

Selective Reactions Using Allylic Metals

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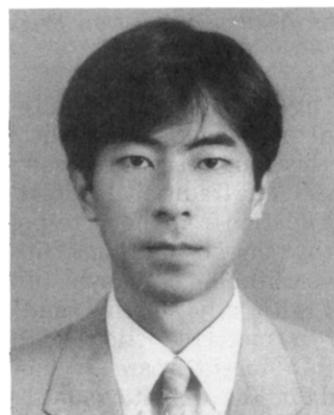
I. Introduction

Prior to the late 1970s, allylic organometallic compounds were studied primarily by a limited number of organometallic chemists¹ 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 anti-selective 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

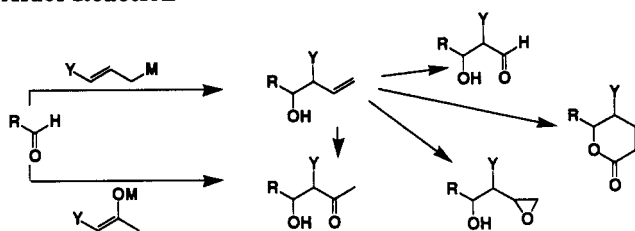


Yoshinori Yamamoto was born in Kobe, Japan, in 1942. He received his B.Sc. degree in 1965 and his Ph.D. degree in 1970 from Osaka University. He joined the faculty of Osaka University as an Instructor in 1970. He was a postdoctoral fellow at Purdue University with Herbert C. Brown from 1970 to 1972. 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 ¹⁰B 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.

the aldol addition of metal enolates, since the resulting homoallyl alcohol can be easily converted to the aldol

Scheme I. Allylmetal-Aldehyde Condensation and Aldol Reaction

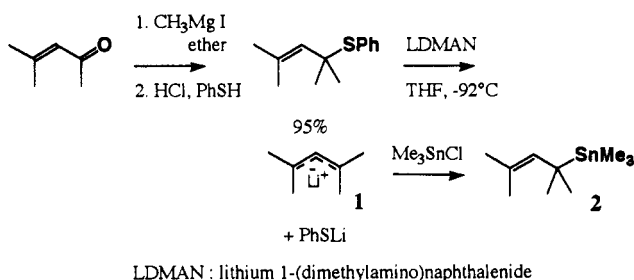
(Scheme I).³ Further, allylmetal additions have significant advantages over aldol condensations since the alkenes may be readily transformed into aldehydes, may undergo a facile one-carbon homologation to δ -lactones via hydroformylation, or may be selectively epoxidized to introduce a third chiral center. 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**

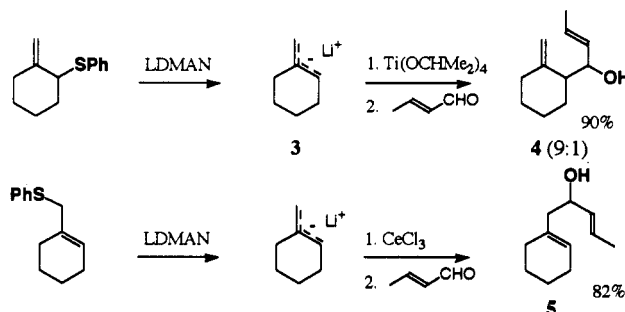
Alkyl and aryllithiums are usually prepared by halogen-metal exchange, but allyllithiums are not available by this route because of competing substitution reactions. The traditional routes to allyllithiums are (i) transmetalation from the corresponding allyltins and allylleads by using allyllithiums,⁶ (ii) ether cleavage with lithium or lithium biphenyl,⁷ (iii) reactions of allyllithiums 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.

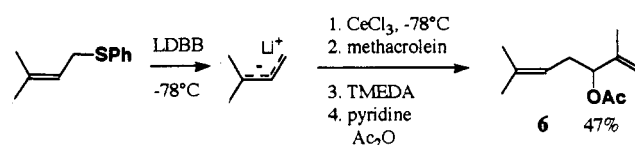


While this radical anion induced reductive metalation has been used for allyllithiums that are substituted at one terminus with ether^{11,12} or thioether¹³ groups, the most important uses have been in the formation of hydrocarbon allyllithiums. The reason is that heteroatom substituted allyllithiums 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,

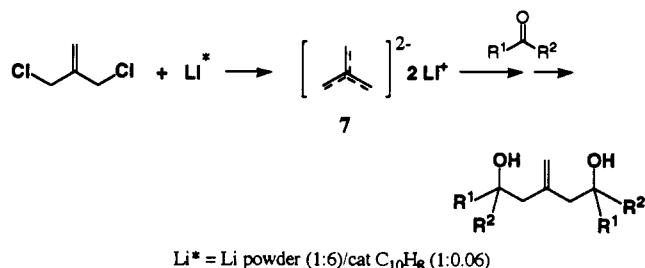


treatment of an unsymmetrical allyllithium with cerium(III) chloride, followed by an enal, results mainly in addition of the least substituted terminus to the carbonyl group;¹⁶ the ratio of 5 to 4 was 18:1. This novel regioselectivity has made possible a highly efficient synthesis of the pheromone of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



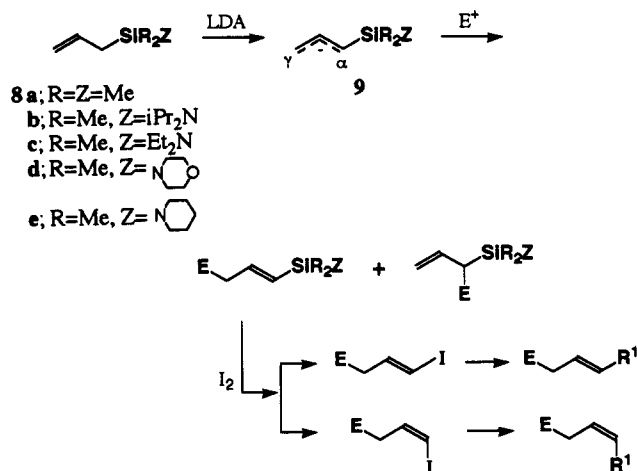
LDBB: lithium *p,p*-di-*tert*-butylbiphenylide

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



2. Heteroatom-Substituted Allyllithiums

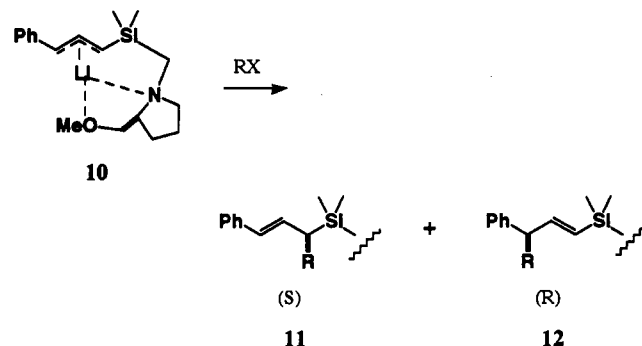
The review article entitled "Heteroatom-Stabilized Allylic Anions" covers papers in this field before late-1988.²⁰ An interesting area for the study of substituent effect is on the regiochemical control in substitution reactions of heteroatom-substituted allyl anion.^{20,21} The [α -(trimethylsilyl)allyl]lithium (**9a**, R, Z = CH₃) can be generated from allyltrimethylsilane (**8a**, R, Z = CH₃) and reacted with electrophiles.²² The regioselectivity



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 MgBr₂^{23b} or Et₃Al.^{21a} The lithio anion of allyl(diisopropylamino)-dimethylsilane (**8b**, R = Me, Z = *i*-Pr₂N), upon treatment with dried ZnCl₂ 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 = Et₂N) 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 MgBr₂, SnCl₂, or Ti(O*i*Pr)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}

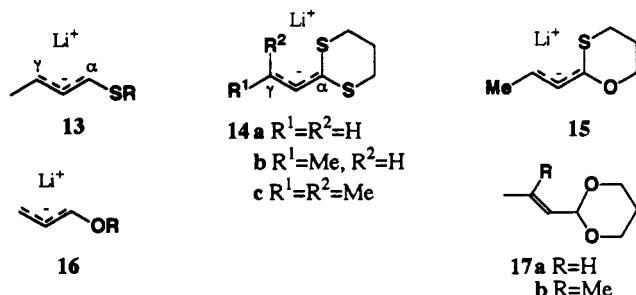
Reactions with alkyl halides are more complicated. Regiocontrol of the alkylation is mentioned here, although this review is primarily concerned with the reactions of C=X. Alkylation of the α -silylallyl anion gave higher γ -regioselection by replacing the methyl groups on silicon by sterically larger 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



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**.

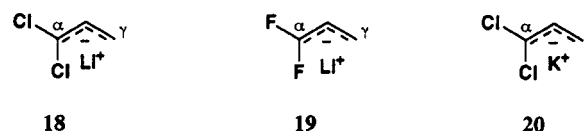
Sulfur-stabilized allyllithiums have been well documented and their regioselective reactions have been investigated.²⁰ Alkyl halides react with **13** predomi-

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 $\text{BF}_3\cdot\text{OEt}_2$.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-elimination 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

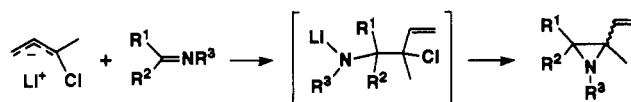


For *gem*-dichloroallyl anions, carbonyl compounds yield different products of attack depending on the substituents on the carbonyl carbon atom, presenting a whole spectrum of product distributions going from a complete α -attack to a complete γ -attack.³⁶ For example, aromatic aldehydes and diaryl ketones 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



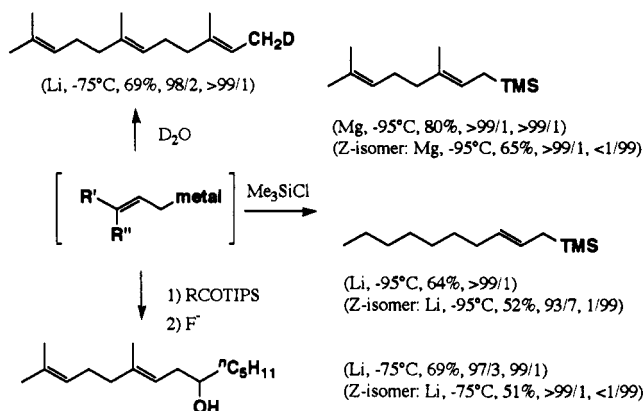
In general, reactions of linear α -alkylaldehydes with allyllithiums are complicated by α -deprotonation of the aldehydes owing to the basic property of the lithium reagents. The use of less basic magnesium and zinc reagents produces higher yields. The reaction of (*gem*-chloro(methyl)allyl)lithium with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



intramolecular $\text{S}_{\text{N}}2$ displacement of chloride via the intermediate lithium amide. The regioselectivity of additions of crotyllithium reagents to aldehydes 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}

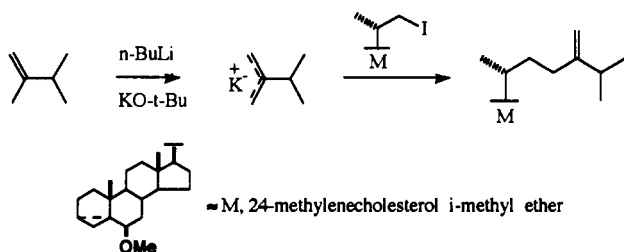
B. Allylic Sodium and Potassium Reagents

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 method⁹ (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 (20S)-20-(iodomethyl)preg-



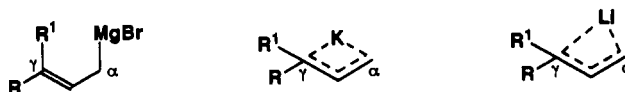
nane *i*-methyl ether followed by deprotection gave, in high yields, a wide variety of Δ^{24} and $\Delta^{24(28)}$ sterols, including the naturally occurring desmosterol, fucosterol, 24(*E*)-propyldenecholesterol, 24-methylenecholesterol, dehydroaplysterol, 25-methyl-24-methylenecholesterol, mutasterol, and 25-methylxestosterol.⁴² The use of unsymmetrical allyl potassiums, 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

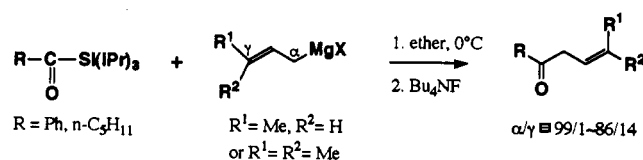
quantity of MgBr_2 causes rapid equilibration.⁹ When butylpotassium is generated in the presence of commercial *cis*-2-pentene and the resulting allylpotassium is captured with PhMe_2SiCl , 1-(phenyldimethylsilyl)-2-pentene is produced in 65% yield with a 98.6:1.4 mixture of *Z* and *E* isomers. When 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**

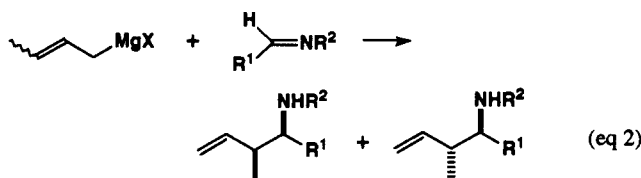
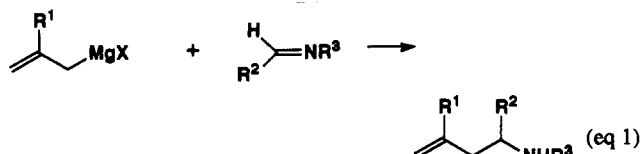
The isotopic perturbation technique has been used to distinguish between the σ - and π -bond structures of allyl- and crotylmagnesium, -potassium, and -lithium reagents.⁴³ The ^{13}C NMR spectra of the deuterated crotyl reagents demonstrate that: (i) crotylmagnesium reagents are σ -structures in which 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.



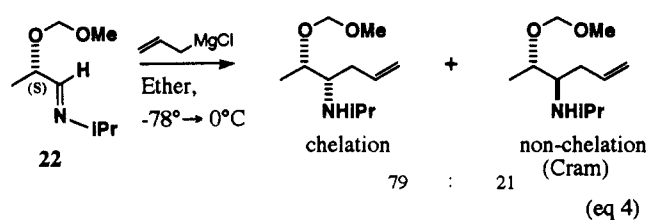
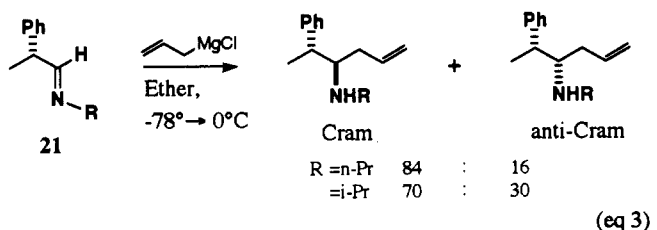
It is well known that crotyl and prenyl Grignard reagents react with aromatic and aliphatic aldehydes at the γ -position.¹ Regioselective α -allylation was accomplished by the reaction of triisopropylsilyl ketones with allyl Grignard reagents.⁴⁴ The corresponding trimethylsilyl ketones gave the γ -product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



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.

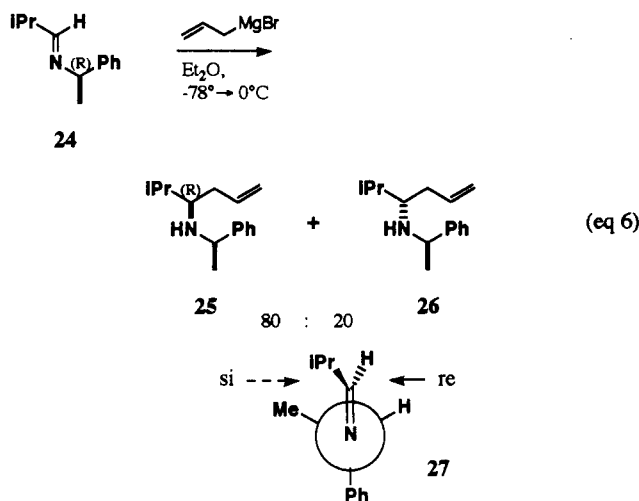
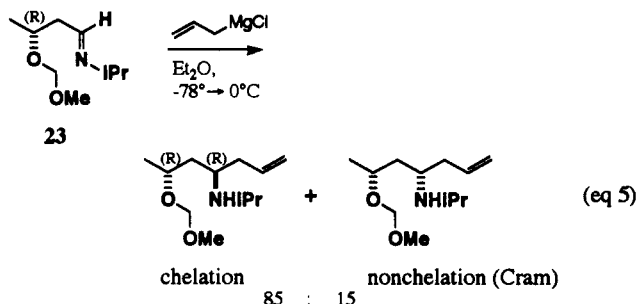


Imines containing one stereocenter at the α -position are treated with allylmagnesium chloride to evaluate the influence of either a nonchelating α -phenyl substituent (eq 3) or a chelating α -alkoxy substituent (eq 4) on reaction diastereofacial selectivity. The Cram product was obtained predominantly 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



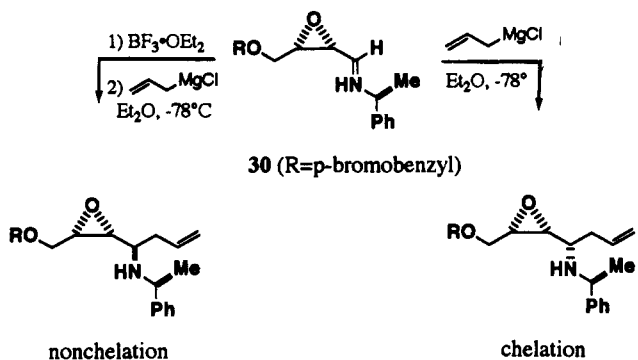
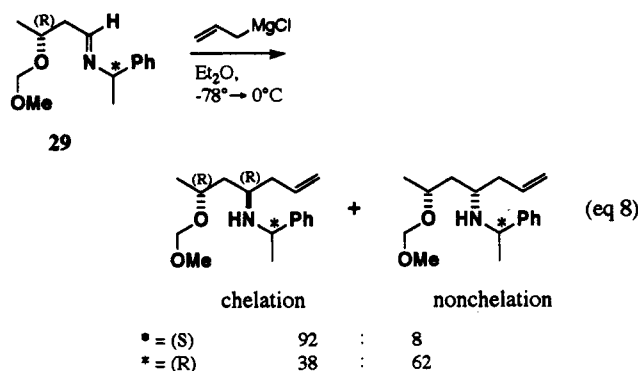
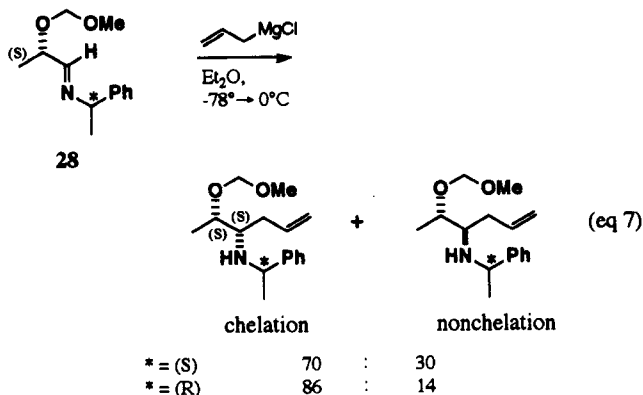
1,3-Asymmetric induction has been investigated by using an imine containing one stereocenter either at the β -position (23) or at the carbon attached to nitrogen atom (24).⁵⁰ Modest chelation control (chelation/nonchelation = 85:15), which is superior to that of the corresponding β -alkoxyaldehydes (chelation/nonchelation = 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

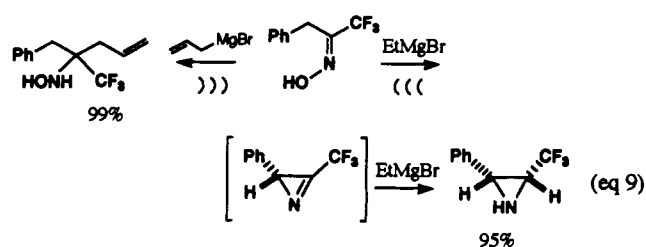


obtained predominantly from 28; the imine derived from (*R*)-1-phenylethylamine gave higher chelation/nonchelation ratio than that from (*S*)-enantiomer (eq 7). However, the chirality of the α -alkoxy center (1,2-asymmetric induction) is the most important determinant of the stereochemical outcome of 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 $\text{BF}_3\cdot\text{OEt}_2$.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 $\text{BF}_3\cdot\text{OEt}_2$ 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 $\text{BF}_3\cdot\text{OEt}_2$ 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

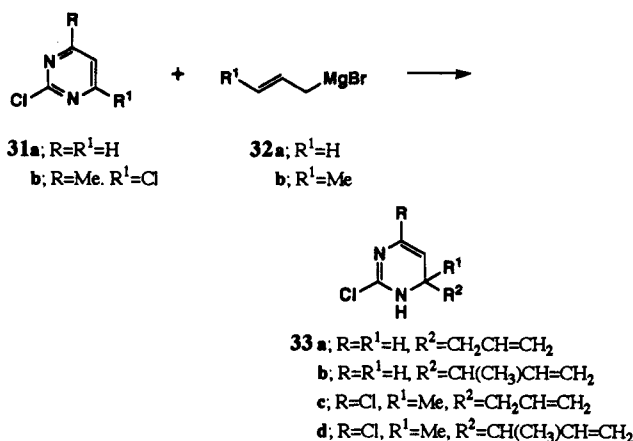


agent toward trifluoromethyl ketones; by using an excess of this Grignard reagent, an exclusive allylation is obtained.⁵² Allylmagnesium bromide smoothly added to trifluoromethyl ketone oximes to produce the corresponding allylated hydroxylamines, whereas the reaction of ethylmagnesium bromide with benzyl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

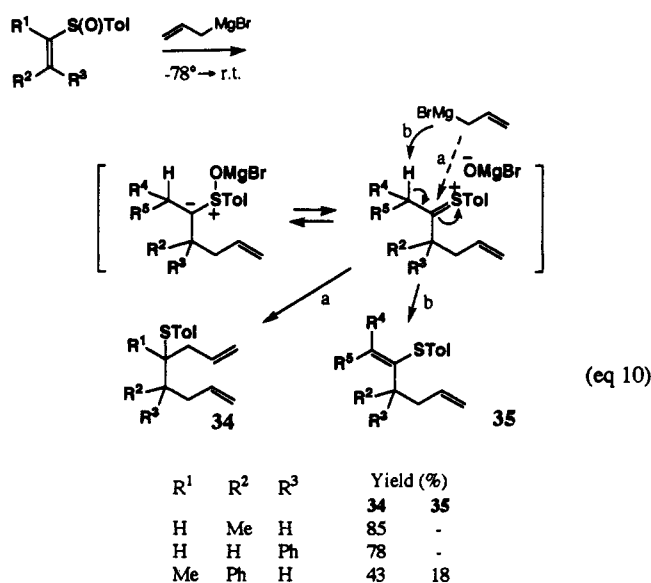


allylation of pyrimidines has been accomplished by reaction with allylic Grignard reagents;⁵³ reactions of 31a and 31b with 32a and 32b lead to allyldihydropyrimidines 33a-d in very good yields. Grignard reagents have been reported to react with pyrimidines furnishing dihydropyrimidines or cross-coupled pyri-

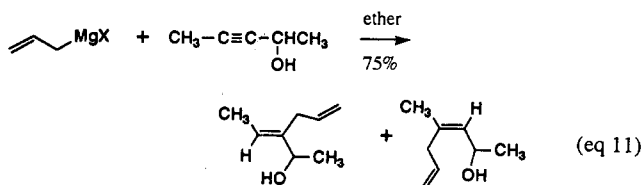
midines,⁵⁴ but this applies only to aryl and primary alkyl Grignards. No secondary or tertiary alkyl group had previously been introduced on the pyrimidine ring.



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



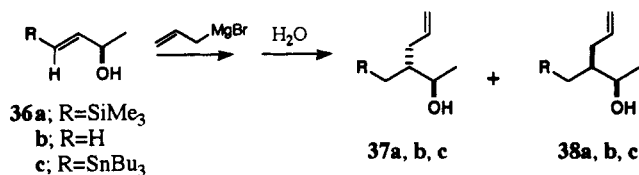
Grignard reagents do not add easily to the triple bond of simple alkynes.⁵⁷ The enhanced reactivity of allylic Grignard reagents enables them to react with acetylenic alcohols by an antiaddition process (eq 11).^{57,58} How-



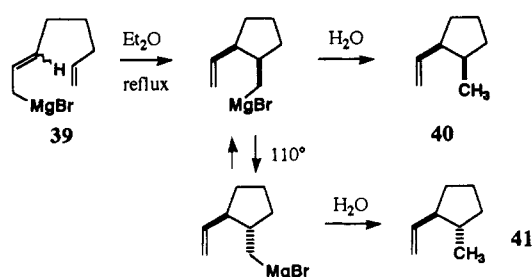
ever, both regioisomers are obtained, making this

allylmatalation 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 allylmagnesiumation 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 Et₂O 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 Et₂O for 170 h to achieve a 16% yield of alcohols **37b** and **38b** (8:1). The corresponding stannane derivative **36c** reacted in refluxing Et₂O (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



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 Et₂O to give, after aqueous workup, selectively *cis*-1-methyl-2-vinylcyclopentane (**40**) in 67% yield.⁶⁵



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

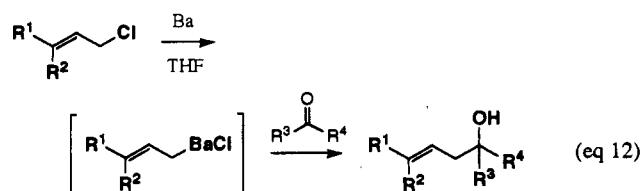
Table I. Intramolecular Allylmagnesium-Ene Reactions

	1) Mg powder, Et ₂ O 2) RT, 20 h 3) O ₂		70%	ref 66
	1) act. Mg -60°C 2) 65°C, 24 h		76%	67
	1) Mg, Et ₂ O 2) 40°C, 14 h 3) MoOPh, -78°C		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
	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 (4*aS*,7*aR*) 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

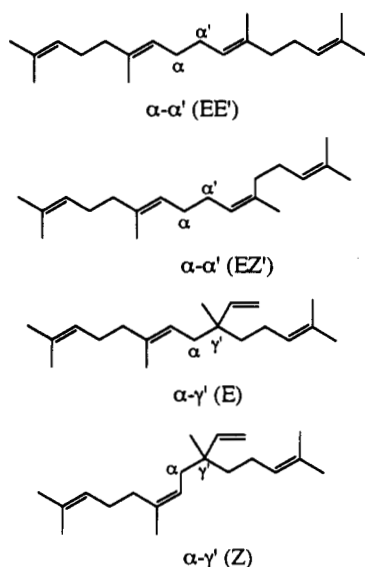
Allylbarium can be prepared directly by the reaction of in situ generated barium metal with various allylic chloride, and the regio- and stereoselective allylation of carbonyl compounds can be accomplished using these allylmetals (eq 12).^{71a} Highly reactive barium was



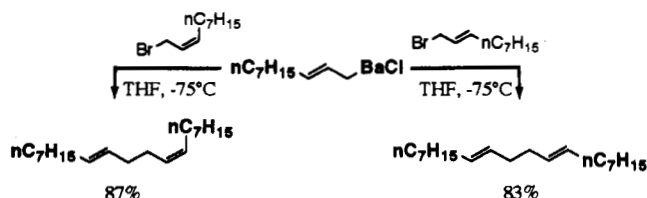
readily prepared by the reduction of barium iodide with

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} $\text{M} = \text{Mg}$, $\alpha/\gamma = <1:99$ (99% yield); $\text{M} = \text{Ca}$, $\alpha/\gamma = 8:92$ (38% yield); $\text{M} = \text{Li}$, $\alpha/\gamma = 47:53$ (36% yield); $\text{M} = \text{Ce}$, $\alpha/\gamma = 72:28$ (52% yield); $\text{M} = \text{Ba}$, $\alpha/\gamma = 92:8$ (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 ($\alpha,\alpha'/\alpha,\gamma' = 97:3$, 47% yield).



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.



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 $78\text{--}95^{\circ}\text{C}$ 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 water⁷³ 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 $\text{NH}_4\text{Cl}/\text{THF}$ 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


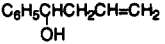

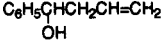

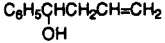


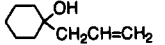

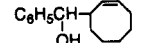
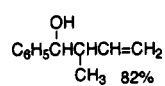
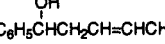

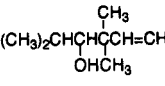

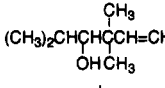

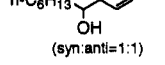

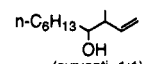
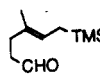

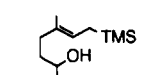
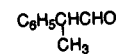

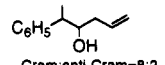
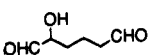

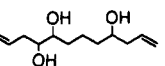
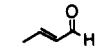

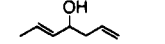
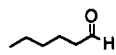

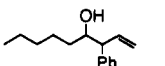

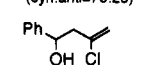
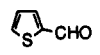

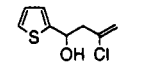
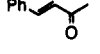

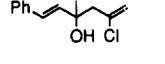
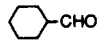

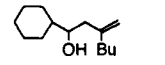
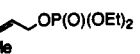
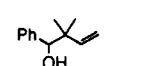
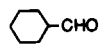
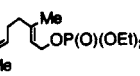
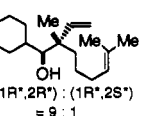


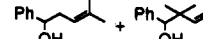

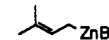





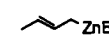

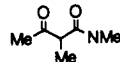

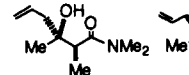
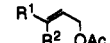
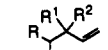
entry	reactant	allyl halide	conditions ^a	product	yield, %	ref(s)
1	C ₆ H ₅ CHO		activated Zn, 95% EtOH, 78 °C		66	72
2	C ₆ H ₅ CHO		activated Zn, t-BuOH, 95 °C		71	72
3	C ₆ H ₅ CHO		Zn, saturated aqueous NH ₄ Cl/ THF, rt, ST		100	73, 74
4			activated Zn, t-BuOH, 95 °C		63	72
5	C ₆ H ₅ CHO		activated Zn, 95% EtOH, 90 °C		48	72
6	C ₆ H ₅ CHO	CH ₃ CH=CHCH ₂ Br	activated Zn, 95% EtOH, 90 °C	 82%  18%	60	72
7	(CH ₃) ₂ CHCHO		Zn, H ₂ O/THF, rt, US		90	73
8	(CH ₃) ₂ CHCHO		Zn, saturated aqueous NH ₄ Cl/ THF, rt, ST		95	73, 74
9	n-C ₆ H ₁₃ CHO		Zn, saturated aqueous NH ₄ Cl, rt, C-18 silica	 (syn:anti=1:1)	85	75
10	n-C ₆ H ₁₃ CHO		Zn, saturated aqueous NH ₄ Cl, rt, C-18 silica	 (syn:anti=1:1)	100	75
11			Zn, saturated aqueous NH ₄ Cl, rt, C-18 silica		68	75
12			Zn, H ₂ O, C-18 silica pyridinium tosylate	 Cram:anti-Cram=8:2	90	75
13			Zn, saturated aqueous NH ₄ Cl, rt, C-18 silica		60	75
14			Zn, DMF, rt		86	76
15		Ph- 	Zn, DMF, rt	 (syn:anti=75:25)	87	76
16	PhCHO		Zn, H ₂ O/toluene HOAc, 45 °C, 1 h		95	77
17			Zn, H ₂ O/toluene HOAc, 45 °C, 1 h		92	77
18			Zn, H ₂ O/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	 (1R*,2R*) : (1R*,2S*) = 9 : 1	78	79

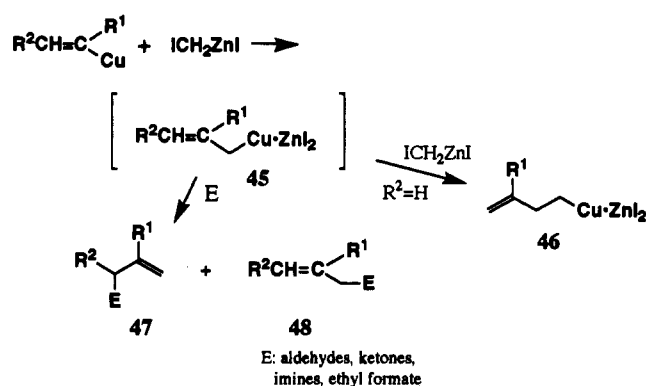
Table II. (Continued)

entry	reactant	allyl halide	conditions ^a	product	yield, %	ref(s)
22			(1) THF, 0 °C, 20–60 min; (2) Bu ₄ NF	 90 : 10	>80	44
23			(1) THF, 0 °C, 20–60 min; (2) Bu ₄ NF	 >99 : 1	>80	44
24			(1) THF, 0 °C, 20–60 min; (2) Bu ₄ NF	 3 : 97	>80	44
25			(1) THF, 0 °C, 20–60 min; (2) Bu ₄ NF	 >99 : 1	>80	44
26			THF, 25 °C	 98 : 2	92	247b
27	RCHO R=Ph, C ₆ H ₁₁		Pd(0)/Zn, dioxane		51~99	79b

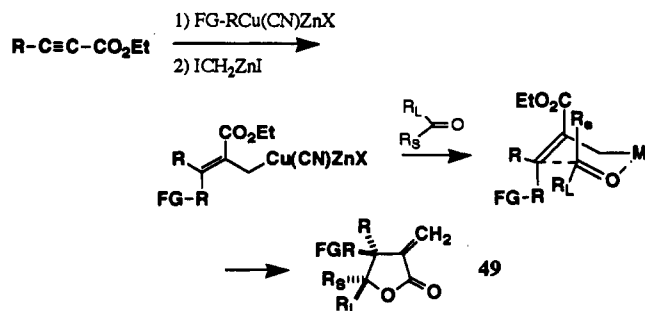
^a Abbreviations are as follows: ST, stirring; US, sonication; rt, room temperature; DMPU, *N,N*-dimethylpropyleneurea; DMA, *N,N*-dimethylacetamide.

