Asymmetric Ene Reactions in Organic Synthesis

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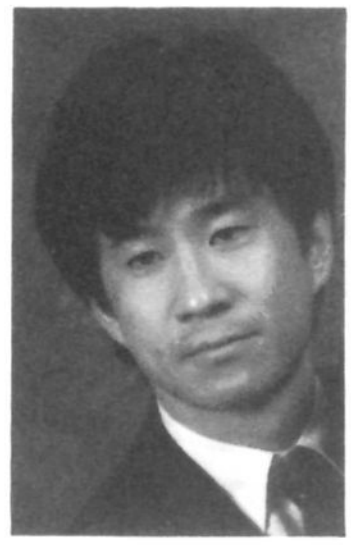
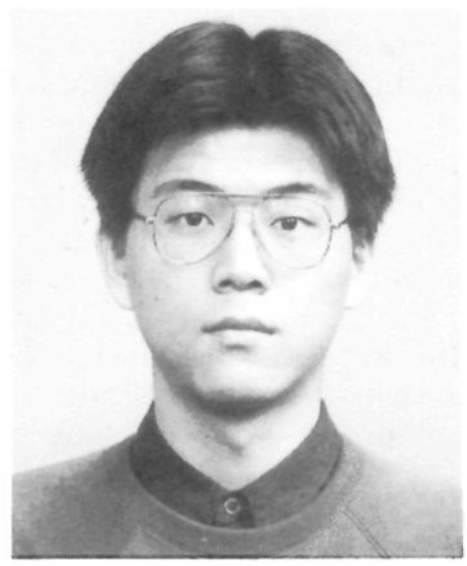
Contents



Koichi Mikami was born in 1953 and received his B.S. degree and Ph.D. from Tokyo Institute of Technology with Takeshi Nakai. He joined the faculty of TIT in 1982 as an Assistant Professor. In 1987, he was promoted to Associate Professor. From 1982 to 1983 he was a postdoctral fellow at the Yale University with Frederick E. Ziegler. His major research interests are the developments of new methods and strategies for organic synthesis, the asymmetric catalysis of synthetic organic reactions, and their application to natural product synthesis.



Masaki Shimizu was born in Tokyo, Japan, in 1965. He graduated from Tokyo Institute of Technology in 1989, where he has now joined the Ph.D. program under the direction of Koichi Mikami.

I. Introduction

C—H bond activation and C—C bond formation are the clues to synthetic exploitation in organic synthesis. In principle, the ene reaction, which converts readily available alkenes with activation of an allylic C—H bond and allylic transposition of the C=C bond into more functionalized products (Scheme 1), is one of the simplest ways for C—C bond formation. The ene reaction was first recognized in 1943[1] by Alder and classified in his Nobel lecture as an "indirect substitution addition" or "ene synthesis" in 1950.[2] Such an ene reaction is defined as a six-electron pericyclic[3] process[4] between an alkene bearing an allylic hydrogen (an "ene") and an electron-deficient multiple bond (an enophile) to form two σ-bonds with migration of the π-bond. The ene reaction is mechanistically related to the much better known "diene synthesis" (the Diels–Alder reaction). In the ene reaction involving a suprafacial orbital interaction (T_1), the two electrons of the allylic C—H σ-bond replace the two π-electrons of the diene in the Diels–Alder reaction. Thus, the activation energy is greater, and higher temperatures are generally required than in the Diels–Alder reactions.[5] That is the main reason why ene reactions, compared to the Diels–Alder counterpart, have remained over-shadowed for a long time.

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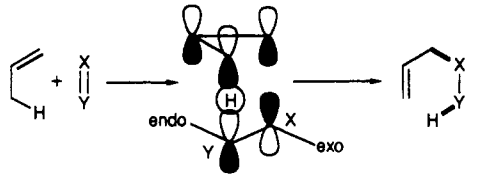
Scheme 1



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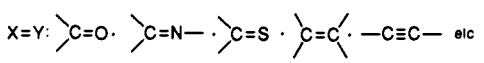
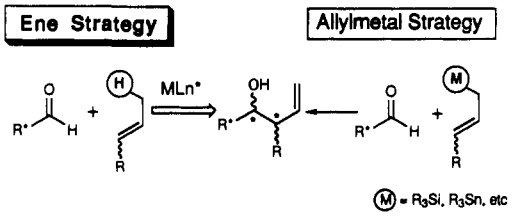


Scheme 2



II. Scope and Limitations

The ene reaction encompasses a vast number of variants in terms of the enophile (X=Y) used.[6] Olefins are relatively unreactive as enophiles; acetylenes are more enophilic. Under high pressure, acetylene reacts with a variety of simple alkenes to form 1,4-dienes.[7] When carbonyl compounds are used as enophiles, alcohols, rather than ethers, are formed exclusively. The imino derivatives of aldehydes also provide homoallylic amines. However, thiocarbonyl compounds react mainly to give allylic sulfides rather than homoallylic thiols. Singlet oxygen, azo, and nitroso enophiles are excluded here since these reactions do not form a C—C bond. In this review, the emphasis will be placed mainly on the ene reactions of carbonyl compounds, aldehydes in particular, as enophiles, which the authors refer to as "carbonyl–ene reactions"[8] where Lewis acids are exploited as promoters or catalysts. A number of Lewis acid promoters have recently been developed, such as $AlCl_3$, $SnCl_4$, $TiCl_4$, and alkylaluminum halides (R_nAlX_{3-n}); the last act as Bronsted bases (proton scavengers) as well as Lewis acids, with the advantage that undesired proton-catalyzed side reactions are prevented.[9]

A. Carbonyl–Ene Reactions

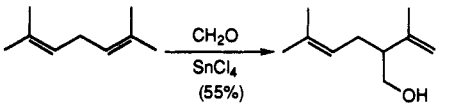
From the synthetic point of view, the carbonyl–ene reaction, should in principle constitute a more efficient alternative to the carbonyl addition reaction of allylmetals which has now become one of the most useful methods for carbon skeletal construction with stereocontrol featuring acyclic stereocontrol (Scheme 2).[10] The synthetic utility of the carbonyl–ene products depends heavily on the functionalities of the enophiles employed. However, the type of carbonyl enophiles developed before 1980 was quite limited; e.g. formaldehyde, chloral, and glyoxylates.

1. Formaldehyde

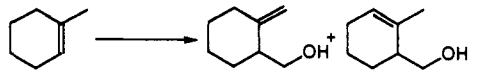
The formaldehyde–ene reaction has been well studied.[11] Thermal ene reactions of paraformaldehyde take place with reactive 1,1-di- and trisubstituted alkenes at 180–220 °C.[12,13] Blomquist has reported the use of acetic anhydride–acetic acid as a solvent system.[14]

$SnCl_4$[15-17] and BF_3·Et_2O[18,19] were exploited as Lewis acid accelerators. $SnCl_4$-promoted reaction with a symmetrical diene provides lavanduol (Scheme 3).[20] Reaction with limonene proceeds selectively at the more reactive 1,1-disubstituted double bond to give the ene product in 80% yield.[18] Recently, Snider has developed a useful method for formaldehyde–ene reactions, paraformaldehyde/Me_2AlCl or $EtAlCl_2$ (Scheme 4).[21] More recently, Yamamoto et al. reported the generation of formaldehyde from trioxane and its stabilization as a complex with an exceptionally bulky aluminum reagent, MAPH which exhibits superior regioselectivity (Scheme 4).[22]

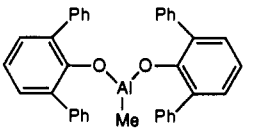
Scheme 3



Scheme 4



CH_2O·$AlMe_2Cl$ (0°C)	92%	41	:	59
CH_2O·MAPH (-78°C)	80%	100	:	0



(MAPH)

2. Chloral

Thermal ene reactions of chloral with 1,1-di- and trisubstituted alkenes take place at lower temperature (90–130 °C) because of the electron-withdrawing trichloromethyl group.[23] The $AlCl_3$- and $SnCl_4$-promoted ene reactions of chloral were also examined.[23] Recently, Gill has reported a complete account on the chloral–ene reaction.[24,25] Lewis acid-catalyzed reactions are best carried out with 2 mol % $AlCl_3$ in CH_2Cl_2 or CCl_4 for reactive alkenes and 6–20 mol % $AlCl_3$ for less reactive alkenes. The order in reactivity of alkenes is as follows: 1,1-disubstituted > trisubstituted > monosubstituted > cis-1,2-disubstituted > alkynes > trans-1,2-disubstituted. Bromal is less reactive.

