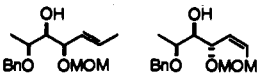
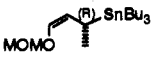
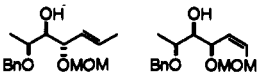
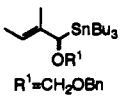
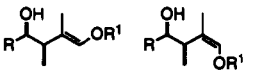
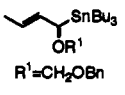
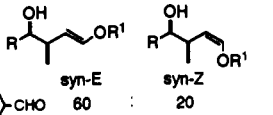
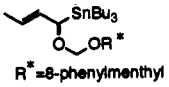
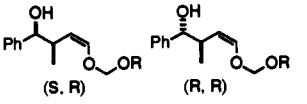
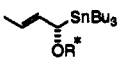
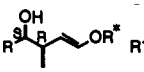
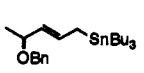
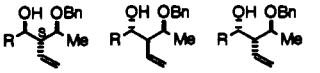
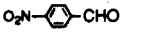
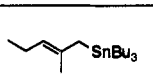
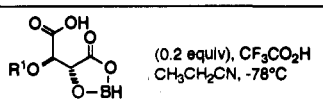
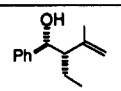
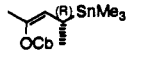
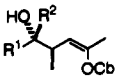
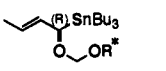
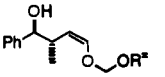
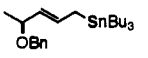
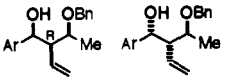
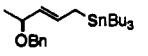
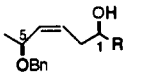
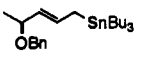
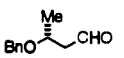
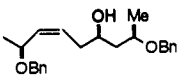
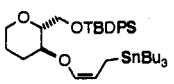
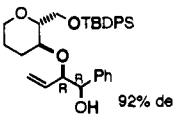
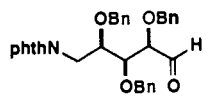
entry	reagent	aldehyde	conditions	product	yield, %	ref
15			$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 (2R, 1S) : (2S, 1S) 20 : 1	88	422
16		n-C_6H_{13}CHO	$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 syn-E 70 syn-Z 27 anti-E <1 anti-Z 3	80	423
17		C_6H_{11}CHO	$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 95 : 5	74	424
18			$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 92 : 8	58	425
19			$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 67 : 33	72	425
20			$MgBr_2$, −23 °C → 23 °C	 93 : 7	74	425
21			$MgBr_2$, −23 °C → 23 °C	 75 : 25	74	425
22		RCHO R=C_6H_{13}, n-C_6H_{13}, sec-C_6H_{13}	$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 syn-E : syn-Z >95 : <5	60–80	426
23		RCHO	$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 syn-E : syn-Z  60 : 20 PhCHO <1 : 95	60–80	426
24		PhCHO	$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 (S, R) (R, R) >95 : <5	75	427
25	 R*=(8-phenylmenthyl)-oxy-methyl	RCHO	$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	 syn-E : syn-Z : anti-E : anti-Z PhCHO <1 : 95 : <1 : 5  82 : 18 : <1 : <1 n-C_6H_{13}CHO 39 : 61 : <1 : <1		427
26		RCHO		 anti-anti anti-syn syn-anti		429
			$BF_3{\cdot}OEt_2$	>95 : <5 : ·	61	
			$MgBr_2{\cdot}OEt_2$	<5 : >95 : ·	35	

Table VII. (Continued)

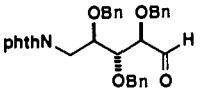
entry	reagent	aldehyde	conditions	product	yield, %	ref
27		PhCHO	 (0.2 equiv), CF_3CO_2H, CH_3CH_2CN, -78°C	 syn : anti = 93 : 7; syn; 70% ee	50	430
28	 Cb = (C=O)N(IPr)$_2$		$TiCl_4$, CH_2Cl_2, −78 °C	 R^1 = IPr, R^2 = H, ee, % = 82; R^1 = C_6H_5, R^2 = CH_3, ee, % = 83	85 83	431
29	 R* = 8-phenylmenthyl	PhCHO	130 °C, 14–15 h, neat	 single stereoisomer	81	432
30		ArCHO Ar=p-$NO_2C_6H_4$	150 °C, 18 h	 73 : 27		433
31		RCHO R=Ph, p-$NO_2C_6H_4$, n-Pr, i-Pr	(1) $SnCl_4$, 5 min, −78 °C; (2) RCHO, 1 h, −78 °C		77–90	434
32			(1) $SnCl_4$, 5 min, −78 °C; (2) RCHO,1 h, −78 °C	 other isomers, < 4%	85	436
33		PhCHO	$AlCl_3$, CH_2Cl_2, −78 °C	 92% de	52	437a

high Cram (Felkin–Anh) selectivity: 89:11 and 90:10, respectively (entry 1).[13] The addition of carbanionic organometallic compounds such as Grignard reagents and organolithiums to the same aldehyde results in the formation of ca. 1:1 to 2:1 mixture of Cram and anti-Cram adducts. The enhanced Cram selectivity in the Lewis acid mediated reaction can be explained by a change in direction of nucleophilic attack towards the carbonyl groups.[414] The BF_3·OEt_2-mediated reaction of crotyltributyltin with 8-phenylmenthyl glyoxylate affords the syn–syn-adduct predominantly (entry 2),[122] which is converted to optically active verrucarinolactone in 91% ee. The reaction of allyltriphenyltin with 3-alkoxybutanals in the presence of $TiCl_4$ provides the chelation-controlled products (the anti-isomer) either predominantly or with very high stereoselectivity (entry 3).[415] In order to obtain high diastereofacil selectivity, the protective group must permit effective bidentate chelation between the aldehyde carbonyl and the ether oxygen, and the protecting group must be sufficiently bulky to force the methyl group into an axial position in the six-membered chelate formed upon bidentate complexation of the Lewis acid. The protecting group of choice is benzyl (Bn). The chelation-controlled addition is also achieved with use of $SnCl_4$ at −78 °C to provide the anti-adduct along with the linear homoallyl alcohol (entry 4).[416] $MgBr_2$-mediated allylation of a series of diprotected unsymmetrized bis(hydroxymethyl)acetaldehyde with allyltin proceeds with good diastereoselectivity (entry 5).[410] The stereochemical outcome is in line with a chelated transition state, where only one of the two CH_2OR appendages, due to the different nature of protecting groups, is capable of coordinating the Lewis acid. The "nonchelating" group is a silyl ether such as Me_2tBuSi, Ph_2tBuSi, or $(i\text{-}Pr)_3Si$, and the "chelating group" is $PhCH_2OCH_2$ (BOM) or p-$MeOC_6H_4CH_2OCH_2$ (PMBOM). When the nonchelating group is used as R^1 and the chelating group as R^2, the anti-isomer is produced predominantly (entry 5). The stereochemical outcome is a reflection of a 1,3-chelation and not of a 1,2-chelation which produces a syn-isomer. This is very clear if the result is compared with the $MgBr_2$-mediated allylation of an α-alkoxyaldehyde (entry 5 of Table VI). Further examples of a chelation-controlled allylation of chiral aldehydes are shown in entries 6 and 7. The allylation of aldehydes with allylic halides and Sn (or Zn) metal in aqueous/organic solvents (entries 29–32 of Table VI) is applied to carbohydrates (entry 8).[419] The reactions proceed with useful diastereoselectivity and permit the synthetic utilization of these water-soluble substrates directly in aqueous solutions without protection. D-Erythrose, D-ribose, D-arabinose, D-glucose, D-mannose, and 2-deoxy-D-glucose are converted to the corresponding allylated compounds with threo preference. The chelation-controlled reaction of chiral 3-[(methylthio)methoxy]butanal with γ-oxo-substituted allyltin produces the syn-anti (syn-chelation) isomer predominantly (entry 9).[420] For the related reaction of the racemic aldehyde, see entry 42 of Table VI. The arabinose derivative also provides the chelation-controlled product as a single stereoisomer upon treatment with the γ-oxo-substituted allyltin in the presence of $MgBr_2$ (entry 10).[196] However, the allylation

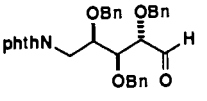
of other stereoisomeric aldehydes such as **339a–c** gives a mixture of diastereoisomers. Another example of a



339a

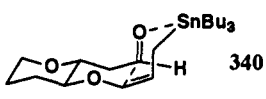


339b



339c

chelation-controlled allylation is illustrated in entry 11. Intramolecular cyclization of chiral allylic tins having γ-oxo group proceeds very stereoselectively to produce seven-membered cyclic ethers in high chemical yields (entries 12 and 13).[397] However, as shown in entry 14, the formation of six-membered cyclic ethers does not proceed in trans stereoselective manner; the BF_3·OEt_2-mediated reaction gives a 33:67 mixture of the trans- and cis-isomers (entry 14).[397] Heating at 120 °C provides the cis-isomer with high diastereoselectivity, presumably via a six-membered cyclic transition state **340**. The BF_3-promoted cyclization of the chiral α-alkoxyallylstannane shown in entry 15 proceeds with high enantioselectivity in the manner predicted by a transition-state geometry **341**.[422] Even though a chelated cyclic transition state is not involved in the reaction of entry 15, the BF_3-promoted reaction shows efficient chiral transfer. Addition of the homochiral (*S*)-[1-(benzyloxy)methoxy-2-(*E*)-hexenyl](tri-*n*-butyl-)stannane to heptanal (see entry 16), (*E*)-2-heptenal, and 2-heptynal under BF_3·catalysts have been investigated.[423] In all cases the addition proceeds by anti S_E' attack to give mainly the *syn–E*-adducts with high ee. The favored formation of the (*E*)-olefin in the intermolecular addition is different from the (*Z*)-olefin preference in the intramolecular cyclization (entry 15). On treatment with BF_3·OEt_2, optically active (*E*)-[α-(alkoxy)allyl]stannanes **342** rearrange stereospecifically to the (Z)-[γ-(alkoxy)allyl]stannanes **343** by 1,3-migration of Bu_3Sn (eq 97).[424] Although the rearrangement from the (*S*)-stannanes to the (S)-[γ-(alkoxy)-allyl]stannanes is shown in eq 97, the corresponding (*R*)-stannanes also provide the (*R*)-[γ-(alkoxy)allyl] derivatives. The rearrangement takes place by an intermolecular anti pathway. Addition of **343** to representative aldehydes affords optically active *syn*-1,2-diol monoethers as the major diastereomers with high anti S_E' stereoselectivity (entry 17).[424] BF_3·OEt_2-promoted addition of the (*R*)-[γ-(alkoxy)allyl]stannane to (*S*)-2-(benzyloxy)propanal gives the syn adduct with 92:8 diastereoselectivity (entry 18), whereas the addition of the *S*-enantiomer to the same aldehyde results in lower diastereoselectivity (entry 19).[425] With $MgBr_2$ as the catalyst addition to the (*S*)-α-alkoxy aldehyde is most selective (93:7) with the (*S*)-[γ-(alkoxy)allyl]-stannane (entry 20) whereas the addition of the (*R*)-stannane produces a diminished diastereoselectivity (entry 21).[425] The addition of [β-methyl-α-(alkoxy)-allyl]stannane to aliphatic aldehydes in the presence of BF_3·OEt_2 produces a uniformly high yield of *syn-E*-isomers out of four possible diastereomers (entry 22, cf. entry 16).[426] It should be noted that the (β-methylallyl)stannane reagent fails to react with benzaldehyde under the same conditions. Fair to good *syn-E* selectivities are observed for the reactions of (α-alkoxycrotyl)stannane with aliphatic aldehydes, whereas excellent *syn-Z* selectivity is observed with benzaldehyde (entry 23).[426] As depicted in Scheme XIII, the relative position of the alkoxy group OR′ determines the facial selection. When the two trigonal carbons approach each other, three staggered rotamers are possible for each facial attack. Among the two antiperiplanar arrangements, rotamer A, which leads to (*E*)-enol ether, is sterically favored since it avoids the repulsion between R and OR′ groups; the rotamer B, however, is favored electronically due to the "inside alkoxy" effect.[428] In the presence of a β-methyl group, the "inside alkoxy" effect is diminished due to the donor ability of the methyl group and the steric effect alone determines the outcome of the reactions. In the absence of a β-methyl group, neither the steric nor the electronic effect is dominant, producing a mixture of *E*- and *Z*-isomers. The electronic effects are much more important in the case of aromatic aldehydes. [[[[(8-Phenylmenthyl)oxy]methyl]oxy]crotyl]stannane produces excellent *syn-Z* diastereoselectivity upon treatment with aromatic aldehydes in the presence of BF_3·OEt_2 (entries 24 and 25). Additions of homochiral [δ-(benzyloxy)allyl]stannane with some aromatic aldehydes produce the anti–anti-isomer with high diastereoselectivity upon treatment with BF_3·OEt_2, whereas the anti–syn-isomer is afforded with excellent selectivity in the presence of $MgBr_2$ (entry 26).[429] The BF_3-mediated addition proceeds through an acyclic