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 ($\sim 7:3$). Allylic acetates are reduced by zinc in the presence of a catalytic amount of Pd(PPh₃)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 Cp₂TiCl₂ (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 ICH₂ZnI to afford the α -methylene- γ -butyrolactone 49.^{81a} The groups R of the alkyne, FG-R of the zinc-

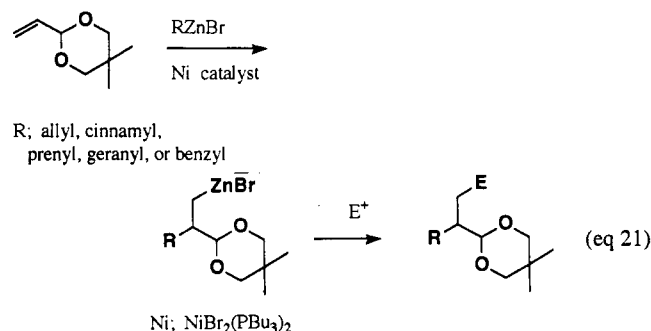


copper organometallic, and R_L of the aldehyde can bear

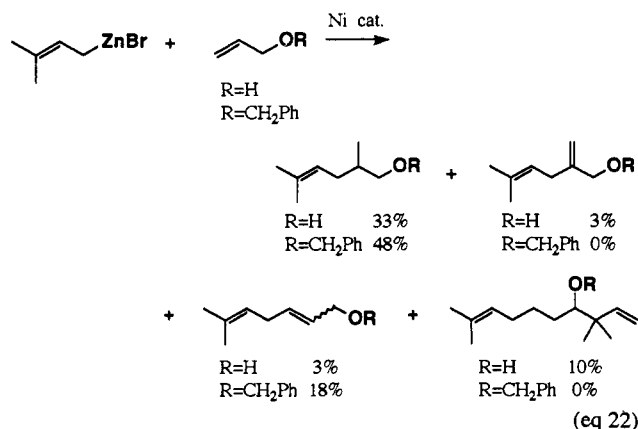
case of preformed iminium salts **59**, α -deprotonation is not a serious problem since yields are generally good even though the iminium salts are enolizable.⁹⁰ The preference for branched homoallylamines follows the trend $\text{Al}_{2/3}\text{X} > \text{ZnX} > \text{MgX} > \text{Li}$, paralleling 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 allylmatalation of allylic alcohol

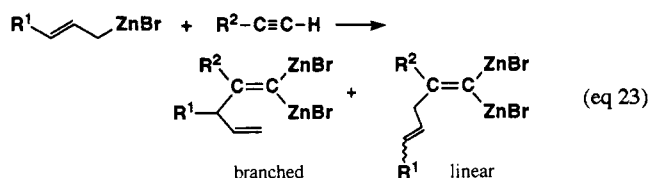


has been accomplished by treatment with allylzinc in the presence of a nickel catalyst, $\text{NiBr}_2(\text{PBu}_3)_2$ (eq 22).⁹² Allyl alcohols were less reactive toward allyl metal reagents than α,β -unsaturated acetal, probably due to its higher basicity. The benzyl allyl ether reacted rapidly with allylzinc reagent, giving a higher C2/C-3 regioselectivity (eq 22). Allylic Grignard reagents or



alkyllithium reagents are known to readily add to allylic alcohols.⁹³ The importance of intramolecular coordination is demonstrated in those reactions. Copper⁹⁴- or nickel⁹⁵-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



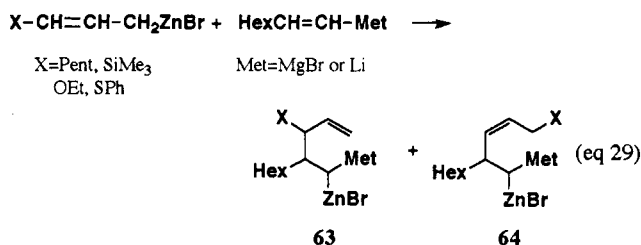
Since the addition is reversible, the amount of the minor thermodynamic linear isomer can be increased by prolonged contact of the reactants. The regiochemistry of the addition is always of the Markovnikov type, whatever the R group of the alkyne. Disubstituted, nonfunctionalized alkynes do not react 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.

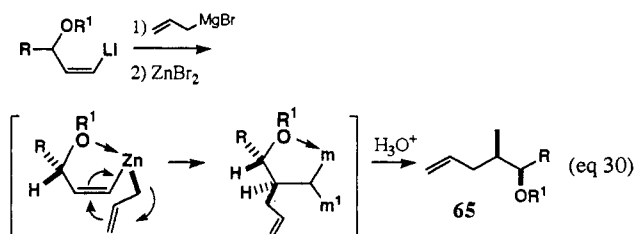
Table III. Allyliczincination of Triple and Double Bonds

entry	zinc reagent	substrate	conditions	product	yield, %	ref(s)
1	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{ZnBr}$	$\text{HC}\equiv\text{CH}$ (excess)	(1) THF, 25 °C, 15 h; (2) H_3O^+		66	98
2	$\text{CH}_3\text{CH}_2\text{CH}_2\text{ZnBr}$	$\text{C}_6\text{H}_{13}\text{C}\equiv\text{CH}$	(1) THF, 30 °C, 24 h; (2) D_2O		70	100
3	$(t\text{-C}_4\text{H}_9)_2\text{Zn}$	$\text{C}_6\text{H}_5\text{C}\equiv\text{CH}$	(1) ether, reflux, 48 h; (2) H_3O^+		70	99
4	$\text{H}_3\text{CC}\equiv\text{C}(\text{CH}_2)_3\text{CH}=\text{CHCH}_2\text{Br}$		(1) Zn/THF, reflux, 24 h; (2) H_3O^+		50	102
5	$\text{CH}_3\text{CH}_2\text{CH}_2\text{ZnBr}$	$(\text{Et})_2\text{N}(\text{CH}_2)_3\text{C}\equiv\text{CH}$	(1) THF, reflux, 23 h; (2) H_3O^+		16	103
6	$\text{CH}_3\text{CH}_2\text{CH}_2\text{ZnBr}$	$(\text{EtO})_2\text{CHC}\equiv\text{CH}$	THF, reflux		37	104
7	$\text{CH}_3\text{CH}_2\text{CH}_2\text{ZnBr}$	$(\text{EtO})_2\text{CHC}\equiv\text{CMgBr}$	THF		37	104
8	$\text{CH}_3\text{CH}_2\text{CH}_2\text{ZnBr}$	$\text{PhOCH}_2\text{C}\equiv\text{CH}$	THF		75	104
9	$\text{CH}_3\text{CH}_2\text{CH}_2\text{ZnBr}$	$\text{C}_6\text{H}_{13}\text{C}\equiv\text{CSiMe}_3$	(1) THF, 60 °C, 18–24 h; (2) I_2		83	105
10	$\text{CH}_3\text{CH}_2\text{CH}_2\text{ZnBr}$	$\text{Pr}-\text{OSiMe}_3-\text{C}\equiv\text{CSiMe}_3$	(1) THF, 60 °C, 18–24 h; (2) saturated aqueous NH_4Cl		52	106
11	$\text{CH}_3\text{CH}_2\text{CH}_2\text{ZnBr}$		(1) THF; 80 °C, 23 h; (2) ClSnMe_3		57	107
12	$\text{CH}_3\text{CH}_2\text{CH}_2\text{ZnBr}$		(1) THF, 80 °C, 45 h; (2) H_2O		80	107
13	$\text{CH}_3\text{CH}_2\text{CH}_2\text{ZnBr}$		(1) THF, 65 °C, 12 h; (2) NH_4Cl , MeOD		60	109
14	$\text{CH}_3\text{CH}_2\text{CH}_2\text{ZnBr}$		(1) THF, 65 °C, 0.5 h; (2) PhCO_2Et ; (3) H_2O		55	109
15	$\text{CH}_3\text{CH}_2\text{CH}_2\text{ZnBr}$	$\text{C}_7\text{H}_{15}\text{C}\equiv\text{C}-\text{Li}$	(1) THF 60 °C, 2 h; (2) H_2O		70	110
16	$\text{CH}_3\text{CH}_2\text{CH}_2\text{ZnBr}$	$n\text{-C}_4\text{H}_9\text{C}\equiv\text{C}-\text{OEt}$	(1) THF, CuBr; (2) $\text{PhSCH}_2\text{NEt}_2$		60	111
17	$\text{CH}_3\text{CH}_2\text{CH}_2\text{ZnBr}$	$t\text{-C}_4\text{H}_9\text{C}\equiv\text{C}-\text{OEt}$	(1) THF; (2) H_2O		70	111
18	$\text{CH}_3\text{CH}_2\text{CH}_2\text{ZnBr}$	$n\text{-C}_4\text{H}_9\text{C}\equiv\text{C}-\text{OEt}$	(1) THF; (2) $i\text{-PrCHO}$; (3) H_2O		75	111
19	$\text{CH}_3\text{CH}_2\text{CH}_2\text{ZnBr}$	$\text{CH}_2=\text{CH}-\text{MgBr}$	(1) THF, 0 °C, 1 h, >95%; (2) $\text{EtO}_2\text{C}-\text{C}\equiv\text{C}-\text{H}$ $\text{EtO}_2\text{C}-\text{C}\equiv\text{C}-(\text{CH}_2)_6\text{OAc}$ THF, 120 °C, 0.5h		80	112

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 regioselective and leads, depending on the substituent X, specifically to products of type **63** or **64** (eq 29).^{113g}



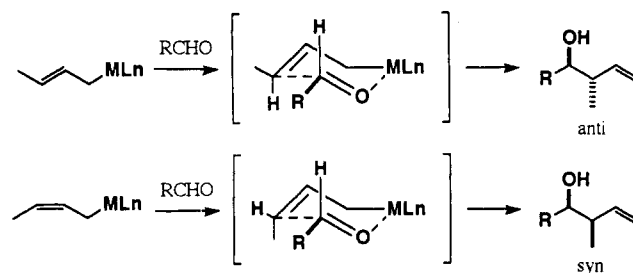
(*Z*)- γ -Lithiovinyl ethers can be added in a stereoselective way to allylic zinc bromide, leading to 1,1-dimetallc species with two asymmetric carbon atoms and, after acidic hydrolysis, to compound **65** (eq 30).¹¹⁴ The high diastereoselectivity observed in this rearrangement is expected by the well-established 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 ZnBr₂ (entries 22 and 23), but no rearrangement takes place between the vinyl-lithium and the Grignard or lithium reagents in the absence of ZnBr₂. Even three asymmetric centers can be obtained with good diastereoselectivity via this metallal Claisen rearrangement (entry 24).¹¹⁵



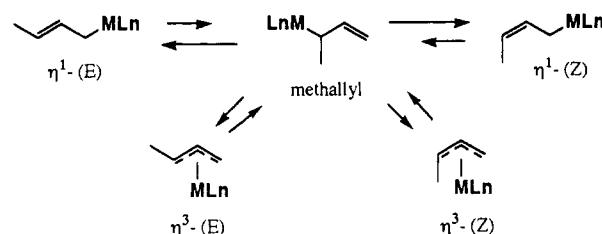
D. Allylic Cadmium Reagents

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/Bu₄NBr/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)

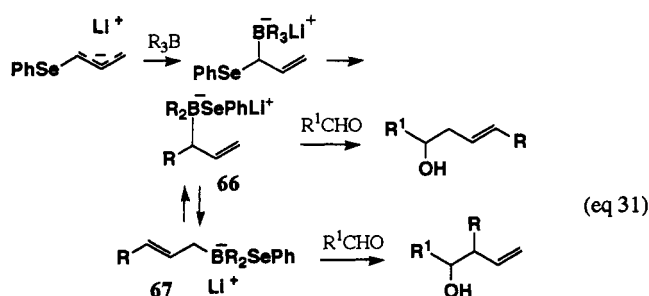
A. Allylic Boron Reagents

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 homoallylic alcohols.¹¹⁹ Crotylboron reagents react with aldehydes presumably via chairlike transition states: from (*E*)-crotyl boron compound an anti homoallylic alcohol is produced, whereas a syn homoallylic 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.

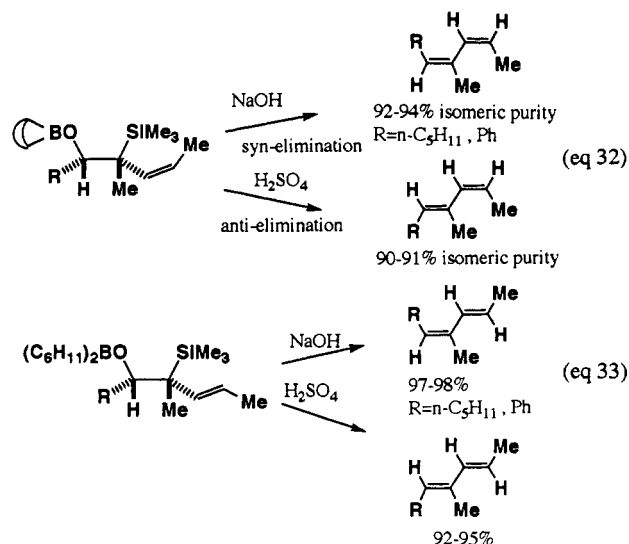
Reactions of nonchiral allylboranes with nonchiral aldehydes and ketones are summarized in Table IV. The dialkylcrotylboranes are the most reactive but also the least configurationally stable among the allylboron reagents.¹²¹ The reaction of crotyl-9-BBN with glyoxylate esters provides the anti diastereomer 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 CO₂R 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 (phenylselenenyl)allyl carbanion with trialkylboranes (entries 5 and 6).¹²⁶ The reaction presumably proceeds as shown in eq 31. A facile

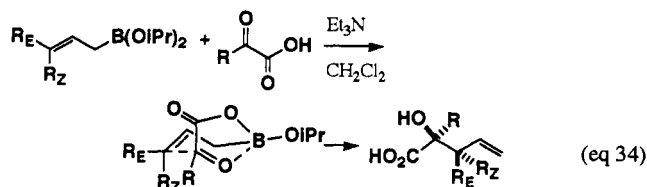


migration of R group from boron to the α -carbon produces **66** (or the uncomplexed borane instead of the PhSe-boronate complex³). The reactions of **66** with aldehydes give linear homoallyl alcohols (entry 5). The allylic rearrangement of the boron atom of **66** takes place after a prolonged period 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-



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



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 $\text{CO}_2\text{-Et}$ 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 ₂ i-Pr	 75 : 25	80	122
2		CH ₃ COCO ₂ R	 R=Ph 80 : 20 R=4- <i>t</i> -Bu-C ₆ H ₄ 100 : 0	89 90	123
3		R ¹ CHO	 >95% anti	52-84	124
4		RCHO (R=Me, Ph, i-Pr)	 68-85% anti	78-91	125
5		PhCHO	 (E:Z=86:14)	88	126
6		PhCHO	 (syn:anti=24:76)	89	126
7		PhCHO	 >98:2 anti	50	127
8		PhCHO		90	127
9		n-C ₅ H ₁₁ CHO		77	128
10		n-C ₅ H ₁₁ CHO		78	128
11		n-C ₅ H ₁₁ CHO		90	129
12				93	130
13		PhCH ₂ CHO		68	131
14		PhCH(OMe) ₂ /TMSOTf		94	132
15		EtCHO	 93:7 anti	62	2b, 133
16		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 ₃ COCH ₂ OH	 97:3 isomeric purity	72	136
20		CH ₃ COCH ₂ OH	 94:6 isomeric purity	65	136
21		PhCOCO ₂ H	 99:1 isomeric purity	97	137
22		PhCOCO ₂ H	 99:1 isomeric purity	96	137
23		Me ₂ CHCHO	 >98:2 anti	77	138
24		Me ₂ CHCHO	 11:89 syn	94	138
25		Me ₂ CHCHO	 >95:5 anti	86	138
26		Me ₂ CHCHO	 11:89 syn	76	138
27		Me ₂ CHCHO	 20:80 syn	90	138
28		PhCHO	 >98:2 anti	89	139
29		PhCHO	 98:2 syn	95	140
30		CH ₃ COCO ₂ Et	 9:1 isomeric mixture	85	141
31		Me ₂ CHCHO	 X		142
			X=Cl 96 : 4	83	
			X=Br 96 : 4	83	
			X=SC ₂ H ₅ 85 : 15	85	
			X=OCH ₃ >95 : 5	55	

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	68	156
23	 SEM=Me ₃ SiCH ₂ CH ₂ OCH ₂		 R=4-MeOC ₆ H ₄ CH 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			 88% ee, >99% anti	87	167
32			 82% ee, 97% syn	80	167
33		 (CO) ₃ Co--Co(CO) ₃	 96% ee, 97% anti	85	168

Table V. (Continued)

entry	allylborane	substrate	isomer ratio	yield, %	ref(s)
34				40 (conversion 80%)	169
35				>90	170
36				81	170
37				93	173
38				86	174
39				47-65	176
40				81	176
41		PhCHO		68	178
42				143b, 152c	
43				52	182
44				51	182
45				56	182
46				55	182
47				44	182
48				178 187	

Table V. (Continued)

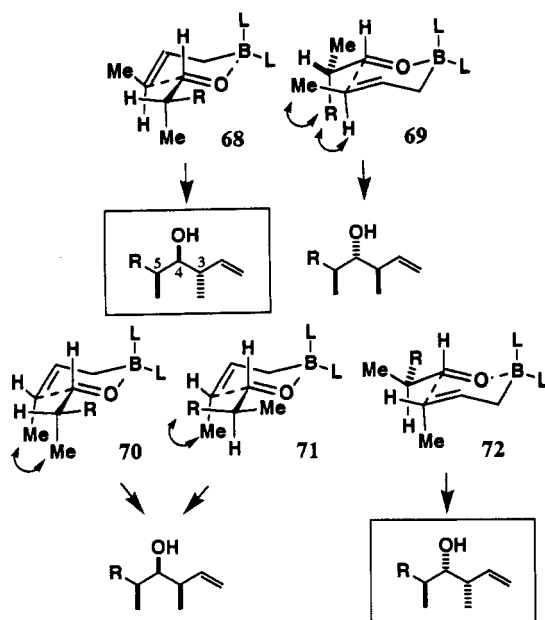
entry	allylborane	substrate	isomer ratio	yield, %	ref(s)
49		BzIO-CHO	 85 : 14 : 1	-	144
50		BzIO-CHO	95 : 5 : 0	-	183 197
51		BzIO-CHO	2 : 98 : 0	-	183, 197
52		CHO	 96 : 4	81	184
53		CHO	5 : 95	81	184
54		BzIO-CHO	 95 : 5	-	
55		BzIO-CHO	83 : 17	-	171
56			 96 : 4	90	165
57			99.7 : 0.3	81	169
58			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)

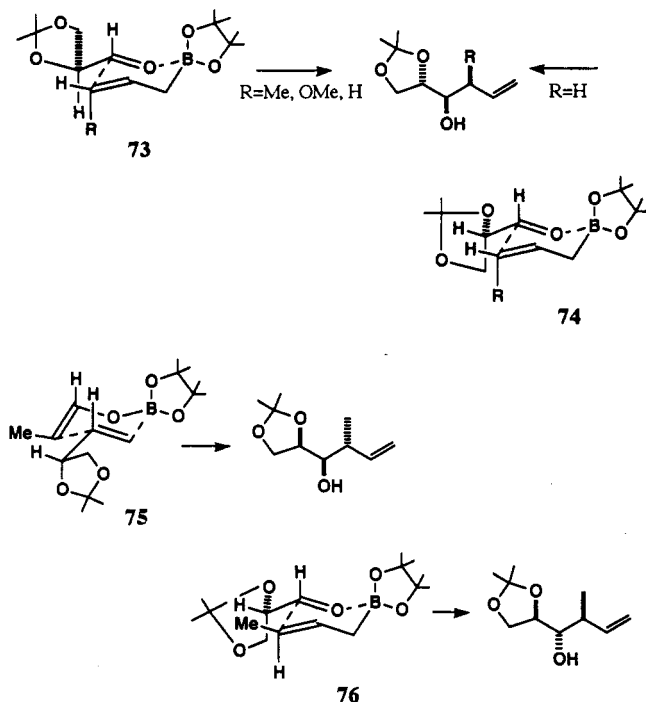
entry	allylborane	substrate	isomer ratio	yield, %	ref(s)
67				66	163, 164
	(R, R)		4 : 2 : 92 : 2		
68				65	163, 164
	(S, S)		- : 2 : 16 : 82		
69				90	173
			96% de		
70				57	198
71				96	186
	(S, S)		99 : 1 (>98% ee) (58% ee)		
72				82	186
	(R, R)		25 : 75 (53% ee) (>97% ee)		
73				95	186
	(R,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

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).¹⁶⁰ 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 -

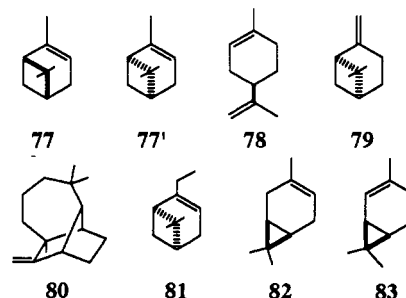
Scheme V. Transition-State Geometries of the Allylboration Reaction of a Chiral Aldehyde


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 intramolecular delivery of the allyl unit (entry 15).¹⁵¹



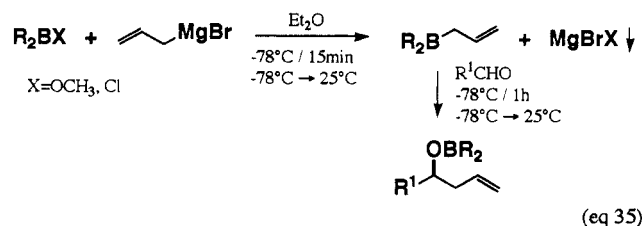
A number of highly enantioselective chiral allylboron reagents have been developed. There are two kind of chiral allylboron reagents: those with conventional, easily introduced chiral auxiliaries as the boron ligands (BLn), and ones in which the chiral center is a structural component of the allylic 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 ($\text{Ipc}_2\text{Ballyl}$) gives consistently excellent results (83–96% ee) in reactions with aldehydes at -78°C : CH_3CHO (93% ee), $\text{C}_2\text{H}_5\text{CHO}$ (entry 18), $\text{C}_3\text{H}_7\text{CHO}$ (87% ee), PhCHO (96% ee), $(\text{CH}_3)_2\text{CHCHO}$ (90% ee), $(\text{CH}_3)_3\text{CCHO}$ (83% ee).¹⁵⁴ Use of isomerically pure (*E*)- or (*Z*)-crotyldiisopinocampheylborane reagent ($\text{Ipc}_2\text{Bcrotyl}$) 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 ($^d\text{Ipc}_2\text{B}$). The use of (–)- α -pinene gives $^l\text{Ipc}_2\text{B}$ which has an absolute configuration opposite to $^d\text{Ipc}_2\text{B}$. 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 $\geq 99\%$ diastereoselectivities and $\geq 95\%$ 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- $^d\text{Icr}_2\text{Ballyl}$, 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 $\text{Ipc}_2\text{Ballyl}$ 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- $^d\text{Icr}_2\text{Ballyl}$. 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 $^d\text{Ipc}_2\text{Ball}$ (entry 18) and 4- $^d\text{Icr}_2\text{Ball}$ (entry 24). Generally, the allylborane reagents in entries 18, 24, and 25 were

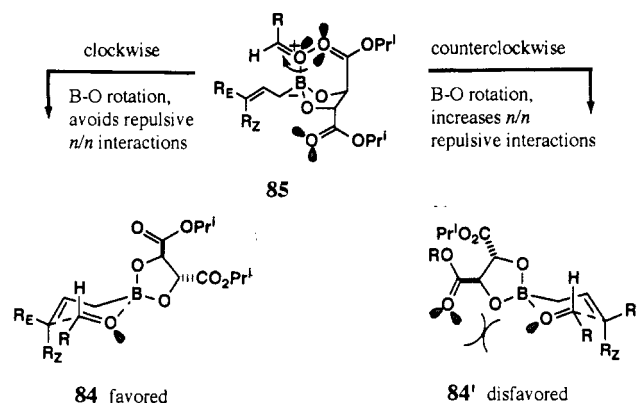
prepared from allylmagnesium bromide (eq 35) and condensed in situ with aldehydes at -78°C . Under



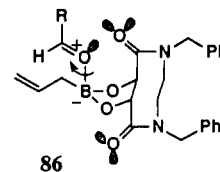
these conditions, magnesium salts are present in the reaction mixture. In the absence of magnesium salts, the chiral allylborane reagents react with aldehydes practically instantaneously at -100°C to give homoallyl alcohols with optically purities approaching 100% ee.^{159a} The short reaction time adopted (<0.5 h) facilitates maintaining the reaction temperature at -100°C . In this way, ^dIpc₂Ballyl gives homoallylic alcohols of >96–99% ee, 4-^dIcr₂Ballyl affords alcohols of ≥98% ee, and 2-^dIcr₂Ballyl 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% BF₃·OEt₂, 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 C₂ 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-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 crotylboronation 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(NO₃)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-

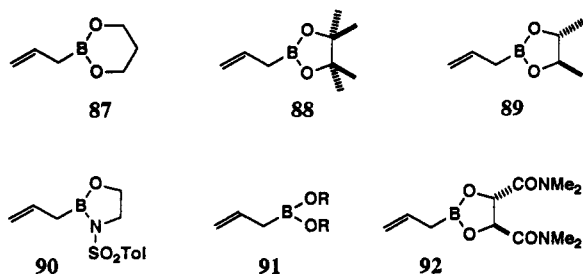


membered ring (cf., 86), the critical conformational features shown in 85 become structural constants, and intermediate aldehyde complexes have no choice but exist in conformations analogous to 86.¹⁶⁹ In fact, this



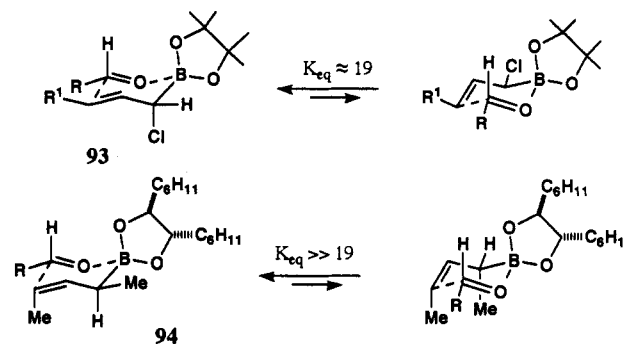
new reagent, derived from *N,N'*-dibenzyl-*N,N'*-ethylenetartramide, was found to be significantly more enantioselective than the corresponding tartrate ester derivative (entry 34 vs 30).¹⁶⁹ However, the tartramide reagent is less reactive and less soluble than the tartrate ester reagent and, consequently, 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 CH₂Cl₂ 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 allylboration, the reactions of benzaldehyde with structurally representative allylboranes were examined under a variety of conditions.¹⁷² Polar solvents, such as HCCl₃, CH₂Cl₂, CS₂, and Et₂O, 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.

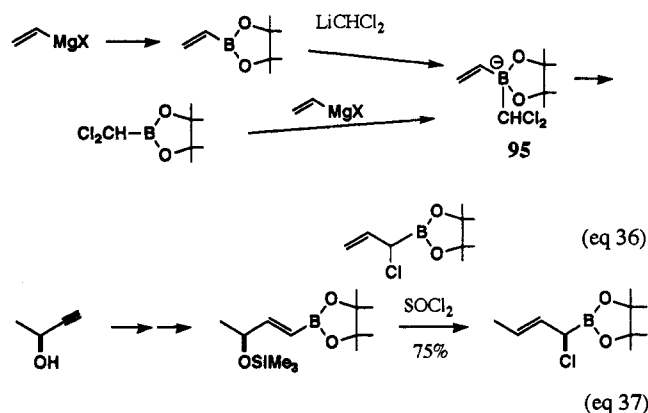


Allylboron compounds with stereocenters at either C-1 or C-4 of the allyl/crotyl unit are frequently less convenient to synthesize than those with conventional auxiliaries as the boron ligand, but the reactions with aldehydes often occur with nearly 100% asymmetric induction. (α -Chloroallyl)boronate 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 OCH₃, Br, SR, and SiMe₃ 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 stereo-electronic 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 dichloromethyl lithium 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



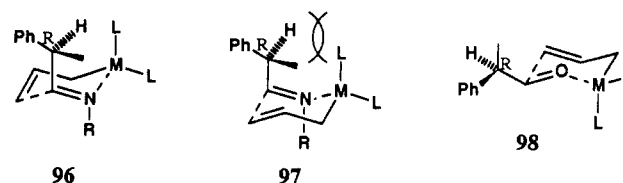
Significant improvement in diastereoselectivity is possible by using double asymmetric synthesis.¹⁸¹ Two types of double asymmetric reactions are known: (1) (matched double asymmetric synthesis) the intrinsic diastereofacial preferences of the carbonyl (or other C=X) electrophile and the chiral allyl 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)₂Ballyl 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 H₂O₂/KF/KHCO₃/MeOH–THF;^{73,198} the conversion of the C–Si bond to C–OH bond proceeds through complete retention. The matched double asymmetric allylations 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 (–)-Ipc₂Ballyl] 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.