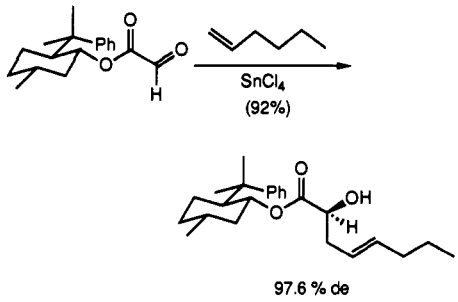
3. Glyoxylates

Thermal glyoxylate–ene reactions take place at 150 °C. $SnCl_4$- and $AlCl_3$-promoted ene reactions of glyoxylates proceed at lower temperature even with cyclohexenes and 1-alkenes.[26] The glyoxylate–ene reactions are synthetically useful, because high asymmetric induction can be obtained with a chiral ester auxiliary (Scheme 5).[27]

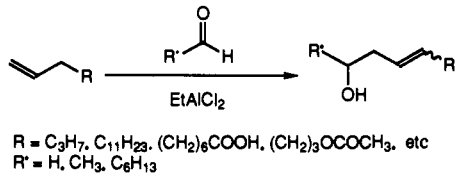
4. Aliphatic and Aromatic Aldehydes

Aliphatic and aromatic aldehydes are much less reactive. Thus, thermal ene reactions cannot be carried out. Snider has reported the use of Me_2AlCl as an

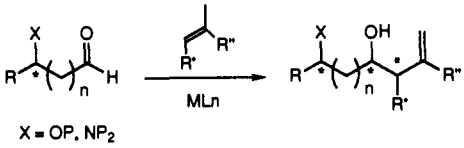
Scheme 5



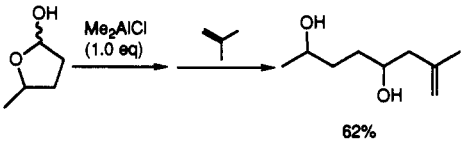
Scheme 6



Scheme 7



Scheme 8

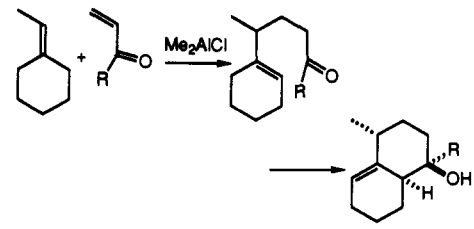


accelerator for ene reactions with reactive 1,1-di-, tri-, and tetrasubstituted alkenes.[21] Mono- and 1,2-disubstituted alkenes are not nucleophilic enough. However $EtAlCl_2$, a stronger Lewis acid than Me_2AlCl successfully promotes ene reactions with monosubstituted alkenes. Reaction of a terminal alkene with an aliphatic aldehyde in the presence of $EtAlCl_2$ in CH_2Cl_2 for a few minutes at 0 °C affords the ene product as a 4:1 trans/cis mixture in 50–60% yield (Scheme 6).[28] Quite recently, Kuwajima et al. reported that ene reactions of 2-(alkylthio)allyl silyl ethers proceed readily with Me_2AlCl to give γ-hydroxy carbonyl compounds as their silyl enol ethers (see Scheme 67).[29]

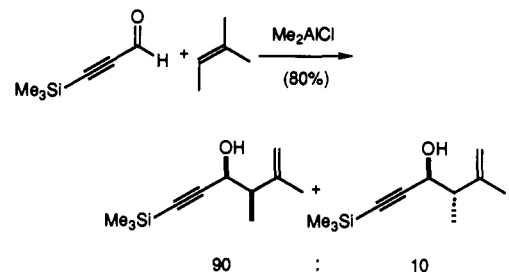
5. Hetero-Substituted Aliphatic Aldehydes

A survey of the literature showed that there was no report on any of hetero-substituted aliphatic aldehydes such as hydroxy and amino aldehydes except for ones with disappointing results. The ene reactions of glycol aldehyde and 3-hydroxybutanal in the presence of a variety of aluminum halides were reported to lead to a complex mixture of products.[30] Quite recently, the authors exploited the ene reactions of protected hydroxy and amino aldehydes with 1,1-di- and trisubstituted alkenes to provide a new entry to the asymmetric synthesis of diols[31] and amino alcohols (Scheme 7).[32] Furthermore, the authors found that γ-lactols, the cyclic equivalent of γ-hydroxy aldehydes, react with 1,1-disubstituted alkenes to give the ene products (Scheme 8).[33]

Scheme 9



Scheme 10



6. α,β-Unsaturated Aldehydes and Ketones

$ZnCl_2$-promoted ene reaction of acrolein with β-pinene gives the "olefin–ene" products rather than the carbonyl–ene products.[34] Reaction of alkylidenecyclopentanes and -cyclohexanes with acrolein derivatives and Me_2AlCl provides the olefin–ene products, which undergo in tandem intramolecular ene reactions of type (2,4) (for the classification of ene cyclizations, see Scheme 81)[35] at 25 °C.[36] The initial ene product can be isolated when the reaction is carried out at −20 °C (Scheme 9).[37,38] However, the authors have recently reported that 3-(trimethylsilyl)propinal reacts with 1,1-di- and trisubstituted alkenes to provide exclusively the carbonyl–ene products (Scheme 10). (For explanation of the syn diastereoselection, see Schemes 20 and 29.)[39,40]

7. Aliphatic Ketones

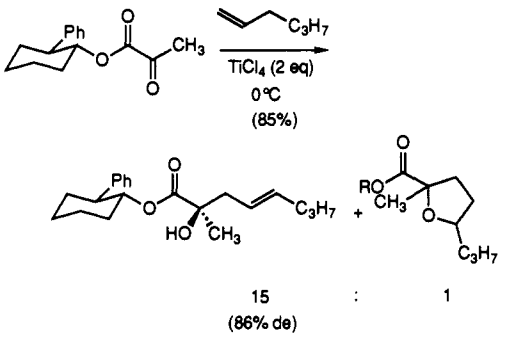
Ketones are less enophilic, and the ene products are tertiary alcohols which are acid labile. However, the ene products can be obtained in moderate yields with $EtAlCl_2$, cycloalkanones, and reactive 1,1-disubstituted alkenes.[41]

8. Oxomalonates and Pyruvates

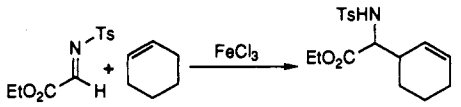
Thermal and Lewis acid-promoted ene reactions of reactive ketones such as dialkyl oxomalonates[42–46] and pyruvate esters[47–49] proceed in good yield. Thermal and $SnCl_4$-promoted ene reactions of diethyl oxomalonate have been well studied by Salomon.[44,45] A variety of alkenes afford the ene products with 1 equiv of diethyl oxomalonate at 80–185 °C. Comparable yields are obtained at 0 °C with $SnCl_4$. The use of clay as a catalyst has also been reported.[50] Thermal ene reaction of β-pinene with methyl pyruvate provides a 1:1 stereoisomeric mixture.[47] This reaction can be carried out in quantitative yield at 40 kbar for 17 h at 25 °C.[48] Reaction of *trans*-2-phenylcyclohexyl pyruvate with 1-hexene and 2 equiv of $TiCl_4$ at 0 °C for 15 min affords the ene product in 86% diastereomeric excess along with the cyclized tetrahydrofuran (Scheme 11).[49]

Dialkyl dioxosuccinate esters,[51] carbonyl sulfide,[52] carbonyl cyanide,[53] hexafluoroacetone,[54–56] and 1,1,1-trifluoromethyl ketones[57] have also been examined. Ene

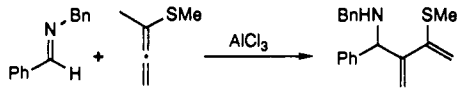
Scheme 11



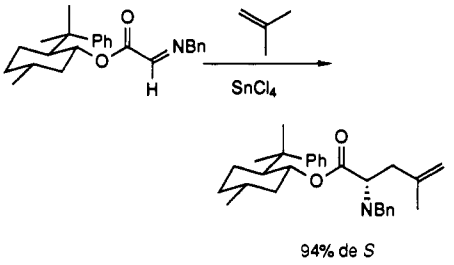
Scheme 12



Scheme 13



Scheme 14



reaction of hexafluoroacetone takes place readily with a variety of alkenes under very mild conditions. 1,1,1-Trifluoromethyl ketones react with terminal alkenes under the influence of $AlCl_3$ even at −78 °C in good yields.