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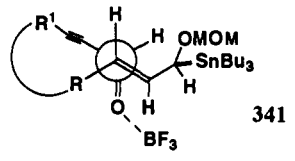

si/re

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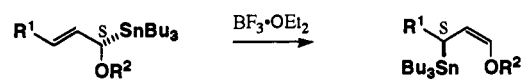
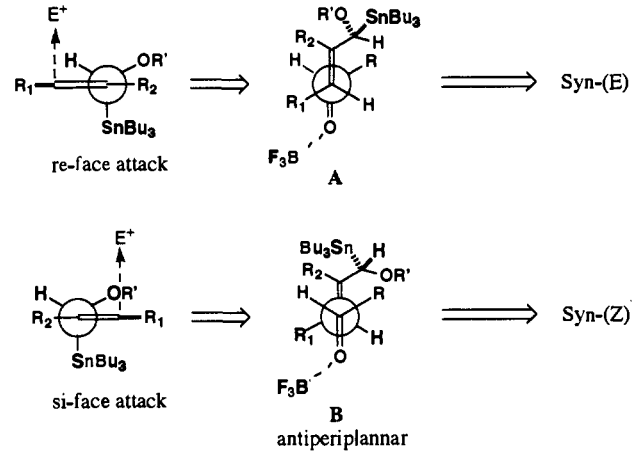


342; R^1=Me, Bu, C_6H_{11}
R^2=MOM, BOM

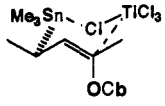
343

(eq 97)

Scheme XIII. Steric and Electronic Effect upon Transition-State Geometries



transition state (either synclinal or antiperiplanar) while the $MgBr_2$-promoted reaction involves chelation of the benzyloxy group of the allylstannane. Additions of achiral allylstannanes to achiral aldehydes in the presence of chiral (acyloxy)borane catalyst and trifluoroacetic anhydride affords homoallyl alcohols with diastereo- and enantioselectivity (entry 27).[430] When an equimolar quantity of the boronate catalyst and excess of $(TFA)_2O$ is employed, the reaction is virtually quantitative (99% yield, syn/anti = 90:10, 85% ee). With aliphatic aldehydes, an equimolar quantity of the catalyst is used to obtain high chemical yields and higher selectivities. The chiral γ-carbamate-substituted allylstannane can be prepared from the corresponding chiral nonracemic 1-lithio-2-alkenyl carbamate, generated by stereospecific deprotonation. This γ-oxo-substituted stannane reacts with aldehydes and ketones in the presence of $TiCl_4$ at −78 °C to give the diastereomerically pure α-addition products with high ee (entry 28).[431] The α-addition (formal allylic retention) contrasts to the regiochemical course of the usual Lewis acid mediated reactions. The result is best explained by assumption of a stereospecific formation (syn-S_E') of the α-trichlorotitanium-substituted intermediate **345** via a transition state **344** followed by the stereospecific aldehyde addition via a six-membered chair transition state in the usual way. The thermal reaction between



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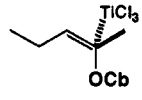
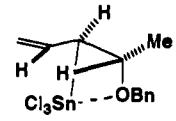


345

the γ-oxo-substituted allylstannane and benzaldehyde does not occur at 150 °C. The thermal reaction of (1*R*)- and (1*S*)-[[(−)-(menthyloxy)methoxy]-(*E*)-crotyl]tributylstannanes with benzaldehyde takes place at 130 °C for 14–15 h (neat) to give (3*S*,4*S*)- and (3*R*,4*R*)-4-hydroxy-3-methyl(*Z*)-1,2-enol ether, respectively (entry 29).[432] The diastereoselectivity of the thermal reaction of the [δ-(alkoxy)allyl]stannane with *p*-nitrobenzaldehyde is not high (entry 30),[433] compared to that of the BF_3-catalyzed addition (entry 26), although the syn–syn-isomer is obtained predominantly. Treatment of the [δ-(alkoxy)allyl]stannane with tin(IV) chloride at −78 °C followed by the addition of an aldehyde gives 1,5-diol derivatives with excellent 1,5-diastereoselectivity (entry 31);[434] less than 2% of the stereoisomer at C-1 position is formed. The reaction between crotyltributyltin and benzaldehyde in the presence of $SnCl_4$, under the exact conditions used for the reaction of entry 31, gives a mixture of all four possible products, suggesting that the benzyloxy group is important in controlling the regioselectivity as well as the stereoselectivity. This view is supported by the selective formation of (3*Z*)-5-alkoxy-1-phenylpent-3-en-1-ol from the $SnCl_4$-induced reaction of a mixture of [4-alkoxy-2-butenyl]- and [1-(alkoxymethyl)-2-propenyl]stannanes with benzaldehyde.[435] It is suggested that the selective formation of the 1,5-diol derivatives (entry 31) involves participation of the allyltrichlorostannane **346** which may be stabilized by a hypervalent Sn–O interaction. The usual six-membered chair transition state involving **346** and an aldehyde, in which the substituent adjacent to the tin is in the preferred axial position, would then give the observed products. The stereospecific formation of **346** is due to intramolecular delivery of the trichlorotin substituent to the double bond by the benzyloxy group (**347**). Excellent, 1,5-



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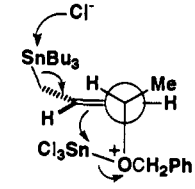
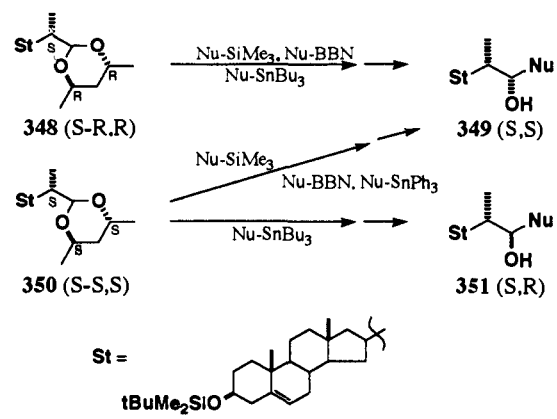


347

diastereoselectivity is also realized in reactions with chiral aldehydes (for example, entry 32); the stereochemical preference of the chiral stannane reagent dominates the course of the reaction. Asymmetric synthesis of *syn*-1,2-diols has been accomplished via the reaction of the chiral γ-alkoxy-substituted allylstannane with aldehydes in the presence of $AlCl_3$ or $AlCl_3$·OEt_2, followed by a five-step operation to remove the chiral auxiliary (entry 33).[437a] Both aromatic and aliphatic aldehydes afford the syn adducts with diastereoselectivities greater than 97:3 upon treatment with BF_3·OEt_2, $AlCl_3$, or $AlCl_3$·OEt_2. The use of $TiCl_4$ and $SnCl_4$ gives unsatisfactory results. The diastereomer excess of the syn-isomers (*R*,*R*-isomer, *S*,*S*-isomer) is high when $AlCl_3$ or $AlCl_3$·OEt_2 is used as Lewis acid while BF_3·OEt_2 leads to decreased de ratios. Three types of optically active allylstannanes, $R^*_2Sn(allyl)_2$ (R* = 2-phenylbutyl, 2-methylbutyl, and 3-phenylbutyl), $R^*R^1Sn(allyl)_2$ (R* = 2-octyl or 2-phenylbutyl, R^1 = phenyl), and $R^*R^1R^2Sn(allyl)$ (R* = 2-phenylbutyl, R^1 = phenyl, R^2 = methyl), have been synthesized. Among these allylstannanes, only diallylbis(2-phenylbutyl)stannane provides allowable enantioselectivity upon treatment with aldehydes in the presence of BF_3·OEt_2.[437b]

2. Reactions with Acetals

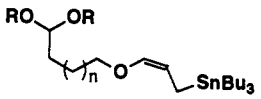
The chiral steroidal acetal **348** (*S*-*R*,*R*), prepared from the steroidal aldehyde and (2*R*,4*R*)-(−)-pentane-2,4-diol, gives **349** (*S*,*S*) upon treatment with nucleophiles including allylsilanes, allyl-9-BBN, and allyltributyltin, while the diastereomeric steroidal acetal **350** (*S*-*S*,*S*) also produces **349** when treated with organometallic reagents with low nucleophilicity such as allylsilanes, allyl-9-BBN, and allyltriphenyltin, but affords **351** (*S*,*R*) with organometallic reagents with high nucleophilicity, for example with allyltributyltin.[289] The high asym-



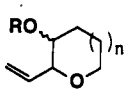
metric induction from **348** to **349** is a reflection of the synergistic effect of the 1,2- and 1,3-chiral centers; the *S* chirality of the newly created chiral center of **349** is expected from Cram's rule of the *S* chirality of the steroidal side chain (1,2-induction) and also from the (R,R)-acetal template (1,3-induction). Predominant formation of **351** from **350** is due to stronger influence of the (*S,S*)-acetal template than that of the 1,2-induction. The conversion of **350** to **349** indicates loss of the effect of the 1,3-chiral center because a late transition state is involved in the reaction of organometallics with low nucleophilicity.[438] The allylation of the β-siloxyacetal **352** (*S-R,R*) with allyltributyltin,

352 **353**

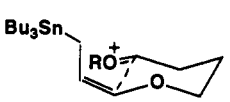
trimethylsilane, and 9-BBN in the presence of $TiCl_4$ gives the chelation product (*S,S*) with very high diastereoselectivity (>90:10), while the (*R-R,R*) isomer **353** also produces the chelation product with fair to good selectivities (>70:30), indicating that the 1,3-asymmetric induction is dictated by chelation rather than the acetal template.[439] The reaction of the ω-trialkylstannyl ether acetals **354–356** in the presence of 2 equiv of $TiCl_3$(Oi-Pr) in CH_2Cl_2 produces the corresponding β-alkoxy-α-vinyl cyclic ethers **357–359**, respectively.[440] The six- and seven-membered cyclic ethers, **357** and **358**, are produced in high yields with slight preference of the trans isomers, but the eight-membered cyclic ether **359** is obtained in only 8% yield. The cyclization of **354** proceeds mainly through a synclinal transition state shown in **360**. Although the use of $TiCl_3$(Oi-Pr), $TiCl_2$(Oi-Pr)$_2$, $TiCl_4$, BF_3·OEt_2, or $MgBr_2$·OEt_2 as a Lewis acid in the cyclization of **354** and **355** affords a mixture of trans- and cis-cyclic ethers, exclusive formation of trans-seven-membered cyclic ether **358** is accomplished by the use of $TiCl_4$·PPh_3 combined Lewis acid system.[302] The $TiCl_4$·PPh_3-



354a; n=1, R⌒R=$(CH_2)_2$
b; n=1, R⌒R=$(CH_2)_3$
c; n=1, R⌒R=$(CH_2)_4$
d; n=1, R=$(CH_2)_3$Ph
355; n=2, R⌒R=$(CH_2)_4$
356; n=3, R⌒R=$(CH_2)_4$



357a; n=1, R=$(CH_2)_2$OH
b; n=1, R=$(CH_2)_3$OH
c; n=1, R=$(CH_2)_4$OH
d; n=1, R=$(CH_2)_3$Ph
358; n=2, R=$(CH_2)_4$OH
359; n=3, R=$(CH_2)_4$OH



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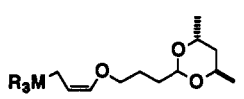
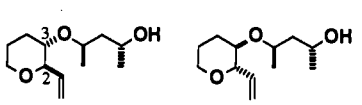


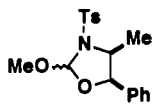
361a; R_3M=Bu_3Sn
b; R_3M=Me_3Ge
c; R_3M=iPr_3Si
d; R_3M=Me_3Si



362 (2R,3S) **363** (2S,3R)

mediated cyclization of **361a** gives a 7:93 mixture of **362** and **363** in 51% yield.[441] The diastereomeric ratio of **362** and **363** is 56:44 in the case of **361b**, and 23:77 in **361c**. Very interestingly, **362** is produced predominantly using **361d**. The stereochemistry at C-2 and C-3 is trans irrespective of the starting material (**361**). The diastereoselectivity change observed above can be explained in terms of S_N1- and S_N2-type mechanism.

The Lewis acid promoted crotylstannane addition to the enantiomerically pure oxazolidine **364** and the subsequent conversion of the resulting adduct **365** provide enantioenriched dithianol **366**.[442] The BF_3·OEt_2-promoted addition of racemic [α- and γ-(alkoxy)allyl]-stannanes **367** or **368** to **364** affords adducts **369** and **370** in diastereomeric ratios up to 95:5 accompanied by enantioenriched [γ-(alkoxy)allyl]stannane (−)-(*R*)-**368**. This observation is consistent with a fast α- to γ rearrangement of the alkoxystannanes (see also eq 97) followed by an enantiomer-discriminating as well as mutual diastereoface-discriminating condensation. This condensation shows a virtually total recognition of the (+)-(*S*) antipodes of **368** from the racemic mixtures when chiral **364** is used. Suitable protection of the α-hydroxy stannane precursors (BOM is best among the three protecting groups) secures a very high mutual diastereoface differentiation of the components, allowing the formation of only two diastereomeric adducts, out of the eight possible, in ratios up to 95:5. The reaction of *S,O*-acetals with allylstannanes is mentioned previously[307] (eq 83).