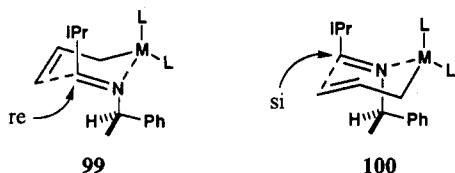
2. Reactions of Imines

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

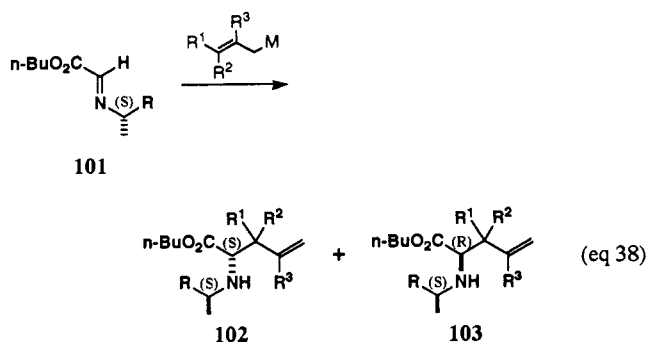


the other hand, the α -chiral carbon occupies the equatorial position (as shown in **98**) in the case of aldehyde addition and avoids the nonbonded interactions, providing low diastereoselectivities. Even in the case of α -alkoxy-substituted aldimines (i.e. **22** in eq 4),⁴⁷ which provide the opportunity 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)AlEt₃MgCl 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-

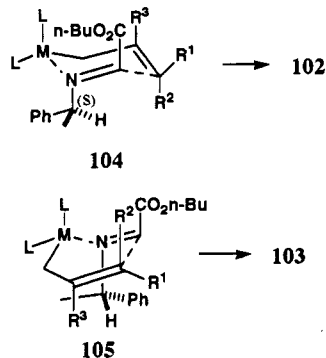
tween the chiral center and the two hydrogen atoms at the axial positions of **99** and **100**, and **99** is more stable than **100**. Actually, the addition mode of **99** is *re*-facial



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-



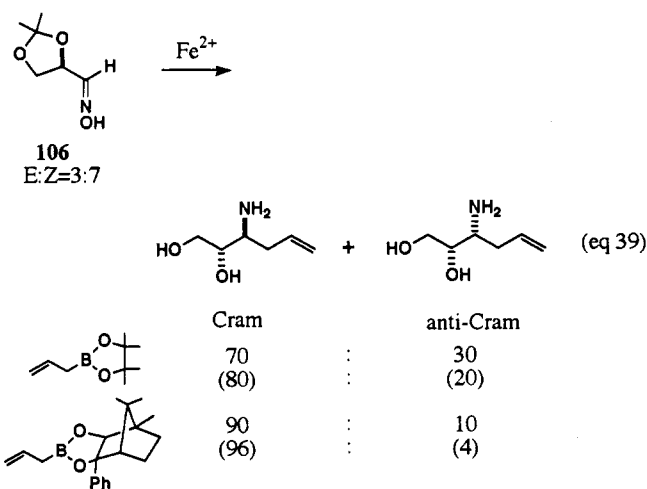
tained in allyl-9-BBN addition to **101** ($R = \text{Ph}$) is in agreement with the cyclic chair transition state shown in **104**. The addition of allylzinc reagents to **101** results in low diastereoselection in all cases. The allyl-9-BBN addition to the α -imino ester derived from (*-*)-1-cyclohexylethylamine (**101**, $R = \text{C}_6\text{H}_{11}$) provides much higher diastereoselection (98:2). Diastereofacial selectivity is reversed in methallyl-9-BBN ($R^1 = R^2 = \text{H}$, $R^3 = \text{CH}_3$) addition to **101** ($R = \text{Ph}$). As a result of additional 1,3-diaxial interactions arising from the methallyl methyl group ($R^3 = \text{CH}_3$) in the chair transition state **104**, a boat transition state **105** is presumably more stable than **104**, leading to amine **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

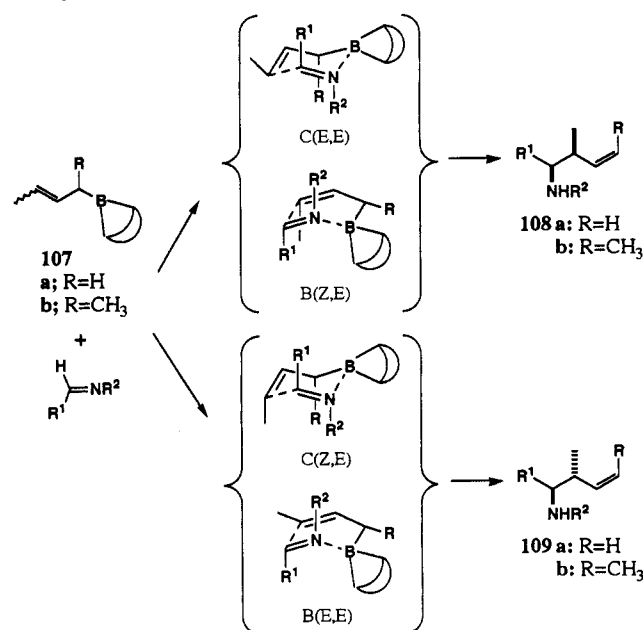
the 9-BBN allylation of **22**). The allylation of β -alkoxyaldehydes (**29**) with allyl-9-BBN produces the nonchelation product predominantly (90:10) in the case of *R*-chirality of the nitrogen auxiliary, whereas it affords the chelation product preferentially (63:37) in the case of *S*-chirality. 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 sulfenimides²⁰¹ 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-



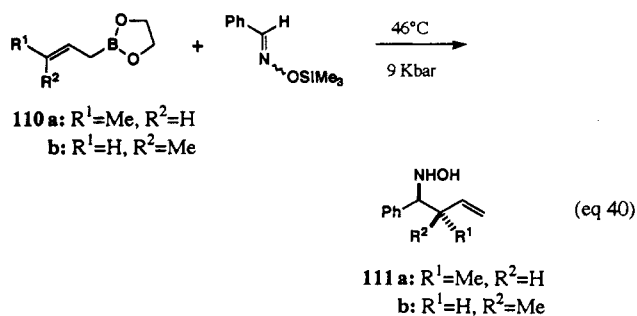
ronates to the corresponding aldehydes are shown in parentheses.] The chiral boronate gives better selectivity than the achiral pinacolboronate.

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 ($R^1 = R^2 = \text{Ph}$) in 93% yield, whereas the syn product **108a** is formed exclusively with the aliphatic imine ($R^1 = n\text{-Pr}$, $R^2 = i\text{-Pr}$) in 97% yield. α -Alkylimines ($R^1 = n\text{-Pr}$, $R^2 = i\text{-Pr}$, and $R^1 = R^2 = n\text{-Pr}$) exhibit syn selectivity when the α -alkyl group is linear, whereas α -arylimines ($R^1 = R^2 = \text{Ph}$ and $R^1 = \text{Ph}$, $R^2 = n\text{-Pr}$) 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 $R^1 = i\text{-Pr}$ and $R^2 = n\text{-Pr}$, or $R^1 = R^2 = i\text{-Pr}$) 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


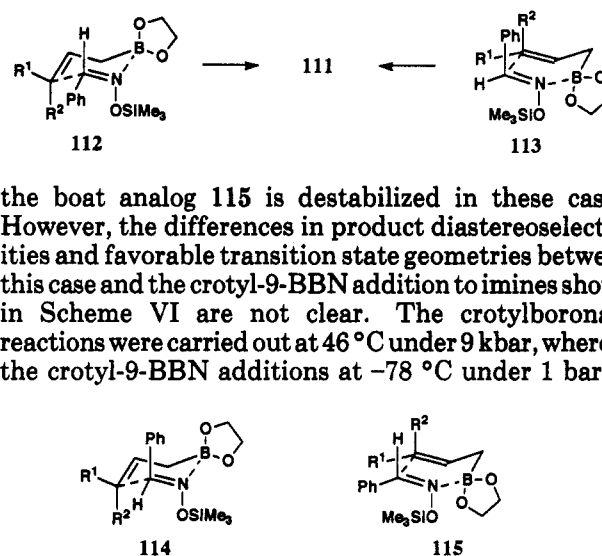
addition of pent-3-en-2-yl-9-BBN (107b) to imines. Syn selectivity is more dominant in these reactions than with crotyl-9-BBN; a small amount of syn product is produced in the reaction of benzylideneaniline (syn/anti = 8:92) which gives 100% anti product using crotyl-9-BBN. The syn product is produced exclusively by the pentenylation of the imine ($R^1 = \text{Ph}$, $R^2 = n\text{-Pr}$), 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 stereochem-



istry defines the site of coordination to the boron atom,

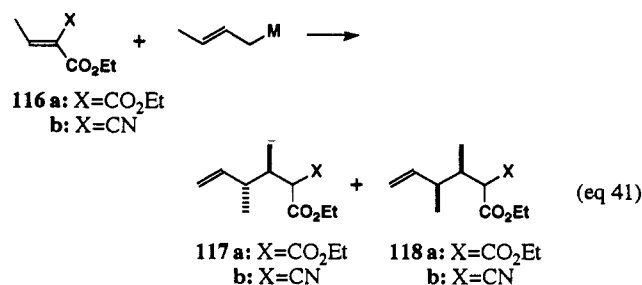
presumably the (*Z*)-oxime reacts predominantly through the chair transition state 112, while the (*E*)-oxime reactions proceed preferentially through the boat transition state 113. The chair transition state 114 or



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.

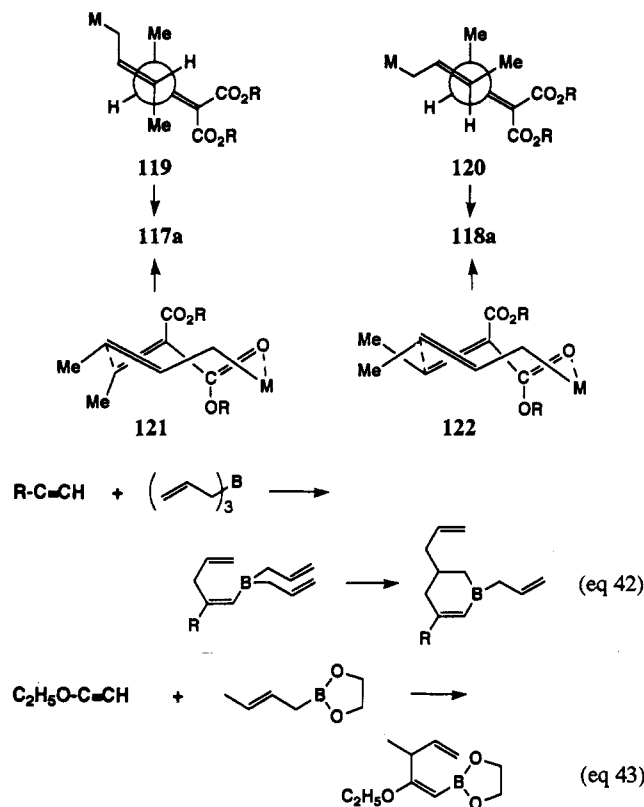
3. Reactions of Alkenes and Alkynes

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}

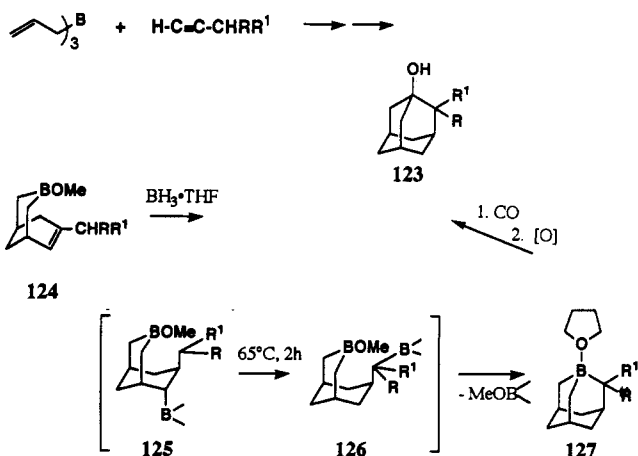


The steric bulk of the ester group does not exert a strong influence upon the selectivity. Reaction of 116b with crotyl-9-BBN does not take place, but it reacts with crotylmagnesium, -titanium, and -zirconium reagents to produce the *anti* adduct 117b preferentially in a ratio of 8:2. The *anti* selectivity 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 alkoxy carbonyl 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)acetylene²⁰⁶ and of ethoxyacetylene²⁰⁸ does allylation stop at the first step

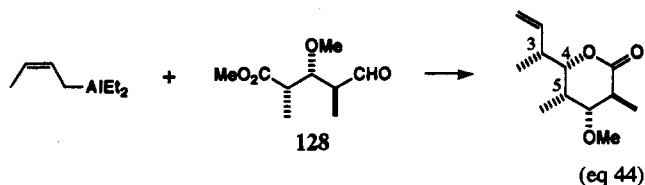


to give the monoallylated product. The reaction occurs with complete allylic rearrangement with crotylborane. The triallylborane-acetylene condensation gives a hardly accessible cage compound 123.^{120c} Heating triallylborane with monosubstituted acetylenes at 130 °C for 2–3 h affords high yields (75–98%) 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.

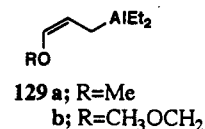


B. Allylic Aluminum Reagents

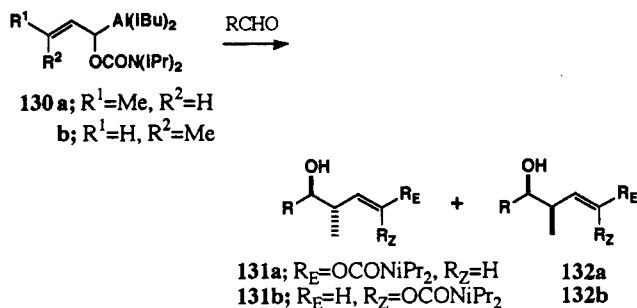
(Z)-Crotyldiethylaluminum, generated by the reaction of (Z)-crotylpotassium with diethylaluminum chloride, reacts with chiral aldehyde 128 to give good 3,4-syn selectivity (3,4-syn/3,4-anti = 3:1) (eq 44).²⁰⁹ The stereoselectivity not only on C-3 and C-4, but also on C-4 and C-5, which is 3,4-syn-4,5-syn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



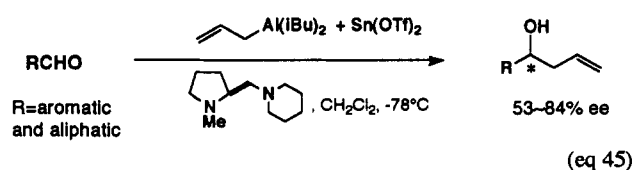
opposite to that of the (Z)-crotylboronate reactions with α -methyl chiral aldehydes which produce 3,4-anti-4,5-anti selectivity predominantly (Table VI, entries 3, 6, and 7). γ -Alkoxy-substituted allyldiethylaluminum reagents 129 are prepared by treatment of the corresponding alkoxy-lithiums with Et_2AlCl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



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 $i-Bu_2AlCl$ 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-

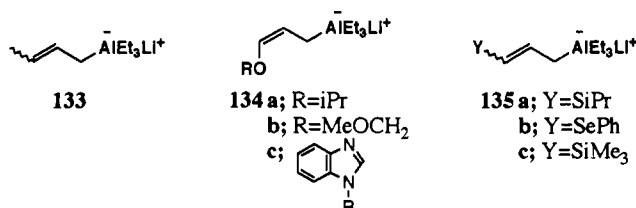


stereoselectivities are consistent with cyclic transition states with preferential equatorial placement of the allylic OCON(i-Pr)₂ group. The equatorial placement is opposite to the axial placement of the α -substituents of allylic boranes (cf. 93 and 94), in which (Z)-alkenes are produced stereoselectively. 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,

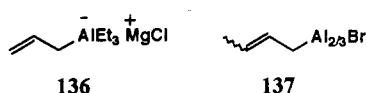


generated from crotyllithium and triethylaluminum, reacts with benzaldehyde with poor diastereoselectivity (56:44, anti/syn).¹²⁵ However, γ -oxygen-substituted allylic aluminum ate complexes 134 exhibit high regio-

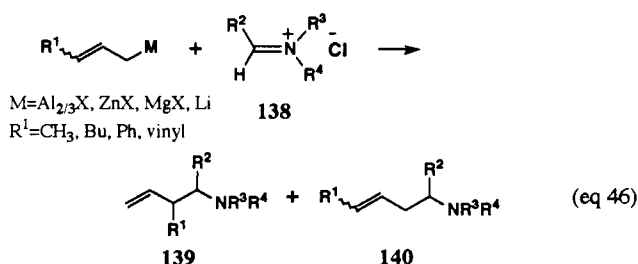
and stereoselectivities in reaction with aldehydes; reagents **134a** and **134b** are quite regioselective in reactions with aliphatic aldehydes to give the γ -adduct exclusively and show >99% syn selectivity, but in reactions with benzaldehyde the syn/anti selectivity is somewhat lower (92:8).^{21a} 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)allyl-aluminum reagent, generated from (trimethylsilyl)-allyllithium and EtAlCl_2 , shows excellent selectivity for the anti diastereomer (86–100%).²¹⁴



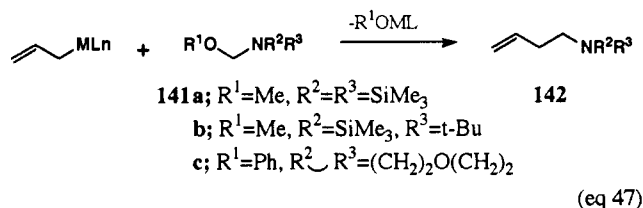
The allyl aluminum ate complex **136**, prepared in situ from allylmagnesium chloride and Et_3Al , reacts with α -chiral imine **22** to give the chelation product in a ratio of 93:7, whereas the corresponding allylmagnesium chloride provides the chelation adduct in a 79:21 ratio (see eq 4).⁵⁰ The chelation 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



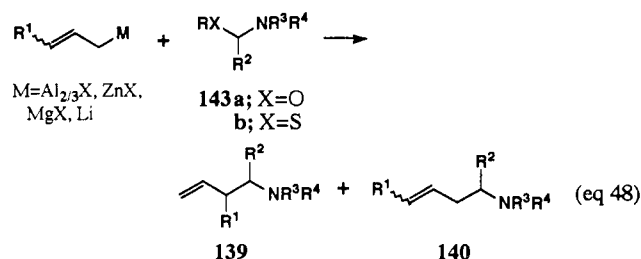
the crotyl aluminum reagent **137** with imines results in low chemical yields and low syn/anti diastereoselectivities (eq 2),⁸⁵ and therefore is not synthetically useful. The iminium salts **138** can be prepared by treatment of the corresponding enamines with hydrogen chloride. The reactions of crotylzinc,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



determined. The preference of the branched homoallylamines **139**, with the exception of vinyl crotyl reagents, follows the trend $\text{Al}_{2/3}\text{X} > \text{ZnX} > \text{MgX} > \text{Li}$, paralleling the covalent character of the carbon-metal bond. With vinyl crotyl reagents ($\text{R}^1 = \text{vinyl}$), 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 allyl aluminum reagent ($\text{CH}_2=\text{CHCH}_2\text{Al}_{2/3}\text{Br}$) with **141a** or **141b** provides **142** in 40–45% yields.²¹⁷ The additions of crotylorgano-

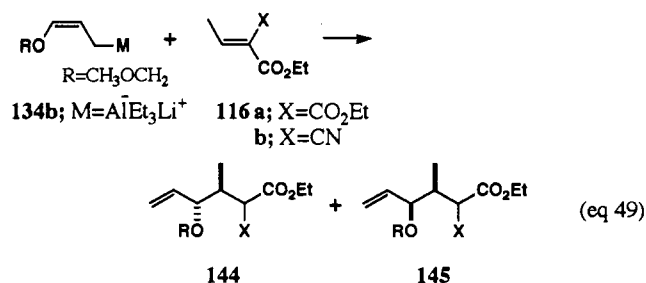


metallics to *gem*-amino ethers **143a** and sulfides **143b** provide the branched adducts **139** predominantly over linear products **140** as in the reactions of preformed iminium salts (eq 48).^{217,219,220} It seems that the reactions

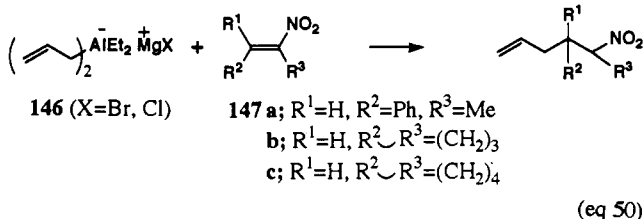


of **143** are somewhat more regioselective than those of **138**. Little difference in regioselectivity is observed between the *gem*-amino ethers **143a** and *gem*-amino sulfides **143b**. As observed in reactions of **138**, the decrease of γ -regioselectivity in reactions of **143** takes place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

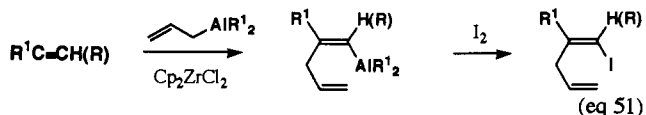
The Michael addition of the γ -oxygen substituted allylic aluminum ate complex **134b** to diesters **116a** produces a 1:1 mixture of anti and syn adducts (**144** and **145**).²⁰⁵ As mentioned later, the titanium reagent provides significantly higher anti selectivity (87:13).



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).



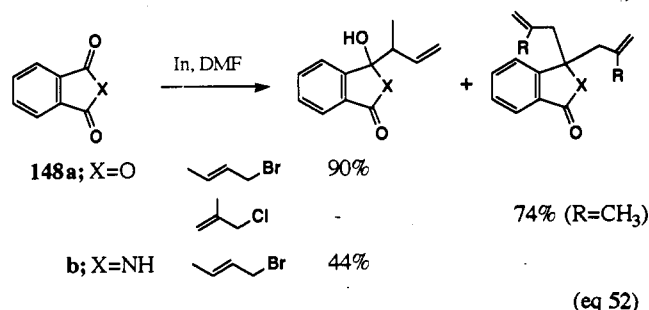
Organoaluminum compounds add in a syn manner to many alkynes, but these reactions are synthetically not useful owing to the poor reactivity of triorganoalanes. The carboaluminum is accelerated remarkably in the presence of catalytic or even stoichiometric amounts of transition metal salts. As shown in 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 allylaluminumation (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}



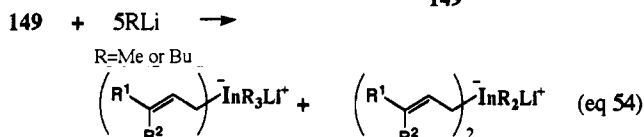
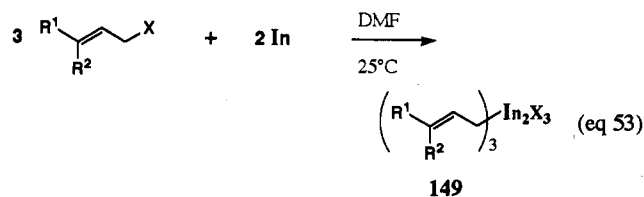
C. Allylic Indium Reagents

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 dial-

lylated products depending on the degree of substitution of the allylic indium reagents used (eq 52).²²⁴ A short



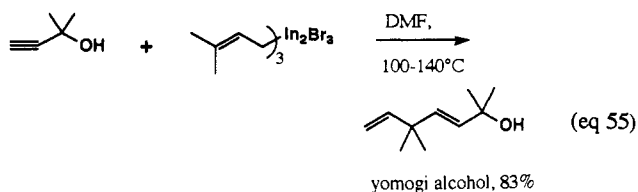
synthesis of (\pm)-bakuchiol has been accomplished by using geranylindium reagent and 2-(4-methoxyphenyl)-acetaldehyde.^{224c} In contrast to allylic magnesium and lithium reagents, the allylic indium reagents 149, prepared from the corresponding allylic chloride, bromide, and iodide, do not react with 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



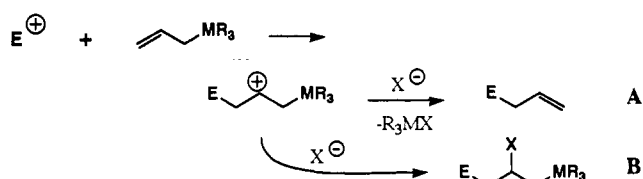
thus prepared are presumably 1:1 mixtures of allyltrialkyl- and diallyldialkylindates. Regio- and stereospecific allylic-allylic coupling has been accomplished using these indates and allylic bromides; only the products coupled at the α -position of allylic bromides and γ -position of allylic indates 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)

Allylsilanes²²⁷ and allylstannanes⁴⁶¹ have been used as extensively allyl anion equivalents during the last two decades. Their regioselective reactions with elec-



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 allylsilanes, -germanes, and -tin compounds has been accomplished.²²⁹ Second-order rate constants for the reactions of para-substituted diarylcarbenium ions ($\text{ArAr}'\text{CH}^+$) with allylsilanes, allylgermanes, and allylstannanes have been determined in CH_2Cl_2 solution at -70 to -30°C . Generally, the attack of $\text{ArAr}'\text{CH}^+$ 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



$\text{H}_2\text{C}=\text{CHCH}_2\text{MPh}_3$, the relative reactivities are 1 ($\text{M} = \text{Si}$), 5.6 ($\text{M} = \text{Ge}$), and 1600 ($\text{M} = \text{Sn}$). From the relative reactivities of compounds with the formula $\text{H}_2\text{C}=\text{CHCH}_2\text{X}$ ($\text{X} = \text{H}, \text{SiBu}_3, \text{SnBu}_3$), the activating effect of an allyl trialkylsilyl (5×10^6) 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 ($\text{An} = \text{CH}_3\text{OC}_6\text{H}_4$). 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.

A. Allylsilane Reagents

1. New Synthetic Methods

According to Fleming's classification,^{227c} the synthetic methods can be 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

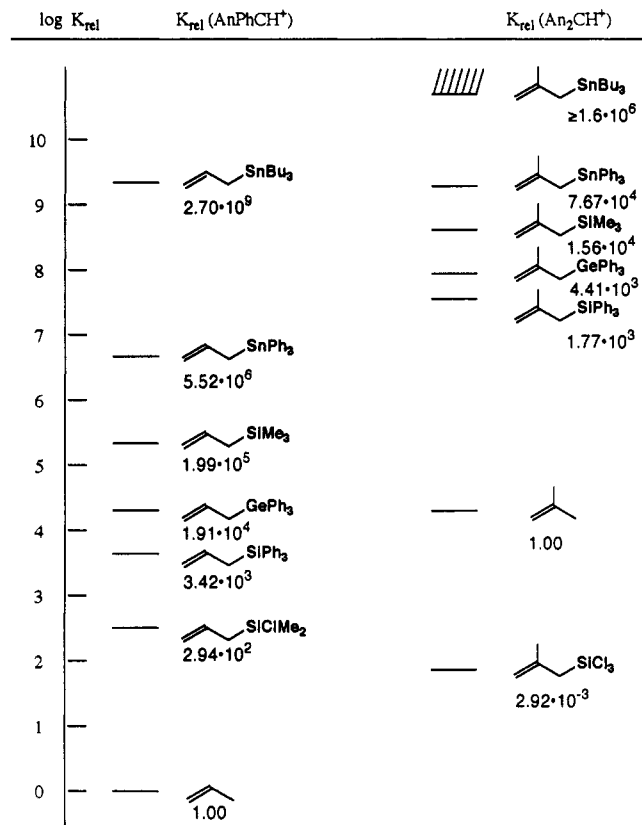
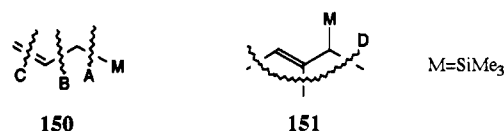
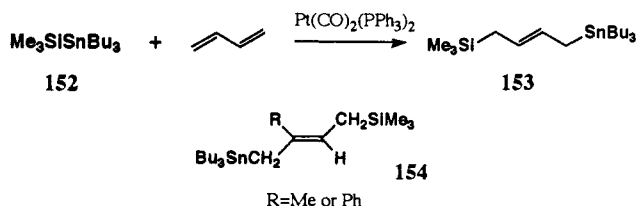


Figure 1. Relative nucleophilicities of allylsilanes, -germanes, and -stannanes with respect to propene (left) and isobutene (right). The graphic representation allows a direct comparison of all compounds; i.e., the nucleophilicities of allyltriphenylgermane and isobutene are almost identical.

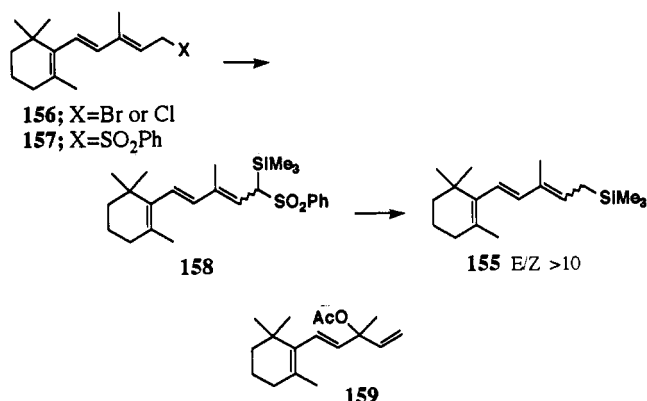


of which involve transition metal catalyzed (or mediated) reactions. Syntheses based on disconnection A are mentioned first. The reaction of $(\text{Me}_3\text{Si})\text{SnBu}_3$ 152 with 3 equiv of 1,3-butadiene in the presence of catalytic amount (5 mol %) of $\text{Pt}(\text{CO})_2(\text{PPh}_3)_2$ gives (*E*)-1,4-silyl-stannylation product 153 in 93% yield as a single stereoisomer.²³⁰ Isoprene and 2-phenyl-1,3-butadiene

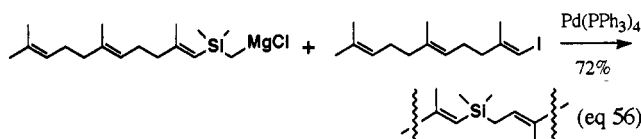


also react with 152 to afford 154 in high yields, in which Me_3Si group bonded to the sterically less bulky carbon. The most direct route for the synthesis of allylsilanes is the silylation of an allylmetal reagent such as a Grignard or lithium reagent.²²⁷ However, the reported general methodologies proved to be unsatisfactory for the synthesis of polyenylsilane;¹⁵⁵ the bromide or chloride 156, on reaction with Mg and $(\text{CH}_3)_3\text{SiCl}$ according to the procedure of Calas,^{231a} did not give 155. An alternative approach using the "counterattacking principles", that is, the reaction of $(\text{Me}_3\text{Si})_2\text{CuLi}$

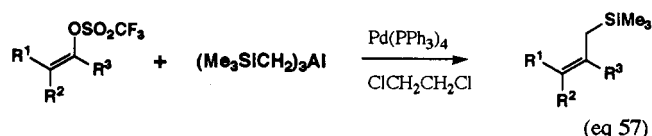
with 159, gives 155 only in 10% yield. The use of sulfone chemistry is effective for the synthesis of 155. Treatment of 157 with *t*-BuLi generated the anion which reacted with Me_3SiCl to give 158 in 80% yield. Sodium amalgam reduction ($\text{Na}/\text{DMAN}/\text{Et}_2\text{NH}$) of 158 in MeOH gives 155 in 84% yield (for DMAN, see 1).^{231b}



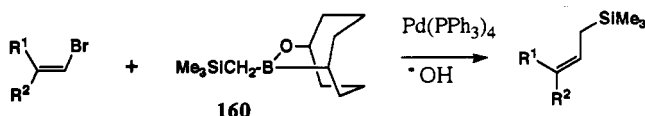
Syntheses based on disconnection B use primarily palladium catalysts. The catalyzed reaction of (trimethylsilyl)methyl Grignard reagent with various substrates, such as esters, enol derivatives, or vinyl halides provides allylsilanes in good yields.²²⁷ The synthesis of silanes bearing both an allylic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



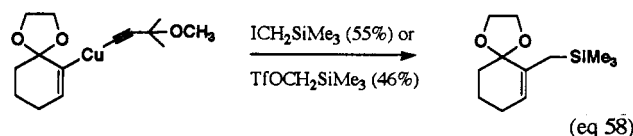
to excellent yields by the Pd(0)-catalyzed cross-coupling of vinyl triflates with $(\text{Me}_3\text{SiCH}_2)_3\text{Al}$, generated in situ from commercially available $\text{Me}_3\text{SiCH}_2\text{Li}$ and AlCl_3 (eq 57).^{232b} The palladium-catalyzed coupling of vinyl



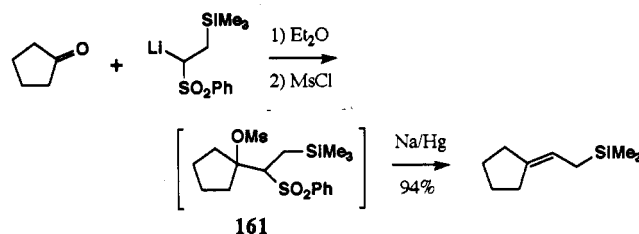
bromides with borinate ester 160, obtained by the trimethylamine *N*-oxide oxidation of the corresponding Me_3SiCH_2 -9-BBN, gives allylsilanes in excellent yields.²³³



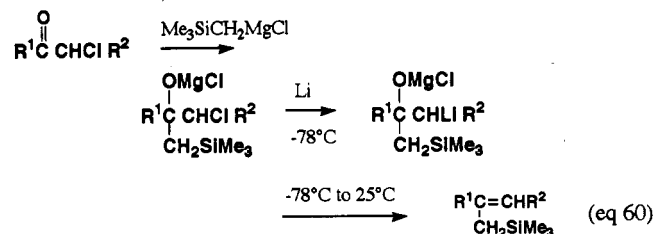
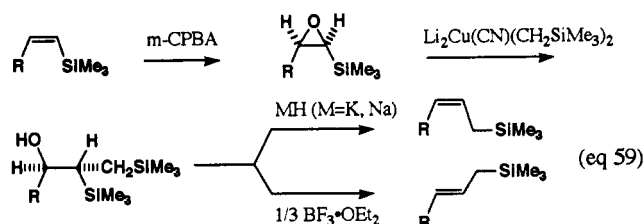
Gilman reagents derived from vinylic nucleophiles react with (iodomethyl)trimethylsilane or (trimethylsilyl)methyl trifluoromethane sulfonate to afford allylsilanes not readily accessible by other procedures (eq 58).²³⁴



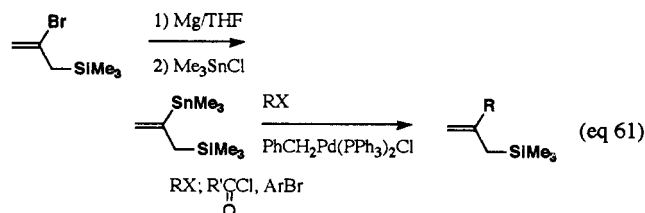
The most simple of the category (disconnection C) is the synthesis based on the Wittig reaction.²²⁷ An alternative approach is reductive desulfonylation of the γ -[(methanesulfonyl)oxyl]- β -sulfonyl derivative 161.^{231b,235} Pure *cis*-vinylsilanes, available from the



hydroboration-protonolysis of silylacetylenes, are efficiently converted to *cis*-epoxysilanes which react smoothly with $\text{Li}_2\text{Cu}(\text{CN})(\text{CH}_2\text{SiMe}_3)_2$ 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.