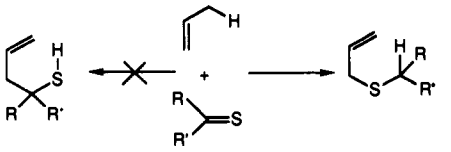
9. Imine Derivatives

Intermolecular ene reactions with Schiff's bases, the nitrogen analogues of aldehydes, provide homoallylic amines. Thus, C—C bond formation takes place site selectively at the imino double bond.[58] However, ene reactions with imine derivatives of aldehydes have been restricted either to reactions employing reactive *N*-sulfonyl imine derivatives of glyoxylate (Scheme 12)[59-61] or to reactions with a highly reactive ene component such as allenyl sulfide (Scheme 13).[62] Recently, the authors found that imine–ene reactions of 1,1-disubstituted alkenes with chiral α-imino esters having an (−)-8-phenylmenthyl auxiliary provide a route to optically active α-amino acids (Scheme 14).[63]

10. Thiocarbonyl Compounds

Thiocarbonyl compounds such as hexafluorothioacetone,[64,65] methyl cyanodithioformate,[66] and thioglyoxylates[67] are particularly reactive enophiles. However, the orientation is the opposite to that for the ene reactions with carbonyl compounds. Ene reactions with thiocarbonyl compounds form C—S rather than C—C bonds. (Scheme 15).[68]

Scheme 15



B. Olefin–Ene Reactions

1. Maleic Anhydride

Maleic anhydride is a widely used olefinic enophile.[69] The scope of the ene reaction has been examined.[70,71] Maleic anhydride reacts with alkyltrimethylsilane or -germane at 200 °C to give vinylsilanes or -germanes.[72]

2. (α-Substituted) Acrylates

Olefins with one electron-withdrawing group such as methyl acrylate are not only relatively unreactive but give mixtures of regioisomers in thermal ene reactions (see Scheme 17). However, reaction with 1-hexene in the presence of $AlCl_3$ at 150 °C for 3.5 h gives the ene product in 39% yield.[73] Snider has reported that the reaction with methylenecyclohexane in benzene with 0.1 equiv of $AlCl_3$ at 25 °C for 48 h gives the ene product in 70% yield.[34] Ene reaction with 1-octene could be accelerated by $AlCl_3$/NaCl/KCl eutectic at 100 °C for 16 h to give the ene product in 40% yield.[74]

More highly functionalized products can be obtained through the ene reaction of α-substituted acrylate esters.[75-77] However, thermal ene reactions of methyl α-haloacrylates are unsuccessful. $EtAlCl_2$ is an effective Lewis acid for these reactions. Acrylates containing a strongly electron-withdrawing α-substituent such as trimethyl α-phosphonoacrylate undergo $EtAlCl_2$-mediated ene reactions in higher yields at 0 °C with a variety of alkenes.[78] By contrast, methyl α-cyanoacrylate gives complex mixtures.[79]

Acrylonitrile reacts with limonene at 200 °C to give ene products in 25% yield.[80] Nitroethylene gives only a low yield of ene product even with β-pinene, the most reactive readily available ene component.[81] Vinyltrichlorosilane reacts as an enophile with terminal alkenes and cycloalkenes at 250 °C.[72]

3. Diene–Iron Complex

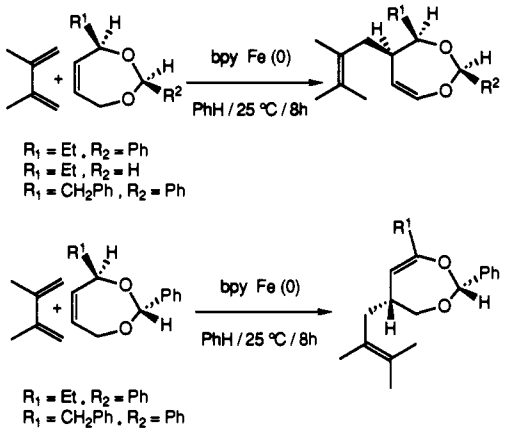
The design of new transition-metal catalysts for olefin–ene reactions has proven to be a challenging problem just like the development of new Lewis acid catalysts for carbonyl–ene reactions (see also "Metallo–Ene Reaction"). Quite recently, Takacs et al. have reported that *formal* ene reactions of 1,3-dienes and allylic ethers catalyzed by soluble iron(0) complexes proceed chemo- and regioselectively (Scheme 16).[82] Each of the phenyl acetal diastereomers reacts with 2,3-dimethyl-1,3-butadiene in the presence of 10 mol % bpy·Fe(0) (bpy = 2,2′-bipyridine) in benzene at 25 °C to yield the formal ene products (40–60%), respectively. Each formal ene reaction proceeds highly diastereoselectively (> 95%), with the formation of isomeric all-cis products, differing only with respect to the regiochemistry of C—C bond formation.

C. Acetylene–Ene Reactions

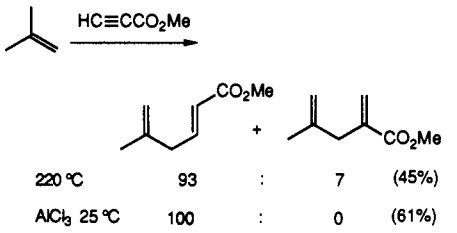
1. Acetylene Dicarboxylates

Thermal ene reaction of acetylenedicarboxylic ester with alkenes proceeds below 200 °C.[83] Dimethyl acet-

Scheme 16



Scheme 17



ylenedicarboxylate (DMAD) undergoes ene reactions with isobutylene at 145–250 °C.[84]

2. Propiolates

Thermal ene reactions with propiolate esters give mixtures of regioisomers. Reaction of methyl propiolate with 1-heptene at 200 °C for 30 h gives a 4:1 regioisomeric mixture in 30% yield.[83] A similar reaction with isobutylene gives a 93:7 of regioisomeric mixture in 45% yield. $AlCl_3$-mediated reactions with 1,1-di-, tri-, and tetrasubstituted alkenes give exclusively the ene products as a single regioisomer (Scheme 17). However, 1,2-disubstituted alkenes give exclusively cyclobutenes. Monosubstituted alkenes give ene products along with cyclobutanes. $EtAlCl_2$ in CH_2Cl_2 was found to be a more effective Lewis acid.[85] Optimal yields are obtained with 1 equiv of Lewis acid since the α,β-unsaturated products are more basic than the propiolate and complex preferentially to the Lewis acid. Similar results are obtained in $ZnCl_2$-promoted reactions of 3-butyn-2-one[86] and $EtAlCl_2$-promoted reactions of ethynyl *p*-tolyl sulfone.[87]

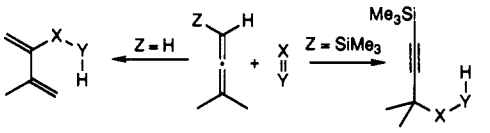
D. Allenes as Enophiles or Enes

Lewis acid-promoted reactions of allenes as enophiles generally give cyclobutanes rather than ene products (see Scheme 27).[88,89] Few examples of allenes as ene components have been reported. Alkylallenes undergo thermal ene reactions with DMAD, hexafluoro-2-butyne,[90] hexafluoroacetone,[91] and 3,3,3-trifluoropropyne to give cross-conjugated dienes.[92] Allenylsilanes are completely different from normal allenes in which an allylic hydrogen is transferred to give a diene (Scheme 18).[93] The trimethylsilyl group causes a reaction at the allenic hydrogen α to the silicon to give a silylalkyne (also see Scheme 13).[72]

III. Mechanistic Aspects

The consideration of the frontier orbital interaction between the HOMO of the ene component and the LUMO of the enophile[4b,c] is of both mechanistic and synthetic importance. The ene process is thus favored by electron-withdrawing substituents on the enophile, by strain in the ene component, and furthermore by geometrical alignments that direct the components in favorable relative positions.