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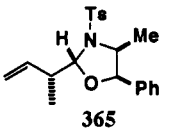

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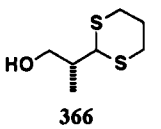

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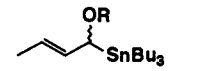
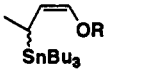


367 R=MOM, BOM, $SiPh_2tBu$



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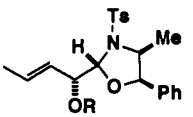

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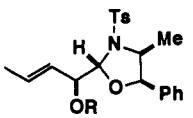

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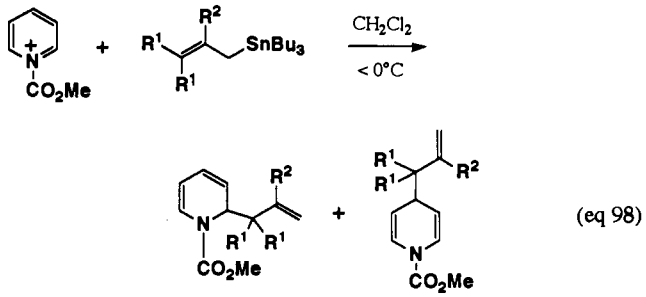
3. Reactions with Imines and Iminium Ions

Allyltributylstannane reacts with aromatic and branched α-alkylimines in the presence of $TiCl_4$ and BF_3·OEt_2 to produce homoallylamines in good to fair yields; the Lewis acid participates by activating the imine, not by transmetalating the tin to other metals (for example titanium).[444] [2-(Acetoxymethyl)allyl]-tributylstannane reacts with imines in the presence of BF_3·OEt_2.[445] The reaction of **21** with allyltributylstannane in the presence of $TiCl_4$ affords a 92–93:8–7 mixture of the Cram and anti-Cram adducts.[46] The $TiCl_4$-mediated addition of allyltributylstannane to **24** produces on 82:18 mixture of **25** and **26** in 70% yields, while the BF_3·OEt_2-mediated reaction affords lower diastereoselectivity (67:33).[46] The BF_3·OEt_2-mediated addition of crotyltributylstannane to aromatic imines (R^1 = R^2 = aromatic in eq 2) provides the syn homoallylamines predominantly (syn/anti = >75:25).[202] The crotylstannane addition to aliphatic and furyl imines (R^1 = i-Pr, c-C_6H_{11}, furyl; R^2 = Bn in eq 2)

produces the syn adducts with very high diastereoselectivity (>20:1).[444] This high syn selectivity can be obtained if Lewis acid–imine complexation is carried out at −78 °C for 2.5 h prior to the addition of crotylstannane, otherwise syn selectivity diminishes to 4:1. These observations are a result of two $TiCl_4$–imine complexes, **371** and **372**, formed kinetically and thermodynamically, respectively.[444] Higher syn selectivity is due to the formation of **371** at lower temperatures, while lower syn selectivity results from **372**. The syn

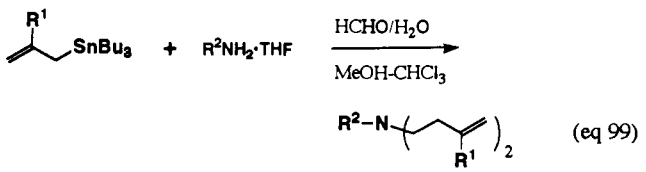
371 **372**

preference in the imine–crotylstannane condensations is consistent with an acyclic transition state similar to the transition states of the aldehyde condensation shown in Scheme X; replacement of aldehyde oxygen to imine NR^2 group affords the transition state of imine additions. Allylstannanes readily react with pyridine and some substituted pyridines activated by alkyl chloroformates to give α-allylated 1,2-dihydropyridines, regioselectively.[448] The regiochemistry of the attack on pyridine nuclei changes from α-addition to α- and γ-addition (nonregioselective) to γ-addition, depending on methyl substituents at the allylic moiety (from allyl to methallyl and crotyl to prenyl groups). The C-C bond formation occurs exclusively at the γ-position of prenylstannane reagent (eq 98).



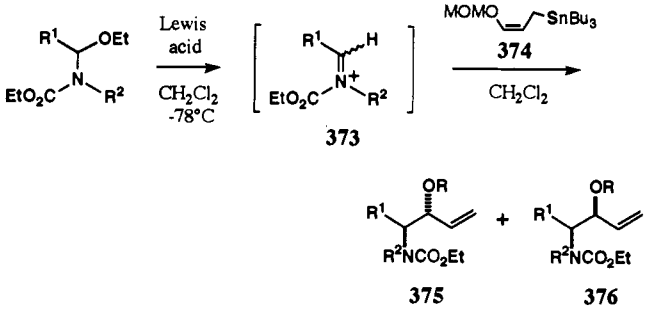
(eq 98)

Reactions of allylstannanes with primary amines and aqueous formaldehyde produce bishomoallylamines (eq 99).[322] Although 4-hydroxypiperidines are obtained in



(eq 99)

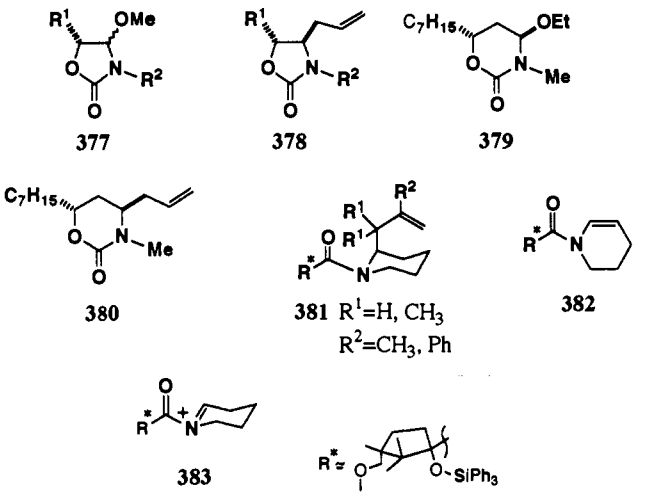
the reaction of primary amines with allylsilanes (eq 84), allylstannanes do not provide such products owing to the higher reactivity of the stannane reagents which add to the derived homoallylamine salt faster than the cyclization process. The Lewis acid mediated reaction of acyliminium ions **373**, generated from the corresponding α-ethoxy carbamates in the presence of Lewis acid, with γ-oxygen-substituted allylstannane **374** provides the amino alcohol derivatives **375** and **376** in good yields.[447] The Lewis acids, $TiCl_4$ and BF_3·OEt_2, are effective. The formation of **373** under these conditions was confirmed by low-temperature NMR.[310] With R^1 = Ph and R^2 = Bn or R^1 = i-Bu and R^2 = Bu, the anti-



373

375 **376**

isomer is produced exclusively, whereas the syn-adduct is obtained exclusively with R^1 = Ph and R^2 = Me. The reactions of the five-membered α-methoxy carbamate **377** with allyltrimethylsilane, allyltributylstannane, and allyl-9-BBN in the presence of $TiCl_4$ or BF_3·OEt_2 afford the trans allylation products **378**, which result from a S_N1 type attack of the allylorganometallics to the intermediate iminium ions, with very high diastereoselectivity.[448] Similarly, the BF_3·OEt_2-mediated allylstannane addition to **379** produces **380** with fair diastereoselectivity (83:17) in 95% yield.[448] Enantiomerically pure 2-substituted piperidines **381** are synthesized by diastereoselective addition of various nucleophiles including allylstannanes to a chiral *N*-acyliminium ion **383** with an *N*-acyl group as chiral auxiliary generated in situ from enamide **382**.[449] The enamide **382** is activated by sequential addition of *O,O*-dimethyldithiophosphoric acid and $TiCl_4$ to produce the acyliminium ion **383**.[450]



377 **378** **379**

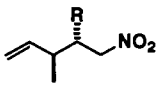
380 **381** R^1=H, CH_3; R^2=CH_3, Ph **382**

383

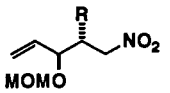
4. Conjugate Addition

Studies on conjugate addition of allylstannanes to Michael acceptors are very few. The Lewis acid ($TiCl_4$, $AlCl_3$, or $SnCl_4$) mediated addition of crotyltributylstannane to **116a** and **116b** affords predominantly **117a** and **117b**, respectively (see eq 41).[205] The highest anti selectivity (90:10) is obtained on treatment with $SnCl_4$, but the other Lewis acids also produce good anti selectivity (>80:20). No addition takes place using BF_3·OEt_2. The Michael addition of the [γ-(alkoxy)-allyl]stannane **374** to **116a** in the presence of $TiCl_4$ or $SnCl_4$ produces the anti-adduct **144a** with good diastereoselectivity (>85:15), but the chemical yield is quite low (10–34%). The Lewis acid ($TiCl_4$, $TiCl_2$(Oi-Pr)$_2$) mediated Michael addition of crotyltributylstannane to nitroolefins affords the anti adducts **384** with low

diastereoselectivity (60:40 to 70:30).[205] Similarly, the anti-isomer **385** is obtained with diastereoselectivity of 65:35 from the addition of **374** to the nitroolefins. The addition of crotyltributylstannane to α,β-unsaturated ketones produces low anti selectivity.[205]



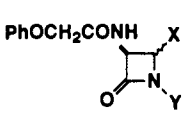
384 (R=Ph, Me)



385 (R=Ph, Me)

5. Radical Allylation

The use of allylstannanes to effect allyl transfer by a radical-chain process is now well documented.[451] The seminal contributions of the radical allylation was made by Kosugi[452] and Pereyre[453] and the initial synthetic application was carried out by Keck.[454] Treatment of **386** with 3 equiv allyltributylstannane and a catalytic amount of AIBN in refluxing benzene produces the allylation product **387** (trans/cis = ca. 2:1) in fair to good yields (50–72%).[455] For the radical allylation, 4-phenylselenyl substituent of **386** is essential. If *cis*-4-chloroazetidinone (X = Cl) was used, **387** could not be obtained and the chloride was expelled from the azetidinone through an ionic mechanism followed by capture of the resulting electron deficient center (iminium ion) by the C-4 secondary amide substituent (see ref 456 for ionic allylation). The free-radical



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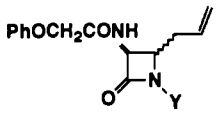
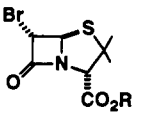


387

X, Y=SePh, $C(CO_2CH_3)=C(CH_3)_2$
SePh, $SiMe_3$
SePh, $Si(tBu)Me_2$

allylation of 6-bromo- and 6,6-dibromopenicillanates, **388** and **389**, in the presence of a catalytic amount of AIBN proceeds in a highly chemo- and stereoselective fashion to give **390a** and **390b**, respectively.[457] Reduction of **390b** with tributyltin hydride gives the corresponding 6-β-allylpenicillanates **391**. In another sequence of reactions, C-allylation was performed on the 6-α-bromopenicillanate 1,1-dioxide esters (SO_2 instead of S of **388**) to give the 6-α-allylpenicillanate 1,1-dioxide esters. Enantiomerically pure 3-oxo-2-(1-phenylethyl)-5-isothiazolidinyl radicals, prepared from the corresponding 5-phenylseleno compound **392**, undergo addition reactions with 2-alkenyltributylstannanes to give a mixture of **393** and **394** with good to excellent diastereoselectivity.[458] In all cases, **393** was produced predominantly, and the highest selectivity (50:1) was obtained in the case of **393c**. For the radical initiator, catalytic amounts of Bu_3SnH/AIBN or AIBN under irradiation are used. As solvents, benzene, ethanol, trifluoroethanol, cyclohexane, and dimethoxyethane are utilized. The crotyl addition leading to **393e** resulted in lower yield (40%) due to the known sensitivity of the crotylstannane to allylic hydrogen abstraction.[459] The radical allylation of the glucosyl bromide **395** with [2-(ethoxycarbonyl)-2-propenyl]tributylstannane produced the corresponding α-allylated glucosyl derivative in 84% yield.[460] Irradiation of 2-(phenylseleno)cycloalkanones **396** with allyltributylstannane in benzene gave the corresponding allylated cycloalkanones in good to excellent yields.[461] Both *cis*- and *trans*-**396** (*n* = 1, R = 3-Me and *n* = 1, R = 3-Bu) yield the same distribution of the *trans*/*cis*-allylated isomers, i.e., ca. 78:22 and 79:21 from each isomer, respectively, indicating the allylation proceeds via the same α-carbon radical intermediate. The thermal reaction of **396** under refluxing toluene in the presence of 10% AIBN also produces the allylation product in high yields.