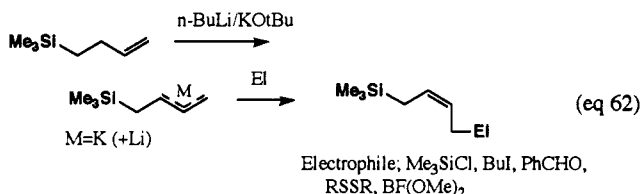


The commonly used procedure of disconnection D is to add substituents to or manipulate substituents on an existing allylsilane system, or alternatively to move the double bond into the allylic position from somewhere else in the molecule.²²⁷ Allylsilanes bearing the various functionalities are prepared 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-



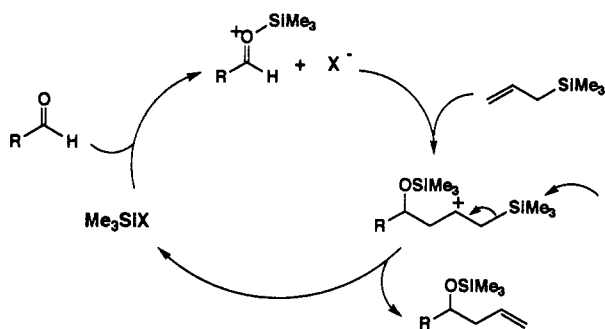
allylsilane, easily prepared by the coupling reaction of allyl bromide and $\text{Me}_3\text{SiCH}_2\text{MgCl}$, with butyllithium/

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 $\text{BF}(\text{OMe})_2$ gives exclusively *Z*-isomers, other electrophiles produce ca. 70:30–80:20 mixture of *Z/E* isomers; trapping with $\text{BF}(\text{OMe})_2$ gives the hydroxy derivative ($\text{E} = \text{OH}$) upon oxidation with $\text{NaOH}/\text{H}_2\text{O}_2$.



2. Intermolecular Reactions of Aldehydes and Ketones

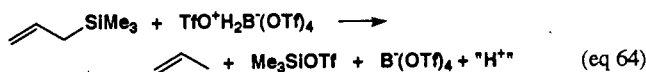
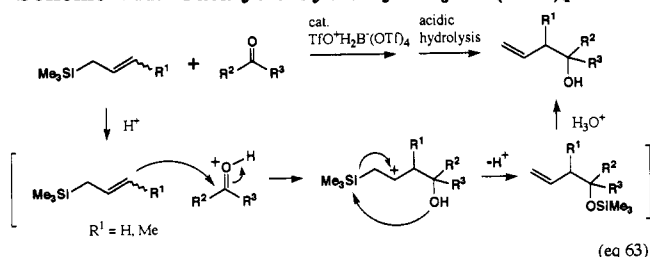
The addition of trialkylallylsilanes to aldehydes and ketones, widely appreciated as a mild method for C–C bond formation, is induced either by stoichiometric amounts of Lewis acids or by catalytic quantities of fluoride ions.^{227,240–242} Allylsilanes are known to be decomposed rapidly by strong protic acids.²⁴³ Therefore, catalysis of the allylation reaction by Brønsted acids has not previously been reported. The superacid $\text{TfOH}_2^+\text{B}(\text{OTf})_4^-$, 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



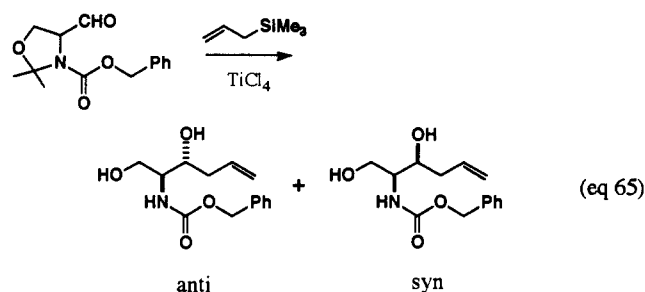
It is proposed that the protonated aldehydes and ketones initiate the catalytic cycle shown in eq 63. The proton is presumably produced by the reaction of allylsilanes with the superacid (eq 64). The allylsilane is presumably unable to quench this proton because its counterion is the highly nonnucleophilic $\text{B}(\text{OTf})_4^-$, which cannot be used to remove the Me_3Si group. The new “supersilylating reagent” $\text{Me}_3\text{SiB}(\text{OTf})_4$, prepared from $\text{B}(\text{OTf})_3$ 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

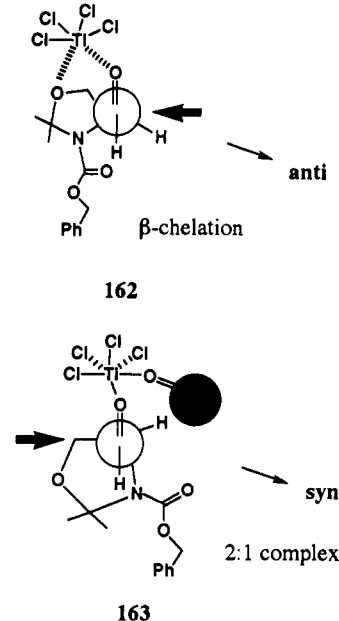
Scheme VII. Catalytic Cycle by $\text{Me}_3\text{SiB}(\text{OTf})_4$



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



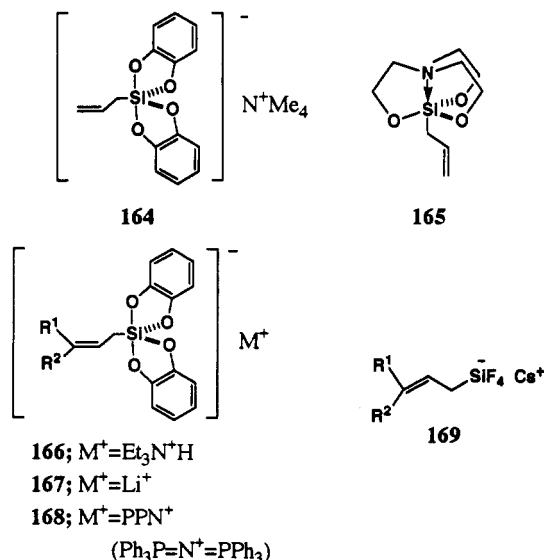
terms of two differently derived species: aldehyde- TiCl_4 , 1:1 (162) and 2:1 complexes (163), which can proceed to their respective transition states. The anti



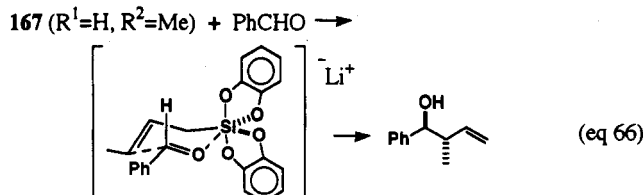
selectivity observed with 1.0 equiv is consistent with β -chelation. The disturbance of β -chelation, with excess TiCl_4 over 1.0 equiv, results in lower anti selectivity. The syn selectivity observed at 0.5 equiv of TiCl_4 is explained by the 2:1 complex shown in 163. Allylation of 2-methyl-3-oxo amides 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.

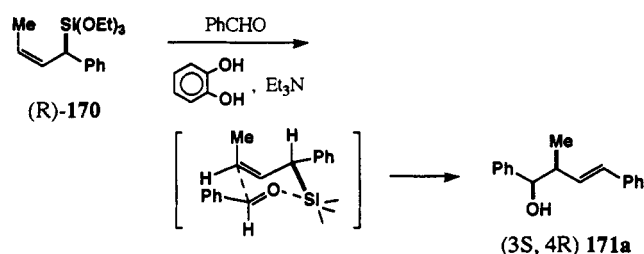
Silicon can expand its coordination number from the normal value of 4 to 5 or 6 to form penta- or hexacoordinated compounds, if the silicon atom carries highly electronegative and sterically compact ligands such as fluorine. The pentacoordinated silicon species bears a unit negative charge, which is delocalized into the electronegative ligands. As a result, the silicon atom becomes rather electron deficient with a significant Lewis acid character.²⁴⁸ 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)allylsilicates 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



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

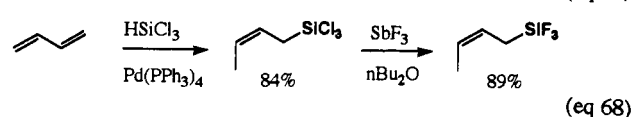
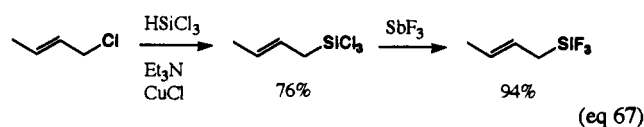


allylic silicates is completely different from that of tetracoordinate allylsilanes in the presence of Lewis acids (this will be mentioned later; see Scheme X). Without isolation of the pentacoordinate species, the allylation of aldehydes can be carried out through the in situ generation of the allylsilicate. 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



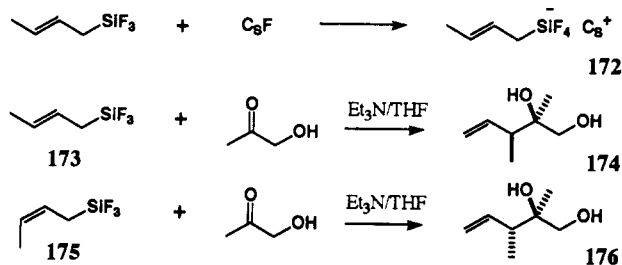
syn stereochemistry of S_{E}' reaction of allylic organometals has been observed only when the reaction is forced to proceed via a cyclic transition state. This is also the case with the allylic silicate reaction. Allylation with (*R*)-(*Z*)-1-phenyl-1-(trifluorosilyl)-2-butene in the presence of cesium 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

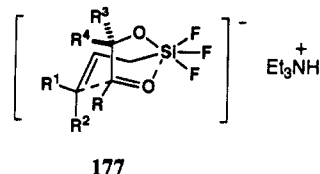


trifluorosilanes are configurationally stable and may be stored for a few months at 0 °C.²⁵² The allylation of aldehydes in the presence of CsF proceeds in high yields with high stereoselectivity. Here also, the pentacoordinate silicate 172 is produced in situ, which reacts with aldehydes to give the 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 catechol, 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.

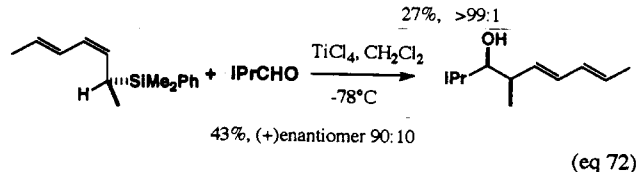
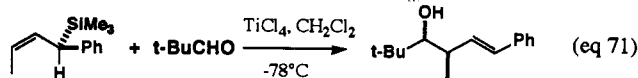
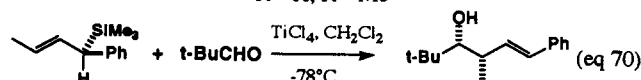
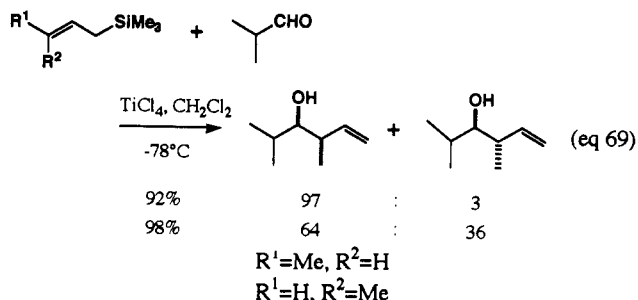
Crotyltrifluorosilanes react with α -hydroxy ketones in the presence of Et_3N without protection of the hydroxy group, producing the tertiary homoallyl alcohols with very high regio- and stereoselectivity; for example, the (*E*)-crotyltrifluorosilane (173) gives 174 in 83% yield with a syn/anti ratio 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

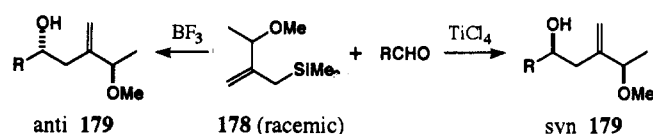


In contrast to the allylic silicate additions, the Lewis acid mediated reaction of allylic silanes (tetravalent silicon) with aldehydes proceeds through an acyclic transition state; *syn*-homoallyl alcohols are obtained predominantly regardless of the geometry of the double bond of crotylsilanes. For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

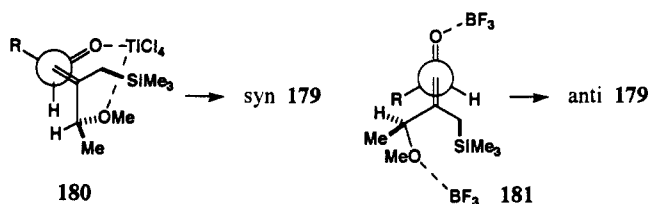


complex, and (*Z*)-crotyltrimethylsilane also affords the *syn*-alcohol predominantly (64% selectivity) (eq 69).²⁵⁶ Mechanisms involving acyclic transition states are discussed in detail in the allylic stannane section. Chiral crotylsilanes react antarafacially; the incoming electrophile attacks the 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- $\text{S}_{\text{E}}2''$ manner to produce the *syn*-(*E*) adduct predominantly (syn/anti = 80:20) (anti- $\text{S}_{\text{E}}2''/\text{syn-S}_{\text{E}}2'' = 90:10$) (eq 72).²⁵⁸ It should be noted that the overall anti- $\text{S}_{\text{E}}2'$ 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-

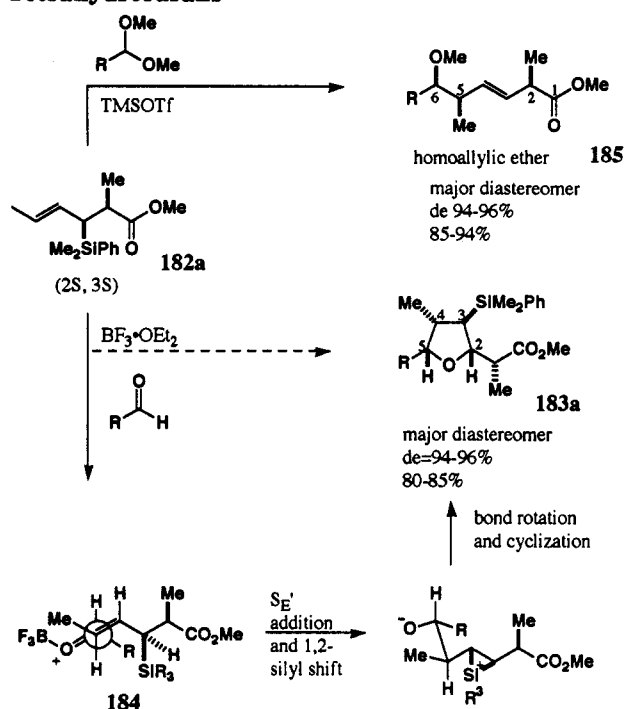


selectivity difference is explained by the different mode of chelation of these two Lewis acids; a bidentate Lewis acid, TiCl_4 , can coordinate the two oxygen atoms and thus the reaction proceeds via 180 to give *syn*-179, whereas the reaction with a monodentate $\text{BF}_3\cdot\text{OEt}_2$ proceeds via 181 to afford *anti*-179. The substituent

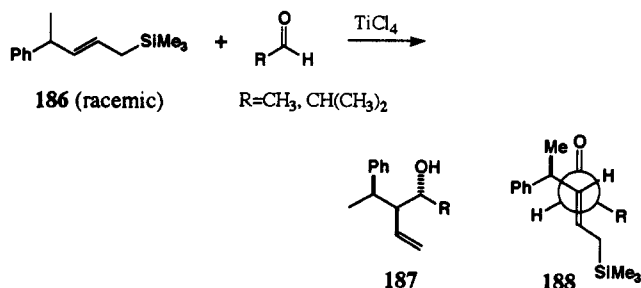


effect at the α -position of allylsilanes upon the diastereoselectivity has also been investigated.²⁶⁰ The asymmetric addition of chiral (*E*)-crotylsilanes to α - and β -benzyloxy aldehydes in the presence of $\text{BF}_3\cdot\text{OEt}_2$ constitutes a remarkably simple procedure for the construction of optically pure 2,5-*cis*-tetrahydrofurans (Scheme VIII).²⁶⁰ The (2*S*,3*S*)-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 $\text{S}_{\text{E}}2'$ 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.

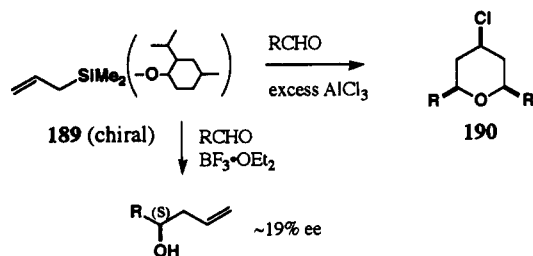
The reaction of allylsilanes, containing a stereogenic center in the δ -position with several electrophiles shows

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.

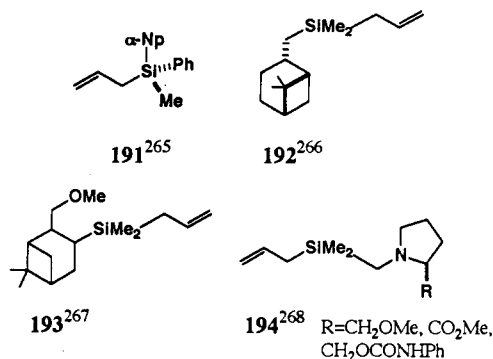


The effect of a stereocenter present on one ligand of the silicon atom, or a stereocenter on the silicon atom (chiral silicon), upon the diastereoselectivity has been studied. The reaction of 189 with aldehydes in the



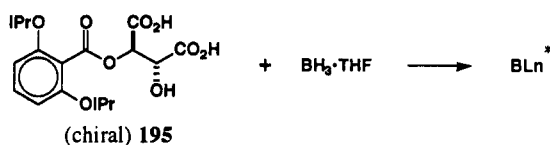
presence of excess (>1 mol) AlCl_3 gives the tetrahydropyran 190 exclusively, whereas the reaction in the

presence of $\text{BF}_3 \cdot \text{OEt}_2$ (<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

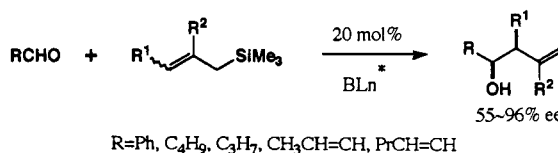


aldehydes produced enantiomeric excess in the range of 5–50%.^{265–268} However, the low asymmetric induction seems to be reasonable, since the Lewis acid mediated reaction proceeds through an acyclic transition state and therefore the chiral silicon center is located away from the carbon where a new 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^* .

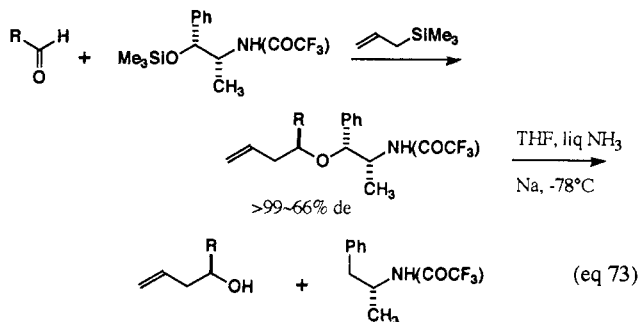


Condensation of aldehydes with allylsilanes is promoted by this catalyst at -78 °C to produce homoallyl alcohols in good to reasonable yields with ee of 55–96%. Simple

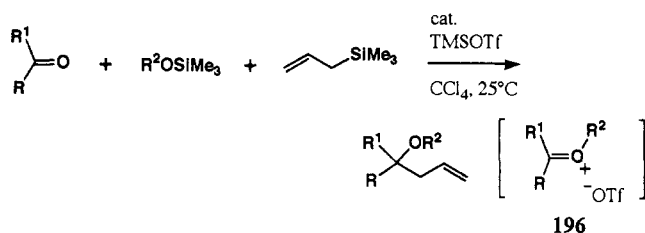


allyltrimethylsilane ($\text{R}^1 = \text{R}^2 = \text{H}$) is not reactive enough to give adducts efficiently, but alkyl substituents on the olefin moiety of allylsilanes increases the reactivity, permitting a lower reaction temperature and improved asymmetric induction. γ -Alkylated allylsilanes produce 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 -

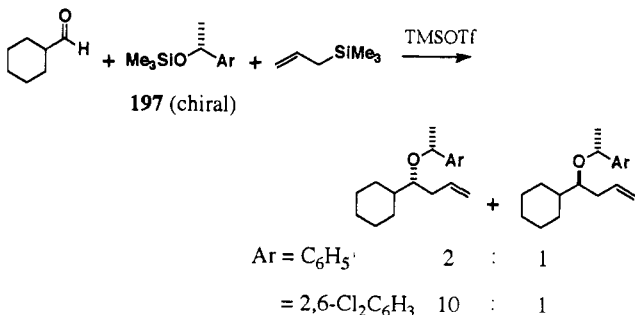
Cl_2 in the presence of 0.1 equiv of TMSOTf, and then the mixture is treated with 2 equiv of allylsilane and 0.1 equiv of TMSOTf at -78°C (eq 73). The homoallylic ethers are obtained in 49–81% yields.



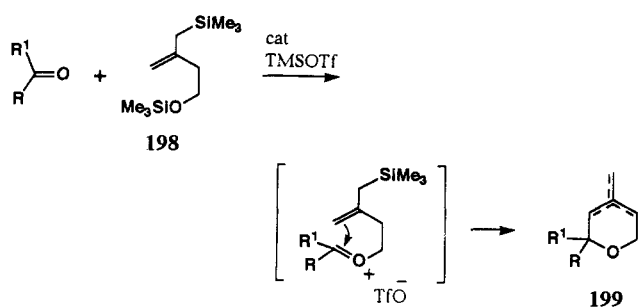
An efficient and versatile preparation of homoallyl ethers from trimethylsilyl ethers, allyltrimethylsilane, and carbonyl compounds has been accomplished.²⁷⁰ It is proposed that the three-component condensation involves the in situ generation of the oxonium cation 196. The diastereoselectivity of this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



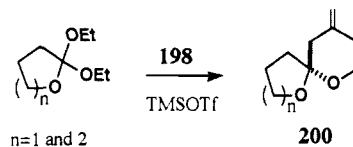
of homoallyl ethers was investigated using the chiral silyl ether 197. The diastereoisomer ratio depended upon the nature of the aromatic group in 197. When



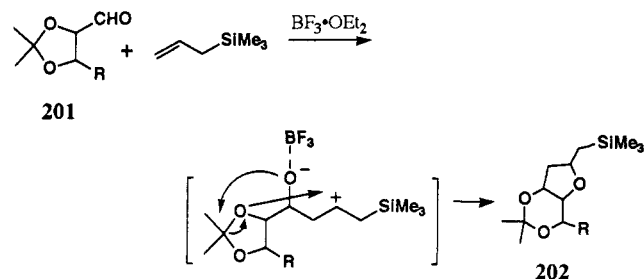
the phenyl-substituted silyl ether was used, a 2:1 ratio of the diastereomers was obtained. Replacement of the phenyl group by a 2,6-dichlorophenyl group lead to a substantially increased ratio of 10:1. By employing the intramolecular version 198 of the reaction shown above, oxocenes including spiroethers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

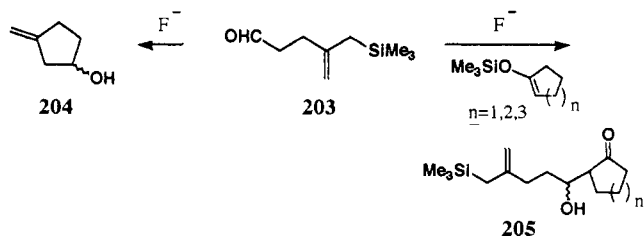


the procedure gives a mixture of regioisomeric olefins 199, the addition of a simple trimethylsilyl ether such as $\text{C}_6\text{H}_{13}\text{OSiMe}_3$ or $\text{C}_2\text{H}_5\text{OSiMe}_3$ to the reaction mixture containing the carbonyl compound, 198, and TMSOTf, dramatically modifies the product 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 $\text{BF}_3\cdot\text{OEt}_2$ 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}



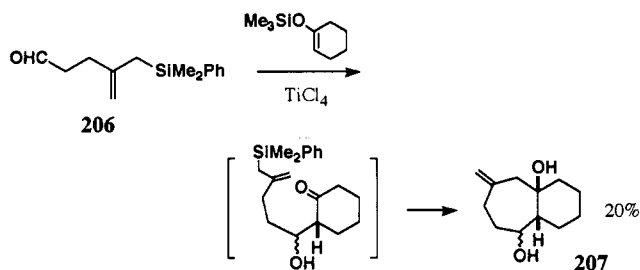
3. Intramolecular Reactions of Aldehydes and Ketones

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

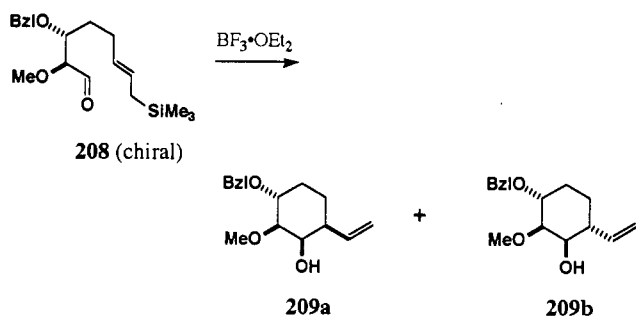


intermolecular attack of the enol silane predominates over the kinetically slower (disfavored) intramolecular cyclization. Further cyclization of 205 is not successful under the influence of F^- , instead the desilylated ketone is isolated. However, the aldehyde allylsilane 206 reacts with the enol trimethylsilyl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

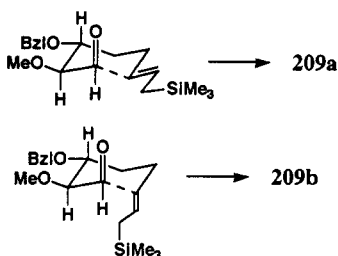
molecular attack by the enol silane takes place, followed by subsequent intramolecular attack upon the initially formed ketone. The $\text{BF}_3 \cdot \text{OEt}_2$ mediated cyclization of



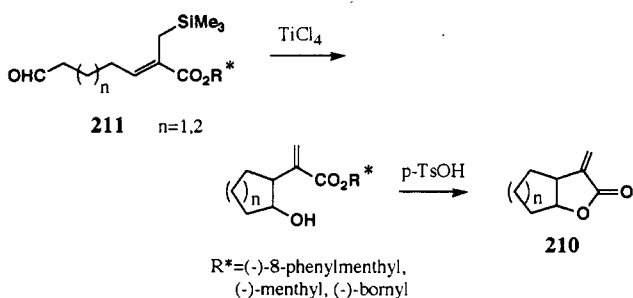
208 gives a mixture of two diastereomers 209a and 209b in a ratio of 47:53 in 82% total yield.²⁷⁶ The stereo-



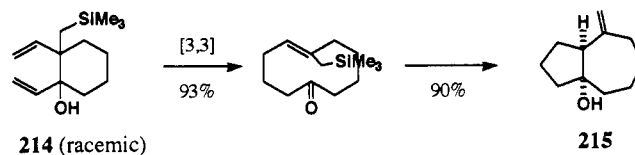
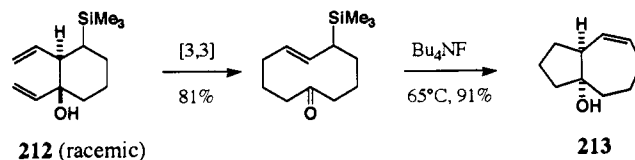
chemical result of the cyclization may be explained by assuming a transition structure with a chair-like conformation where the two alkoxy groups occupy equatorial positions. The carbonyl group must point in the axial direction, since this corresponds to a Cram-Felkin-type transition structure. Thus,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



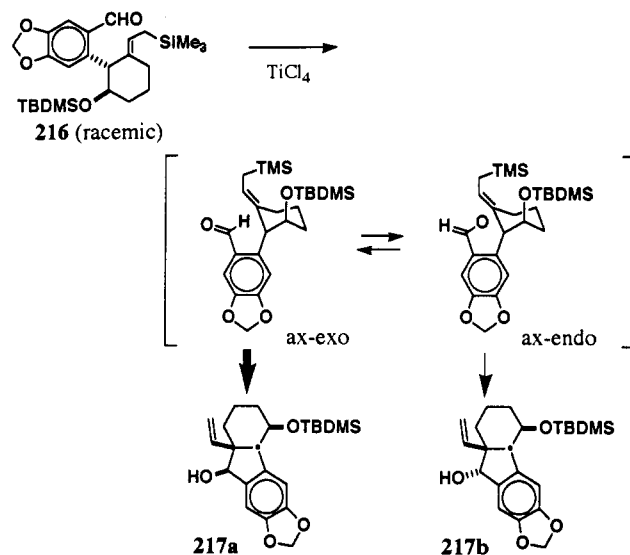
Optically active α -methylene- γ -butyrolactones 210 fused to five- or six-membered carbocyclic ring are synthesized in 62–92% enantiomeric excess using the intramolecular reaction of ω -formylated β -(chiral)-(alkoxycarbonyl)allylsilanes 211.²⁷⁷ Intramolecular cyclization of the allylsilanes produced from anionic oxy-



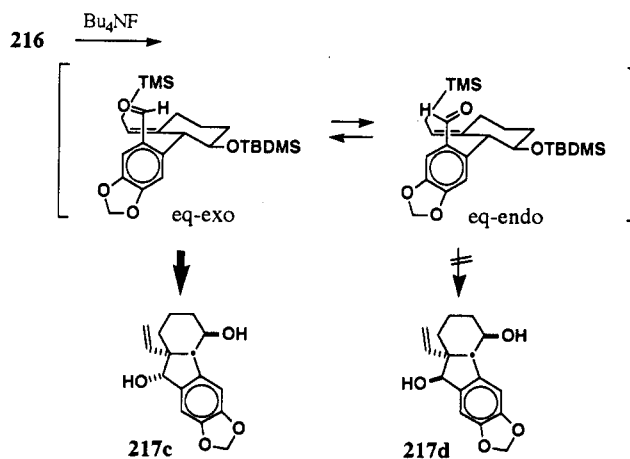
Cope rearrangements of 1,2-divinylcyclohexanols led to hydroazulenols with the cis ring fusion.²⁷⁸ The reaction of 212 with 5 equiv of KH and 0.4 equiv of I_2 in THF at 60 °C gives cyclodecenone with the trans double bond, which is converted to 213 upon treatment with Bu_4NF at 65 °C. Similarly, 214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



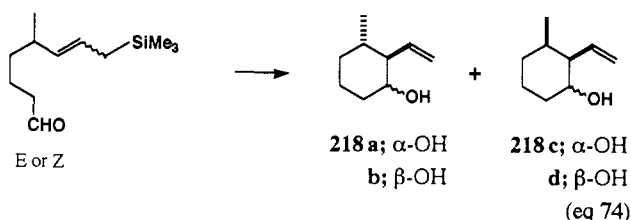
affords a 4:1 mixture of cis-fused alcohols 217a and 217b in 70% yield.²⁷⁹ No trans-fused products are obtained. This diastereoselectivity can be reasonably explained by the transition-state geometries (ax-exo and ax-endo). However, the reaction of 216 with excess



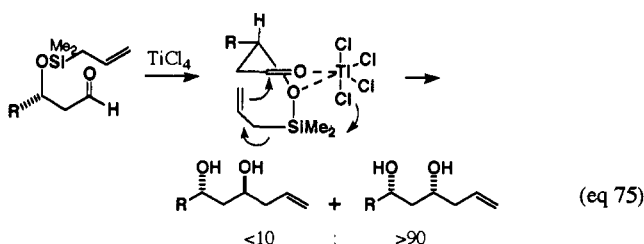
Bu_4NF in THF provides a ca. 10:1 mixture of diols 217c and 217d in 86% yield. The selectivity for the F⁻-induced trans fusion process is between 5–7:1.