Scheme 18



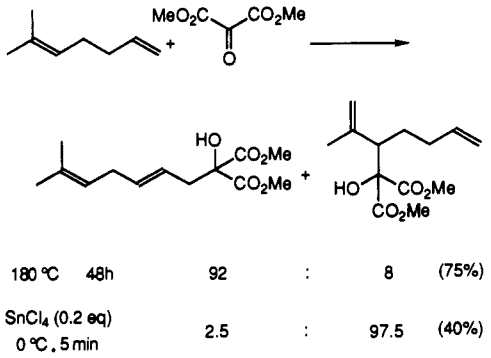
Intermolecular ene reactions exhibit the highly negative entropies of activation[94] and "cis addition" to the enophile[83] that are expected for a concerted process. The ene reaction of deuterated 2,3,3-trimethyl-1-butene with maleic anhydride proceeds through "cis addition" of the ene component and deuterium to the double bond of maleic anhydride.[95] The ene products of 1-alkenes with acetylenedicarboxylates are derivatives of maleic rather than fumaric esters, and propiolates afford derivatives of acrylic ester containing a trans double bond. However, there are some *thermal* reactions that appear to involve a stepwise biradical pathway. The ene reaction of cyclopentene and cyclohexene with diethyl azodicarboxylate can be catalyzed by free-radical initiators.[96,97] Cyclopentene and cyclohexene are relatively rigid and it is therefore difficult to achieve the optimum geometry for a concerted process. Alternatively, the stability of the cyclopentenyl and cyclohexenyl radicals[98] favors a stepwise process.

A. Thermal vs Lewis Acid-Promoted Reactions

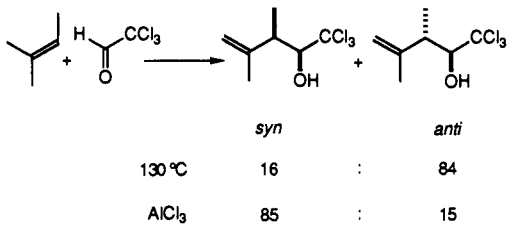
Thermal ene reactions generally require higher temperatures than Diels–Alder reactions. That is the main reason why ene reactions have been relatively less explored for a long time. Thus, Lewis acid-promoted versions have recently been exploited, and the mechanistic differences from thermal reactions have been examined carefully. Whether the mechanism is concerted or stepwise, positive charge is developed to some extent at the ene component in Lewis acid-promoted reactions. Thus, alkenes with at least 1,1-disubstituted double bond are much more reactive than mono- or 1,2-disubstituted alkenes. At this point, the Lewis acid-promoted ene reactions differ from thermal ene reactions where steric accessibility of the double bond and allylic hydrogen is the primary concern. These differences have been quantified by Salomon, who showed that the reaction constant $\rho = -1.2$ for the thermal ene reaction of para-substituted 1-arylcyclopentenes with diethyl oxomalonate, while $\rho = -3.9$ for the reaction catalyzed by $SnCl_4$.[44] The influences of steric effects in thermal reactions vs electronic effects in Lewis acid-promoted reactions are shown in the different product ratios obtained with diethyl oxomalonate and 6-methyl-1,5-heptadiene (Scheme 19).

Lewis acid-mediated ene reactions of methyl acrylate or propiolate with alkenes are regiospecific, giving only one regioisomer in marked contrast to the thermal reactions which give a regioisomeric mixture (see Scheme 17). Complexation of a Lewis acid to the ester, makes the double bond electron deficient and polarizes

Scheme 19



Scheme 20



it so that reaction occurs regiospecifically at the electron deficient β-carbon.

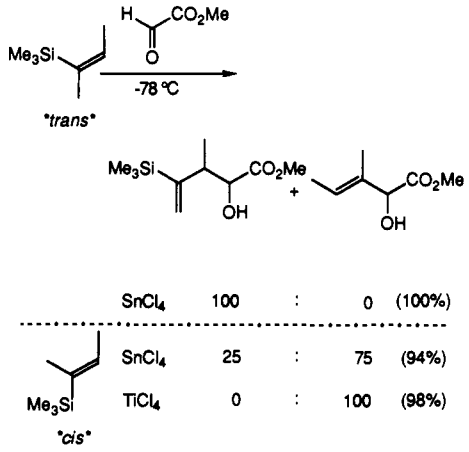
Diastereoselectivity (see "Internal Asymmetric Induction") in the thermal and $AlCl_3$-catalyzed ene reactions of chloral has been exploited (Scheme 20).[25] Reaction of 2-methyl-2-butene at 130 °C gives the anti isomer in 84% diastereoselectivity. By contrast, Lewis acid-catalyzed reaction affords syn diastereomer in 85% selectivity. (For the mechanistic explanation, see Scheme 29.)

B. Continuum from Concerted to Cationic Mechanism

The mechanism of Lewis acid-promoted ene reactions has been the subject of controversial discussions. The Lewis acid-promoted ene reaction is usually discussed in terms of the continuum from concerted to cationic mechanism. In one end, an ene reaction is considered to proceed through a concerted mechanism, namely a single-barrier process. In the other, a reaction can be considered to be stepwise via a cationic intermediate. The formation of the intermediate can be either fast and reversible followed by a slow hydrogen transfer as a rate-determining step or the formation of the intermediate can be the slow rate-determining step followed by a fast hydrogen transfer.

The formation of chloro alcohols from Me_2AlCl-promoted ene reactions of formaldehyde implied a cationic mechanism (see Scheme 28).[21] The ene reaction of 8-phenylmenthyl glyoxylate was reported to be cationic, rather than concerted since *cis*-2-butene was isomerized to *trans*-2-butene under the reaction conditions (see Scheme 75).[9c] Stephenson and Orfanopoulos have found negligible primary isotope effects (k_H/k_D)[99] in the $SnCl_4$-promoted ene reaction of diethyl oxomalonate but suggested that the reaction was concerted with C—H bond breaking only slightly progressed at the transition state.[100] Kwart and Brechbiel have examined the temperature dependence of kinetic isotope effect in the ene reaction of diethyl oxomalonate with allylbenzene and claimed that the temperature-independent isotope effect (k_H/k_D = 2.56) indicates a pseudopericyclic transition state involving nonlinear H transfer.[101,102] However, their interpretation has been challenged on theoretical grounds.[103] They have also found that the $SnCl_4$-promoted reaction of diethyl oxomalonate with allylbenzene gives an oxetane and proposed that the rate-determining step is the formation of a π-complex.[104] Stephenson has developed a stereochemical isotope test comparing inter- and intramolecular kinetic isotope effects and demonstrated that singlet oxygen ene-type reactions proceed through stepwise mechanism involving perepoxide intermediate.[105] Stephenson's test was also used to show that the Lewis acid-promoted ene reactions of methyl propiolate/$EtAlCl_2$ (intermolecular k_H/k_D = 1.1–1.2; intramolecular k_H/k_D = 1.6–2.5) and formaldehyde/Me_2AlCl (intermolecular k_H/k_D = 1.3–1.4; intramolecular k_H/k_D = 2.7–3.3) proceeded through a stepwise reaction involving cationic (zwitterionic) π-complex intermediate.[106,107]

Scheme 21

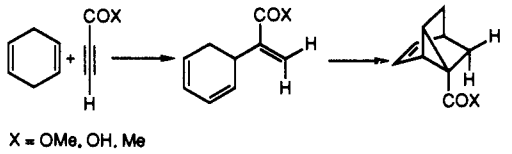


Recently the authors have reported that vinylsilanes provide a novel mechanistic probe for Lewis acid-promoted ene reactions; cationic processes with vinylsilanes should provide the vinylsilane substitution products via β-silyl cations.[108] However, the reaction of formaldehyde with vinylsilanes provides exclusively the ene products rather than the vinylsilane substitution product. By contrast, the reaction modes of vinylsilanes with glyoxylates largely depend on the geometry of the vinylsilane and the Lewis acid employed. In sharp contrast to the exclusive formation of ene product with "*trans*"-vinylsilane, "*cis*"-vinylsilane provides not only the ene product but also the substitution product (Scheme 21).[109,110] More significantly the use of $TiCl_4$ instead of $SnCl_4$ provides only the substitution product. Thus, the cationic process (presumably via zwitterionic intermediate) may occur, when the optimum geometry of the transition state is inaccessible and the cationic intermediate is generated by the stronger Lewis acid.