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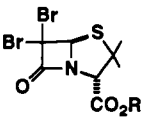

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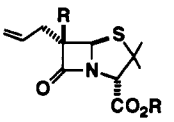
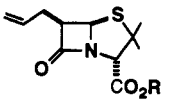


390a; R=H
b; R=Br



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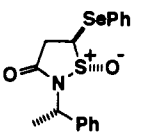

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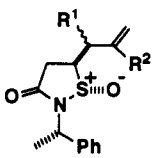
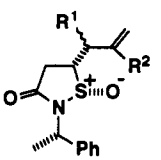
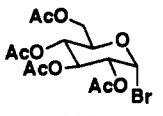




393a; R^1=R^2=H
b; R^1=H, R^2=CH_3
c; R^1=H, R^2=n-Bu
d; R^1=H, R^2=CO_2Bn
e; R^1=CH_3, R^2=H

394



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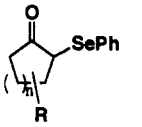
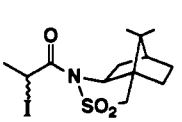


396 n=1 or 2
R=3-Me, 3-Bu, 4-tBu, 2-Me

Heating of (α-iodopropionoyl)camphorsultam (**397**), allyltributylstannane, and 10% AIBN at 80 °C (benzene-d_6) gives a mixture of the allylated derivatives **398a** and **399b** in a ratio of 12:1 in virtually quantitative yield.[462] This level of selectivity (85% de) is remarkable



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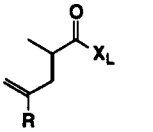
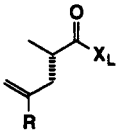


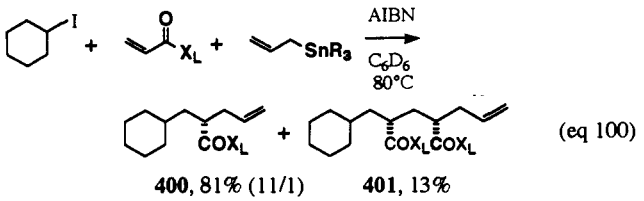
398a; R=H
b; R=Me
c; R=CO_2Me



399a; R=H
b; R=Me
c; R=CO_2Me

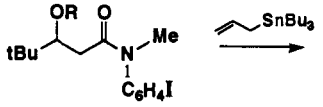
X_L=L-(+)2,10-camphor sultam

for a reaction conducted at 80 °C in the absence of chelating Lewis acid. Reactions at 25 °C or below are initiated with triethylboron in CH_2Cl_2. A decrease in temperature from +80 to −78 °C gives a slow and steady increase in the ratio of **398a**/**399a**, and finally a > 30/1 ratio is achieved at −78 °C. The asymmetric allylation can be placed in sequence with an addition reaction of an alkyl iodide to acryloylsultam (eq 100). The 1/1/1

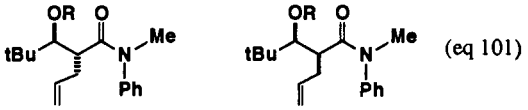


(eq 100)

adduct **400** was obtained as an 11:1 mixture of diastereomers in 81% yield, and 1/2/1 adduct **401** as largely a single product in 13% yield. Asymmetric stereoselection in radical additions to α,β-unsaturated amides and esters has also been reported by the groups of Porter[463] and Giese,[464a] although allylstannanes have not been used in the addition.[464b] Radical allylation of β-hydroxy anilide **402a** (racemic) under Keck's standard thermal conditions (80°C) provided an inseparable mixture of isomers **403a**-anti/syn in a ratio of 86/14 (eq 101). By using photolytic conditions (25°C), the ratio



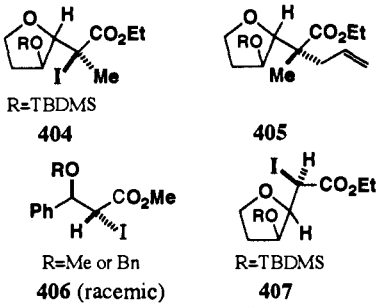
402a; R=H
b; R=Ac



403a-anti **403b-anti** **403a-syn** **403b-syn**

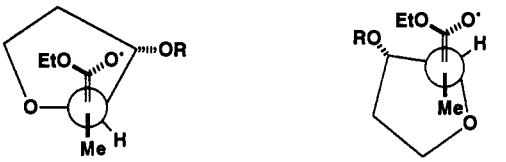
(eq 101)

increased to 93/7. In sharp contrast, allylation of the β-acetoxy anilide **402b** under the photolytic conditions provided *anti/syn*-**403b** in a reversed ratio of 15:85 (eq 101).[465] The allylation may proceed through a rapid translocation of radicals derived from *o*-iodoanilides to the radical α to the carbonyl group. The reaction of tertiary iodide **404** with allyltributylstannane in combination with AIBN at 60 °C gave **405** in 55% yield and with excellent diastereoselectivity (>30:1).[466] Reactions of secondary iodides **406** (racemic) and **407** at 50 °C exhibit modest to good diastereoselectivities (5:1 for **406** and >30:1 for **407**). These ratios could be improved



R=TBDMS
404 **405**
R=Me or Bn R=TBDMS
406 (racemic) **407**

by lowering the reaction temperature to −78 °C and using Et_3B as an initiator. Some mechanistic aspects of the diastereocontrol have been discussed.[466] The radical is not pyramidalized and delocalized through the carbethoxy group. Rotamer **408** suffers from severe interaction between the ester appendage and the tetrahydrofuran ring residue. Rotamer **409** not only lacks such destabilizing interactions but the intramolecular electrostatic or dipole–dipole interactions between the two electronegative groups are alleviated through their anti orientation. Delivery of allyl group from the least hindered face of the radical would lead to the observed diastereoselection.

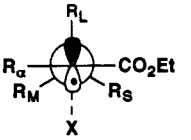


Rotamer **408** Rotamer **409**

The free radical allylation of **410a** and **410b** with allyltributylstannane at −78 °C (AIBN, *hν*, THF) gives a 62:38 and 82:18 mixture of **411** and **412**, respectively, whereas the allylation of **410c** under the same conditions afforded a 26:74 mixture of **411** and **412**.[467] The radicals derived from **410c** did not behave as expected, the reason for which is not clear. There may be little difference in size between methyl and phenyl groups within the context of the radical derived from **410c**. The stereochemical course of the radical allylation of **410a** and **410b** is consistent with model **413**, in which allylation (or reduction with Bu_3SnH) occurs anti to the largest substituent to minimize torsional strain in the transition state. The free-radical allylation using

410a; R_L=tBu, R_M=Me
b; R_L=$SiMe_2Ph$, R_M=Me
c; R_L=Ph, R_M=Me

411; R^1=$CH_2CH=CH_2$, R^2=H
412; R^1=H, R^2=$CH_2CH=CH_2$

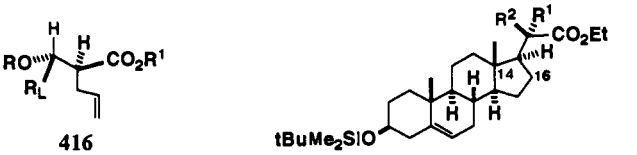


413; Rα=H
X=allylstannane

substrates **414** with electron-withdrawing β-substituents (OR) produces **415** predominantly; the ratio of **415** and **416** is 90:10 from the reaction of **414a**, 83:17 from **414b**, and 89:11 from **414c**. The stereochemical outcome of

414a; R=Me, R_L=Ph, R^1=Me, Z=Br
b; R=Me, R_L=Me, R^1=Et, Z=Br
c; R=Ac, R_L=tBu, R^1=Et, Z=PhSe

415



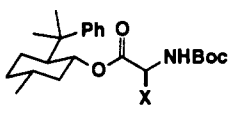
416

417a; R^1, R^2 = SePh, H (20S:20R=1:18)
417b; R^1, R^2 = H, •
417c; R^1=H, R^2=$CH_2CH=CH_2$
417d; R^1=$CH_2CH=CH_2$, R^2=H

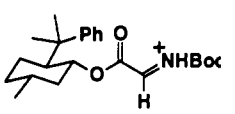
the allylation of **414** is consistent with the model **413** if the electron-withdrawing β-substituent plays the role of R_M, which just corresponds to rotamer **409**. Ally-

lations of β-hydroxy-α-carbalkoxy radicals are not accommodated by the model **413**; they do not parallel the results of **414** in all cases. The stereochemical course of these reactions show solvent dependency. There is a shift in product distribution from the model **413** toward an intramolecular hydrogen-bonded model as one moves from THF to toluene as solvent. The allylation of a C(20) steroidal α-carbethoxy free radical **417b**, prepared from **417a** using AIBN in THF under irradication at −60 °C, with allyltributylstannane produces a 9:1 diastereoselectivity (**417c**/**417d**).[468] The stereochemical outcome can be interpreted by the model **413**.

Reactions of the 8-phenylmenthyl ester of the *N*-Boc derivative of 2-bromoglycine **418** with allyl-, methallyl-, and crotylstannanes at room temperature give **419** with very high diastereoselectivities in high chemical yields; the chiral induction (% *S*) of **419a** is 96, that of **419b** is 95, and that of **419c** is not clear.[469] It is possible that the new allylation reaction does not involve radicals but occurs instead by the nucleophilic addition of the organometallic compound to an intermediate iminium species **420**. Similar, but Lewis acid catalyzed, reactions of this type have been described for the synthesis of alkynylglycine derivatives.[470] The reaction of **421** with allyltributylstannane proceeds at low temperatures both in the presence of $ZnCl_2$ and in the presence of AIBN, and significantly high asymmetric induction is produced in both cases.[471a] It is not clear whether the reaction



418; X=Br



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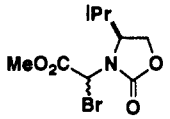
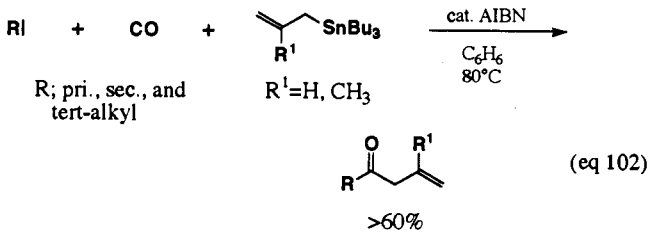


421

419 (X= $RCHC(R^1)=CH_2$)
a; $R=R^1=H$
b; $R=H$, $R^1=CH_3$
c; $R=CH_3$, $R^1=H$

proceeds through a radical process or not. The ionic reaction of α-haloglycine derivatives and organometallics including allylsilanes or -stannanes has been reported previously.[471b] The three-component coupling reaction of alkyliodides, carbon monoxide, and allylstannanes by free-radical carbonylation leads to a convergent synthesis of β,γ-unsaturated ketones (eq 102).[472] The use of enhanced CO pressure gives better

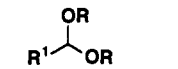


(eq 102)

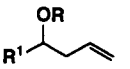
selectivity of carbonylated products relative to allylated alkanes, which are presumably produced by the Keck-type allylation. The three-component coupling reaction probably proceeds through the formation of acyl radicals, generated from R· and CO, followed by allylation with allylstannanes. Allylation of quinones via photoinduced electron-transfer reactions of allylstannanes has been investigated from the mechanistic point of view.[473] Irradiation of aromatic α,β-epoxy ketones in the presence of allyltributylstannane affords α-allyl-β-hydroxy ketones by a single electron transfer mechanism.[474]

D. Allylic Plumbum Reagents

A lead-promoted allylation of carbonyl compounds with allyl bromide in Pb/Bu_4NBr/Me_3SiCl/DMF system has been performed in good yields with high chemoselectivity; the order of reactivity of substrates is following: $RCHO > R^1R^2CO > R^1CH(OH)CO_2R^2 \gg R^1CO_2R^2$, lactone, $(RCO)_2O$, and RCOCl.[475a] An in situ method for preparing a reactive allyllead reagent is attractive from the standpoint of convenience since it avoids the need to isolate the organometallic reagent. The reagent, which is formed by treatment of allyl bromide with aluminum foil (1.0 equiv), $AlBr_3$ (0.1 equiv), and a catalytic amount of lead(II) bromide (0.03–0.1 equiv) in THF, reacts with acetals **422** to give the allylated ethers **423** in good to high yields.[476] In the case of dimethyl acetals of cinnamaldehyde or of some aromatic aldehydes, small amounts of double allylated products are obtained as byproducts. The allylation of the *N*,*O*-acetal **424a** affords **424b** in 52% yield. The



422; R^1=Ar, Cinnamyl, C_6H_{11}

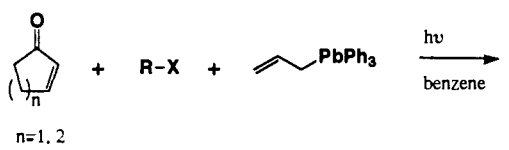


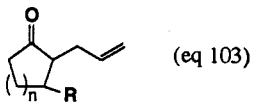
423

424a; X=OAc
b; $X=CH_2CH=CH_2$

allylation of imines is accomplished by the electroreductive "Barbier-type" allylation using allyl bromide (3 equiv) in THF containing $PbBr_2$ (0.05 equiv) and Bu_4NBr (0.1 M).[477] In place of $PbBr_2$, $PbCl_2$, and $BiCl_3$ can be used successfully, while $ZnCl_2$ and $SnCl_2$ are less effective. As a cathode Pt is used, and Al or Zn anodes are employed. By this electroreductive method, allylation of aromatic and α-branched aliphatic aldimines proceeds smoothly to afford the corresponding homoallylamines in 85–98% yields. Details of the structure of the reactive allyllead species and its mechanism of formation are not quite clear. The allylation of imines was also carried out with a combination of a catalytic amount of $PbBr_2$ (~0.1 equiv) and Al (1 equiv) in Et_2O containing $BF_3{\cdot}OEt_2$.[475b]

2-Cyclopenten-1-one and 2-cyclohexen-1-one react with various alkyl bromides and iodides (primary, secondary, and tertiary) (6 equiv) in the presence of allyltriphenylplumbum (3 equiv) under irradiation to give α-allylated-β-alkylated cyclopentanones and cyclohexanones, respectively, in good to high yields (eq 103).[478] The use of allystannanes, instead of allylplumbum, significantly decreases the yield of the product. The trans/cis ratios of the product are at least 80:20 and 99.7:0.3 at best. To accelerate radical reactions, 5 mol % of hexaphenyldiplumbum was used. Not only the cycloalkenones, but also methyl crotonate and acrylonitrile undergo the three-component coupling reaction (α-allylation-β-alkylation) under similar conditions. Higher reactivity of allylplumbum than allylstannane toward carbon radicals α to the carbonyl





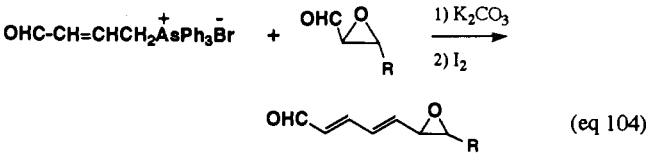
(eq 103)

was confirmed in the reactions of α-(phenylseleno)-carbonyl compounds. A 0.025 M benzene solution of α-(phenylseleno)-γ-butyrolactone and 1.5 equiv of allyltriphenylplumbum in the presence of hexaphenyldiplumbum (5 mol %) was irradiated for 5 min to give α-allyl-γ-butyrolactone in 95% yield, whereas irradiation of a 1 M benzene solution of the same substrate and 2.0 equiv of allyltributylstannane in the presence of hexabutyldistannane (5 mol %) took 1 h for complete consumption of the starting lactone giving the allylbutyrolactone in 90% yield.