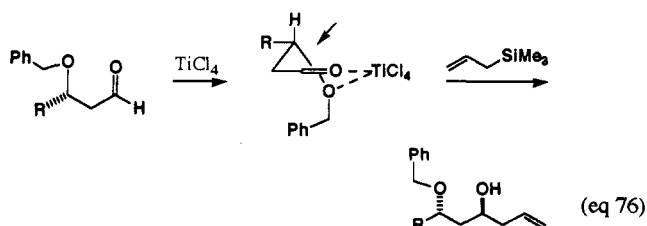
Generally speaking, all annulation reactions which generate small rings (≤ 7) are expected to form *cis* ring fusions. Accordingly, the fluoride-induced annulation seems to be a rare case. The cyclization of (*E*)-5-methyl-8-(trimethylsilyl)-6-octenal in the presence of SnCl_4 or $\text{CF}_3\text{CO}_2\text{H}$ provides *trans*-hydroxy product **218a** preferentially; **218a**/**218b** = $>5:1$ in reactions of $\text{CF}_3\text{CO}_2\text{H}$ 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 $\text{CF}_3\text{CO}_2\text{H}$ and $>3:1$ in SnCl_4 .²⁸⁰



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 $\text{BF}_3\cdot\text{OEt}_2$ 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

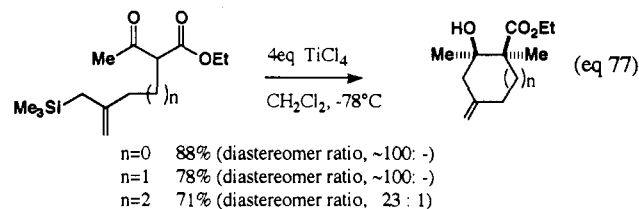


This selectivity (*syn*) is opposite to that observed in intermolecular allylsilane additions to the related chelates (*anti* preference) (eq 76). The switch from

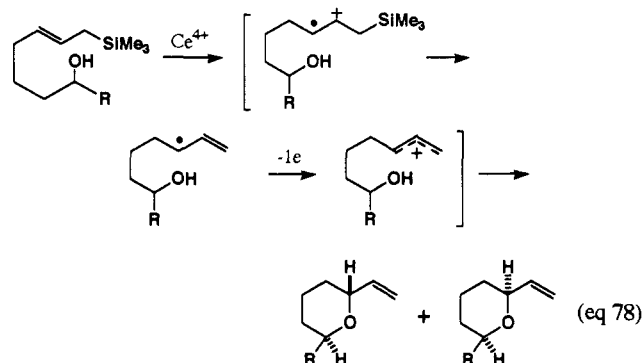


TiCl_4 to SnCl_4 in the intramolecular reaction (eq 75) results in the reversal of diastereofacial selectivity and an intermolecular allyl transfer which gives the anti-product.²⁸³ Although the mechanistic picture of the intermolecular SnCl_4 induced allylation is less clear, the formation of 2:1 complex (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

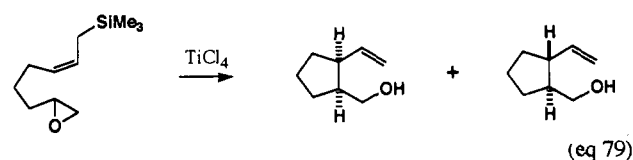
intramolecular additions of allylsilanes to β -dicarbonyl compounds.²⁸⁴ Cyclizations occur under mild conditions and are highly chemoselective, providing direct routes to highly functionalized five-, six-, and seven-membered carbocycles (eq 77). Allylsilanes containing



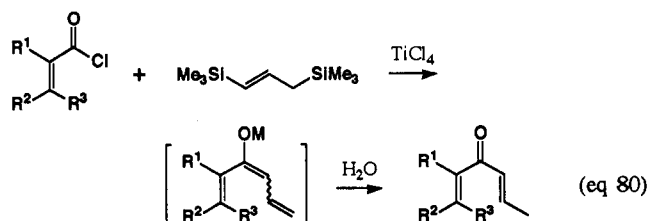
heteroatom nucleophiles yield cyclic products when treated with $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$ (eq 78).²⁸² The cyclization



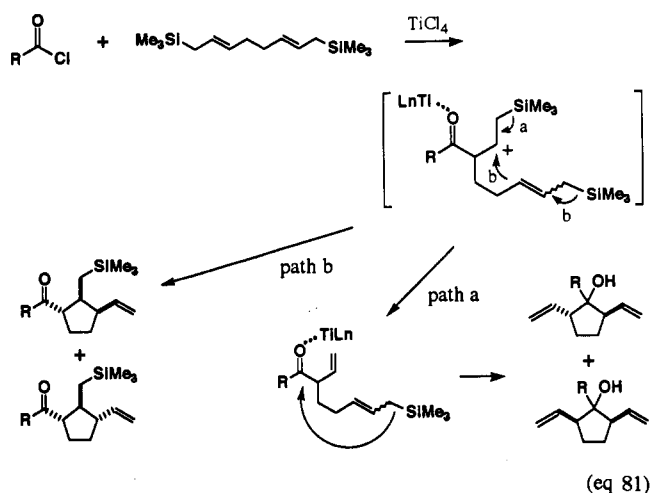
presumably proceeds through direct oxidation of the double bond of the allylsilane unit rather than formation of an oxy radical intermediate due to the hydrogen abstraction from the hydroxy group. The resulting radical cation is converted to the allyl radical via removal of trimethylsilyl cation. Further 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



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-vinylcyclopentanols (eq 81). The cyclo-

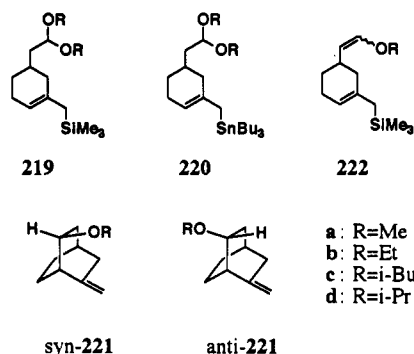


pentanol derivatives, in which the trans-isomer predominates, are formed via path a, whereas the cyclopentane derivatives are produced via path b where the trans-cis isomer is, in general, a major isomer.²⁸⁷



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

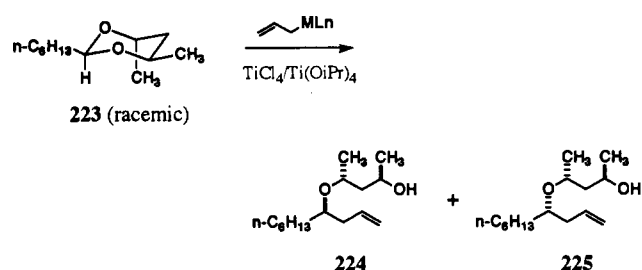
The mechanism and stereochemical outcome of allylsilane-acetal addition reaction have been investigated, but it seems to be difficult to draw clear-cut and firm conclusions. The first series of experiments addresses the Lewis acid dependence of cyclization stereochemistry with **219** and **220**. The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



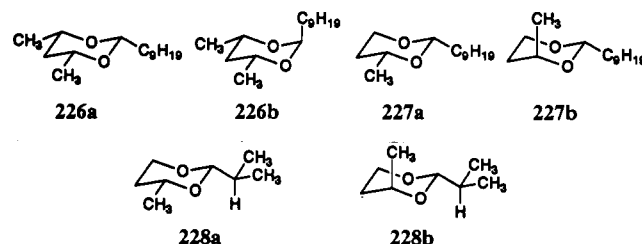
selectivities from highly syn selective (**221**, in the presence of TMSOTf) to unselective (TiCl_4) strongly suggested the involvement of the Lewis acid in the stereochemistry-determining step and argues against a common oxocarbenium ion intermediate.²⁸⁸ The effect of the acetal structure on the stereochemical 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: $\text{S}_{\text{N}}2$ via a complex and $\text{S}_{\text{N}}1$ 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 $\text{S}_{\text{N}}2$ -like mechanism, whereas that of allyltrimethylsilane proceeds via a $\text{S}_{\text{N}}1$ -like mechanism.²⁸⁹ Similar conclusions were reached in the study of the stereoselective opening of **223** with allylmetals. Here



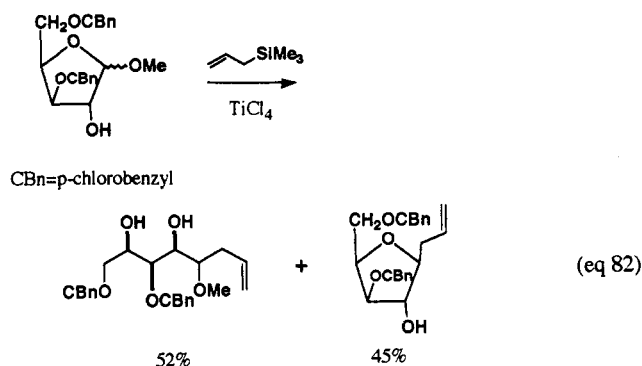
also, the stereoselectivity (**224/225**) is highly dependent on the nature of the allylmetal reagent: $\text{L}_n\text{M} = \text{Ph}_3\text{Si}$ (19:1), Me_3Si (58:1), Ph_3Sn (90:1), Me_3Ge (100:1), $n\text{-Bu}_3\text{Sn}$ (>300:1).²⁹² The TiCl_4 -promoted reactions of allyltrimethylsilane with **226**–**228** were investigated to clarify the mechanism of the acetal cleavage. Seemingly minor



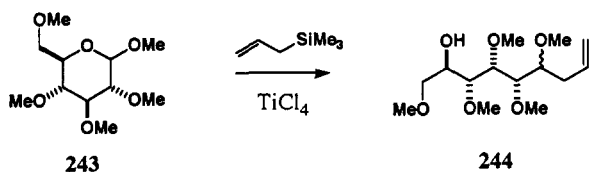
perturbations in the structure of the acetal can substantially change the outcome and mechanism of the reaction. It is difficult to draw firm conclusions regarding the mechanism, but it is clear that an oxocarbenium ion mechanism displays lower selectivity than a direct displacement mechanism ($\text{S}_{\text{N}}2$ like).^{293a} More recently, it was demonstrated by the experiments using deuterated chiral acetals that the Lewis acid ($\text{TiCl}_n(\text{OiPr})_{4-n}$, $n = 4, 3, 2$) 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}

2-Azido C-glycosyl sugars can be prepared by the $\text{BF}_3 \cdot \text{OEt}_2$ -mediated reaction of allylsilanes to the nitrate glycosides of 2-azido sugars.³⁰⁵

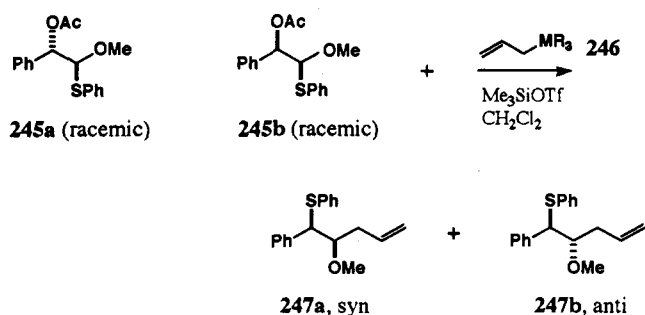
As noted above, most of the reactions of glycosides have promoted the substitution of the exocyclic C–O bond, thereby leading to cyclic products (C-glycosides). By contrast, the formation of chain-extended acyclic products, that is the regiocontrolled substitution of the endocyclic C–O bond in glycosides 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



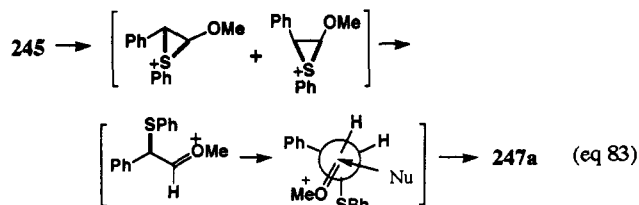
protected xylofuranoside with allylsilane in the presence of TiCl_4 gives the open-chain alditol derivative as the major product (eq 82). Although per-O-alkylated glucopyranosides are known to undergo C-allylation with exocyclic C–O-bond cleavage only on reaction with allyltrimethylsilane and Me_3SiOTf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



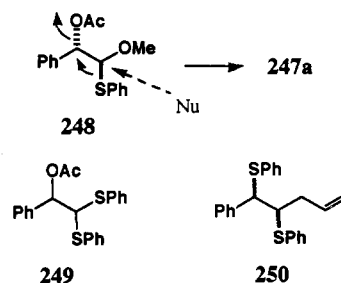
The mechanism of allylmetal–thioacetal reactions has been investigated by using 2-acetoxy-2-phenylacetaldehyde thioacetals in the presence of TMSOTf .³⁰⁷ Upon treatment with the monoethioacetal **245**, allyltrimethylsilane **246a** and allyltrimethylgermane **246b** provide allylation products **247**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



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

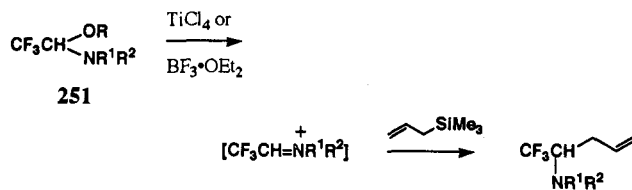


indicate that reactions of the less nucleophilic silicon and germanium compounds proceed through a $\text{S}_{\text{N}}1$ mechanism while the allyltins react through a $\text{S}_{\text{N}}2$ -type mechanism.²⁸⁹ Apparently, the reactions with the silyl and germlyl reagents produce an oxonium intermediate ($\text{S}_{\text{N}}1$ 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 $\text{S}_{\text{N}}2$ -type mechanism. Reaction of the dithioacetal **249** furnishes predominantly the syn product **250** with both allylsilane and -stannanes, indicative of an $\text{S}_{\text{N}}2$ -type mechanism. These results

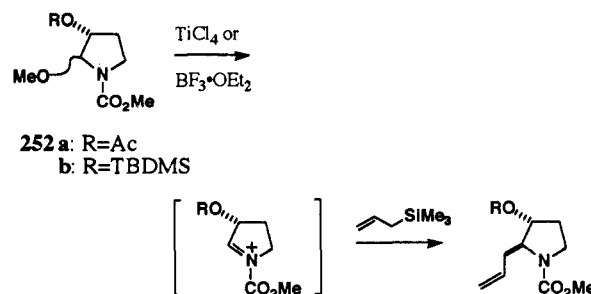


reflect the inferior ability of a sulfenyl group to stabilize an α -carbocation, relative to a methoxy group. The reaction of anodically prepared β -trifluoromethylated O,S-acetals with allyltrimethylsilane produces the corresponding allylated sulfides in good yield.^{308a}

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

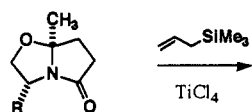


of Lewis acids gives **253** in high yields.^{309a} It was established from low-temperature NMR experiments that *N*-acyliminium ion intermediates are produced



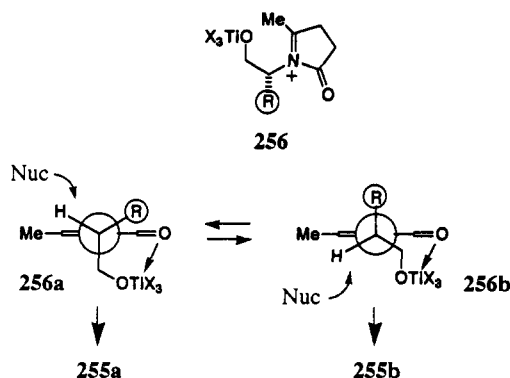
from α -methoxylated carbamates.³¹⁰ The trans isomer **253a** is obtained predominantly from **252a**, while the cis isomer **253b** is formed preferentially from **252b**.

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

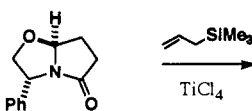
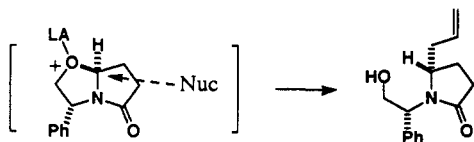
**254** (chiral)

R	255a (retention)	255b (inversion)
Me	8	1
Ph	5	1
<i>i</i> -Pr	1	2
<i>t</i> -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

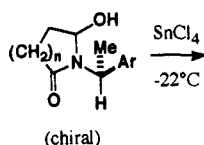


254, the allylation of the angular hydrogen lactam **257** gives the product with inversion at the angular position (S_N2 -like product).

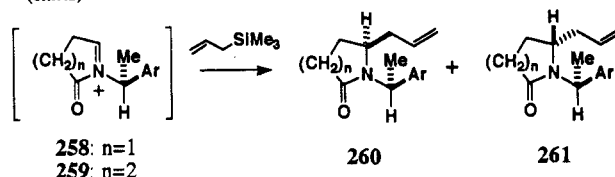
**257**

(*S*)-(-)- α -Phenylethylamine (Ar = C₆H₅), (*S*)-(-)-1-(2-Cl-C₆H₄), (*S*)-(-)-1-(2,6-dichlorophenyl)ethylamine (Ar = 2,6-Cl₂C₆H₃), and (*S*)-(-)-1-(2,3,4,5,6-pentachlorophenyl)ethylamine (Ar = Cl₅C₆) have been incorpo-

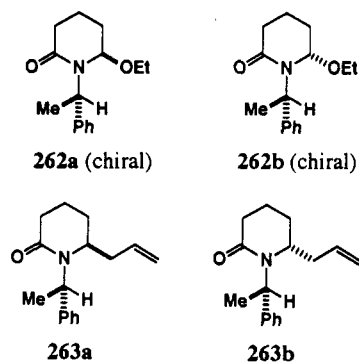
rated into acyliminium ions of structural type **258** and **259**. The chlorinated derivatives of **258** provide **260** predominantly, whereas the nonchlorinated five-membered iminium ion of **258** affords **261** preferentially.



(chiral)

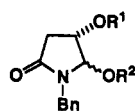
**258**: n=1**259**: n=2**260****261**

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 TiCl₄ in CH₂Cl₂ 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 Me₃-

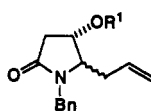
**262a** (chiral)**262b** (chiral)**263a****263b**

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 Me₃-SiOTf-mediated allylation to benzylether **264d**. Prevalent formation of the cis isomer of **265** is possible by using **264c** and MgBr₂ as a Lewis acid. The best cis selectivity (4:1) is achieved by the MgBr₂-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 BF₃·OEt₂ yielded an 11:1 mixture of **267** and its cis-isomer.^{316a} The use of TiCl₄ 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 BF₃·OEt₂. Several 2-(phenylsulfonyl)piperidines and -pyrrolidines **268** react with allyltrimethylsilane in the presence of Lewis acids such as

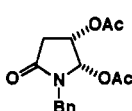
AlCl_3 and MgBr_2 to give the corresponding allylated products **269** in good to high yields.³¹⁷ Not only allylsilane but also allylmagnesium bromide in the presence of ZnCl_2 produces **269** in high yield. The $\text{BF}_3 \cdot \text{OEt}_2$ -mediated reaction of allylsilanes with *N*-(alkoxycarbonyl)- α -methoxyglycinamides leads to the corresponding α, δ -unsaturated α -amino carboxamides.^{316b} The $\text{S}_{\text{N}}1$ character of this process was proven in the case of α -methoxyglycine methyl ester.



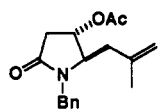
264 a: $\text{R}^1 = \text{Ac}$, $\text{R}^2 = \text{Et}$
 b: $\text{R}^1 = \text{Ac}$, $\text{R}^2 = \text{Ac}$
 c: $\text{R}^1 = \text{Bn}$, $\text{R}^2 = \text{Ac}$
 d: $\text{R}^1 = \text{Bn}$, $\text{R}^2 = \text{Et}$



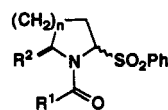
265; $\text{R}^1 = \text{Ac}$



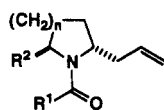
266 (chiral)



267 (chiral)

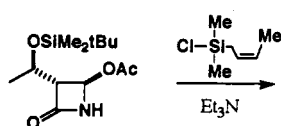


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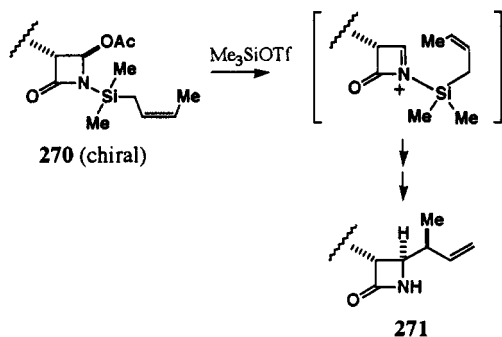


269

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 $\text{MeOH}/\text{Et}_3\text{N}$ gives **271** in 84% yield.³¹⁸ Reaction of

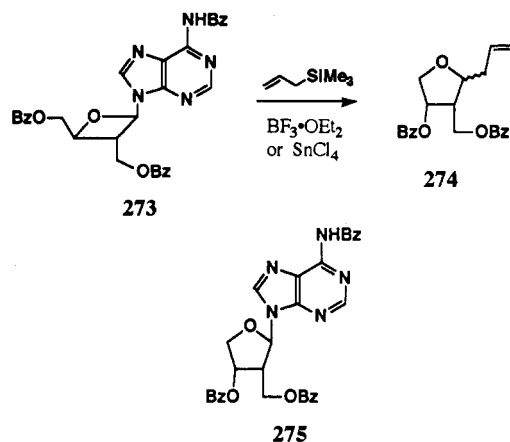


272

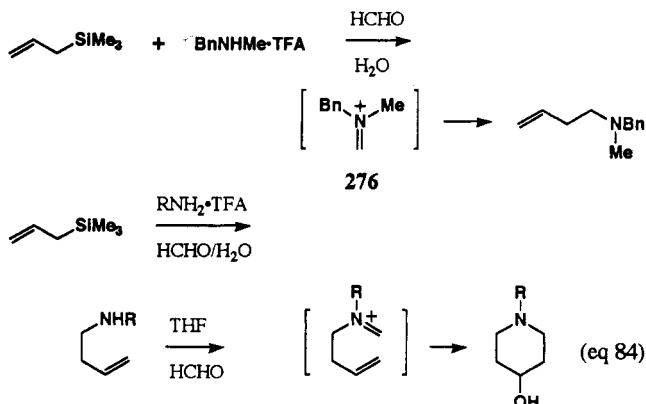


272 with crotyltrimethylsilane in the presence of Lewis acids gave a 1:1 mixture of **271** and (4*R*)-4-[(1*R*)-1-methylallyl]-isomer regardless of the geometry of the double bond of crotylsilane. Further, the intermolecular reaction of **272** with 2-(trimethylsilyl)-2-butenyltrimethylsilane in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ 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 $\text{BF}_3 \cdot \text{OEt}_2$ 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**

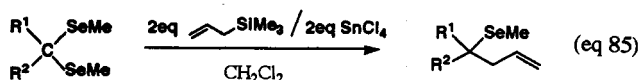
under the similar conditions used for **273** gave **274**. Generally the C-O bond cleavage of *N,O*-acetals is observed in the Lewis acid mediated allylation, but this example clearly indicates that the C-N bond cleavage



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).



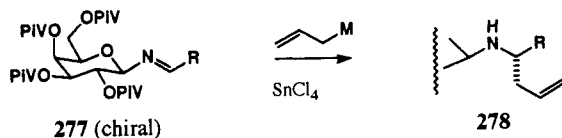
Lewis acid activation of bis(methylseleno)alkanes causes them to react with allylsilane to produce the corresponding homoallyl selenides in moderate to good yields, depending on the structure of the starting selenoacetals (eq 85).³²³



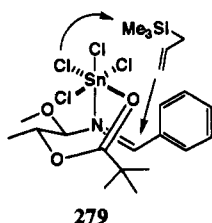
5. Reactions of Imines

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

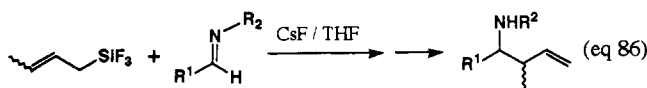
reaction of aldehydes. As mentioned above, the reaction of iminium salts (particularly acyliminium ions) proceeds smoothly in contrast to that of uncharged imines. Aromatic *N*-galactosyl imines **277** ($R = Ar$) react with 1 equiv of allyltrimethylsilane in THF in the presence of 2.2 equiv of $SnCl_4$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



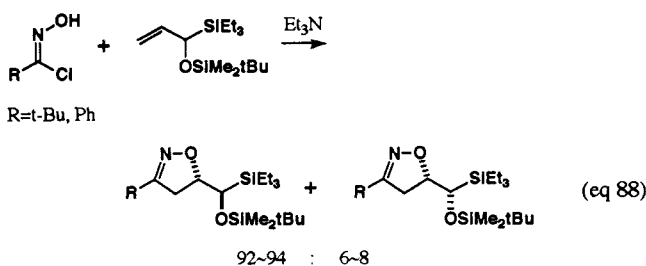
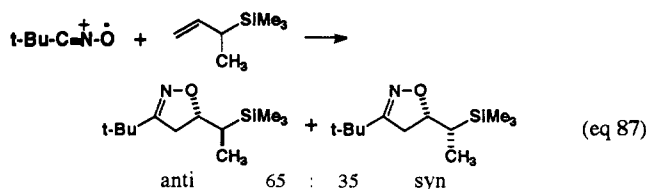
($R = alkyl$) do not react with allyltrimethylsilane under the same conditions, but more the nucleophilic allyl-tributyltin reacts with those imines in allowable yields. The high diastereoselectivity observed in the allylsilane reaction is explained by the transition state shown in **279**. Two coordination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



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 crotyltri-fluorosilanes with aldimines in the presence of cesium fluoride affords the corresponding homoallylamines in good to high yields (except for a hindered imine such as $n\text{-PrCH=N-i-Pr}$) in a regiospecific manner, but the diastereoselectivity is not high (eq 86).³²⁵ The cycload-



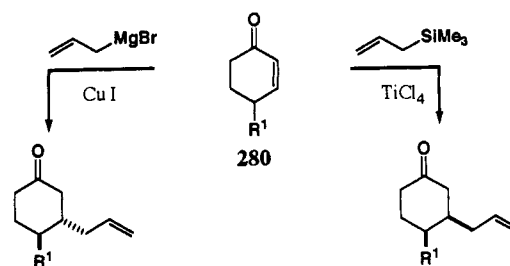
dition reactions of nitride oxides with α -chiral butenylsilanes provide Δ^2 -isoxazolines with low diastereoselectivity (eq 87).³²⁶ However, (α -siloxyallyl)silane



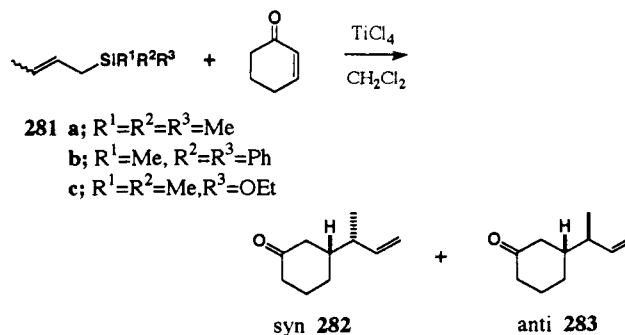
produces high anti selectivity (eq 88).³²⁷ 2,2-Dimethylpropane- and -benzonitrile oxide are generated in situ from the corresponding oxime chloride and Et_3N . The use of [α -(acyloxy)- or -(alkoxy)carbonyl]oxy]allyl]-silanes results in low diastereoselectivity. The high anti selectivity in reactions 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

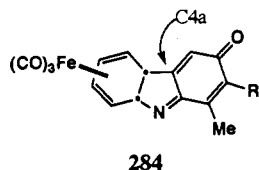


the 5-substituted cyclohexenone give the *trans*-3-allyl-5-substituted product predominantly irrespective of the reagent types. It is proposed that the major products formed in the allylsilane additions are those favored for stereoelectronic reasons, whereas the copper-catalyzed addition affords less 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*)-

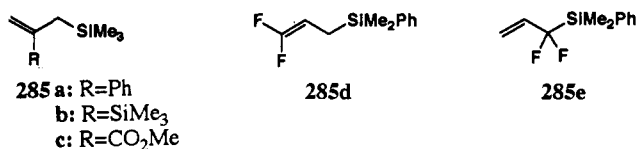


281 predominantly (11:1 from **281a**, 15.6:1 from **281b**, and 6:1 from **281c**), while the syn-isomer **282** is produced from (*Z*)-**281** with lower diastereoselectivities (3:1 from

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

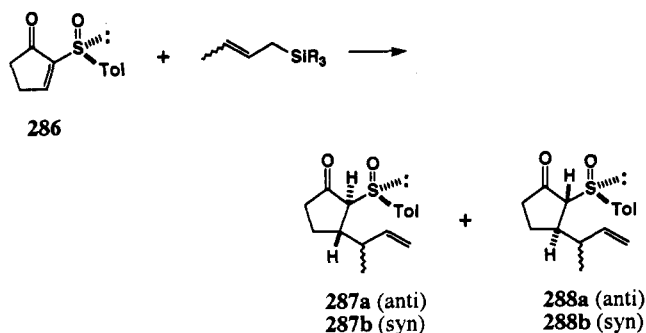


Previously it was reported that the allylation of aldehydes with allylsilanes in the presence of catalytic amounts of Bu_4NF would proceed through the intermediacy of an allyl anion.³³² However it was later proposed that there was no allylic anion but a nucleophilic intermediate of hypervalent silicon 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 under TASF catalysis ($(\text{Et}_2\text{N})_3\text{S}^+\text{Me}_3\text{SiF}_2^-$) at room temperature in DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) and an equilibrium between 285d and 285e is not observed under the reaction conditions. Accord-

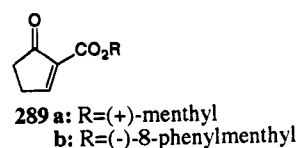


ingly, a metal-free *gem*-difluoroallyl anion as the common intermediate, although *gem*-difluoroallyllithium 19 exists only at low temperature of -95°C ,³⁷ is involved in this TASF-catalyzed (6 mol %) reaction.^{333b}

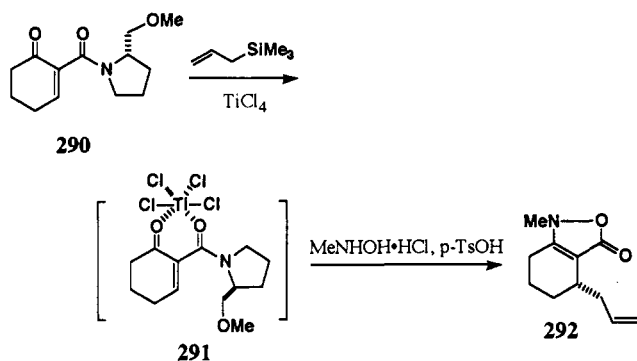
The Lewis acid mediated addition of crotylsilanes to 2-cyclopentenone derivatives (286 and 289) having chiral auxiliaries at 2-position was investigated.³³⁵ As observed previously in the case of simple cycloalkenones (see the additions of 281), the anti diastereoselectivity is obtained from the reaction 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



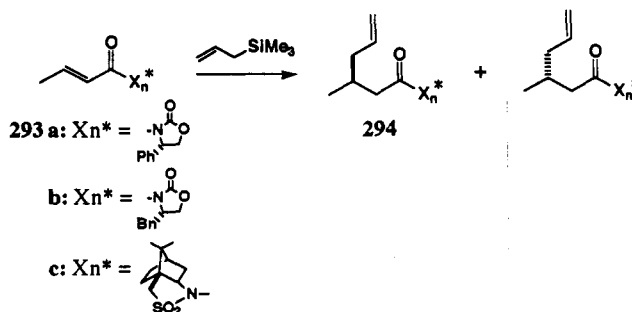
the reactions with (*E*)- and (*Z*)-crotylsilanes, and the 3*S*-enantiomers (287a and 287b) are obtained as high as 99% de. Although the diastereofacial selectivities (leading to 3*S*-isomers) observed in the reaction of 289a are moderate for both (*E*)- and (*Z*)-crotylsilanes, those (leading to 3*R*-isomers)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



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.

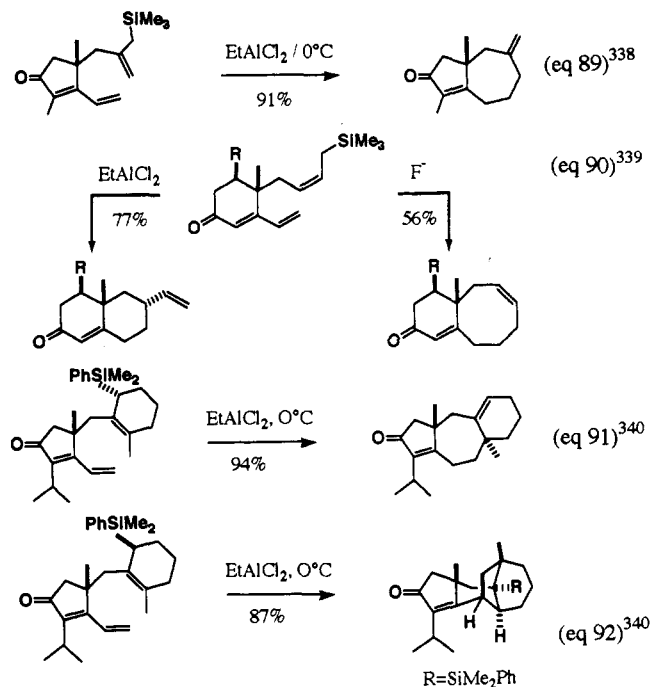


The 1,4-addition reaction of allyltrimethylsilane to α,β -unsaturated *N*-acyloxazolidinones or *N*-enoyl sul-tams in the presence of Lewis acids proceeds in good chemical yield with high diastereomeric excess.³³⁷ The TiCl_4 -mediated addition to 293a at -78°C provides a

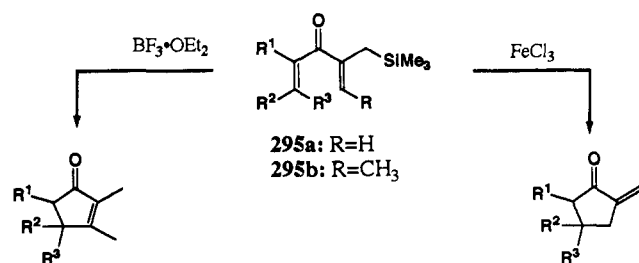


89:11 mixture of **294** and its diastereomer in 88% yield. The diastereoselectivity decreases in the reactions of **293b** (70:30) and **293c** (78:22).