C. Side Reactions and Byproducts

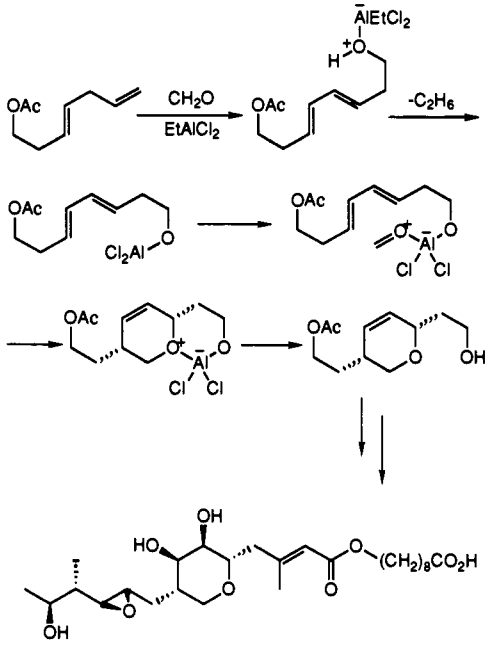
An initial ene product may react as the ene component with a second molecule of enophile to give a 2:1 product. Alder found that reaction of even excess 1-propene with methyl acrylate at 230 °C gives a 7:1 mixture of 2:1 and 1:1 ene products in 30% yield.[83] However, the carbonyl-

Scheme 22



X = OMe, OH, Me

Scheme 23



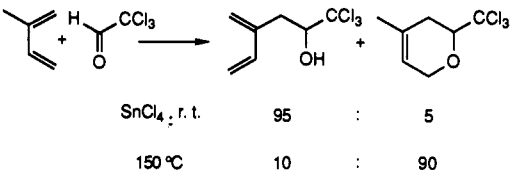
ene products, homoallylic alcohols, are less nucleophilic than the starting alkene and rarely undergo a second ene reaction under Lewis acidic conditions. However, carbonyl–ene products sometime cyclize to a tetrahydrofuran by protonation of the resultant double bond (see Scheme 11).

Alder also found a tandem ene–intramolecular Diels–Alder reaction where 1,4-cyclohexadiene reacts with DMAD at 185 °C to give the ene product which reacts further to give the intramolecular Diels–Alder product.[111] The conditions for this reaction have been optimized and extended to monoactivated acetylenes (Scheme 22).[112]

Tandem ene–quasi-intramolecular Diels–Alder reaction with formaldehyde has been applied to a formal synthesis of pseudomonic acids A and C.[113] Treatment of acetate with 3 equiv of paraformaldehyde and 4.5 equiv of $EtAlCl_2$ in 1:1 dichloromethane/nitromethane at 25 °C for 12 h affords the key intermediate as a 16:1 regioisomeric mixture in 37% yield (Scheme 23).

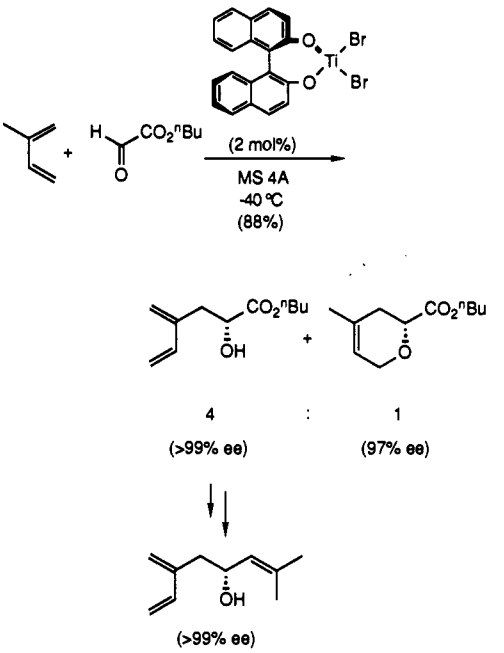
The Me_2AlCl-promoted reaction of isovaleraldehyde with isoprene gives the ene product ipsenol[114] in only 16% yield and the Diels–Alder product in 60% yield.[9] A similar reaction of isoprene with chloral in the presence of $SnCl_4$ at room temperature affords 95% ene and 5% Diels–Alder products (Scheme 24).[17b,c] In the absence of Lewis acid, the reaction requires higher temperatures (150 °C) and the ratio is reversed. In the course of studies on the asymmetric catalysis of carbonyl–ene reaction, the authors have recently found that the reaction of isoprene and glyoxylate catalyzed by a binaphthol-derived chiral titanium complex at −40 °C provides a 4:1 ratio of the carbonyl–ene and the hetero Diels–Alder products along with extreme-

Scheme 24



$SnCl_4$, r. t.	95	:	5
150 °C	10	:	90

Scheme 25



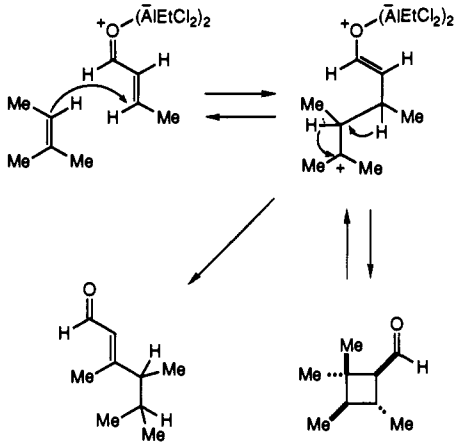
ly high enantioselectivity (>99% ee) (Scheme 25).[115] The ene product has been converted to optically pure ipsdienol.[114]

In the reactions of α,β-unsaturated carbonyl compounds, the β-substituent stabilizes the enal– or enone–Lewis acid complex and sterically retards the reaction with an alkene. However, a complex of these aldehydes and ketones with 2 equiv of $EtAlCl_2$ reacts reversibly with alkenes to give a zwitterion, which reacts reversibly to give a [2 + 2] product or undergoes two 1,2-hydride shifts to give irreversibly a β,β-disubstituted-α,β-unsaturated carbonyl compound (Scheme 26).[116] 2,3-Butadienoates undergo $AlCl_3$- and $EtAlCl_2$-promoted stereospecific [2 + 2] cycloadditions with a wide variety of alkenes to give alkyl cyclobutylideneacetates in good yields (Scheme 27).[117–119]

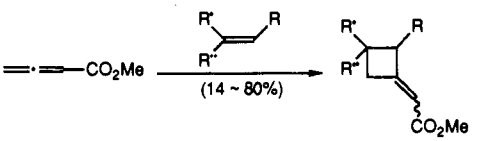
Some reported [2 + 2] cycloadditions[120] have, however, been shown to be incorrect. $AlCl_3$-promoted reaction of isobutylene or 2,3-dimethyl-2-butene with methyl acrylate in benzene gives only the ene products.[121] In nitromethane/dichloromethane, the ene products easily undergo isomerization or rearrangement but are obtained under carefully controlled conditions to prevent isomerization of the double bond.[122]

Secondary chlorides are formed in the Me_2AlCl-promoted reaction with formaldehyde with the stereospecific cis addition of CH_2OH and Cl on the double bond (Scheme 28).[21,123] These chloro alcohols can be isolated in varying amounts with 1 equiv of Me_2AlCl. With an excess of Me_2AlCl, the Lewis acid assists the regeneration of the carbenium ion intermediate. Reaction with 1.5–2 equiv of Me_2AlCl for 1–2 h gives only ene product.