VI. Group 15 (As, Sb, and Bi)

A. Allylic Arsenic Reagents

(3-Formylallyl)triphenylarsonium bromide was used for formyl enyl olefination of an epoxyaldehyde (eq 104).[479a] An allylic arsonium bromide, derived from

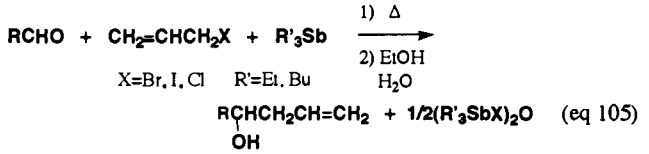


(eq 104)

triphenylarsine and 5-bromo-3-penten-2-one, condensed with a variety of aldehydes in the presence of K_2CO_3 to give exclusively ω-acyl-substituted polyenones in good yields.[479b] Treatment of allylic arsonium ylides with LDA gave the corresponding ylides (R^1R^2-CH=CHCHAsPh$_3$), which react with aldehydes to afford the vinyl epoxides in good yields.[479d]

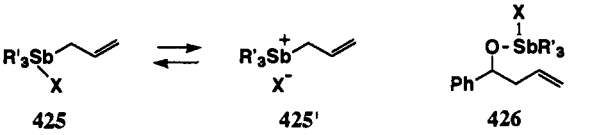
B. Allylic Stibine Reagents

On heating equivalent amount of aldehydes, allyl halides, and trialkylstibine at 80 °C, homoallylic alcohols are obtained in high yields after hydrolysis, along with bis(bromotrialkylantimony) oxide (eq 105).[480]



(eq 105)

Aromatic and aliphatic aldehydes react smoothly. Crotyl chloride reacts with *p*-bromobenzaldehyde in the presence of tributylstibine and a catalytic amount of I_2 to produce a 75:25 mixture of the syn and anti homoallyl alcohols. The allylation proceeds through pentavalent organoantimony salt, allyltriethylstibonium bromide **425**, generated from triethylstibine and allyl bromide at room temperature. The salt **425** reacts with benzaldehyde at 80 °C, forming a moisture-sensitive oil, (bromoalkoxy)triethylstiborane (**426**).



Related to **425'**, quaternary stibonium salts [n-Bu_3Sb-CH_2E]$^+X^-$ (E = Ph, CH=CH_2, CH=$CHCO_2$Et, CO_2Et, CN) are prepared from the corresponding halides and n-Bu_3Sb. On treatment with RLi (R = n-Bu, t-Bu, Ph) the salts afford pentaalkylstiboranes, n-Bu_3Sb(R)-CH_2E, which react with aromatic aldehydes to give, after subsequent hydrolysis, homobenzylic alcohols, homoallylic alcohols, ethyl 5-aryl-5-hydroxypent-2-enoates, ethyl β-aryl-β-hydroxypropionates, and β-aryl-β-hydroxypropionitriles, respectively, in good to excellent yields.[481] Allyltetrabutylstiborane reacts with acid chlorides to produce the corresponding allylic ketones, and crotyltetrabutylstiborane which is prepared by reaction of butylmagnesium bromide with crotyltributylstibonium bromide (resulting from the reaction of crotyl bromide and tributylstibine) also reacts with acyl chlorides to give the branched ketones **427** instead of the linear ketones **428**.[462] The reaction

of these pentavalent allylstiboranes with ketones is generally very low, but the reaction can be promoted by the Lewis acid $AlCl_3$ to give the corresponding tertiary homoallyl alcohols in good yields.[462] Active zerovalent antimony generated from antimony(III) chloride/metallic iron ($SbCl_3$/Fe),[483] antimony(III) chloride/metallic aluminum ($SbCl_3$/Al), or metallic antimony/THF/HMPA[479c] induces allylation of aldehydes with allylic halides at room temperature to give high yields of the corresponding homoallyl alcohols with high regio- and chemoselectivity. Less relative allyl bromide needs higher temperatures (60 °C), but addition of NaI allowed the reaction temperature to be reduced to ambient. DMF is used as a solvent in the $SbCl_3$/Fe system, and DMF/H_2O medium is effective in the $SbCl_3$/Al or $SbCl_3$/Zn system.[484] When methyl and ethyl alcohols are used as solvent instead of DMF/H_2O, the acetalization product is obtained in almost quantitative yield. Catalytic amounts of $SbCl_3$ are effective for this purpose; catalytic $SbCl_3$/Fe and catalytic $SbCl_3$/Al are needed, and the reaction does not occur in the absence of Fe or Al.[464] This method can also be applied to ethylene glycol and propylene glycol to give the corresponding cyclic acetals.

C. Allylic Bismuth Reagents

In the presence of metallic bismuth Bi(0) (1.2 equiv), allyl bromide and iodide (1.2 equiv) react with aliphatic and aromatic aldehydes in DMF at room temperature to give the corresponding homoallyl alcohols in good to excellent yields.[485] Acetophenone is not allylated under these conditions. The allylation also proceeds very smoothly by $BiCl_3$/Zn(0) in THF, $BiCl_3$/Fe(0) in THF, and $BiCl_3$/Al(0) in THF/H_2O, at room temperature.[486] The allylation of aldehydes containing a hydroxyl group has been accomplished by the last system ($BiCl_3$/Al(0)

in THF/H_2O). Also, only a catalytic amount of $BiCl_3$ is needed to effect the allylation in the aqueous medium; 10 mole % $BiCl_3$, Al (2 equiv), THF/H_2O (2.5:1). The addition of crotyl bromide to benzaldehyde produces the syn-adduct predominantly in any procedure, but the $BiCl_3$/Fe(0) procedure gives higher anti selectivity than others.

VII. Group 16 (Te)

A. Allyltelluronium Reagents

Allyldialkyltelluronium bromides are converted to diphenyltelluronium allylides **429**, which reacts with aldehydes to produce α,β-unsaturated epoxides.[467] In

$R_2\overset{+}{T}e\text{-}\overset{-}{C}HCH{=}CH_2$

429; R=Me, n-Bu, i-Bu

the presence of solid KOH, allyldi-isobutyltelluronium bromide reacts directly with aromatic aldehydes at room temperature under solid–liquid phase-transfer conditions to afford α,β-unsaturated epoxides in excellent yields (eq 106).[488a] The allyltelluronium salt is easily

$$[\overset{+}{I}Bu_2TeCH_2CH{=}CH_2]\overset{-}{B}r + RCHO \xrightarrow[\text{KOH}\\ \text{-}iBu_2Te]{\text{THF(trace } H_2O)} R\text{-}\underset{\diagdown O \diagup}{CH}\text{-}CHCH{=}CH_2 \quad \text{(eq 106)}$$

obtained by the reaction of diisobutyl telluride and allyl bromide without solvent at room temperature. In general, the cis epoxides are produced predominantly, but the stereoselectivity is low. Trimethylsilylated diisobutyltelluronium allylide, generated from [3-(trimethylsilyl)prop-2-enyl]diisobutyltelluronium bromide with lithium 2,2,6,6-tetramethylpiperidide, reacts with α,β-unsaturated esters to afford trimethylsilylvinylcyclopropane derivatives via Michael addition in excellent yields with high stereoselectivity.[488b]

VIII. Group 3 (Ce, La, Nd, Sm, and Yb)

A. Allylic Lanthanoid Reagents

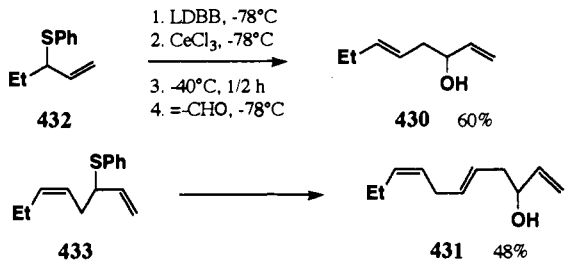
Cerium amalgam Ce-(Hg) or Ce-($HgCl_2$) is an effective reagent for the chemoselective preparation of homoallyl alcohols from allyl halides and carbonyl compounds (eq 107).[469] The same reagent can also be satisfactorily

$$\underset{\text{allyl, benzyl, propargyl iodides and bromides}}{RX} + \underset{\text{aldehydes ketones}}{R'COR''} \xrightarrow[\text{THF}]{\text{Ce-(Hg) or Ce-(HgCl}_2\text{)}} R\text{-}\underset{OH}{\overset{R'}{\underset{|}{C}}}\text{-}R'' \quad \text{(eq 107)}$$

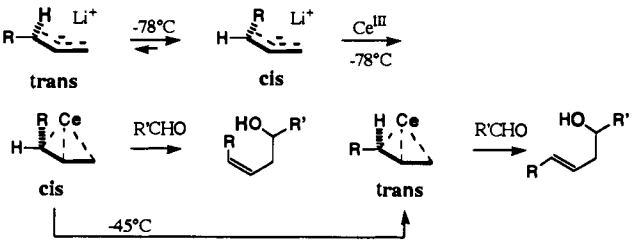
employed for the Reformatsky-type reaction of α-halo esters with carbonyl compounds. The reaction of alkyl- and phenyllithiums with 1 equiv of CeI_3, prepared in situ by the reaction of Ce metal with iodine in THF, produces organocerium(III) reagents (eq 108). The reagents are less basic than organolithiums and Grignard reagents, and they react cleanly at −78 to −65 °C with various carbonyl compounds to afford the addition

$$RLi + CeI_3 \xrightarrow[-65°C]{\text{THF}} \text{"}RCeI_2\text{"} \quad \text{(eq 108)}$$

products in high yields, even though the substrates are susceptible to enolization or metal–halogen exchange with simple organolithiums. The same reagents react also with α,β-unsaturated carbonyl compounds to yield 1,2-addition products in high regioselectivity. Instead of the in situ prepared CeI_3, the use of commercially available lanthanoid chlorides was attempted; $CeCl_3 \cdot 7H_2O$, $LaCl_3 \cdot 7H_2O$, $NdCl_3 \cdot 6H_2O$, $PrCl_3 \cdot 7H_2O$, $SmCl_3 \cdot 6H_2O$, $YbCl_3 \cdot 6H_2O$. These hydrated salts were dried in vacuo at 140 °C and treated with a n-BuLi at −78 °C (see eq 108). The resulting reagents were subjected to reaction with carbonyl compounds. Cerium, lanthanium, neodymium, and ytterbium chlorides give excellent results, while the use of praseodymium and samarium chlorides result in lower yields probably owing to insufficient dehydration of the salts. The X-ray crystal structural analysis indicates that an allylcerium is a π-complex.[490] Treatment of unsymmetrical allyllithiums with cerium(III) chloride at −78 °C presumably produces the corresponding allylceriums which react with aldehydes at the less-substituted allylic terminus to give linear homoallyl alcohols regioselectively (see **5** and **6**).[9] In general, *cis*-allyl anions are more stable than trans-isomers.[491a] Cis-isomers of heteroatom-substituted allyl anions (i.e. O- or S-substituted systems) are quite stable due to chelation of lithium to the heteroatom. Remarkably, *trans*-allyl anions can be produced with high selectivity simply by warming the solutions of *cis*-allylceriums from −78 to −40 °C. Thus, **430** and **431** can be generated from **432** and **433**, respectively.[16] This stereochemical control is



possible because of the fortunate circumstance that the mainly ionic allyllithiums are more stable in the cis configuration[5] while the allylcerium π-complexes are more stable in the trans configuration (eq 109).[9] Allylic,

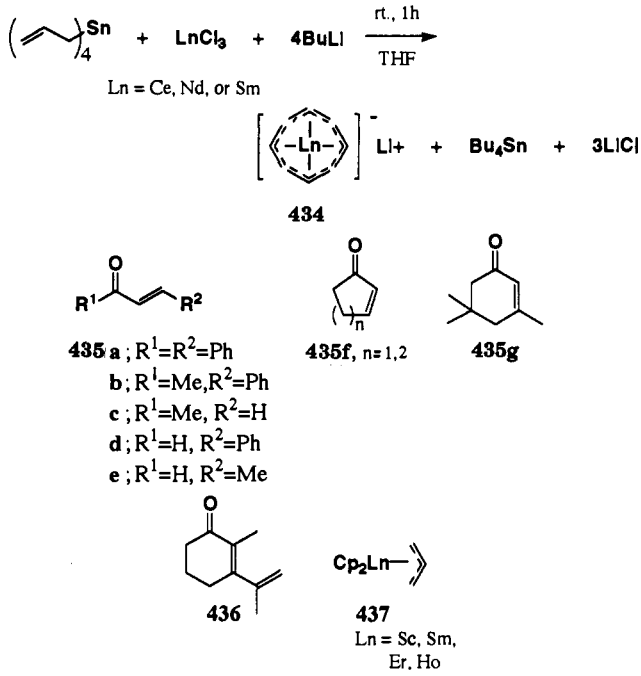


(eq 109)

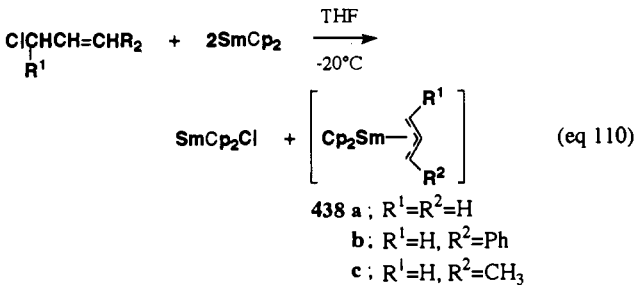
benzylic, and propargylic halides easily react with ketones in the presence of SmI_2.[491] Yields are often appreciable (60–80%) under standard conditions at room temperature and can be rendered quantitative using an excess of SmI_2 and organic halides. Allylic or

propargylic halides lead to mixtures of the two isomeric tertiary alcohols (linear or branched alcohols in the case of allylic halides). The major product formally arises from reaction of unrearranged halide.