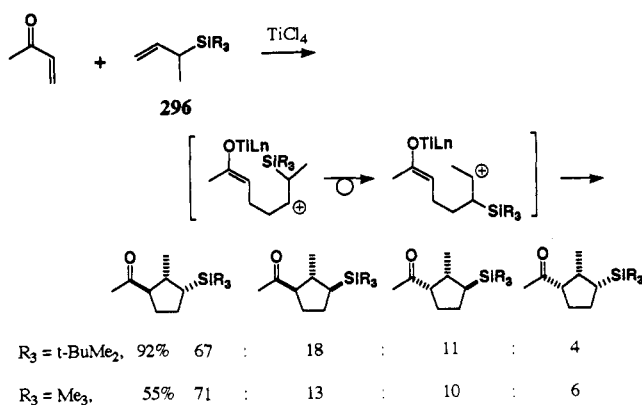
The intramolecular version of the Lewis acid of F⁻-mediated conjugate addition of allylsilanes to α,β -unsaturated carbonyl systems has been studied extensively primarily for the synthesis of carbocyclic compounds including natural products. Excellent reviews have appeared recently,²⁷⁴ and they cover 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.



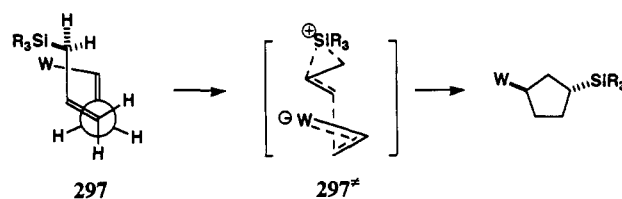
The reaction of **295a** with anhydrous FeCl₃ in dichloromethane gives the corresponding α -methylenecyclopentanones.³⁴¹ A completely different regioselectivity on the double-bond formation is found in the reaction of **295b** with BF₃·OEt₂.³⁴² Allylsilanes can serve



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 SiR₃ group such as Me₃Si 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⁺**). As



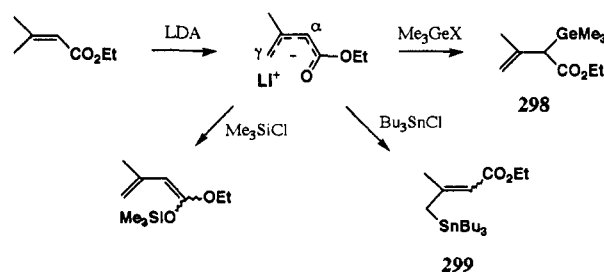
mentioned above, allylsilanes bearing large R₃Si group are essential for the desired [3 + 2] annulation. For example, even the reaction of methyl vinyl ketone with allyltriisopropylsilane produces the desired cyclopentane derivatives in 77% yield along with small amounts of the ordinary conjugate adduct. 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}

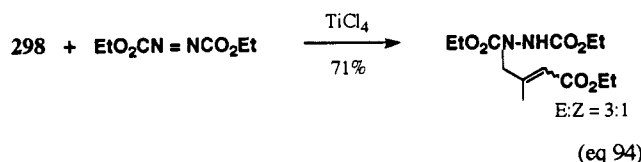
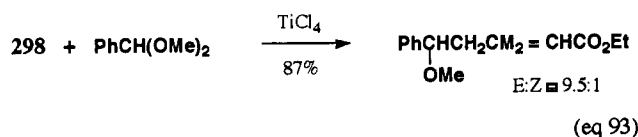
B. Allylgermanium Reagents

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-butenolate, with Me₃GeX (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 Bu₃SnCl provides the γ -stannylated derivative **299** and trapping with Me₃SiCl affords the O-silylated compound as expected from the reactivity of Me₃SiCl.

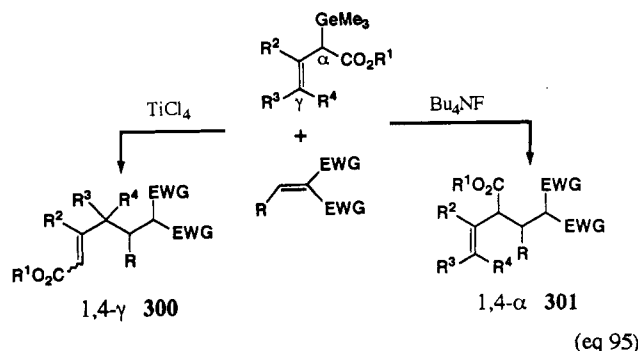


Alkylation of the lithium dienolate produces the α -alkylated product due to higher electron density at the α -position than that at the γ -position. Accordingly, the regioselective formation of **298** is reasonable and the formation of **299** is presumably due to the fact that the γ -regioisomer is 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-



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-butenolate 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



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 $\text{TiCl}_4/\text{PPh}_3$ -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, $\text{PPh}_3/\text{TiCl}_4$, provide **238a** in 98:2 selectivity with **237** and in 87:13 diastereoselectivity with the trimethylgermane derivative.

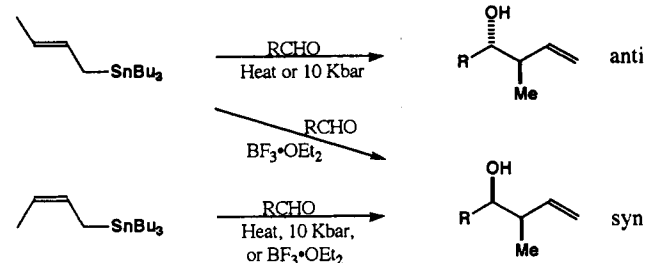
C. Allylic Stannane Reagents

1. Reactions of Aldehydes and Ketones

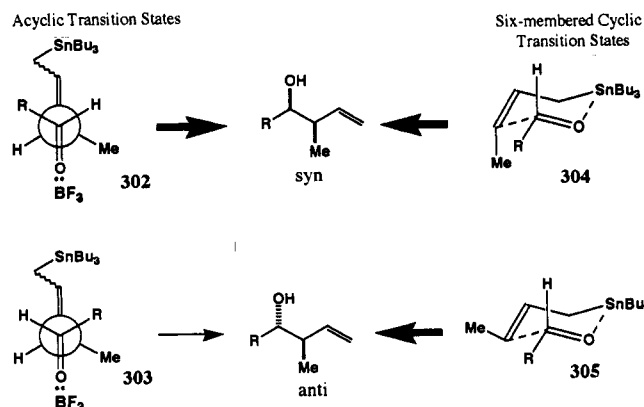
The stereochemical outcomes of allylic tin-aldehyde condensation reactions are summarized in Scheme IX. The Lewis acid mediated reaction of allylic tins and silanes (cf. the silicate case eq 66) produces syn-homoallyl alcohols predominantly regardless of the geometry of the but-2-enyl unit.^{2c} (In 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

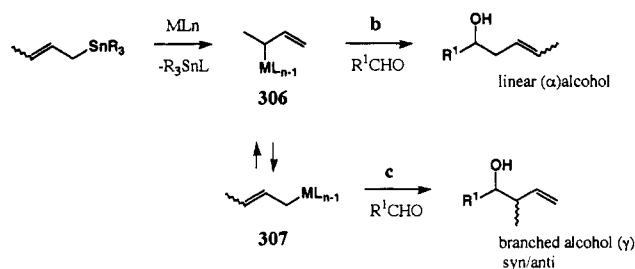
Scheme IX. Stereochemical Outcome of Allylic Tin-Aldehyde Condensation



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 allylmethyl 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 allylmethyl 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 $\text{AlCl}_3/\text{i-PrOH}$ 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 $\text{BF}_3\cdot\text{OEt}_2$, 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 $\text{AlCl}_3/\text{i-PrOH}$. Transmetalation from crotyltin with the acid of $\text{AlCl}_3/\text{i-PrOH}$, presumably $\text{AlCl}_2(\text{Oi-Pr})$, would proceed via an $\text{S}_{\text{E}}2'$ process to produce the α -methallyl aluminum intermediate 306 ($\text{M} = \text{Al}$), 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 ($\text{M} = \text{Al}$) 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 $\text{AlCl}_3/\text{i-PrOH}$ 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, $\text{AlCl}_3/\text{i-PrOH}$, causes transmetalation, and the reactive aldehydes react immediately via path b. Relatively

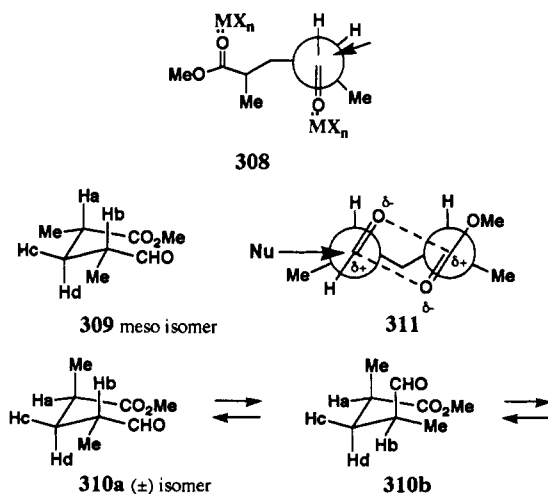
unreactive aldehydes and ketones permit further rearrangement to crotylaluminum compound, resulting in the reaction via path c. Accordingly, the sequence of addition is important; the addition of aldehydes to Lewis acids prior to the addition of crotyltin makes path a favorable.

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 , $\text{BF}_3\cdot\text{OEt}_2$, 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 $\text{BF}_3\cdot\text{OEt}_2$ -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 $\text{BF}_3\cdot\text{OEt}_2$ -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 $\text{BF}_3\cdot\text{OEt}_2$, *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 $\text{BF}_3\cdot\text{OEt}_2$, 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 ($\text{M} = \text{Ti}$)], 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 $\text{BF}_3 \cdot \text{OEt}_2$ (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 diastereofacial 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 $\text{BF}_3 \cdot \text{OEt}_2$ -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 $\text{BF}_3 \cdot \text{OEt}_2$, 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 $(\text{CH}_3\text{O})_2\text{SiCH}_3\text{Cl}$, 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 $\text{BF}_3 \cdot \text{OEt}_2$ 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 $\text{BF}_3 \cdot \text{OEt}_2$ -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 (\pm)-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 (\pm)-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 (\pm)-dimethylglutaric hemialdehyde is explained as follows. The fact that the Felkin-Anh syn selectivity in the reaction of the (\pm)-isomer (entry 24) does not depend upon the amount of $\text{BF}_3 \cdot \text{OEt}_2$ 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 (\pm)-isomer a rapid equilibrium between **310a** and **310b** exists as an



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 $\text{BF}_3 \cdot \text{OEt}_2$ -mediated

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

entry	allyltin	aldehyde	conditions	product	yield, %	ref(s)
1		HCOCO_2iPr	$\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -78°C	 syn:anti = 90:10	80	122
2		MeCOCO_2Me	$\text{BF}_3 \cdot \text{OEt}_2$, 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		$\text{BF}_3 \cdot \text{OEt}_2$, 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			$\text{BF}_3 \cdot \text{OEt}_2$ (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			$\text{BF}_3 \cdot \text{OEt}_2$ (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	85	362
11	 E:Z = 90:10		MgBr_2 , CH_2Cl_2 , -78°C	 syn-anti syn-syn	76 : 24	85
12			SnCl_4 , CH_2Cl_2	 syn-anti syn-syn	93 : 7	85
13		PhCHO	$\text{Co}^{\text{II}}\text{Cl}_2$, 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	 Et 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)











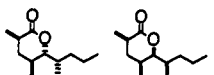




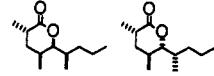




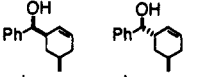










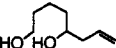
entry	allyltin	aldehyde	conditions	product	yield, %	ref(s)
16		PhCHO	BuSnCl ₃ , CH ₂ Cl ₂ , -78 °C	 Z-linear : branched 96 : 4	96	366
17		n-HexCHO	BuSnCl ₃ , CH ₂ Cl ₂ , -78 °C	 Z-linear : branched 95 : 5	94	366
18		PhCHO	CH ₃ SiCl ₃ , CH ₂ Cl ₂ , rt, 22 h	 ~100	~100	370
19		PhCHO	150 °C, neat, 18 h	 anti-Z : others >99 : 1	72	367
20		PhCHO	BF ₃ ·OEt ₂ , -78 °C, CH ₂ Cl ₂ , 4 h	 syn-E : syn-Z : anti-E : anti-Z 73 : 15 : 6 : 6  anti-syn syn-syn anti-syn : syn-syn : anti-anti : syn-anti	62	367
21		MeO ₂ C-CH ₂ -CH ₂ -CHO	(1) BF ₃ ·OEt ₂ ; (2) H ₂ /Pd-C	83 : 10 : 7 : -	80	368,369
22		MeO ₂ C-CH ₂ -CH ₂ -CHO	(1) 2 equiv of TiCl ₄ (inverse addn); (2) H ₂ /Pd-C	12 : - : 88 : -		368,369
23		MeO ₂ C-CH ₂ -CH ₂ -CHO	(1) 1 equiv of TiCl ₄ ; (2) H ₂ /Pd-C	89 : - : 11 : -		368,369
24		MeO ₂ C-CH ₂ -CH ₂ -CHO	(1) 1 equiv of TiCl ₄ ; (2) H ₂ , Pd-C	 syn-syn anti-syn syn-syn : anti-syn : anti-anti : syn-anti 86 : 7 : - : 7	70	368
25		MeO ₂ C-CH ₂ -CH ₂ -CHO	(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 ₂ O, 3 days; (2) H ₂ O	 anti:syn = 65:35	41	372
27	 cis:trans 67:33	PhCHO	(1) 9 kbar, neat, 30 °C; (2) H ₂ O	 cis-syn trans-syn cis-syn : cis-anti : trans-syn : trans-anti 64 : 4 : 30 : 4	85	373
28		PhCHO	BuSnCl ₃ , CH ₂ Cl 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 ₂ O (2 mL) H ₂ O (1 mL)	 syn:anti = 60:40	87	377
30		PhCHO	Sn-Al, ether/H ₂ O, (HBr)	 anti:syn = 100:-	72	378
31		PhCHO	BF ₃ ·OEt ₂ , CH ₂ Cl ₂ , -78 °C	 anti:syn = 99:1	76	379
32			Sn/THF-H ₂ O (1:4), rt,), 30-60 min		79	380

Table VI. (Continued)



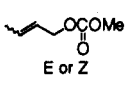



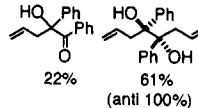
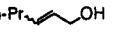
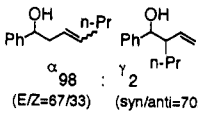
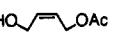
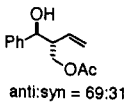
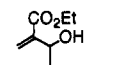
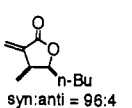
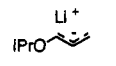
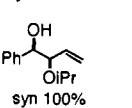
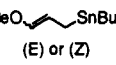
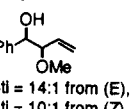
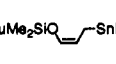

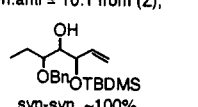
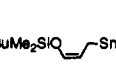

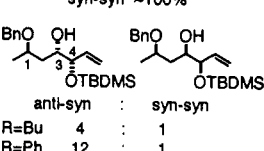
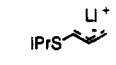

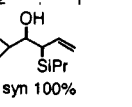
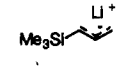
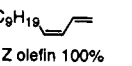
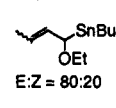

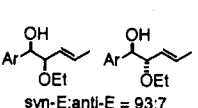
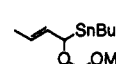
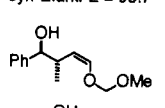
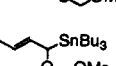
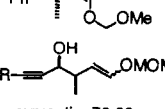
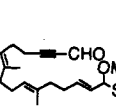

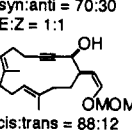
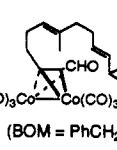

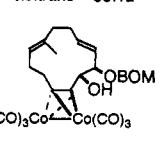
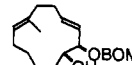
entry	allyltin	aldehyde	conditions	product	yield, %	ref(s)
33		RCHO R=Ph, n-C ₈ H ₁₇ , PhCH=CH	cat. PdCl ₂ (PhCN) ₂ , SnCl ₂ , DMI*, 25–60 °C		52~82	381
34	 E or Z	PhCHO	cat. PdCl ₂ (PhCN) ₂ , SnCl ₂ , DMI, 25 °C	 from E carbonate syn:anti=33:67 from Z carbonate syn:anti=48:52	80 42 83	382
35			cat. PdCl ₂ (PhCN) ₂ , SnCl ₂ , DMI, 50 °C	 22% (anti 100%)	83	384
36	n-Pr- 	PhCHO	cat. PdCl ₂ (PhCN) ₂ , SnCl ₂ , Et ₂ O, 10–15 °C Ultrasound	 α 98 : γ 2 (E/Z=87/33) (syn/anti=70/30)	57	385
37	HO- 	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 ₂ O, 80 °C	 syn:anti = 96:4	40	387
39		PhCHO	Bu ₃ SnCl/BF ₃ ·OEt ₂ , -78 °C, THF	 syn 100%	89	211
40	MeO-  (E) or (Z)	PhCHO	BF ₃ ·OEt ₂ , CH ₂ Cl ₂ , -78 °C	 syn:anti = 14:1 from (E), syn:anti = 10:1 from (Z),	87 86 67	388a
41	t-BuMe ₂ SiO- 		MgBr ₂ ·OEt ₂	 syn-syn ~100%	89	389
42	t-BuMe ₂ SiO- 		MgBr ₂ ·OEt ₂	 anti-syn : syn-syn R=Bu 4 : 1 R=Ph 12 : 1	75 72 89	359
43			Bu ₃ SnCl/BF ₃ ·OEt ₂ , -78 °C, THF	 syn 100%	89	211
44		n-C ₉ H ₁₉ CHO	Bu ₃ SnCl/BF ₃ ·OEt ₂ , -78 °C, THF	nC ₉ H ₁₉ -  Z olefin 100%	85	211,214
45	 E:Z = 80:20	Br-  -CHO	BF ₃ ·OEt ₂ , CH ₂ Cl 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) ₃ OTBS)	BF ₃ ·OEt ₂ , CH ₂ Cl ₂ , -78 °C	 syn:anti = 70:30 E:Z = 1:1	—	394,395
48			BF ₃ ·OEt ₂ , CH ₂ Cl ₂ , -78 °C	 cis:trans = 88:12	88	394,395
49	 (BOM = PhCH ₂ OCH ₂)		BF ₃ ·OEt ₂ , -78 °C, CH ₂ Cl ₂	 (CO) ₃ Co-  -Co(CO) ₃	70	396

Table VI. (Continued)

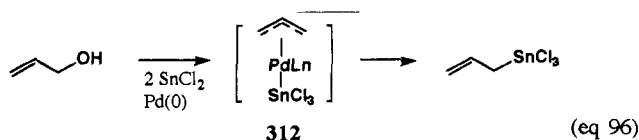
entry	allyltin	aldehyde	conditions	product	yield, %	ref(s)
50			BF ₃ ·OEt ₂ , -78 °C, CH ₂ Cl ₂		95	397
51		PhCHO	BF ₃ ·OEt ₂ , CH ₂ Cl ₂ , -78 °C Bu ₄ NF, THF		~100	398
52		PhCHO	Bu ₄ NF, THF or BF ₃ ·OEt ₂ , CH ₂ Cl ₂ , -78 °C		65	398
53		PhCHO	room temp		70	398
54		PhCHO	Bu ₄ NF room temp	syn:anti = 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 (ΔV^\ddagger) leading to the syn and anti adducts, the difference of the activation volumes ($\Delta\Delta V^\ddagger = \Delta V^\ddagger_{\text{anti}} - \Delta V^\ddagger_{\text{syn}}$), 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 cm³ 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 cm³ 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 BuSnCl₃, 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 BF₃·OEt₂ (entry 31).³⁷⁹ The BF₃·OEt₂-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 BF₃·OEt₂) 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/H₂O, 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)/SnCl₂ 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

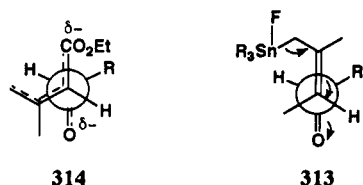
or an ester group; for example, the allylation of 10-oxo-undecanal provides 13-oxotetradec-1-en-4-ol in 68% yield.³⁸¹ In the case of crotyl, 1-methylallyl, cinnamyl, and 1-phenylallyl acetates, benzaldehyde regioselectively attacks the more substituted allylic position to give a single regioisomer (branched 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 $\text{PdCl}_2(\text{PhCN})_2/\text{SnCl}_2$, 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 $\text{PdCl}_2(\text{PhCN})_2/\text{SnCl}_2$ -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 $\text{PdCl}_2(\text{PhCN})_2/\text{SnCl}_2$ 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 NMR spectra of the reaction of allyl alcohol with $\text{PdCl}_2(\text{PhCN})_2/\text{SnCl}_2$ in $\text{DMF}-d_7$ correspond to those of the reaction of allyl chloride with $\text{PhCl}_2(\text{PhCN})_2/\text{SnCl}_2$ in $\text{DMF}-d_7$.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



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 $\text{PdCl}_2(\text{PhCN})_2/\text{SnCl}_2$ 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 $\text{Me}_3\text{SiCl}/\text{NaI}/\text{H}_2\text{O}$ -Sn system, giving linear homoallyl alcohols in good yields.^{387b}

The [(isopropoxy)allyl]lithium is once trapped with tributyltin chloride, and subsequent treatment with aldehydes in the presence of $\text{BF}_3\cdot\text{OEt}_2$ provides the syn-1,2-diol derivatives with very high diastereoselectivity (entry 39). Presumably, (*Z*)-[γ -(isopropoxy)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 $\text{BF}_3\cdot\text{OEt}_2$ to produce the syn vicinal diol monomethyl ether unit (entry 40).³⁸⁸ The key intermediate to *exo*-brevicomine 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 $\text{MgBr}_2\cdot\text{OEt}_2$ 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 ($\text{CH}_3\text{OCH}_2\text{OCH}=\text{CHCH}_2\text{SnBu}_3$) 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 $\text{BF}_3\cdot\text{OEt}_2$ (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 $\text{BF}_3\cdot\text{OEt}_2$ 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 $\text{BF}_3\cdot\text{OEt}_2$,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 $\text{BF}_3\cdot\text{OEt}_2$ 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

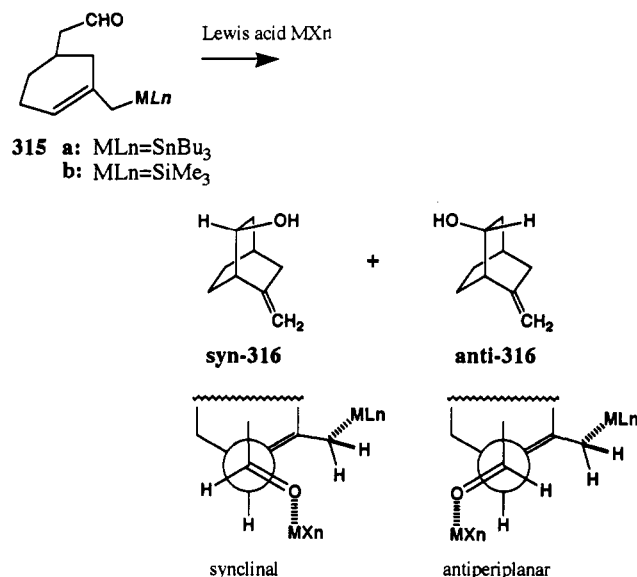
cyclic transition state in which the anti stereochemistry is a consequence of the *E*-geometry of the tin, and the (*Z*)-enol ether geometry is due to a preference of the α -methoxymethoxy substituent to adopt an axial position (see also entry 19). The [α -(methoxymethoxy)-crotyl]tin reacts with the acetylenic aldehyde in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ 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 $\text{BF}_3 \cdot \text{OEt}_2$ -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 $\text{BF}_3 \cdot \text{OEt}_2$ 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 $\text{BF}_3 \cdot \text{OEt}_2$ -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-butenolate, 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 $\text{BF}_3 \cdot \text{OEt}_2$ -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 $\text{BF}_3 \cdot \text{OEt}_2$ or Bu_4NF (entry 52). Similarly, the SnBuCl_2 derivative gives the syn-adduct exclusively in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ 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 $\text{BF}_3 \cdot \text{OEt}_2$ -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



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

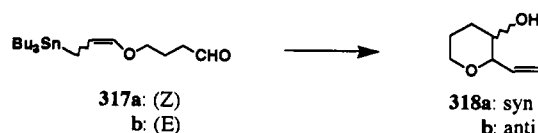
steric and electronic points of view, resulting in the predominant formation of the anti isomer.

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



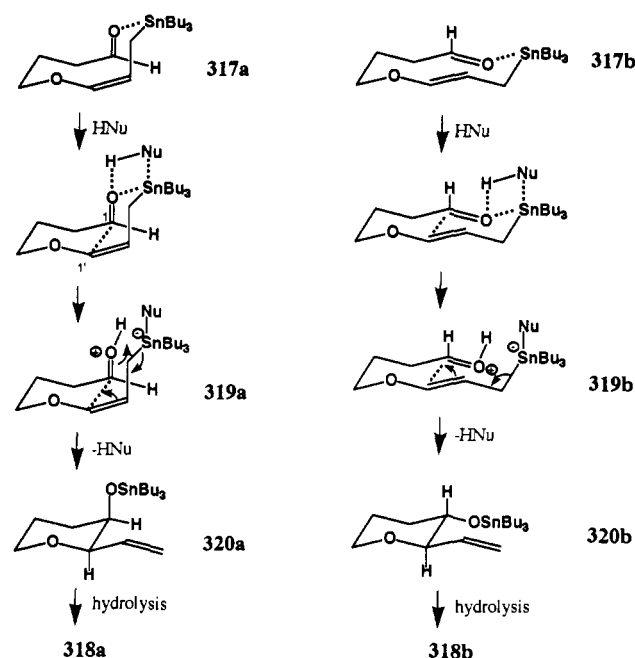
syn selective and relatively insensitive to the nature of the Lewis acid ($\text{BF}_3 \cdot \text{OEt}_2$, AlCl_3 , Et_2AlCl , ZrCl_4 , SnCl_4 , FeCl_3 , 87–98% *syn*^{399,400}), indicating a significant preference for the synclinal orientation. On the other hand, variable *syn* selectivity (47–99%) 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



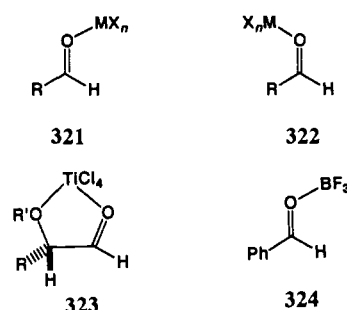
protic acids TfOH , $\text{CF}_3\text{CO}_2\text{H}$, $\text{CCl}_3\text{CO}_2\text{H}$, $\text{ClCH}_2\text{CO}_2\text{H}$, $\text{CH}_3\text{CO}_2\text{H}$, and HCl can be used, and even a catalytic amount of TfOH can induce the cyclization of **317**. As

Scheme XII. "Push-Pull" Mechanism

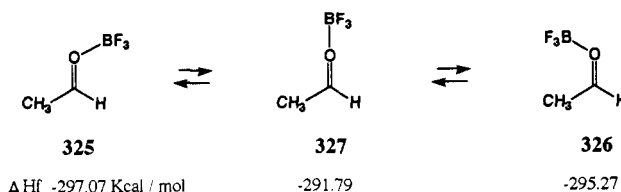


expected, the Lewis acid induced cyclization using TiCl_4 or $\text{BF}_3 \cdot \text{OEt}_2$ affords **318b** predominantly regardless of the double-bond geometry. The observed stereochemical results can be explained by a new "push-pull" mechanism via cyclic transition state (Scheme XII). In the presence 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 alkoxy-stannane **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 TiOH 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 $\text{Bu}_4\text{NF}/\text{TiCl}_4$ 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 $\text{CF}_3\text{CO}_2\text{H}$.^{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 frag-

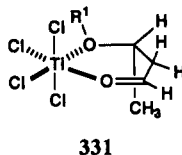
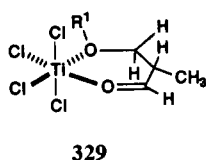
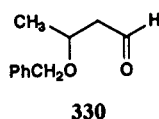
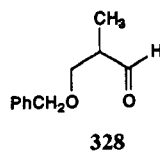


ment lies essentially in a common place. Anti complexation also pertains in solution, as shown by a heteronuclear Overhauser experiment.⁴⁰⁴ MNDO calculations of the acetaldehyde- BF_3 adduct show that anti complexation **325** does indeed lead to the lowest energy species.⁴⁰⁴ However, the *syn*-adduct **326** lies only 1.8 kcal/mol higher in energy. On the other hand, the difference between anti and *syn* $\text{PhCHO} \cdot \text{BF}_3$ 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.

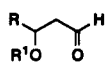


BF_3 complexation lowers the energy of the π^*_{CO} orbital, rendering the molecule more susceptible to nucleophilic attack. The extent of LUMO lowering is a little greater in the anti complex than in the *syn* isomer. The coefficient of the orbital at the carbonyl C atom in π^*_{CO} increases in magnitude 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 $\text{PhCHO} \cdot \text{BF}_3$ and $\text{CH}_3\text{CHO} \cdot \text{BF}_3$ is their B-O bond lengths. The B-O bond distances have the following order: *anti*- $\text{PhCHO} \cdot \text{BF}_3$ (1.62 Å) < *syn*- $\text{PhCHO} \cdot \text{BF}_3$ (1.63 Å) < *anti*- $\text{CH}_3\text{CHO} \cdot \text{BF}_3$ \approx *syn*- $\text{CH}_3\text{CHO} \cdot \text{BF}_3$ (1.65 Å). The BF_3 complexes have the following order of stability: *anti*- $\text{PhCHO} \cdot \text{BF}_3$ > *anti*- $\text{CH}_3\text{CHO} \cdot \text{BF}_3$ > *syn*- $\text{CH}_3\text{CHO} \cdot \text{BF}_3$ > *syn*- $\text{PhCHO} \cdot \text{BF}_3$.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*- $\text{PhCHO} \cdot \text{BF}_3$ complex (steric repulsion between ortho phenyl H and the BF_3 group).

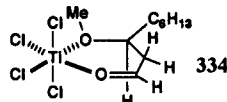
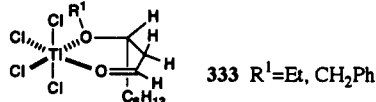
The structure of Lewis acid complexed intermediates derived from alkoxy carbonyl compounds in solution was studied by variable-temperature NMR spectroscopy.⁴⁰⁷ The TiCl_4 complex of **328** adopts the bidentate chelate conformation **329** in which the CH_3 group occupies a pseudoequatorial position, 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



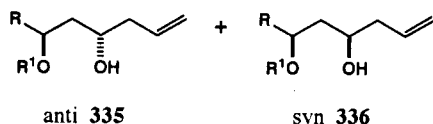
plays a critical role in determining the conformation of chelates derived from β -alkoxyaldehydes in solution.⁴⁰⁸ With **332a**, where the methyl substituent of **330** is replaced by *n*-hexyl, the TiCl_4 or MgBr_2 complex takes a bidentate chelated structure **333** similar to **331**. However, simply 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



- 330** $\text{R}=\text{CH}_3$, $\text{R}'=\text{CH}_2\text{Ph}$
332a $\text{R}=\text{n-C}_6\text{H}_{13}$, $\text{R}'=\text{CH}_2\text{Ph}$
332b $\text{R}=\text{n-C}_6\text{H}_{13}$, $\text{R}'=\text{CH}_3$
332c $\text{R}=\text{n-C}_6\text{H}_{13}$, $\text{R}'=\text{CH}_2\text{CH}_3$
332d $\text{R}=\text{n-C}_6\text{H}_{13}$, $\text{R}'=\text{Si}(\text{t-Bu})\text{Me}_2$

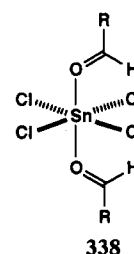
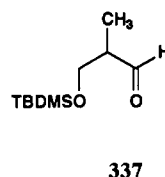


of the Lewis acids (TiCl_4 , MgBr_2 , and SnCl_4) is not formed.⁴⁶⁹ The nonchelating ability of sterically demanding siloxy group was utilized for the stereocontrolled allylation of diprotected bis(hydroxymethyl)-acetaldehyde.^{358,360,410} The diastereoselectivity in additions of allyltriphenyltin to 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



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 $\text{BF}_3\cdot\text{OEt}_2$, high levels of stereoselectivity are not expected. Most of the results agree with the predictions. ^1H 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).