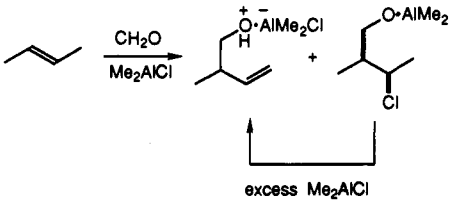
Scheme 26



Scheme 27



Scheme 28



It is rather surprising that alkenes are more nucleophilic than the methyl group of Me_2AlCl in the ene reaction conditions. With aliphatic and aromatic aldehydes, addition of a methyl group from Me_2AlCl to aldehyde competes with the ene reaction of nucleophilic alkenes. Addition of the Me group to the aldehyde is more problematic with sterically hindered aldehydes. $Me_3Al_2Cl_3$ or $EtAlCl_2$ sometimes gives better results. Use of 2 equiv of $EtAlCl_2$ gives the ene product as a 3:1 *E*/*Z* mixture in 70% yield (see Scheme 6).

IV. Stereochemical Aspects

A. Transition-State Models

The thermal ene reaction maximizes allylic resonance by tuning the axis of the breaking C—H bond parallel to the p orbitals of the neighboring double bond in the *early* transition state. In fact, STO-3G and 3-21G calculations by Houk on the *thermal* ene reaction of propene with formaldehyde and ethylene have shown that the exothermicities of both reactions are so large that very early transition states are predicted.[124] The transition-state geometry resembles that proposed by Hoffmann,[6a] although the C–O—H angle is 155°, not 180° (Figure 1). The transition structure is characterized as an envelope conformation.

However, the authors have recently proposed a 6-membered chairlike transition-state model for the *Lewis acid-promoted* carbonyl–ene reactions which should proceed with relatively *late* transition states.[125] Another

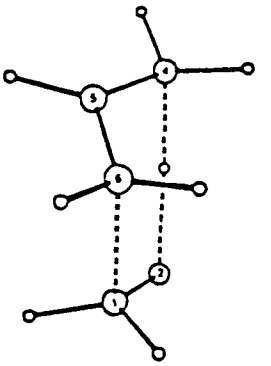
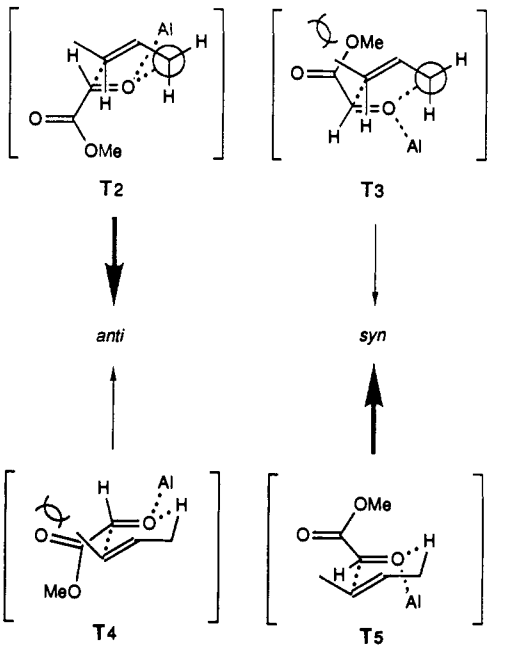


Figure 1. View of the 3-21G transition structure of the propene formaldehyde–ene reaction (from ref 124; copyright 1987 American Chemical Society).

Scheme 29

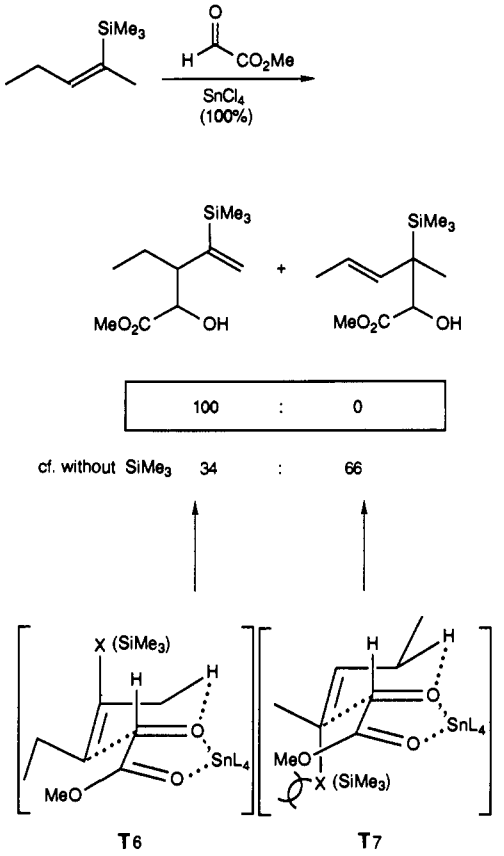


reason is that the envelope model cannot explain the syn diastereoselectivity observed in the aluminum-promoted glyoxylate–ene reactions (Scheme 29).[125] Anti selectivity should be predicted by an envelope model at least in the reaction of *trans*-2-butene with an aluminum reagent because of the steric repulsion of Me and CO_2Me in T_3 leading to syn diastereomer. Furthermore with the chairlike mode, one can easily visualize the steric parameters such as 1,3-diaxial and 1,2-diequatorial repulsions as shown in T_4.

B. Regioselection

Ene reactions often suffer a serious drawback in terms of regiochemistry, for which the steric accessibility of the hydrogen is an important determining factor. Methyl and methylene hydrogens are abstracted much more easily than methine hydrogens. In thermal ene reactions, a primary hydrogen is abstracted more readily than a secondary and much faster than a tertiary one, irrespective of the thermodynamic stability of the internal olefin product.[96] In Lewis acid-promoted reactions, the relative ease of abstraction of methyl vs methylene hydrogens depends on the enophile/Lewis acid employed. With formaldehyde/Me_2AlCl, methylene hydrogens are abstracted more easily, presumably

Scheme 30



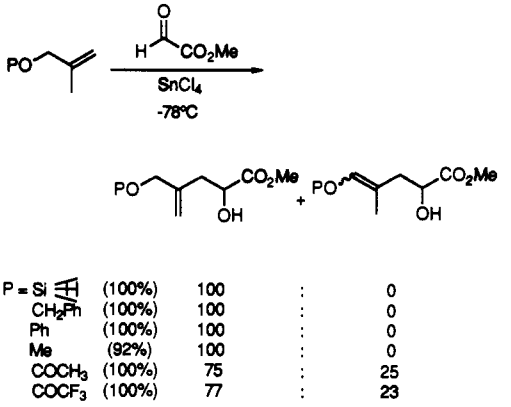
T6 T7

because of product development control. With methyl propiolate/$EtAlCl_2$, methyl and methylene hydrogens are abstracted with equal rates.

By contrast, functionalization of ene components leads to the high level of regiocontrol, because of the steric and/or electronic effects of the functional groups. Thus, the regiochemistry can be controlled by the introduction of a silyl, alkoxy, or amino group in the ene component. The synthetic advantages of the directed carbonyl–ene reaction are highly regiocontrolled introduction of multifunctionality and remarkably high levels of stereoselectivity. The authors have recently reported that the introduction of a silyl group controls the regiochemical course in the carbonyl–ene reaction to give the vinylsilane product as a single regioisomer (Scheme 30).[40] The highly regiocontrolled ene reaction with vinylsilanes is in sharp contrast to the ene reaction of the alkene without the silyl group, which gives a 1:2 mixture of regioisomers under the same reaction conditions. The high level of regiocontrol can be visualized in terms of the chairlike transition state model. Steric interaction of Me_3Si and CO_2Me is greatly enhanced relative to that of H and CO_2Me in the transition state (T_7). Thus, vinylsilane would be formed regioselectively via the regioisomeric transition state (T_6).