π-Allyl lanthanoid ate complex **434**, which is prepared in situ by transmetalation of tetraallylstannane using the lanthanoid trichloride and n-BuLi in THF, reacts smoothly with α,β-unsaturated carbonyl compounds **435–436** with a high degree of 1,2-regioselectivity to give the corresponding 3-hydroxy-1,5-dienes in good to excellent yields.[492] The 1,2-regioselective allylation may

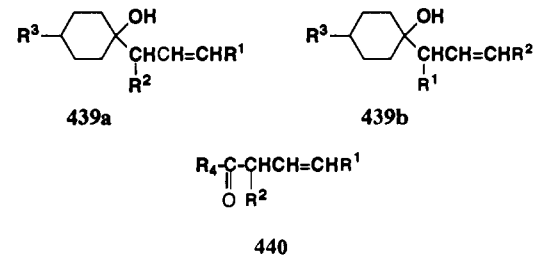


be rationalized by the strong oxophilicity and hardness of lanthanoid metal species. Complexes **434**[493] and **437** (Cp = cyclopentadienyl) have been isolated and their structure determined. As mentioned above, alkyl and allyl lanthanides complexes are usually prepared from some Ln(III) compounds such as $CeCl_3$ and $SmCl_3$. Allyl chlorides react with Cp_2Sm to afford an allyl samarium intermediate **438** (eq 110), the η^3-allyl structure of which has been assigned upon its reactivity with ketones;



(eq 110)

cyclohexanones are converted to the corresponding homoallyl alcohols **439** and acid chlorides to the corresponding allylated ketones **440**.[495] Reaction of **438b** (from cinnamyl chloride) and **438c** (from crotyl chloride) with cyclohexanone (R^3 = H) produces the branched homoallyl alcohols **439a** in high yield; **439a**/**439b** = >100:1 for **438b**, and 4:1 for **438c**. This regioselectivity is in contrast with product distribution in Barbier-type conditions with SmI_2, in which a mixture



of the two alcohols with linear isomer in major amount is obtained.[496] Further, this regioselectivity is also opposite to the selectivity in cases of allylcerium reagents (eq 109). Formation of **439a** and **439b** with the same diastereoisomer ratio for the reactions of crotyl chloride and 3-chloro-1-butene on $SmCp_2$ followed by addition of cyclohexanone is consistent with formation of common intermediate **438c**. Branched ketones **440** are obtained either exclusively or predominantly, but addition of nonanoyl chloride on **438a** yields only double allylated tertiary alcohol; further allylation of the resulting allylated ketone takes place. Lanthanide(II) iodides such as SmI_2 and YbI_2 show high catalytic activity for the photochemical allylation of aldehydes with allylic halides to give the corresponding homoallyl alcohols.[497]

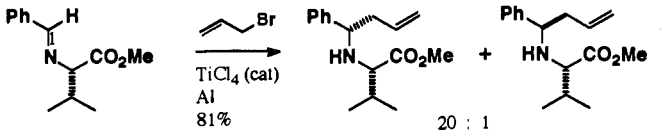
IX. Group 4 (Ti and Zr)

A. Allylic Titanium Reagents

If the counterion (Li, Na, K, etc.) of allyl carbanions is replaced by titanium metal (or zirconium metal), high regio- and stereoselectivity are often produced by the resulting allyltitanium reagents (for example see **3** and **4**). The immense progress in this field has been surveyed in a series of general,[4,498] and more specific[499] review articles. Impressive diastereo- and regiocontrol can be achieved with achiral allyltitanium reagents.[500] A six-membered cyclic transition state with chair conformation (Scheme III) explains the diastereoselectivity of the aldehyde–allyltitanium condensation reaction. Titanium tetraalkoxides $Ti(OR)_4$, partially chlorinated alkoxides $Ti(OR)_nCl_{4-n}$, and Cp- and even Cp_2-substituted titanium complexes can be used as the titanium metal for replacement of the main group counterion. Ketones can be allylated with high diastereocontrol as well.[501] Excellent enantioface control of the allylation of carbonyl compounds has been accomplished if the chirality is incorporated in the ligand of titanium metal. The successful results in the enantioselective allylations have been covered by a recent review of Duthaler and Hafner,[502] and by their most recent full paper.[503] Accordingly, the allylation of aldehydes and ketones with achiral or chiral titanium reagents is not picked up, but the allylation of other electrophiles is surveyed.

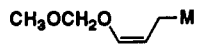
The allylation of **22** with allyltitanium triisopropoxide gives a 23:77 mixture of chelation and nonchelation products. Predominant formation of nonchelation product is also observed in the allylation with allyl-9-BBN and allyl-$B(OMe)_2$. Perhaps, the titanium triisopropoxide reagent has weaker chelating ability toward the nitrogen and oxygen atoms of **22** than allylmagnesium or zinc halides (see eq 4).[50] The allylation of **23** with the same titanium reagent affords

a 30:70 mixture of chelation and nonchelation adducts.[50] Further, the nonchelation isomer is produced predominantly from the reaction of **29** with allyl-Ti(Oi-Pr)$_3$;[350] the ratio of chelation/nonchelation is 6:94 for the (*S*)-phenylethyl derivative of **29** and 20:80 for the *R*-isomer. The addition of crotyl-Ti(Oi-Pr)$_3$ or γ-methoxy-substituted allyl-Ti(Oi-Pr)$_3$ to certain activated imines analogous, **101**, results in low syn/anti diastereoselectivities.[46,199b] "Barbier-type" allylation of imines with allyl bromide is carried out by the action of aluminum (1 equiv) and titanium chloride (0.05 equiv) in THF.[504] It is proposed that low-valent titanium(0) is produced by the reduction of Ti(IV) using Al(0), and this Ti(0) inserts into allyl bromide to give allyltitanium halide intermediate which reacts with imines (or iminium ions activated by the resulting Al(III)), giving the homoallyl amines. Very high 1,3-asymmetric induction has been accomplished by the $TiCl_4$ (cat)/Al-promoted allylation (eq 111).



(eq 111)

The conjugate addition of crotyl-Ti(Oi-Pr)$_3$ to **116a** affords the anti-isomer **117a** predominantly in high yields.[205] γ-Oxygen-substituted allyl-Ti(Oi-Pr)$_3$ **441** adds to **116a** and **116b** in an anti selective manner.[205]

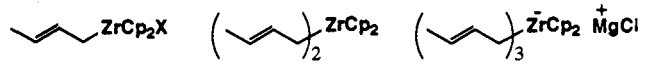


441; M = Ti(OiPr)$_3$

Allyltitanium triphenoxide, generated in situ from allylmagnesium chloride and $ClTi(OPh)_3$ in THF at −78 °C, reacts with various substituted oxiranes regioselectively at the more substituted carbon atom to give the corresponding allylated alcohols in good yields.[505] The use of allyl-Ti(Oi-Pr)$_3$ results in the loss of the regioselectivity and the formation of considerable amounts of reduction product of epoxides.

B. Allylic Zirconium Reagents

Crotylzirconium reagents **442**–**444** have been prepared in situ by the addition of 1, 2, and 3 equiv of crystallithium or crotylmagnesium chloride to Cp_2ZrCl_2 in THF.[506,507] Low-temperature NMR studies indicate

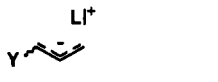


442; X=Cl
b; X=OC_5H_{11}

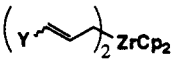
443

444

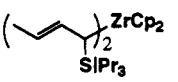
that **443** is a 60:40 mixture of *E*- and *Z*-isomers at 30 °C and an 87:13 mixture at −78 °C, and **442** and **444** are 85:15 and 55:45 mixtures of isomers at −70 °C.[507] These reagents produce the anti homoallyl alcohols predominantly upon treatment with aldehydes, and the diastereoselectivity closely paralleles the isomeric composition of these crotyl reagents, suggesting the reaction proceeds through a six-membered chair transition state. The addition of crotylmagnesium chloride to $Zr(OR)_4$ produces crotyl-$Zr(OR)_3$ reagents, which are in general less diastereoselective than **442**–**444**.[507] This is in marked contrast to the high diastereoselectivity often realized by allylic-$Ti(OR)_3$ reagents. Among the alkoxy-substituted zirconium reagent, the most selective is **442b**. Heteroatom-substituted allylic anions **445a,b** are trapped with Cp_2ZrCl_2 to produce **446a,b** in situ, respectively.[211] These reagents also afford the anti-adduct predominantly upon treatment with aldehydes, suggesting a major stereoisomer of **446a** and **446b** possesses *E* geometry. The use of PhCHO/BF_3 complex in the reaction of **447** affords the syn-isomer **448** predominantly, while the reaction of **447** with PhCHO gives, as usual, the anti-isomer preferentially.[211] As in



445a; Y=CH_3OCH_2O
b; Y=iPrS



446a; Y=CH_3OCH_2O
b; Y=iPrS



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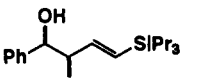
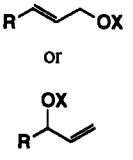


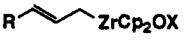
448

the case of the allylic stannane reactions, the Lewis acid mediated condensation of the allylic zirconium reagent presumably proceeds via an acyclic transition state. Allylic zirconium reagents **449** can be prepared in situ by treating allylic ether derivatives **450a** with zirconocene "Cp_2Zr", generated from Cp_2ZrCl_2 and 2 equiv of *n*-butyllithium.[508a] Reactions of **449** with aldehydes proceed in highly regio- and diastereoselective manner to give anti homoallyl alcohols predominantly. The bulkiness of the alkoxy group (OX) has a notable effect on the anti diastereoselectivity: a bulkier alkoxy group such as OTBDMS gives higher selectivity than OMe or OBn group. The conjugate addition of **443** to **116a** and **116b** produces predominantly the anti-adduct **117a** and **117b**, respectively.[205] Alkoxy allylic zirconium reagents, prepared from acetals **450b** of α,β-unsaturated aldehydes and "Cp_2Zr", react with carbonyl compounds to give 1,2-diol derivatives **451** with low anti diastereoselectivity.[508b] Intervention of a γ-alkoxy allylic zirconium intermediate was confirmed by an NMR experiments.

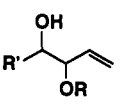


450a; X=alkyl, benzyl, SiR_3

450b; R=Et, -CH_2CH_2-



449



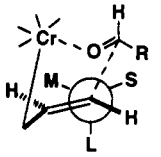
451

X. Group 6 (Cr and Mo)

A. Allylic Chromium Reagents

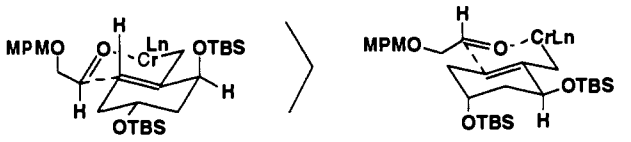
The additions of an alkenyl, alkynyl, allyl, or vinylchromium compound to an aldehyde have been re-

viewed recently.[509] Allylic halides add to aldehydes in the presence of chromium(II) salts; $CrCl_2$ is generated in situ by the $LiAlH_3$ reduction of $CrCl_3$ in THF.[510] The reaction is highly stereoselective and affords the *anti*-homoallyl alcohols regardless of the geometry of the starting allylic halides.[2a,511] This behavior can be explained by assuming that the intermediate organometallics (*E*)-**307** and (*Z*)-**307** (ML_{n-1}=CrX_2) equilibrate rapidly via the chromium(III) intermediate **306** (ML_{n-1}=CrX_2) before reacting with an aldehyde (Scheme XI).[4] The anti diastereoselectivity is produced through a six-membered chair transition state involving (*E*)-**307**. Since the initial report of Hiyama and Nozaki,[510a] the addition of allylic chromium reagents to aldehydes has led to numemrous useful synthetic studies (Table VIII). The Cram (or Felkin–Anh) product is produced predominantly from α-chiral aldehydes (entries 1–3), and chelation control is not involved in the allylic chromium reaction.[512,513] The nature of the large substituent on the α-carbon of the aldehyde is the predominant factor for the diastereoselectivity. Treatment of ethyl α-(bromoethyl)acrylate with Cr(II) produces the corresponding allylic chromium reagent which adds to aldehydes efficiently to give α-methylene-γ-butyrolactones (entry 4).[514] The chromium(II)-mediated addition of the chiral allylic bromides to achiral (or chiral) aldehydes proceeds with high Felkin–Anh selectivity with respect to the stereocenter at Cγ in the bromide (entries 5 and 6).[515] By double stereodifferentiation experiments it was shown that the bromide is the stereodominating component in the addition. The diastereoselectivity can be explained in terms of the Felkin–Anh model **452**, although