The possibility of a metathesis process was studied by Tagliavini,³⁵⁴ Keck,⁴⁰⁸ Yamamoto³⁵³ (Scheme XII), and Pereyre³⁹² 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 $\text{BF}_3\cdot\text{OEt}_2$ may occur depending upon the amount of trimeric aldehyde present under the reaction conditions, and the degree of trimerization at $\sim 80^\circ\text{C}$ 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 $\text{BF}_3\cdot\text{OEt}_2$ 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 $\text{BF}_3\cdot\text{OEt}_2$. 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 [$(\text{328})_2\text{SnCl}_4$, $(\text{330})_2\text{SnCl}_4$, and $(\text{337})_2\text{SnCl}_4$] and the chelate complexes do not promote metathesis, and this Keck's observation is in conflict with Denmark's results; Denmark concludes that with $(\text{RCHO})_2\cdot\text{SnCl}_4$ complex metathesis with allyl SnMe_3 or allyl SnBu_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) $_2\text{SnCl}_2$). 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

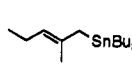
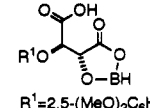
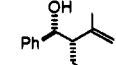
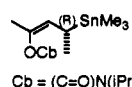

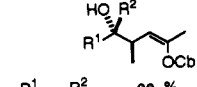
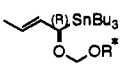
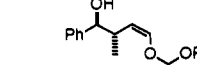
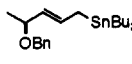
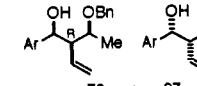
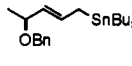
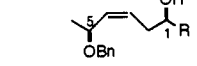
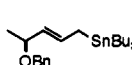
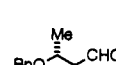
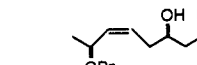
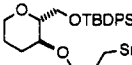
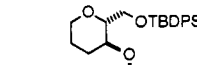
Table VII. Reactions of Chiral Aldehydes and/or Chiral Allyltins or in the Presence of a Chiral Catalyst

entry	reagent	aldehyde	conditions	product	yield, %	ref
1			TiCl ₄ , CH ₂ Cl ₂ , -78 °C	 Cram:anti-Cram = 99:1	85	413
2		 R* = <i>s</i> -phenylmenthyl	BF ₃ ·OEt ₂ , CH ₂ Cl ₂ , -78 °C		80	122
3		 P = Bn(CH ₂ Ph) = BOM (CH ₂ OPh) = MTM (CH ₂ SCH ₃)	TiCl ₄ , CH ₂ Cl ₂ , -78 °C	 anti : syn 29 : 1 9 : 1 2 : 1	75 — —	415
4		 PMB = <i>p</i> -methoxyphenyl	SnCl ₄ , -78 °C	 (+ linear isomer 20%)	60	416
5			MgBr ₂ , CH ₂ Cl ₂ , -78 °C → 0 °C	 anti:syn = 87 : 13 (R ¹ = SiPh ₂ tBu, R ² = CH ₂ OBn)	92	410
6			MgBr ₂ , CH ₂ Cl ₂	 single stereoisomer	92	417
7			MgBr ₂ , CH ₂ Cl ₂ , -25 °C	 single stereoisomer	95	418
8			Sn powder, 9:1 EtOH/H ₂ O, ultrasonification	 3.5~6.5 : 1	52~90	419
9		 MTM = CH ₂ SCH ₃	MgBr ₂ ·OEt ₂ , CH ₂ Cl ₂ , -23 °C	 4.1:1 mixture	46	420
10		 phthN = phthalimido	MgBr ₂ ·OEt ₂ , CH ₂ Cl ₂ , -78 °C → 0 °C		87	196
11		 PMB = <i>p</i> -MeOC ₆ H ₅	MgBr ₂ ·OEt ₂ , CH ₂ Cl ₂ , -40 °C	 syn-syn : another isomer = 7.5 : 1	71	421
12			BF ₃ ·OEt ₂ , CH ₂ Cl ₂ , -78 °C	 ~100% de	99	397
13			BF ₃ ·OEt ₂ , CH ₂ Cl ₂ , -78 °C	 ~100% de	97	397
14			BF ₃ ·OEt ₂ , 120 °C	 trans : cis 33 : 67 3 : 97		397

Table VII. (Continued)

entry	reagent	aldehyde	conditions	product	yield, %	ref
15			$\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -78°C		88	422
16	$n\text{Bu}-\text{CH}=\text{CH}-\text{SnBu}_3$ $\text{R}=\text{CH}_2\text{OBn}$	$n\text{-C}_6\text{H}_{13}\text{CHO}$	$\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -78°C		80	423
17		$\text{C}_6\text{H}_{11}\text{CHO}$	$\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -78°C		74	424
18			$\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -78°C		58	425
19			$\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -78°C		72	425
20			MgBr_2 , $-23^\circ\text{C} \rightarrow 23^\circ\text{C}$		74	425
21			MgBr_2 , $-23^\circ\text{C} \rightarrow 23^\circ\text{C}$		74	425
22		RCHO $\text{R}=\text{C}_6\text{H}_{13}$, $n\text{-C}_6\text{H}_{13}$, $\text{sec-C}_6\text{H}_{13}$	$\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -78°C		60–80	426
23		RCHO	$\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -78°C		60–80	426
24		PhCHO	$\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -78°C		75	427
25		RCHO	$\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -78°C			427
26		RCHO	$\text{BF}_3 \cdot \text{OEt}_2$		61	429
		$\text{O}_2\text{N}-\text{C}_6\text{H}_4-\text{CHO}$	$\text{MgBr}_2 \cdot \text{OEt}_2$		35	

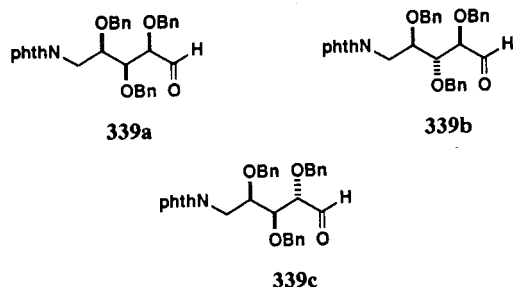
Table VII. (Continued)

entry	reagent	aldehyde	conditions	product	yield, %	ref
27		PhCHO	 (0.2 equiv), CF ₃ CO ₂ H CH ₃ CH ₂ CN, -78 °C R ¹ = 2,5-(MeO) ₂ C ₆ H ₃ CO	 syn : anti = 93 : 7 syn; 70% ee	50	430
28	 Cb = (C=O)N(i-Pr) ₂		TiCl ₄ , CH ₂ Cl ₂ , -78 °C	 R ¹ R ² ee, % i-Pr H 82 C ₆ H ₅ CH ₃ 83	85 83 81	431
29	 R* = 8-phenylmenthyl	PhCHO	130 °C, 14–15 h, neat	 single stereoisomer		432
30		ArCHO Ar = p-NO ₂ C ₆ H ₄	150 °C, 18 h	 73 : 27		433
31		RCHO R = Ph, p-NO ₂ C ₆ H 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 ₂ Cl ₂ , -78 °C	 92% de	52	437a

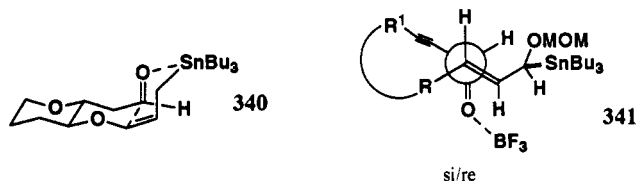
high Cram (Felkin–Anh) selectivity: 89:11 and 90:10, respectively (entry 1).¹³ The addition of carbanionic organometallic compounds such as Grignard reagents and organolithiums to the same aldehyde results in the formation of ca. 1:1 to 2:1 mixture of Cram and anti-Cram adducts. The enhanced Cram selectivity in the Lewis acid mediated reaction can be explained by a change in direction of nucleophilic attack towards the carbonyl groups.⁴¹⁴ The BF₃·OEt₂-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 TiCl₄ provides the chelation-controlled products (the anti-isomer) either predominantly or with very high stereoselectivity (entry 3).⁴¹⁵ In order to obtain high diastereofacial 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 SnCl₄ at -78 °C to provide the anti-adduct along with the linear homoallyl alcohol (entry 4).⁴¹⁶ MgBr₂-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 CH₂OR 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 Me₂tBuSi, Ph₂tBuSi, or (i-Pr)₃Si, and the “chelating group” is PhCH₂OCH₂ (BOM) or *p*-MeOC₆H₄CH₂OCH₂ (PM-BOM). When the nonchelating group is used as R¹ and the chelating group as R², 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 MgBr₂-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 three 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 MgBr₂ (entry 10).¹⁹⁶ However, the allylation

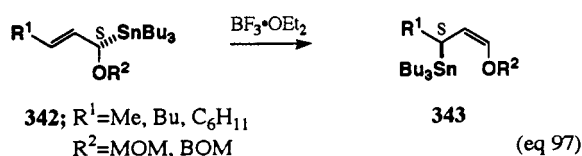
of other stereoisomeric aldehydes such as 339a–c gives a mixture of diastereoisomers. Another example of a



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 $\text{BF}_3\cdot\text{OEt}_2$ -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 che-

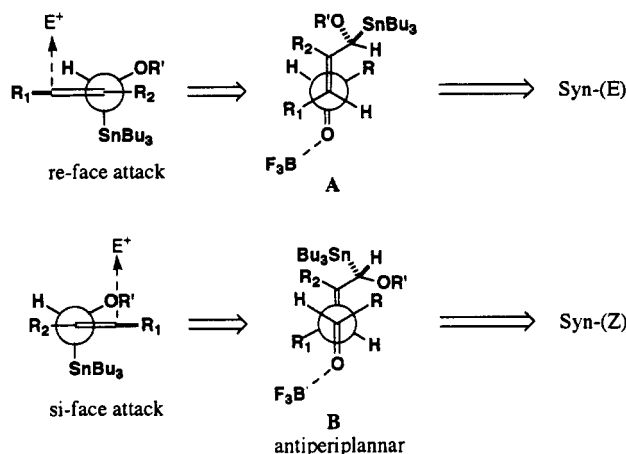


lated cyclic transition state is not involved in the reaction of entry 15, the BF_3 -promoted reaction shows efficient chiral transfer. Addition of the homochiral (*S*)-[1-(benzyloxy)methoxy-2-(*E*)-hexenyl](tri-*n*-butyl)stannane to heptanal (see entry 16), (*E*)-2-heptenal, and 2-heptynal under BF_3 -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 $\text{BF}_3\cdot\text{OEt}_2$, 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 rearrange-



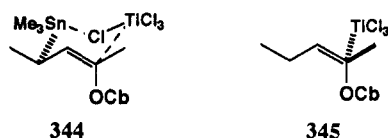
ment from the (*S*)-stannanes to the (*S*)-[γ -(alkoxy)allyl]stannanes is shown in eq 97, the corresponding (*R*)-stannanes also provide the (*R*)-[γ -(alkoxy)allyl] derivatives. The rearrangement takes place by an intermolecular anti pathway. Addition of 343 to representative aldehydes affords optically active *syn*-1,2-diol monoethers as the major diastereomers with

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



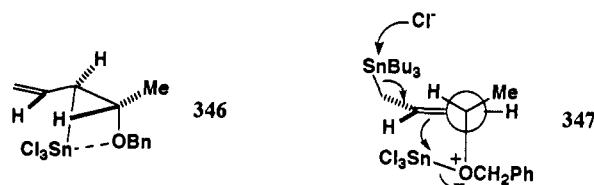
high anti S_{E}' stereoselectivity (entry 17).⁴²⁴ $\text{BF}_3\cdot\text{OEt}_2$ -promoted addition of the (*R*)-[γ -(alkoxy)allyl]stannane to (*S*)-2-(benzyloxy)propanal gives the *syn* adduct with 92:8 diastereoselectivity (entry 18), whereas the addition of the *S*-enantiomer to the same aldehyde 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 $\text{BF}_3\cdot\text{OEt}_2$ 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. [1-(8-Phenylmenthyl)oxy]methyl[oxy]crotyl]stannane produces excellent *syn-Z* diastereoselectivity upon treatment with aromatic aldehydes in the presence of $\text{BF}_3\cdot\text{OEt}_2$ (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 $\text{BF}_3\cdot\text{OEt}_2$, 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

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 $(\text{TFA})_2\text{O}$ 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



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 crotyl-tributyltin 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

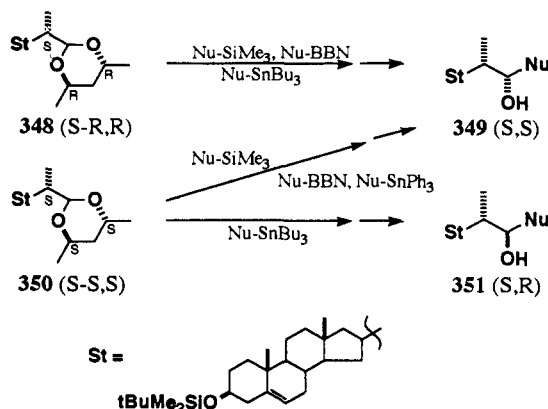
position, would then give the observed products. The stereospecific formation of 346 is due to intramolecular delivery of the trichlorotin substituent to the double bond by the benzyloxy group (347). Excellent, 1,5-



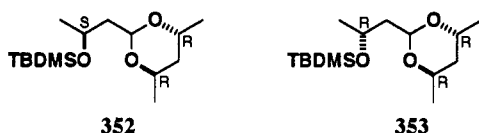
diastereoselectivity is also realized in reactions with chiral aldehydes (for example, entry 32); the stereochemical preference of the chiral stannane reagent dominates the course of the reaction. Asymmetric synthesis of syn-1,2-diols has been accomplished via the reaction of the chiral γ -alkoxy-substituted allylstannane with aldehydes in the presence of AlCl_3 or $\text{AlCl}_3\cdot\text{OEt}_2$, 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 $\text{BF}_3\cdot\text{OEt}_2$, AlCl_3 , or $\text{AlCl}_3\cdot\text{OEt}_2$. 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 $\text{AlCl}_3\cdot\text{OEt}_2$ is used as Lewis acid while $\text{BF}_3\cdot\text{OEt}_2$ leads to decreased de ratios. Three types of optically active allylstannanes, $\text{R}^*\text{Sn}(\text{allyl})_2$ ($\text{R}^* = 2$ -phenylbutyl, 2-methylbutyl, and 3-phenylbutyl), $\text{R}^*\text{R}^1\text{Sn}(\text{allyl})_2$ ($\text{R}^* = 2$ -octyl or 2-phenylbutyl, $\text{R}^1 = \text{phenyl}$), and $\text{R}^*\text{R}^1\text{R}^2\text{Sn}(\text{allyl})$ ($\text{R}^* = 2$ -phenylbutyl, $\text{R}^1 = \text{phenyl}$, $\text{R}^2 = \text{methyl}$), have been synthesized. Among these allylstannanes, only diallylbis(2-phenylbutyl)stannane provides allowable enantioselectivity upon treatment with aldehydes in the presence of $\text{BF}_3\cdot\text{OEt}_2$.^{437b}

2. Reactions with Acetals

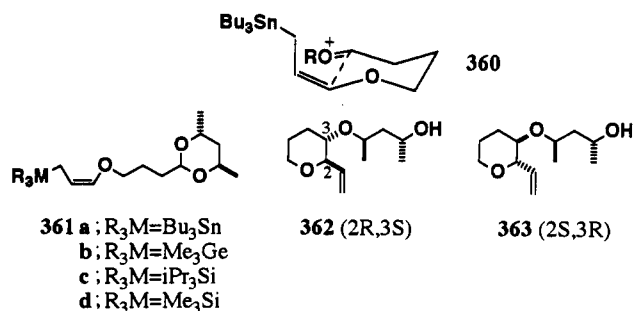
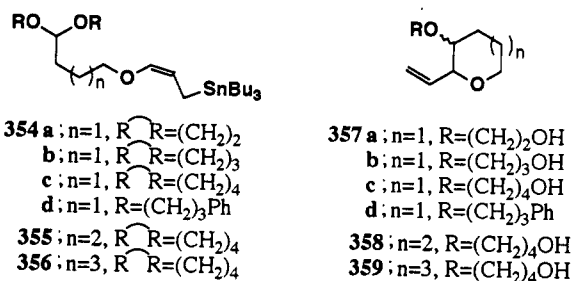
The chiral steroidal acetal 348 (*S-R,R*), prepared from the steroidal aldehyde and (2*R*,4*R*)-(-)-pentane-2,4-diol, gives 349 (*S,S*) upon treatment with nucleophiles including allylsilanes, allyl-9-BBN, and allyltributyltin, while the diastereomeric steroidal acetal 350 (*S-S,S*) also produces 349 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,



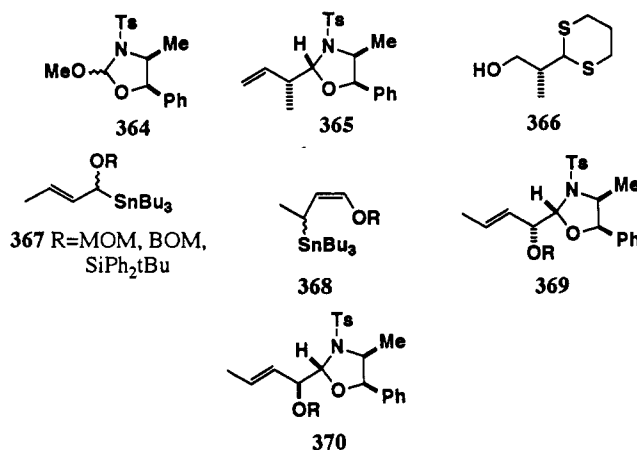
trimethylsilane, and 9-BBN in the presence of TiCl_4 gives the chelation product (*S,S*) with very high diastereoselectivity (>90:10), while the (*R,R,R*) isomer **353** also produces the chelation product with fair to good selectivities (>70:30), indicating that the 1,3-asymmetric induction is dictated 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 $\text{TiCl}_3(\text{Oi-Pr})$ 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 $\text{TiCl}_3(\text{Oi-Pr})$, $\text{TiCl}_2(\text{Oi-Pr})_2$, TiCl_4 , $\text{BF}_3\cdot\text{OEt}_2$, or $\text{MgBr}_2\cdot\text{OEt}_2$ 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 $\text{TiCl}_4\cdot\text{PPh}_3$ combined Lewis acid system.³⁰² The $\text{TiCl}_4\cdot\text{PPh}_3$ -



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 $\text{S}_{\text{N}}1$ - and $\text{S}_{\text{N}}2$ -type mechanism.

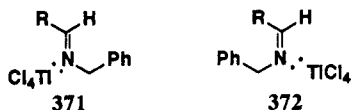
The Lewis acid promoted crotylstannane addition to the enantiomerically pure oxazolidine **364** and the subsequent conversion of the resulting adduct **365** provide enantioenriched dithianol **366**.⁴⁴² The $\text{BF}_3\cdot\text{OEt}_2$ -promoted addition of racemic [α - and γ -(alkoxy)allyl]-stannanes **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 previously³⁰⁷ (eq 83).



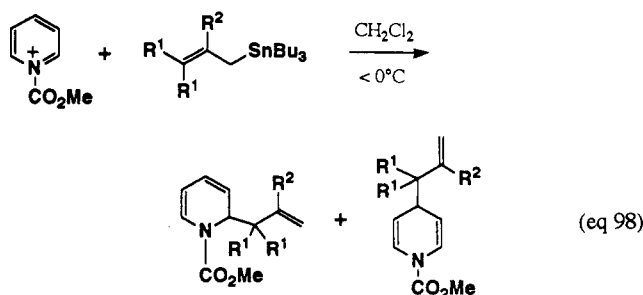
3. Reactions with Imines and Iminium Ions

Allyltributylstannane reacts with aromatic and branched α -alkylimines in the presence of TiCl_4 and $\text{BF}_3\cdot\text{OEt}_2$ 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 $\text{BF}_3\cdot\text{OEt}_2$.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 an 82:18 mixture of **25** and **26** in 70% yields, while the $\text{BF}_3\cdot\text{OEt}_2$ -mediated reaction affords lower diastereoselectivity (67:33).⁴⁶ The $\text{BF}_3\cdot\text{OEt}_2$ -mediated addition of crotyltributylstannane to aromatic imines ($R^1 = R^2 = \text{aromatic}$ in eq 2) provides the syn homoallylamines predominantly (syn/anti = >75:25).²⁰² The crotylstannane addition to aliphatic and furyl imines ($R^1 = \text{i-Pr, c-C}_6\text{H}_{11}, \text{furyl}$; $R^2 = \text{Bn}$ in eq 2)

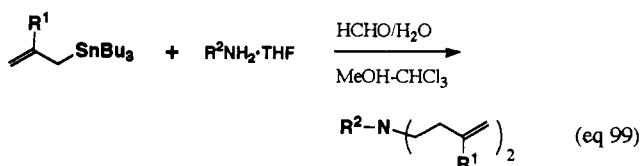
produces the syn adducts with very high diastereoselectivity (>20:1).⁴⁴⁴ This high syn selectivity can be obtained if Lewis acid-imine complexation is carried out at -78 °C for 2.5 h prior to the addition of crotylstannane, otherwise syn selectivity diminishes to 4:1. These observations are a result 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



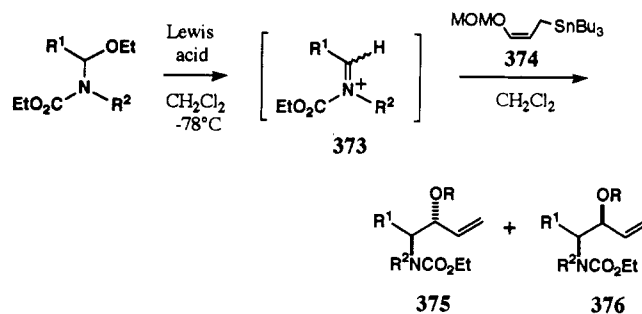
preference in the imine-crotylstannane condensations is consistent with an acyclic transition state similar to the transition states of the aldehyde condensation shown in Scheme X; replacement of aldehyde oxygen to imine NR^2 group affords the transition state of imine additions. Allylstannanes readily react with pyridine and some substituted pyridines activated by alkyl chloroformates to give α -allylated 1,2-dihydropyridines, regioselectively.⁴⁴⁶ 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).



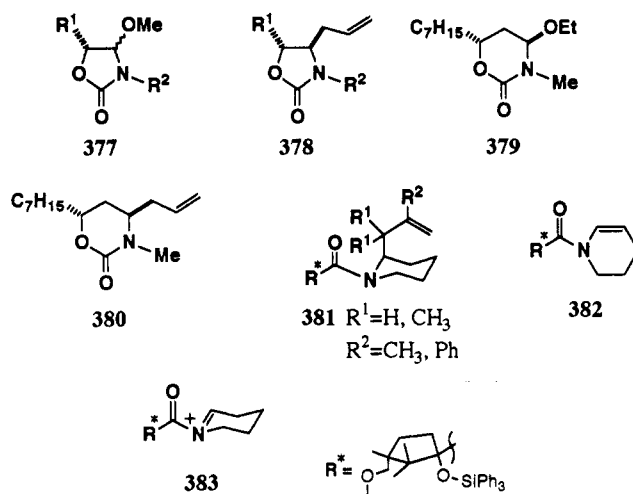
Reactions of allylstannanes with primary amines and aqueous formaldehyde produce bishomoallylamines (eq 99).³²² Although 4-hydroxypiperidines are obtained in



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 $\text{BF}_3 \cdot \text{OEt}_2$, are effective. The formation of **373** under these conditions was confirmed by low-temperature NMR.³¹⁰ With $\text{R}^1 = \text{Ph}$ and $\text{R}^2 = \text{Bn}$ or $\text{R}^1 = i\text{-Bu}$ and $\text{R}^2 = \text{Bu}$, the anti-



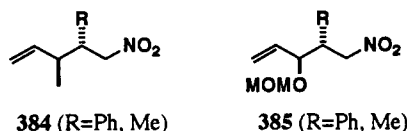
isomer is produced exclusively, whereas the syn-adduct is obtained exclusively with $\text{R}^1 = \text{Ph}$ and $\text{R}^2 = \text{Me}$. The reactions of the five-membered α -methoxy carbamate **377** with allyltrimethylsilane, allyltributylstannane, and allyl-9-BBN in the presence of TiCl_4 or $\text{BF}_3 \cdot \text{OEt}_2$ afford the trans allylation products **378**, which result from a $\text{S}_{\text{N}}1$ type attack of the allylorganometallics to the intermediate iminium ions, with very high diastereoselectivity.⁴⁴⁸ Similarly, the $\text{BF}_3 \cdot \text{OEt}_2$ -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



4. Conjugate Addition

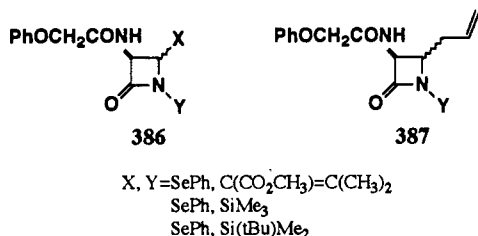
Studies on conjugate addition of allylstannanes to Michael acceptors are very few. The Lewis acid (TiCl_4 , AlCl_3 , or SnCl_4) mediated addition of crotyltributylstannane to **116a** and **116b** affords predominantly **117a** and **117b**, respectively (see eq 41).²⁰⁵ The highest anti selectivity (90:10) is obtained on treatment with SnCl_4 , but the other Lewis acids also produce good anti selectivity (>80:20). No addition takes place using $\text{BF}_3 \cdot \text{OEt}_2$. 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 , $\text{TiCl}_2(\text{Oi-Pr})_2$) 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



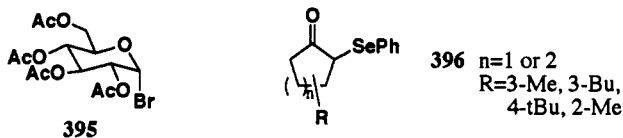
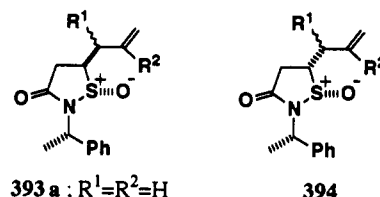
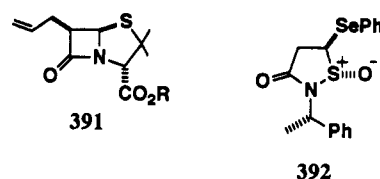
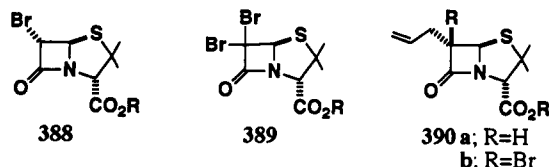
5. Radical Allylation

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 Kosugi⁴⁵² and Pereyre⁴⁵³ 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-phenylselenenyl 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

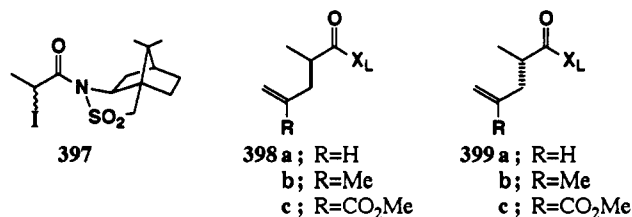


allylation of 6-bromo- and 6,6-dibromopenicillanates, **388** and **389**, in the presence of a catalytic amount of AIBN proceeds in a highly chemo- and stereoselective fashion to give **390a** and **390b**, respectively.⁴⁵⁷ Reduction of **390b** with tributyltin hydride gives the corresponding 6- β -allylpenicillanates **391**. In another sequence of reactions, C-allylation was performed on the 6- α -bromopenicillanate 1,1-dioxide esters (SO₂ 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 Bu₃SnH/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)cy-

cloalkanones **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.

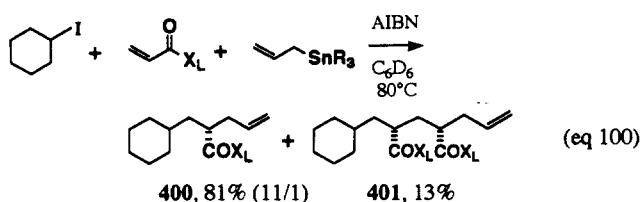


Heating of (α -iodopropionyl)camphorsultam (**397**), allyltributylstannane, and 10% AIBN at 80 °C (benzene-*d*₆) gives a mixture of the allylated derivatives **398a** and **399b** in a ratio of 12:1 in virtually quantitative yield.⁴⁶² This level of selectivity (85% de) is remarkable

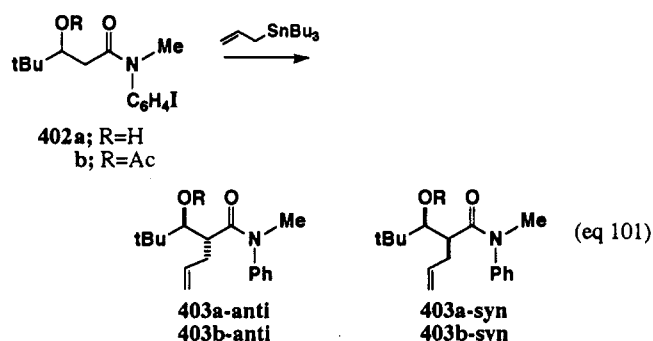


X_L=L-(+)-2,10-camphor sultam

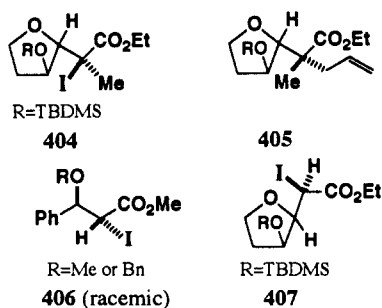
for a reaction conducted at 80 °C in the absence of chelating Lewis acid. Reactions at 25 °C or below are initiated with triethylboron in CH₂Cl₂. A decrease in temperature from +80 to -78 °C gives a slow and steady increase in the ratio of **398a/399a**, and finally a > 30/1 ratio is achieved at -78 °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



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 Porter⁴⁶³ 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

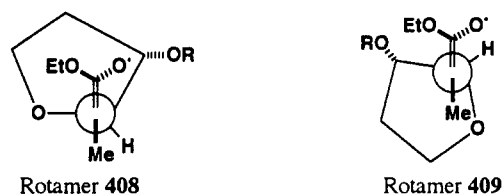


increased to 93/7. In sharp contrast, allylation of the β -acetoxy anilide **402b** under the photolytic conditions provided *anti/syn*-**403b** in a reversed ratio of 15:85 (eq 101).⁴⁶⁵ The allylation may proceed through a rapid translocation of radicals derived from *o*-iodoanilides to the radical 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

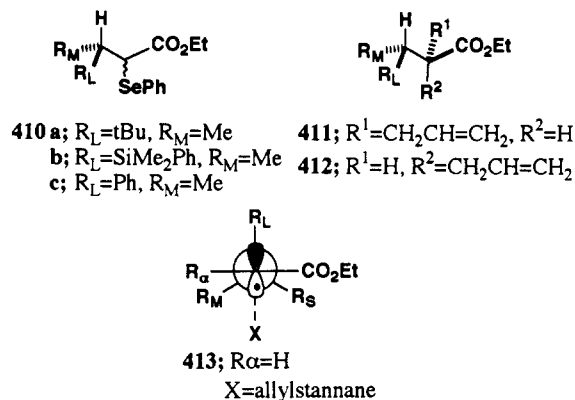


by lowering the reaction temperature to -78°C and using Et_3B as an initiator. Some mechanistic aspects of the diastereocontrol have been discussed.⁴⁶⁶ The radical is not pyramidalized and delocalized through the carbethoxy group. Rotamer **408** suffers from severe interaction between the ester appendage 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

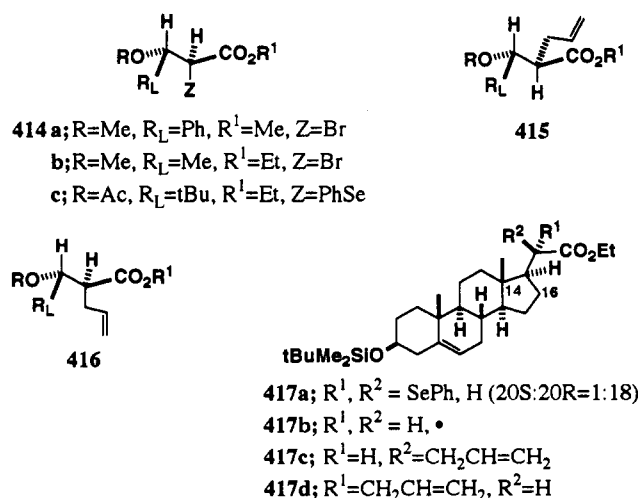
through their anti orientation. Delivery of allyl group from the least hindered face of the radical would lead to the observed diastereoselection.