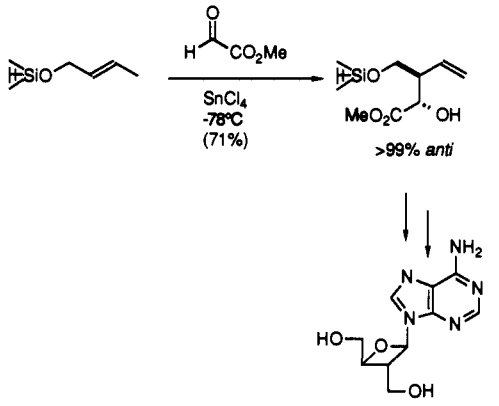
The authors have also found that carbonyl–ene reactions with allylic ethers give single regioisomers with a wide range of protecting groups except for trifluoroacetate which provides a 1:3 regioisomeric mixture (Scheme 31).[126] High levels of regio- and stereocontrol are also obtained with 1,2-unsymmetrically disubstituted allylic component which give exclusively the anti ester (Scheme 32). The ene product could serve as a synthetic precursor for oxetanocin A.[127,128]

Scheme 31

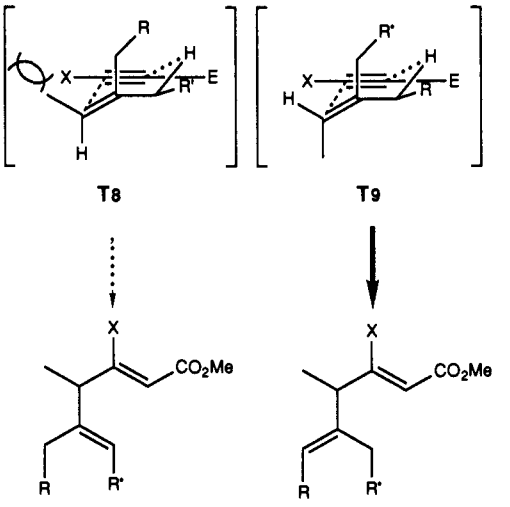


P = Si	(100%)	100	:	0
CH_2Ph	(100%)	100	:	0
Ph	(100%)	100	:	0
Me	(92%)	100	:	0
$COCH_3$	(100%)	75	:	25
$COCF_3$	(100%)	77	:	23

Scheme 32

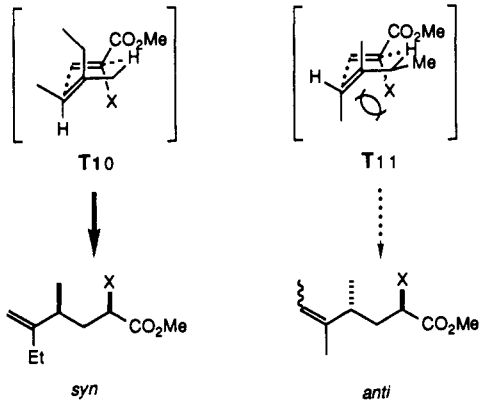


Scheme 33

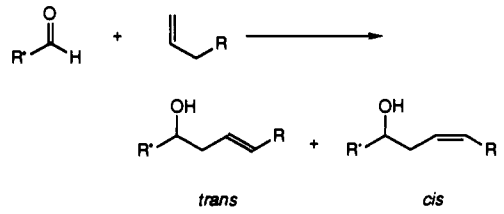


With trisubstituted alkenes, the $EtAlCl_2$-promoted ene reaction with DMAD, but not with methyl propiolate, is regiospecific (Scheme 33). A hydrogen is abstracted from the alkyl group trans to the alkenyl hydrogen. Similar reactions of methyl α-bromo- and α-chloroacrylate (but not acrylate itself) with these alkenes are also regio- and stereospecific (Scheme 34).[75,76] However, a hydrogen is abstracted from the alkyl group cis to the alkenyl hydrogen. These enophiles react stereoselectively (85–95%) with the carbomethoxy group *equatorial* (T_{10} vs T_{11}). 1,3-Diaxial interactions are operative between Me and X in the transition state (T_{11}). By contrast, the transition state (T_{10}) leading to the observed product has no significant steric interactions.[129,130] Formaldehyde–ene reactions with trisub-

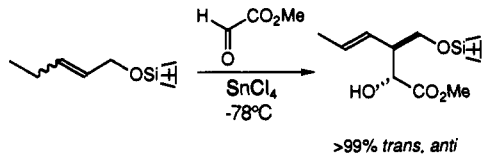
Scheme 34



Scheme 35



Scheme 36



stituted alkenes also shows a preference for hydrogen transfer from the alkyl group cis to the alkenyl hydrogen. However, the selectivity is only modest except with 2-methylethylidenecyclopentane (see Scheme 59).

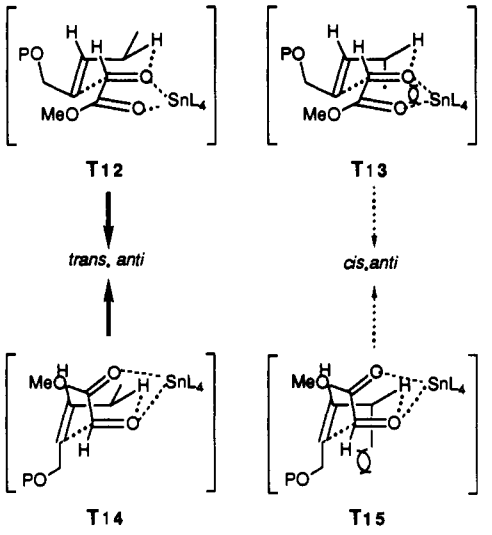
C. Olefinic Diastereoselection

The geometry of the newly formed double bond in the ene product will be considered first. Trans selectivities in the range of 70–90% have generally been obtained in the ene reactions (Scheme 35). 1,2-Disubstituted double bonds are formed ~90% trans via formaldehyde–ene reactions with Me_2AlCl and 75% trans with $EtAlCl_2$ (see Scheme 6). Trisubstituted double bonds are formed ~70% trans.

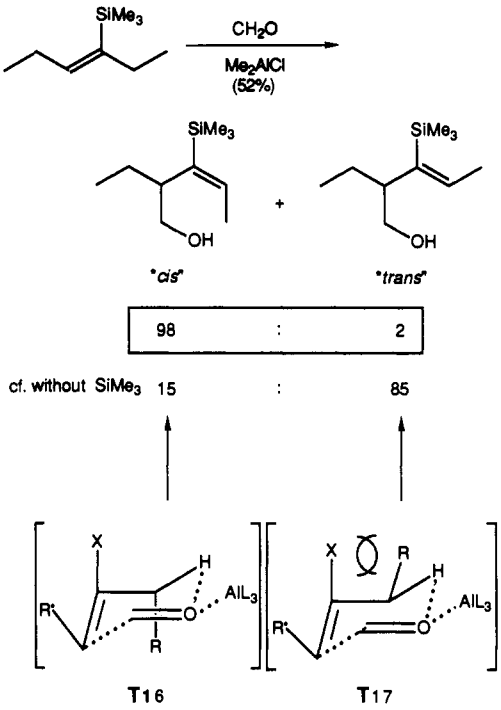
Reaction of 9-decenoic acid with 1 equiv of acetaldehyde and 2.2 equiv of $EtAlCl_2$ affords the ene product as a 4:1 trans/cis mixture in 60% yield. Lactonization of the trans isomer provides recifeolide.[130] Reaction of 10-undecanoic acid with 1 equiv of heptanal and 2.2 equiv of $EtAlCl_2$ provides a 4:1 mixture of ricinelaidic acid and ricinoleic acid in 41% yield (see Scheme 6, R = $(CH_2)_3OCOCH_3$).[28] Ene reaction of 8-phenylmenthyl glyoxylate with 1-alkenes and a stoichiometric amount of $SnCl_4$ gives the ene product in ~90% yield with >97% diastereomeric excess.[131] The newly formed double bond is 94% trans (see Scheme 5).