452

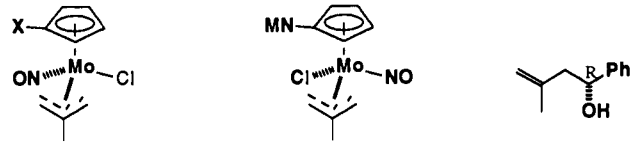
this result is somewhat surprising as the Felkin–Anh model normally is considered as characteristic of electron deficient reaction sites. The reaction of γ-disubstituted allylic phosphates with aldehydes in the presence of $CrCl_2$/cat LiI in DMPU is not stereoconvergent (in contrast to γ-monosubstituted allylic chromium reagents) and proceeds with high stereoselectivity (entry 7).[516] The presence of the two substituents at the γ-position slows down the equilibrium process (Scheme XI, **306** and **307**). The use of a phosphate as a leaving group is not responsible for the high stereodivergent process, as the reaction of (*E*)- and (*Z*)-monosubstituted allylic phosphates with benzaldehyde in the presence of $CrCl_2$ always affords the *anti*-alcohol as major diastereoisomer. γ-Trimethylsilyl-substituted allylchromium reagent, prepared from a 2:1 mixture of 3-(trimethylsilyl)- and 1-(trimethylsilyl)-prop-2-ene, affords the anti-adduct as a single stereoisomer (entry 8).[517] However, trimethylsilyl substitution in the 2-position of a crotylchromium reagent give the syn-adduct predominantly (entry 9).[517] The γ-halo-substituted allylic chromium reagent gives, upon treatment with benzaldehyde, a mixture of branched and linear homoallyl alcohols along with 1-phenyl-1,4-butadiene (entry 10).[518] Although the reaction proceeds predominantly with allylic transposition in accord with results obtained with non-halogenated reagents, the halogen substituent serves to diminish this selectivity. The *syn*- and *anti*-halohydrin isomers are formed in approximately equal amounts. β,γ-Dioxygen-substituted chromium reagent also provides a mixture of branched and linear alcohols (entry 11), but in this case a single stereoisomeric branched alcohol is produced.[518] The very high stereoselective condensation shown in entry 12 is rationalized by assuming transition state **453** is preferred over **454** because of minimization of $A^{1,2}$ type of steric interaction.[519] A vinyl-substituted β-hydroxy carbanion synthon is produced by reduction of 1,3-diene monoepoxide with $CrCl_2$ in the presence of LiI (entry 13).[520] The reagent reacts with aldehydes to afford *R*,R** adducts stereoselectively.



453 **454**

B. Allylic Molybdenum Reagents

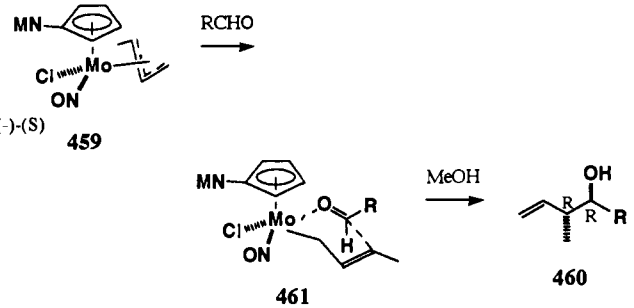
Treatment of CpMo(NO)Cl(η^3-2-methallyl) complex **455** with aldehydes (2–3 equiv) in the presence of MeOH in $CDCl_3$ (in NMR tubes) yield the corresponding homoallyl alcohols in high yields (90–100%).[521] Homochiral complexes, **456** [(−)-(*S*)] and **457** [(+)-(*R*)], were isolated via fractional crystallization. Treatment of >98% de **456** with benzaldehyde gives (+)-(*R*)-**458** in >98% de. The reaction of the *R*-epimer **457** with



455 X=H
456 X=neomenthyl (NM)

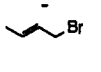
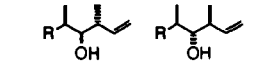
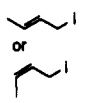
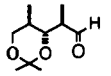
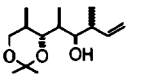
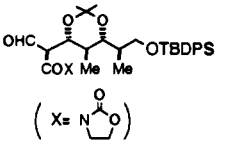
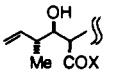
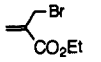
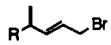
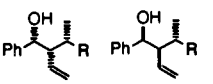
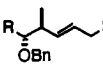
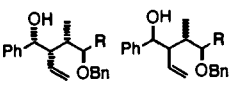
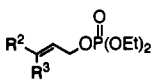
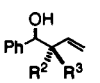
457 **458**

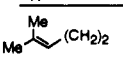
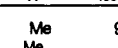
benzaldehyde affords (−)-(*S*)-3-methyl-1-phenyl-3-buten-1-ol with 97% de. Treatment of benzaldehyde (2 equiv) with CpMo(NO)(Cl)(η^3-(*E*)-crotyl) in methanol/CH_2Cl_2 yields a 22:1 mixture of the *anti*- and *syn*-homoallyl alcohols.[522] Homochiral (−)-(*S*)-NMCpMo(NO)(Cl)(η^3-(*E*)-crotyl) **459** reacts with benzaldehyde to yield (*R*,*R*)-2-methyl-1-phenyl-3-buten-1-ol (**460**) in 90% ee and 92% de. The origin of this extraordinary

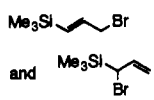
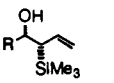
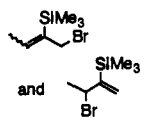
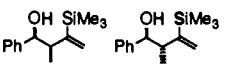
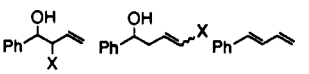
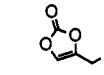
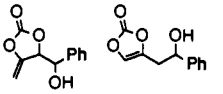
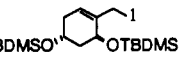
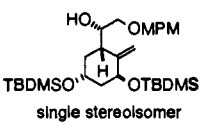
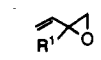
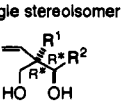


selectivity lies in the electronic asymmetry created by the differential backbonding capabilities of the nitrosyl and chloride ligands. As anticipated by the distortion toward a π-σ-crotyl in the solid structure (X-ray), the

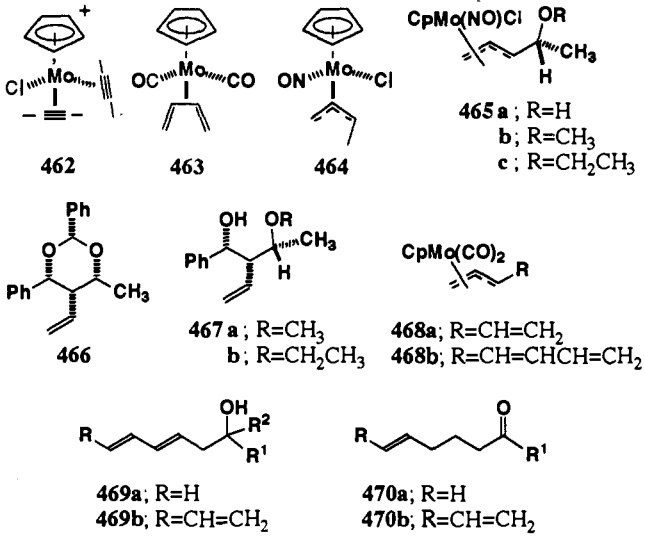
Table VIII. Reactions of Allylic Chromiums with Aldehydes

entry	allylic substrate	aldehyde	conditions	product	yield, %	ref
1			$CrCl_2$, THF	 R=Ph 2.6 : 1; R=CH_2OTHP 1 : 1; R=  11 : 1		512
2	 or		$CrCl_2$, THF	 > 10:1 (other isomers)	86	513
3			$CrCl_2$, THF, 25 °C	 anti : syn= 4-5 : 1	75–84	194
4		PhCHO	$CrCl_2$, THF, 25 °C		94	514
5	 R = CH_2OSiPh_2tBu, CH_2OBn	PhCHO	$CrCl_2$, THF, 0 °C	 82-83 : 18-17	68–88	515
6	 R = CH_2OBn, 	PhCHO	$CrCl_2$, THF, 0 °C	 91~96 : 9~4	75–84	515
7		PhCHO	$CrCl_2$, cat Li(I), DMPU, 25 °C			516

R^2	R^3	isomeric ratio	
	Me	97 : 3	94
		99 : 1	98
Me	Bu	93 : 7	66
Pr	Pr	>99 : 1	75
Bu			

entry	allylic substrate	aldehyde	conditions	product	yield, %	ref
8	 2:1 mixture	RCHO	$CrCl_2$, THF, rt	 R=Ph, C_3H_7, C_6H_{11} single stereoisomer	54–69	517
9		PhCHO	$CrCl_2$, THF, rt	 67 : 33	91	517
10	 X=Cl, Br	PhCHO	$CrCl_2$, THF, rt	 X=Cl 65% 13% 2% (syn:anti=1.1:1); X=Br 46% 34% 20% (syn:anti=1:1.8)		568
11		PhCHO	$CrCl_2$, THF	 1.6 : 1 (one isomer)	90	518
12	 (chiral)	MPMOCHO	$CrCl_2$, THF, rt	 single stereoisomer	97	519
13	 R^1=Me, n-$C_{11}H_{23}$	RCHO R=Ph, $PhCH_2CH_2$ n-C_6H_{17}, c-C_6H_{11} $PhCH{=}CH_2$	$CrCl_2$, Li(I), THF, 0 °C	 (R*, R*) : (R*, S*) > 90 : 1	95	520

σ-bond forms at the terminus cis to the nitrosyl, which opens the latent coordination site for the aldehyde trans to the nitrosyl **461**. A chairlike transition state and attack from the *re* face of the aldehyde accounts for the formation of the *R,R*-isomer. CpMo(NO)(Cl)(η^3-(*Z*)-crotyl) complex adds to aldehydes with high diastereoselectivity to yield *syn*-β-methyl homoallyl alcohols in up to 98% de.[523] The usual route for preparation of (*Z*)-crotyl organometallic reagents is via the Schlosser metalation of *cis*-butene,[5] but the rearrangement of (*Z*)-crotylpotassium to the more stable *E*-isomer generally leads to some loss of isomeric purity. Hydride addition to thermodynamically stable cationic *s-cis*-butadiene or 2-butyne complexes, **463** and **462**, respectively, and subsequent ligand exchange afford the η^3-(*Z*) complex **464**. Stirring of **465a** with 2.5 equiv of benzaldehyde in CH_2Cl_2 in the presence of CH_3OH stereospecifically produces the acetal **466** in 52% yield. Similarly, **465b** and **465c** give the anti adducts **467a** and **467b**, respectively, as one single stereoisomer.[524] The reaction of η^3-allylmolybdenum complexes [$MoCp(CO)_2(\eta^3$-allyl-R)] (**468**) undergoes BF_3-catalyzed carbon–carbon bond formation with aldehydes, ketones, and α,β-unsaturated ketones; the η^3-pentadienyl complex **468a** affords 1,3-diene derivatives **469** upon treatment with aldehydes and ketones in the presence of $BF_3{\cdot}OEt_2$, and alkenyl ketones **470a** with α,β-unsaturated ketones in the presence of $BF_3{\cdot}OEt_2$; the η^3-heptatrienyl complex **468b** provides trienyl derivatives **469b** with aldehydes and the conjugate adducts **470b** with enones.[525]



XI. Group 7 (Mn)

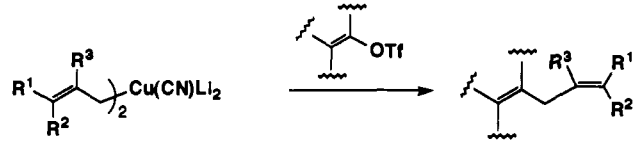
A. Allylic Manganese Reagents

Treatment of "Mn(0)" reagent, prepared in situ from anhydrous manganese(II) chloride and $LiAlH_4$ in THF at 0 °C, with allylic bromide and then with aldehydes or ketones provides homoallyl alcohols with allylic rearrangement.[526] α,β-Unsaturated aldehydes and ketones undergo 1,2-addition. With crotyl bromide, carbonyl addition produces a mixture of syn- and anti-isomers; the diastereoselectivity is low to moderate and normally syn-isomers are formed predominantly. Addition to 4-*tert*-butylcyclohexanone occurs predominantly from the equatorial direction. Reaction of prenyl bromide is less effective than allyl or crotyl bromide. Allyl phosphate and chloride can be used in place of the bromide. Metallic manganese powder, suspended in THF containing iodine under reflux, is also applicable to C–C bond formation including the Barbier-type allylic carbonyl addition.[527]

XII. Group 11 (Cu)

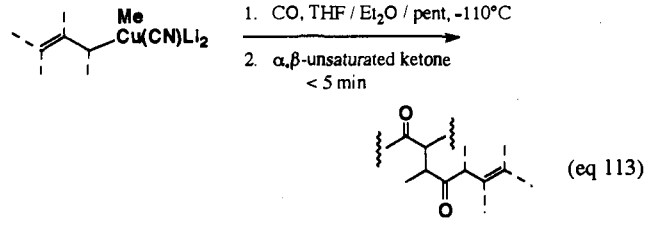
A. Allylic Copper Reagents

^{13}C NMR spectroscopy has unequivocally established the σ-bound nature of the bonding in both higher order (HO) allyl cuprates, $(allyl)_2Cu(CN)Li_2$, and lower order (LO), $(allyl)_2CuLi$.[528] It has also been demonstrated that $(allyl)_2CuLi$ has limited thermal stability while no such problem exists with $(allyl)_2Cu(CN)Li_2$. The extent to which ligand reorganization between α- and γ-termini occurs is a function of temperature and substitution on the allyl unit. HO diallyl cuprates, easily prepared and handled even at 0 °C or above, are among the most reactive copper reagents known. Treatment of a vinyl triflate with a HO cuprate prepared from lithium chloride solubilized CuCN and either allyllithium, methallyllithium, crotyllithium, or prenyllithium (2 equiv) in THF at −78 °C affords the corresponding 1,4-dienes virtually upon mixing (eq 112).[529] Prenyl