The free radical allylation of **410a** and **410b** with allyltributylstannane at -78°C (AIBN, $h\nu$, 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



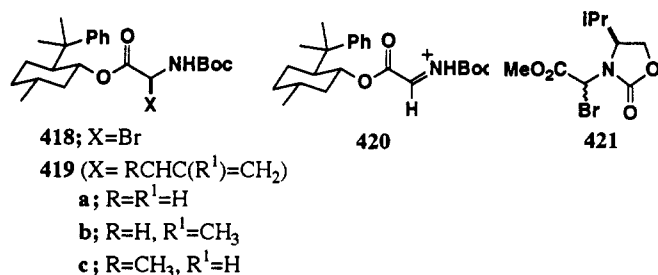
substrates **414** with electron-withdrawing β -substituents (OR) produces **415** predominantly; the ratio of **415** and **416** is 90:10 from the reaction of **414a**, 83:17 from **414b**, and 89:11 from **414c**. The stereochemical outcome of



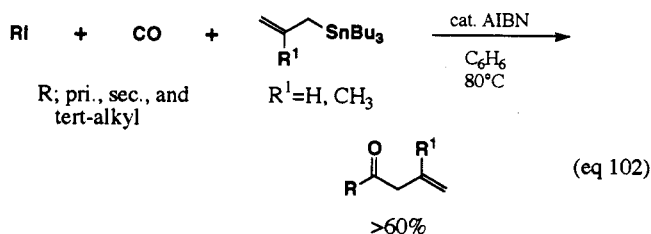
the allylation of **414** is consistent with the model **413** if the electron-withdrawing β -substituent plays the role of R_M , which just corresponds to rotamer **409**. Ally-

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 irradiation 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



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 alkyl iodides, 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

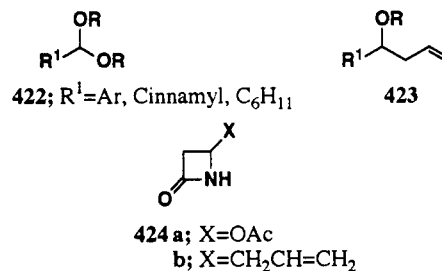


selectivity of carbonylated products relative to allylated alkanes, which are presumably produced by the Keck-type allylation. The three-component coupling reaction probably proceeds through the formation of acyl radicals, generated from R[•] and CO, followed by allylation with allylstannanes. Allylation 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

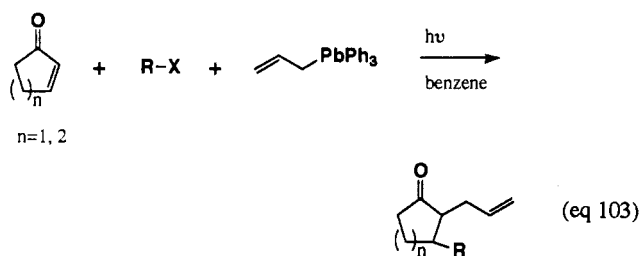
D. Allylic Plumbum Reagents

A lead-promoted allylation of carbonyl compounds with allyl bromide in $\text{Pb}/\text{Bu}_4\text{NBr}/\text{Me}_3\text{SiCl}/\text{DMF}$ system has been performed in good yields with high chemoselectivity; the order of reactivity of substrates is following: $\text{RCHO} > \text{R}^1\text{R}^2\text{CO} > \text{R}^1\text{CH}(\text{OH})\text{CO}_2\text{R}^2 \gg \text{R}^1\text{CO}_2\text{R}^2$, lactone, $(\text{RCO})_2\text{O}$, 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



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 $\text{BF}_3\cdot\text{OEt}_2$.^{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 allylstannanes, 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

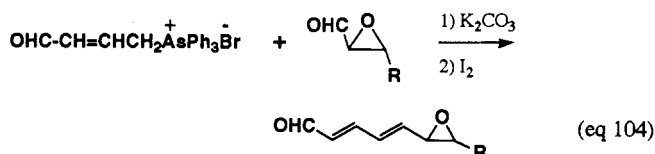


was confirmed in the reactions of α -(phenylseleno)-carbonyl compounds. A 0.025 M benzene solution of α -(phenylseleno)- γ -butyrolactone and 1.5 equiv of allyltriphenylplumbum in the presence of hexaphenyldiplumbum (5 mol %) was irradiated for 5 min to give α -allyl- γ -butyrolactone in 95% yield, whereas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

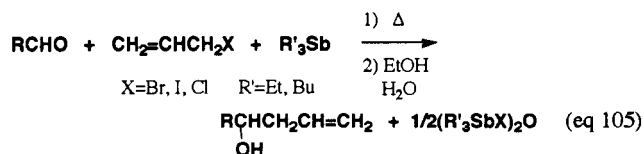
(3-Formylallyl)triphenylarsonium bromide was used for formyl enyl olefination of an epoxyaldehyde (eq 104).^{479a} An allylic arsonium bromide, derived from



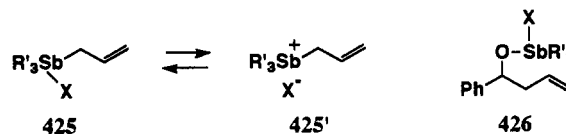
triphenylarsine and 5-bromo-3-penten-2-one, condensed with a variety of aldehydes in the presence of K_2CO_3 to give exclusively ω -acyl-substituted polyenones in good yields.^{479b} Treatment of allylic arsonium ylides with LDA gave the corresponding ylides ($R^1R^2CH=CHCHAsPh_3$), which react with aldehydes to afford the vinyl epoxides in good yields.^{479d}

B. Allylic Stibine Reagents

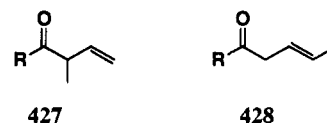
On heating equivalent amount of aldehydes, allyl halides, and trialkylstibine at 80 °C, homoallylic alcohols are obtained in high yields after hydrolysis, along with bis(bromotrialkylantimony) oxide (eq 105).⁴⁸⁰



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 -Bu₃Sb-CH₂E]⁺X⁻ (E = Ph, CH=CH₂, CH=CHCO₂Et, CO₂-Et, CN) are prepared from the corresponding halides and n -Bu₃Sb. On treatment with RLi (R = *n*-Bu, *t*-Bu, Ph) the salts afford pentaalkylstiboranes, n -Bu₃Sb(R)-CH₂E, 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**.⁴⁸² 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.⁴⁸² 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/H₂O 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/H₂O, 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.⁴⁸⁴ This method can also be applied to ethylene glycol and propylene glycol to give the corresponding cyclic acetals.

C. Allylic Bismuth Reagents

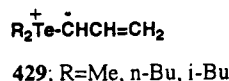
In the presence of metallic bismuth Bi(0) (1.2 equiv), allyl bromide and iodide (1.2 equiv) react with aliphatic and aromatic aldehydes in DMF at room temperature to give the corresponding homoallyl alcohols in good to excellent yields.⁴⁸⁵ Acetophenone is not allylated under these conditions. The allylation also proceeds very smoothly by $BiCl_3/Zn(0)$ in THF, $BiCl_3/Fe(0)$ in THF, and $BiCl_3/Al(0)$ in THF/H₂O, 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/H₂O). Also, only a catalytic amount of BiCl₃ is needed to effect the allylation in the aqueous medium; 10 mole % BiCl₃, Al (2 equiv), THF/H₂O (2.5:1). The addition of crotyl bromide to benzaldehyde produces the syn-adduct predominantly in any procedure, but the BiCl₃/Fe(0) procedure gives higher anti selectivity than others.

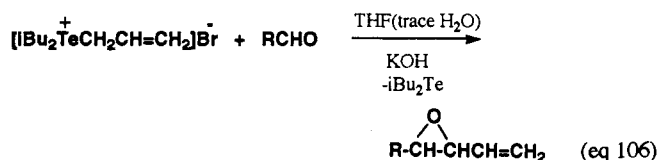
VII. Group 16 (Te)

A. Allyltelluronium Reagents

Allyldialkyltelluronium bromides are converted to diphenyltelluronium allylides **429**, which reacts with aldehydes to produce α,β -unsaturated epoxides.⁴⁸⁷ In



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

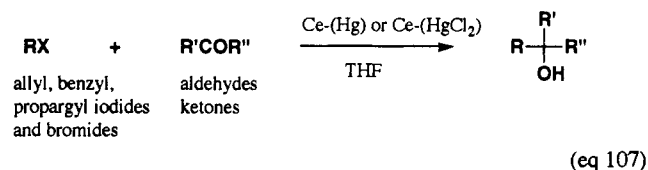


obtained by the reaction of diisobutyl telluride and allyl bromide without solvent at room temperature. In general, the cis epoxides are produced predominantly, but the stereoselectivity is low. Trimethylsilylated diisobutyltelluronium allylide, generated from [3-(trimethylsilyl)prop-2-enyl]diisobutyltelluronium 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}

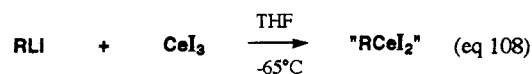
VIII. Group 3 (Ce, La, Nd, Sm, and Yb)

A. Allylic Lanthanoid Reagents

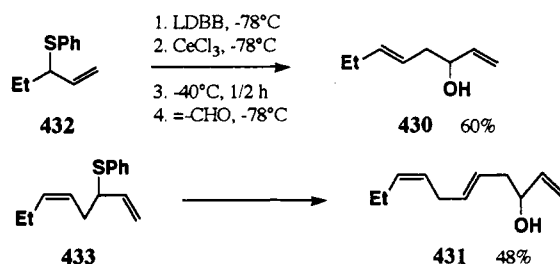
Cerium amalgam Ce-(Hg) or Ce-(HgCl₂) is an effective reagent for the chemoselective preparation of homoallyl alcohols from allyl halides and carbonyl compounds (eq 107).⁴⁸⁹ The same reagent can also be satisfactorily



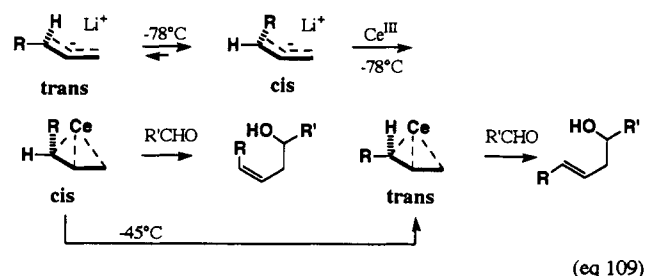
employed for the Reformatsky-type reaction of α -halo esters with carbonyl compounds. The reaction of alkyl- and phenyllithiums with 1 equiv of CeI₃, prepared in situ by the reaction of Ce metal with iodine in THF, produces organocerium(III) reagents (eq 108). The reagents are less basic than organolithiums and Grignard reagents, and they react cleanly at -78 to -65 °C with various carbonyl compounds to afford the addition



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 CeI₃, the use of commercially available lanthanoid chlorides was attempted; CeCl₃·7H₂O, LaCl₃·7H₂O, NdCl₃·6H₂O, PrCl₃·7H₂O, SmCl₃·6H₂O, YbCl₃·6H₂O. 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, lanthanum, 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



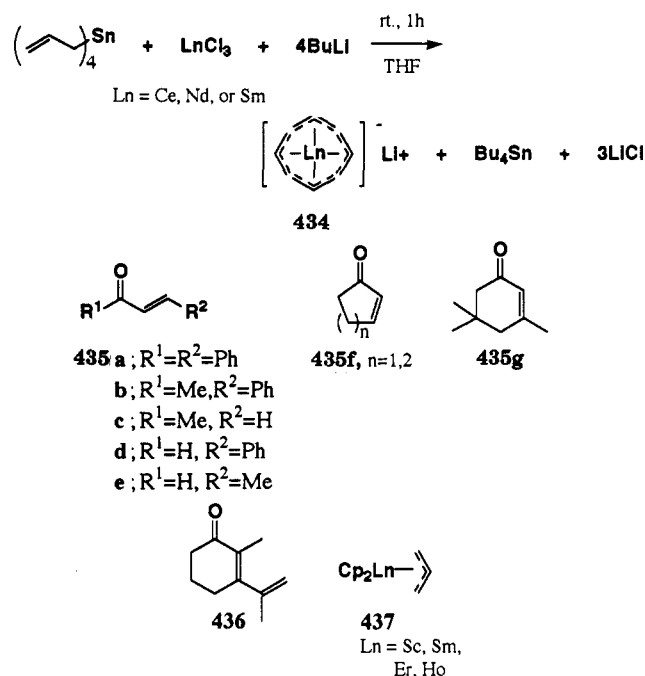
possible because of the fortunate circumstance that the mainly ionic allyllithiums are more stable in the *cis* configuration⁵ while the allylcerium π -complexes are more stable in the *trans* configuration (eq 109).⁹ Allylic,



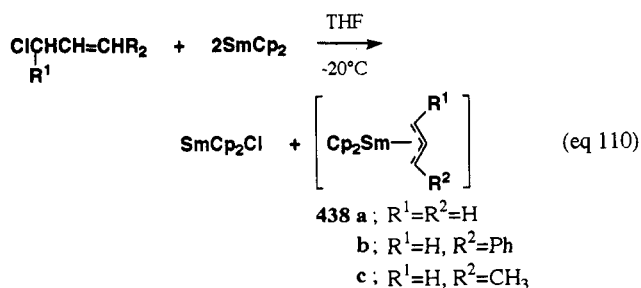
benzylic, and propargylic halides easily react with ketones in the presence of SmI₂.⁴⁹¹ Yields are often appreciable (60–80%) under standard conditions at room temperature and can be rendered quantitative using an excess of SmI₂ and organic halides. Allylic or

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.

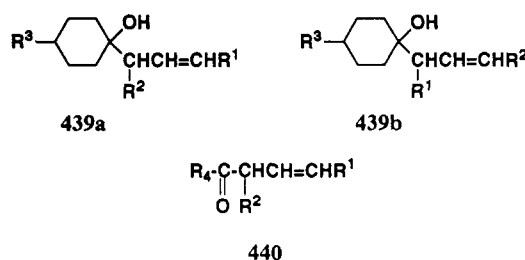
π -Allyl lanthanoid ate complex **434**, which is prepared in situ by transmetalation of tetraallylstannane using the lanthanoid trichloride and *n*-BuLi in THF, reacts smoothly with α,β -unsaturated carbonyl compounds **435**–**436** with a high degree of 1,2-regioselectivity to give the corresponding 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 CeCl₃ and SmCl₃. Allyl chlorides react with Cp₂Sm to afford an allyl samarium intermediate **438** (eq 110), the η^3 -allyl structure of which has been assigned upon its reactivity with ketones;



cyclohexanones are converted to the corresponding homoallyl alcohols **439** and acid chlorides to the corresponding allylated ketones **440**.⁴⁹⁶ Reaction of **438b** (from cinnamyl chloride) and **438c** (from crotyl chloride) with cyclohexanone (R³ = 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 SmI₂, 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 SmCp₂ 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 SmI₂ and YbI₂ show high catalytic activity for the photochemical allylation of aldehydes with allylic halides to give the corresponding homoallyl alcohols.⁴⁹⁷

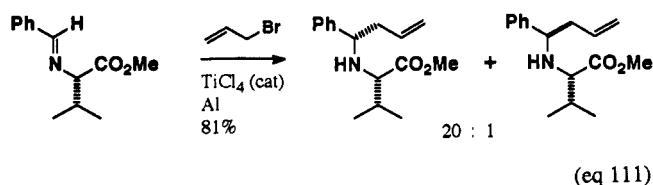
IX. Group 4 (Ti and Zr)

A. Allylic Titanium Reagents

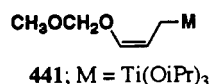
If the counterion (Li, Na, K, etc.) of allyl carbanions is replaced by titanium metal (or zirconium metal), high regio- and stereoselectivity are often produced by the resulting allyltitanium reagents (for example see **3** and **4**). The immense progress in this field has been surveyed in a series of general,^{4,498} and more specific⁴⁹⁹ 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 Cp₂-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 TiCl₄ (cat)/Al-promoted allylation (eq 111).



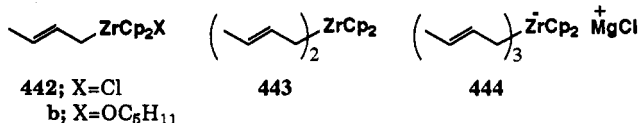
The conjugate addition of crotyl-Ti(Oi-Pr)₃ to **116a** affords the anti-isomer **117a** predominantly in high yields.²⁰⁵ γ -Oxygen-substituted allyl-Ti(Oi-Pr)₃ **441** adds to **116a** and **116b** in an anti selective manner.²⁰⁵



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.

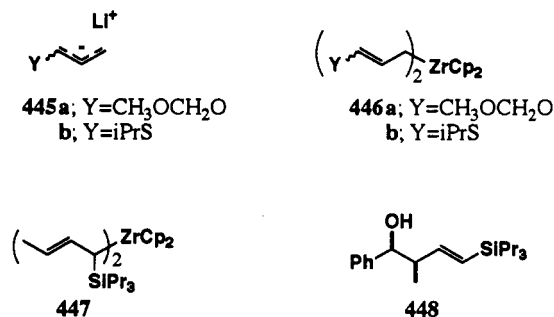
B. Allylic Zirconium Reagents

Crotylzirconium reagents **442**–**444** have been prepared in situ by the addition of 1, 2, and 3 equiv of crystalline lithium or crotylmagnesium chloride to Cp₂ZrCl₂ in THF.^{506,507} Low-temperature NMR studies indicate

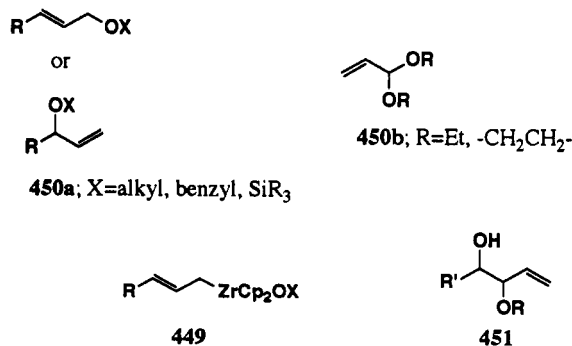


that **443** is a 60:40 mixture of *E*- and *Z*-isomers at 30 °C and an 87:13 mixture at -78 °C, and **442** and **444** are 85:15 and 55:45 mixtures of isomers at -70 °C.⁵⁰⁷ These reagents produce the anti homoallyl alcohols predominantly upon treatment with aldehydes, and the diastereoselectivity closely parallels 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 Cp₂ZrCl₂ 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/BF₃ 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



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 "Cp₂Zr", generated from Cp₂ZrCl₂ 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 "Cp₂Zr", 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.

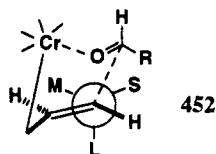


X. Group 6 (Cr and Mo)

A. Allylic Chromium Reagents

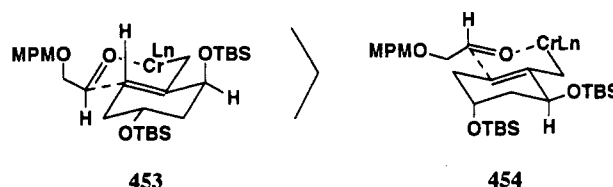
The additions of an alkenyl, alkynyl, allyl, or vinyl-chromium compound to an aldehyde have been re-

viewed recently.⁵⁰⁹ Allylic halides add to aldehydes in the presence of chromium(II) salts; CrCl_2 is generated in situ by the LiAlH_4 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** ($\text{ML}_{n-1}=\text{CrX}_2$) equilibrate rapidly via the chromium(III) intermediate **306** ($\text{ML}_{n-1}=\text{CrX}_2$) 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 numerous 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 $\text{Cr}(\text{II})$ 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 C_γ 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



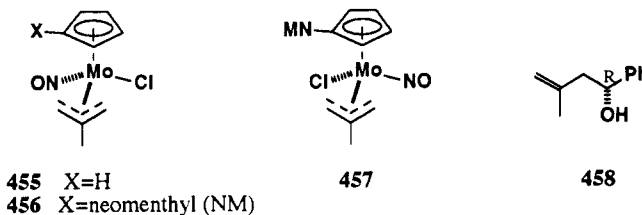
this result is somewhat surprising as the Felkin-Anh model normally is considered as characteristic of electron deficient reaction sites. The reaction of γ -disubstituted allylic phosphates with aldehydes in the presence of $\text{CrCl}_2/\text{cat LiI}$ in DMPU is not stereoconvergent (in contrast to 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 $\text{A}^{1,2}$ 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.

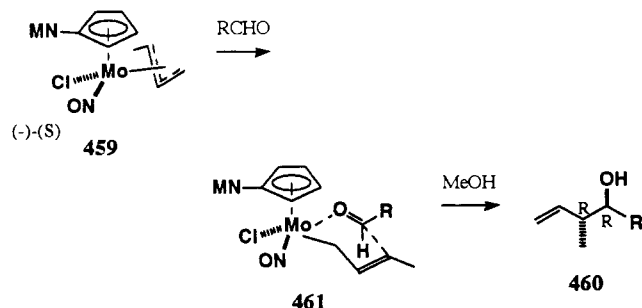


B. Allylic Molybdenum Reagents

Treatment of $\text{CpMo}(\text{NO})\text{Cl}(\eta^3\text{-2-methylallyl})$ 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



benzaldehyde affords (–)-(*S*)-3-methyl-1-phenyl-3-buten-1-ol with 97% de. Treatment of benzaldehyde (2 equiv) with $\text{CpMo}(\text{NO})\text{Cl}(\eta^3\text{-}(E)\text{-crotyl})$ in methanol/ CH_2Cl_2 yields a 22:1 mixture of the *anti*- and *syn*-homoallyl alcohols.⁵²² Homochiral (–)-(*S*)- $\text{NMCPMo}(\text{NO})\text{Cl}(\eta^3\text{-}(E)\text{-crotyl})$ **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

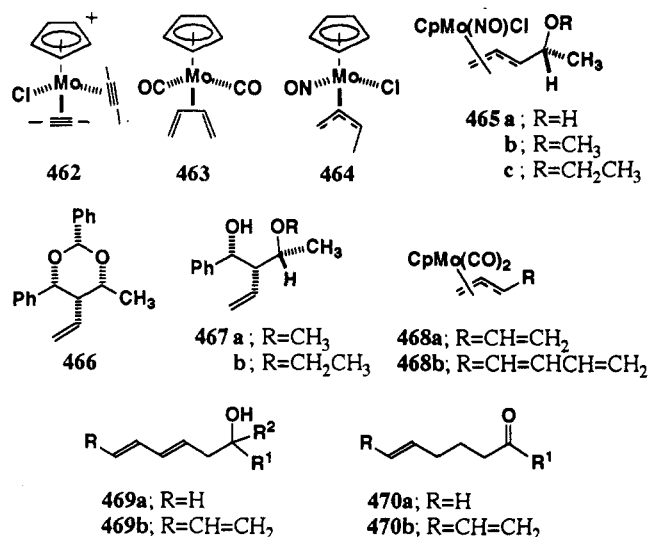


selectivity lies in the electronic asymmetry created by the differential backbonding capabilities of the nitrosyl and chloride ligands. As anticipated by the distortion toward a π - σ -crotyl in the solid structure (X-ray), the

Table VIII. Reactions of Allylic Chromiums with Aldehydes

entry	allylic substrate	aldehyde	conditions	product	yield, %	ref															
1		$R-CHO$	$CrCl_2$, THF	 R=Ph 2.6 : 1 R=CH ₂ OTHP 1 : 1 R=		512															
2	 or 		$CrCl_2$, THF	 > 10:1 (other isomers)	86	513															
3		 (X=)	$CrCl_2$, THF, 25 °C	 anti : syn= 4-5 : 1	75-84	194															
4		PhCHO	$CrCl_2$, THF, 25 °C		94	514															
5	 R = CH ₂ OSiPh ₂ tBu, CH ₂ OBn	PhCHO	$CrCl_2$, THF, 0 °C	 82-83 : 18-17	68-88	515															
6	 R = CH ₂ OBn,	PhCHO	$CrCl_2$, THF, 0 °C	 91-96 : 9-4	75-84	515															
7		PhCHO	$CrCl_2$, cat Li(I), DMPU, 25 °C	 R ² R ³ isomeric ratio <table><tr><th>R²</th><th>R³</th><th>isomeric ratio</th></tr><tr><td>Me</td><td>Me</td><td>97 : 3</td></tr><tr><td>Me</td><td>Me</td><td>99 : 1</td></tr><tr><td>Pr</td><td>Bu</td><td>93 : 7</td></tr><tr><td>Bu</td><td>Pr</td><td>>99 : 1</td></tr></table>	R ²	R ³	isomeric ratio	Me	Me	97 : 3	Me	Me	99 : 1	Pr	Bu	93 : 7	Bu	Pr	>99 : 1		516
R ²	R ³	isomeric ratio																			
Me	Me	97 : 3																			
Me	Me	99 : 1																			
Pr	Bu	93 : 7																			
Bu	Pr	>99 : 1																			
8	 and 2:1 mixture	RCHO	$CrCl_2$, THF, rt	 R=Ph, C ₃ H ₇ , C ₆ H ₁₁ single stereoisomer	54-69	517															
9	 and	PhCHO	$CrCl_2$, THF, rt	 67 : 33	91	517															
10	 X=Cl, Br	PhCHO	$CrCl_2$, THF, rt	 X=Cl 85% (syn:anti=1.1:1) 13% 2% X=Br 46% (syn:anti=1:1.8) 34% 20%		568															
11		PhCHO	$CrCl_2$, THF	 1.6 : 1 (one isomer)	90	518															
12	 (chiral)	MPMO~CHO	$CrCl_2$, THF, rt	 single stereoisomer	97	519															
13	 R ¹ =Me, n-C ₁₁ H ₂₃	RCHO R=Ph, PhCH ₂ CH ₂ n-C ₈ H ₁₇ , c-C ₆ H ₁₁ PhCH=CH ₂	$CrCl_2$, Li(I), THF, 0 °C	 (R ¹ , R ²) : (R ³ , S ³) > 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. $\text{CpMo}(\text{NO})(\text{Cl})(\eta^3\text{-(Z)-crotyl})$ 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 $\eta^3\text{-(Z)}$ 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 $[\text{MoCp}(\text{CO})_2(\eta^3\text{-allyl-R})]$ (**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 $\text{BF}_3\cdot\text{OEt}_2$, and alkenyl ketones **470a** with α,β -unsaturated ketones in the presence of $\text{BF}_3\cdot\text{OEt}_2$; 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

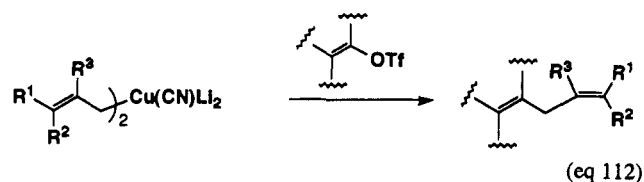
Treatment of "Mn(0)" reagent, prepared *in situ* from anhydrous manganese(II) chloride and LiAlH_4 in THF at 0 °C, with allylic bromide and then with aldehydes or ketones provides homoallyl alcohols with allylic rearrangement.⁵²⁶ α,β -Unsaturated aldehydes and ketones undergo 1,2-addition. With crotyl 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

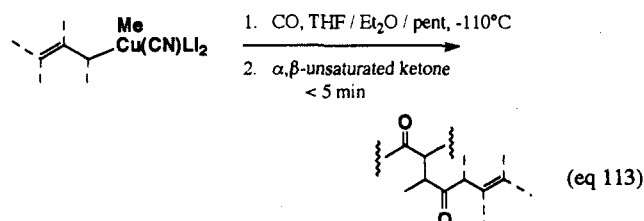
XII. Group 11 (Cu)

A. Allylic Copper Reagents

¹³C NMR spectroscopy has unequivocally established the σ -bound nature of the bonding in both higher order (HO) allyl cuprates, $(\text{allyl})_2\text{Cu}(\text{CN})\text{Li}_2$, and lower order (LO), $(\text{allyl})_2\text{CuLi}$.⁵²⁸ It has also been demonstrated that $(\text{allyl})_2\text{CuLi}$ has limited thermal stability while no such problem exists with $(\text{allyl})_2\text{Cu}(\text{CN})\text{Li}_2$. 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

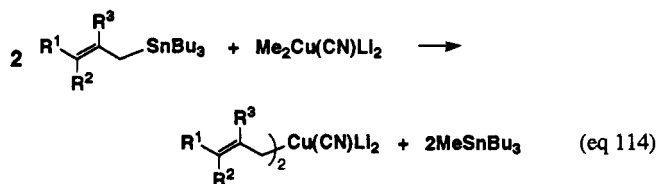


couplings occur with >99% α -attack, whereas crotyl cuprates reacts both regio- and stereorandomly as 2-3:1 mixtures of *Z/E* products, along with ca. 1~2:1 ratios of α/γ attack. Exposure of HO mixed allylic cyanocuprates (Me as a second dummy ligand) to an atmosphere of CO at low temperatures followed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



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 ($\text{allylCu}\cdot\text{TMSCl}$).⁵³¹ Attempts to deliver a simple allyl ligand to cyclohexenone by using either $(\text{allyl})_2\text{Cu}(\text{CN})\text{Li}_2$ or $(\text{allyl})\text{Cu}(\text{CN})\text{Li}$ 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 Me₂Cu(CN)Li₂ at 0 °C for 30 min affords HO allylic cyanocuprates essentially quantitatively (eq 114). Di-

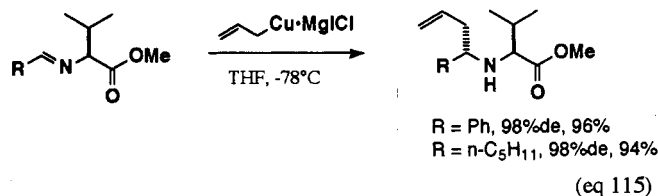


prenylcyanocuprates, which react with epoxides by way of α -attack, reverse this trend with halides where attachment at the γ -carbon prevails. Dicrotylcyanocuprates likewise react preferentially with halides at the γ -position. Cyclic epoxides, highly prone toward Li⁺-induced rearrangement to cyclic ketones, undergo clean displacement with minimal Lewis acid related side product formation. Even primary unactivated chlorides can be displaced by the HO allylic cyanocuprates, although the use of lower order Gilman-like cuprates tends not 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 naphthalene 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

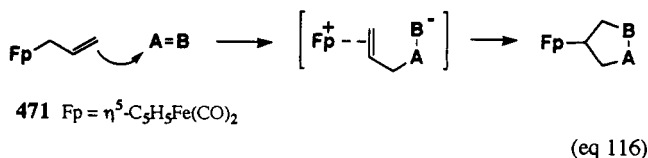
The conventional method for the synthesis of allyl copper reagents has been the reaction of allylic magnesium (or lithium) reagents with copper salts (Li₂-CuCl₄, CuX, or catalytic amounts of CuX in the case of the magnesium reagents).⁵³⁶ Treatment of secondary allylic chlorides or allylic phosphates 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



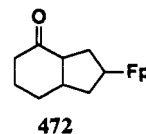
XIII. Groups 8–10 (Fe, Co, and Ni)

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-

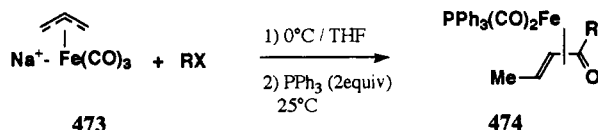


minum bromide catalyzed reaction of 471 with cyclohexenone provides cyclopentane annulation product 472 in 45% yield.⁵⁴¹ Cycloaddition of 471 with enones,

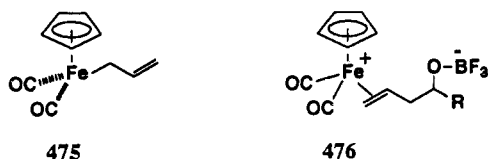


in the absence of Lewis acid, is possible by further substitution of the acceptor olefin with electron-withdrawing groups. As shown above electron-deficient olefins readily react with 471. 2-Carbethoxycycloalkenones serve as useful models in these cycloaddition reactions.

Electron-rich aromatic and heteroaromatic compounds react with $(\eta^3\text{-allyl})\text{Fe}(\text{CO})_4\text{BF}_4$, which is a cationic π -allyl complex, to produce allylated aromatics in moderate to good yields.⁵⁴² The reaction of an anionic allyl complex $(\eta^3\text{-allyl})\text{Fe}(\text{CO})_3^-$ 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).



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 ($\text{BF}_3\cdot\text{OEt}_2$, TiCl_4 , SnCl_4 , AlBr_3 , TMS triflate), $\text{BF}_3\cdot\text{OEt}_2$ is the most effective. The allylation reactions do not occur in the absence of Lewis acid. The $\text{BF}_3\cdot\text{OEt}_2$ -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

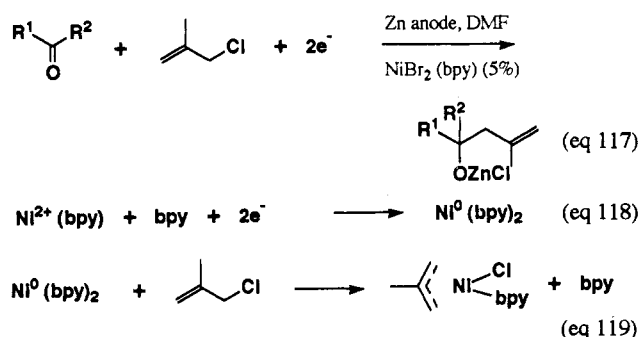


B. Allylic Nickel Reagents

π -Allylnickel halides react with electron-poor centers and may thus be classed as nucleophilic allylic 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 $\text{C}=\text{X}$ 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 elec-

trophiles, the reagents have not been used widely in organic synthesis. A major reason seems to be that very toxic $\text{Ni}(\text{CO})_4$ 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 $\text{NiBr}_2\cdot(\text{bpy})$ complex (bpy = 2,2'-bipyridine) was achieved in a one-compartment cell fitted with a sacrificial zinc anode (eq 117).⁵⁴⁹ The $\text{Ni}^0(\text{bpy})_2$ complex is produced by reduction of $\text{Ni}^{2+}(\text{bpy})$ (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 $\text{Ni}^{2+}(\text{bpy})$ 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 $\text{C}=\text{X}$ 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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