(eq 112)

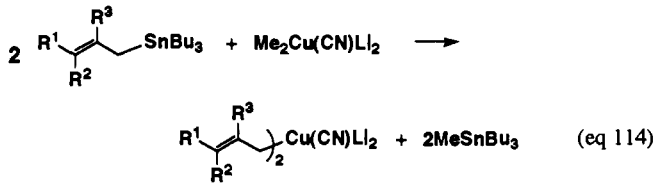
couplings occur with >99% α-attack, whereas crotyl cuprates reacts both regio- and stereorandomly as 2–3:1 mixtures of *Z*/*E* products, along with ca. 1∼2:1 ratios of α/γ attack. Exposure of HO mixed allylic cyanocuprates (Me as a second dummy ligand) to an atmosphere of CO at low temperatures followed by an enone leads to products of 1,4-acylation which contain the unit "allyl-CO" (eq 113).[530] Good yields can be



(eq 113)

expected employing allyl, methallyl, and crotyl mixed cyanocuprates, but highly hindered enones are not amenable to this process. Crotyl reagents react predominantly at the γ-site to afford a diastereomeric mixture of products, an observation contrary to the 1,4-addition of crotylcopper·TMSCl to α,β-unsaturated ketones, which adds with virtually complete α-selectivity (see below). Michael additions of allylic ligands, including allyl, methallyl, crotyl, and prenyl systems, to a variety of α,β-unsaturated ketones can be effected in synthetically useful yields with allylcopper reagents in the presence of trimethylchlorosilane (allylCu·TMSCl).[531] Attempts to deliver a simple allyl ligand to cyclohexenone by using either $(allyl)_2Cu(CN)Li_2$ or (allyl)Cu(CN)Li were unsuccessful. Allylcopper was

normally prepared from allyltributylstannane and MeLi- and LiCl-solubilized CuI in THF. In many situations, allylcopper was also prepared from allyllithium (or allyl Grignard) and CuI. As the steric bulk is increased about the reactive site, however, products of 1,2-addition and reduction are competitive in the cyclohexenone series. Prenyl- and crotylcopper reagents couple predominantly, if not exclusively, at the α-position. The crotylcopper derivative affords an ca. 3:1 mixture of olefinic isomers favoring the *E* form, which is similar to the preference of crotyllithium to exist as a 3:2 mixture of *E*/*Z* isomers. A new method for forming relatively thermally stable allylic cuprates has been discovered.[532] Treatment of allylic tributylstannanes with 0.5 equiv of MeLi-derived cyanocuprate $Me_2Cu(CN)Li_2$ at 0 °C for 30 min affords HO allylic cyanocuprates essentially quantitatively (eq 114). Di-

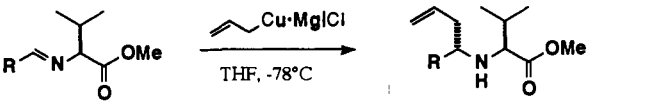


(eq 114)

prenylcyanocuprates, which react with epoxides by way of α-attack, reverse this trend with halides where attachment at the γ-carbon prevails. Dicrotylcyanocuprates likewise react preferentially with halides at the γ-position. Cyclic epoxides, highly prone toward Li^+-induced rearrangement to cyclic ketones, undergo clean displacement with minimal Lewis acid related side product formation. Even primary unactivated chlorides can be displaced by the HO allyllic cyanocuprates, although the use of lower order Gilman-like cuprates tends no to effect these displacements. Although acyclic HO allylic cyanocuprates can be prepared as described above, the direct transmetalation from allylic stannanes is not effected in the case of cyclic analogs. Cyclic allylic stannanes are once transmetalated to the corresponding lithium derivatives upon treatment with MeLi, which are subsequently treated with 0.5 equiv of CuCN·LiCl in THF to give HO cyclic allylic cuprates.[533]

The direct formation of highly functionalized allylic organocopper reagents has been carried out using a highly active form of zerovalent copper (Cu*).[534] The cold-temperature reduction of CuCN·*n*LiX complexes by lithium naphthalenide in THF under an argon atmosphere produces the Cu* complex, which reacts rapidly with primary and secondary allyl chlorides at −100 °C with little homocoupling. Allyl, methallyl, and crotyl acetates also oxidatively add with Cu* at low temperatures to afford the corresponding organocopper reagent. The allyl chlorides can contain a wide array of functional groups including ketones, α,β-unsaturated ketones, epoxides, alkyl acetates, esters, alkyl chlorides, nitriles, and carbamates. The cross-coupling of the highly functionalized allylic organocopper reagents with various electrophiles including aldehydes, ketones, acid chlorides, imines, and epoxides proceeds in excellent yields.[534] The reactive zerovalent copper reacts directly with 2,3-dichloropropene to yield a new bisorganocopper species containing both a nucleophilic allylic and vinylic moiety. This new bisorganocopper reagent undergoes selective one-pot addition to two different electrophiles in good to excellent yields.[535]

The conventional method for the synthesis of allyl copper reagents has been the reaction of allylic magnesium (or lithium) reagents with copper salts (Li_2CuCl_4, CuX, or catalytic amounts of CuX in the case of the magnesium reagents).[536] Treatment of secondary allylic chlorides or allylic phosphates in THF with prenyl Grignard reagent in the presence of CuCN·2LiCl gives geraniol or farnesol derivatives with high S_N2' selectivity. Phosphate leaving groups are highly trans selective for the formation of (*E*,*E*)-farnesol derivatives. Furthermore, complete anti-S_N2' selectivity is observed in the alkylation of optically active allylic phosphates.[537] The regioselectivity of trimethylsilyl-substituted allyllithium is controlled by adding copper salts;[538] by adding 1 equiv of CuCN or CuI a wide range of electrophiles, such as aldehydes, acid chlorides, α,β-unsaturated ketones (1,4-addition takes place with the substrates), and epoxides, react at the γ-position of the allylic lithiums. (see also **9**).[23d] The addition of allylcopper reagents, prepared in situ from allyl Grignard reagents and CuI, to imines derived from (*S*)-valine occurs with excellent diastereoselectivity (eq 115).[539]



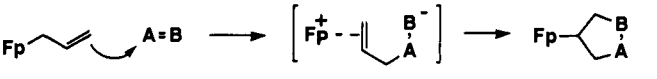
R = Ph, 98%de, 96%
R = n-C_5H_{11}, 98%de, 94%

(eq 115)

XIII. Groups 8–10 (Fe, Co, and Ni)

A. Allylic Iron and Cobalt Reagents

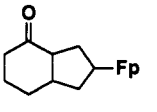
Monohaptoallyl iron complex **471** reacts with electrophiles such as TCNE, dichlorodicyanoquinone, β,β-dicyano-*o*-chlorostyrene, and dimethyl methylenemalonate to give [3 + 2] cycloaddition products;[540] **471** and its congeners behave as 1,3-dipoles in nonconcerted [3 + 2] cycloadditions, affording both carbocyclic and heterocyclic five-membered rings (eq 116). The alu-



471 Fp = η^5-$C_5H_5Fe(CO)_2$

(eq 116)

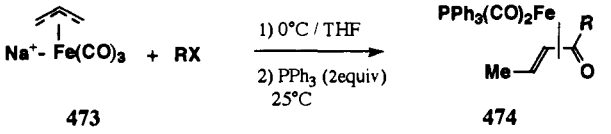
minum bromide catalyzed reaction of **471** with cyclohexenone provides cyclopentane annulation product **472** in 45% yield.[541] Cycloaddition of **471** with enones,



472

in the absence of Lewis acid, is possible by further substitution of the acceptor olefin with electron-withdrawing groups. As shown above electron-deficient olefins readily react with **471**. 2-Carbethoxycycloalkenones serve as useful models in these cycloaddition reactions.

Electron-rich aromatic and heteroaromatic compounds react with (η^3-allyl)$Fe(CO)_4BF_4$, which is a cationic π-allyl complex, to produce allylated aromatics in moderate to good yields.[542] The reaction of an anionic allyl complex (η^3-allyl)$Fe(CO)_3^-$ **473** with alkyl halides leads to α,β- or β,γ-unsaturated ketones.[543] Treatment of **473** (Na salt) with RX followed by addition of PPh_3 gives **474**. Free α,β-unsaturated ketones may be readily obtained by treating **474** in CH_3CN under reflux (80–85%, R = Me, $PhCH_2$, i-Pr, allyl, Bu).



473 **474**

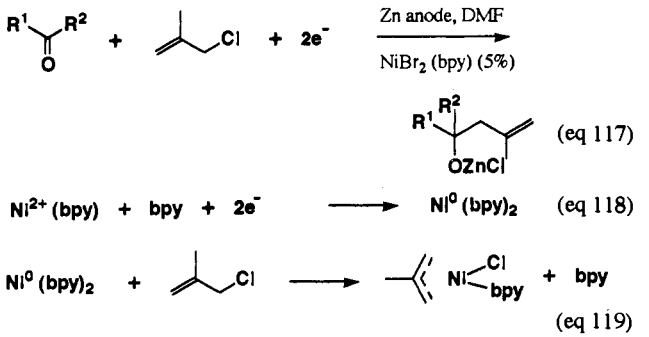
The Lewis acid promoted addition of allyliron(II) reagent **475** to aldehydes provides zwitterionic iron–olefin complex **476** as isolable yellow salts. Treatment of the iron complexes with NaI in wet acetone affords homoallylic alcohols.[544] Of the Lewis acids examined (BF_3·OEt_2, $TiCl_4$, $SnCl_4$, $AlBr_3$, TMS triflate), BF_3·OEt_2 is the most effective. The allylation reactions do not occur in the absence of Lewis acid. The BF_3·OEt_2-promoted allylation of ketones also affords the corresponding iron–olefin complexes.[545] In the deoxygenation reaction of allylic alcohols to alkenes using H_2, $CoCl_2$, KCN, KCl, β-cyclodextrin, and KOH, σ- and π-allylic cobalt intermediates are proposed as intermediates.[546]

475 **476**

B. Allylic Nickel Reagents

π-Allylnickel halides react with electron-poor centers and may thus be classed as nucleophilic allyllic reagents, whereas π-allylpalladium complexes react with electron-rich centers (normally stabilized anions) and may be considered to be electrophilic allylic reagents. The reactions of π-allylnickel complexes with C=X electrophiles, organic halides, epoxides, an related substrates have been reviewed previously.[547] π-Allylnickel halides react with 1,2-diketones, ketones, and aldehydes to give the expected homoallylic alcohols. With 1,2-diketones, only one addition occurs, even in the presence of a large excess of the nickel reagent, and α,β-unsaturated ketones gives only 1,2-addition products even in the presence of added CuI.[548] 1,2-Diketones are the most reactive substrates toward the nickel reagents, while cyclic ketones are less reactive, and both simple ketones and α,β-unsaturated ketones are less reactive. Aryl ketones are more reactive than their alkyl counterparts, and both esters and acid chlorides fail to react with the reagents. These reactivities are in contrast to those of the allyllithium, -zinc, and -magnesium reagents, which normally attack both carbonyls in 1,2-disubstituted ketones, are highly reactive toward aliphatic and α,β-unsaturated ketones, and may add in a 1,4-manner to the latter substrates under suitable conditions. Although π-allylnickel complexes possess some interesting and useful reactivities toward electrophiles, the reagents have not been used widely in organic synthesis. A major reason seems to be that very toxic $Ni(CO)_4$ has to be used for the synthesis of the nickel complexes and handling the π-allylnickel reagents is not convenient in comparison with other allylic reagents.

An efficient electrosynthesis of homoallylic alcohols from allylic chlorides or acetates and carbonyl compounds in the presence of catalytic amounts of $NiBr_2$(bpy) complex (bpy = 2,2′-bipyridine) was achieved in a one-compartment cell fitted with a sacrificial zinc anode (eq 117).[549] The $Ni^0(bpy)_2$ complex is produced by reduction of Ni^{2+} (bpy) (eq 118), which reacts with methallyl chloride to afford π-allylnickel complex (eq 119). The π-allylnickel complex reacted with ketones and aldehydes in the presence of Zn^{2+} to produce Ni^{2+} (bpy) and zinc alkoxide (eq 117). The catalytic process may be useful since the stoichiometric use of π-allylnickel complexes is not required. Nickel-catalyzed metallo-ene cyclizations have been summarized recently.[62]



XIV. Summary

Over the last 15 years, many approaches to the stereoselective C—C bond formation via the reaction of allylic metals with C=X electrophiles have been investigated. A variety of very successful methods have been developed for diastereoselective C—C bond formation between allylic metals and carbonyl compounds, imines, and alkenes. In many instances, high enantioselectivities have been achieved via the reactions of allylic boranes and stannanes. More recently, asymmetric allylation with catalytic amounts of certain Lewis acids has been reported. Main-group allylmetals always act as nucleophilic allyl transfer reagents, but transition-metal allyl reagents exhibit both nucleophilic and electrophilic property depending on the metal (this review does not cover the latter reactions via π-allylpalladium complexes). New selectivities and reactivities have been observed in the reactions of transition-metal allyl reagents including group 3 and Zr. Perfect regioselectivity has been accomplished with Ba reagents. Accordingly, in addition to the useful and common allyl reagents (B, Si, Sn, Ti, Cr), research on new types of allylmetals has just begun. Further investigations of the chemistry of allylmetals will provide us with a number of synthetically useful and selective reactions.

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