The introduction of an alkoxy group in the ene component leads to a high level of olefinic stereocontrol. Significantly, the carbonyl–ene reaction with an allylic ether provides the trans,anti ester as a single isomer, irrespective of the ene geometry (Scheme 36). The remarkably high level of trans,anti stereoselection can be explained in terms of the chairlike model

Scheme 37



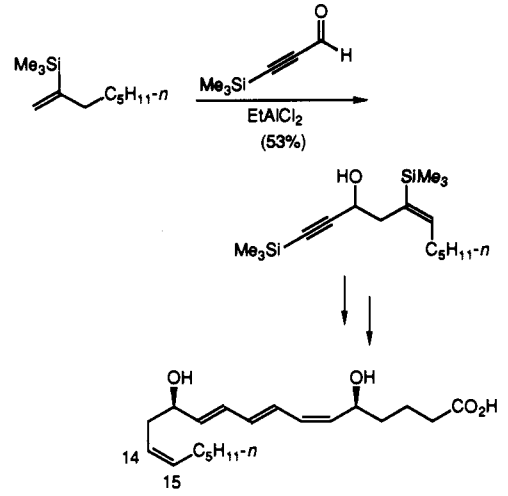
Scheme 38



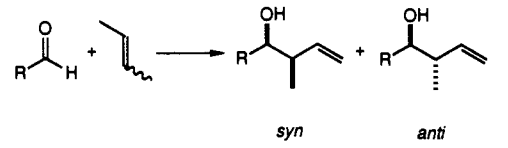
(Scheme 37). The Me-axial transition states (T_{13}, T_{15}) would be disfavored by steric repulsions. Thus, the trans,anti product would be formed via either Me-equatorial transition state (T_{12}, T_{14}).

The controlling effect of the silyl group on the stereo- and regioselectivity is highlighted by the changeover of the olefinic stereoselectivity from trans to "cis" (Scheme 38).[39] In the context of leukotriene synthesis,[132] the (trimethylsilyl)propynal–ene reaction provides a high level of cis-olefinic stereoselectivity at C-14 and -15. On the basis of the chairlike model, the changeover into "cis" selectivity is predicted. The equatorial transition state (T_{17}) leading to "trans" product would be less favorable because of the large 1,2-repulsion between the bulky silyl and α-alkyl substituents. Thus, the anomalous "cis" selectivity would be obtained via the axial transition state (T_{16}). Using $EtAlCl_2$ in toluene, the propynal–ene reaction does provide the

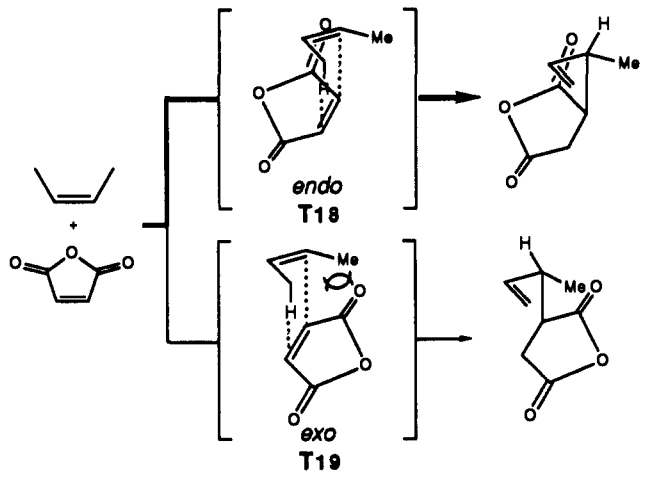
Scheme 39



Scheme 40



Scheme 41



key intermediate for leukotriene B_4 with virtually complete "cis" selectivity (Scheme 39).

D. Internal Asymmetric Induction: Endo Preference?

The diastereoselection with respect to the newly created chiral centers, namely internal asymmetric induction is the most basic problem from the standpoint of acyclic stereocontrol (Scheme 40).

Berson showed that maleic anhydride reacts with *cis*-2-butene to give two diastereomeric thermal ene products in a ratio of 80–85:20–15 (Scheme 41). *trans*-2-Butene, by contrast, affords a ratio of 43:57. The thermal ene reaction of cyclopentene shows a 78:22 preference for the endo transition state (T_{18}).[133] Nahm and Cheng have also determined the endo/exo, trans/cis, and regioselectivities of the thermal ene reaction with all nine decenes.[134] Their results are consistent with Berson's as follows. *cis*-Decene shows a ca. 85:15 endo preference leading to the anti isomer with a trans

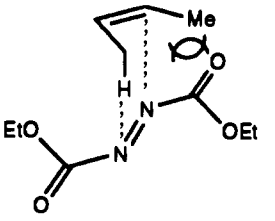
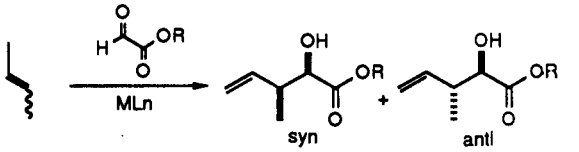


Figure 2.

Table 1. Glyoxylate–Ene Reactions with 2-Butene



butene	R	MLn	syn:anti
trans	Me	$SnCl_4$	18:82 (quant)
cis			28:72 (quant)
trans	i-Pr		8:92 (quant)
cis			29:71 (quant)
cis	Me	Me_2AlOTf	91:9 (65%)
trans			79:21 (29%)
		$MeAl(OTf)_2$	65:35 (41%)

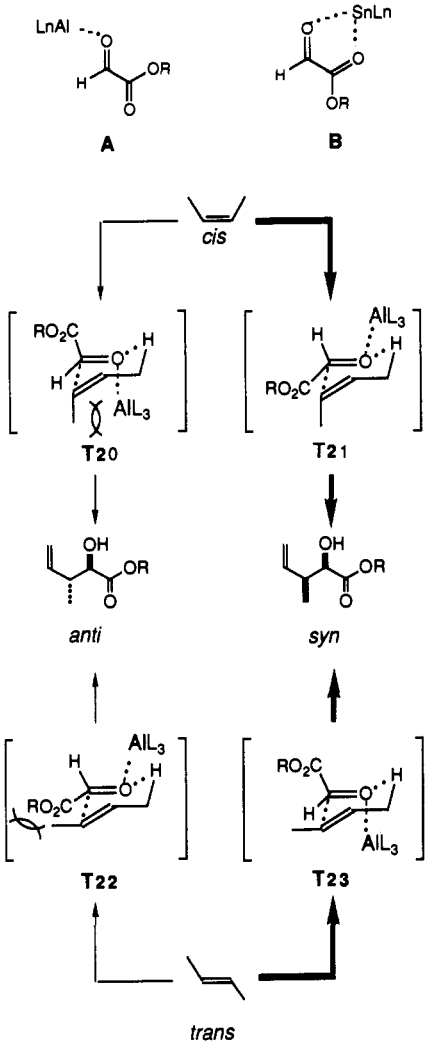
double bond exclusively. *trans*-Decene exhibits only a ca. 60:40 endo preference leading to the syn isomer as a 81:19 mixture of trans/cis isomers. The endo preference is qualitatively observed but sensitive to steric effects.

Steric effects are obvious in the thermal reaction with diethyl azodicarboxylate. In sharp contrast to maleic anhydride which reacts more readily with *cis*-2-butene, *trans*-2-butene reacts about 3.7 times faster than the cis isomer. One ethoxycarbonyl group of the azo ester and the opposing methyl group of the *cis*-2-butene disfavor the transition state (Figure 2).[96] In contrast, no such repulsion is present in the reaction of *trans*-2-butene. All these differences are of steric origin rather than electronic origin.

Diastereoselectivity in the thermal and $FeCl_3$-promoted ene reactions of methyl glyoxylate was examined.[135] Thermal reaction with *cis*-2-butene at 200 °C for 60 h gives a 88:12 anti/syn diastereomeric mixture in 54% yield. Similar reaction of *trans*-2-butene gives a 36:64 mixture in 20% yield. However, Lewis acid-promoted reactions show lower selectivity and yield along with the formation of chloro alcohols as significant byproduct. $FeCl_3$-promoted ene reaction with *cis*-2-butene affords only a 58:42 diastereomeric mixture of ene products in 31% yield.

In connection with the synthesis of the acyclic side chain of brassinosteroids,[136,137] the authors are interested in the glyoxylate–ene reaction, which hopefully will provide the 22(*R*)-hydroxy-23-carbonyl product with a high syn selectivity. Thus, the diastereoselectivity of glyoxylate–ene reactions has been investigated with 2-butene using various Lewis acids such as (alkoxy)titanium chloride, boron trifluoride, etc. Interestingly, a dramatic changeover in diastereoselectivity has been observed by changing the Lewis acid from stannic chloride to aluminum reagents (Table 1).[125] The $SnCl_4$-promoted reactions exhibit anti selectivity, irrespective of the ene geometry. By contrast, the Me_nAlL_{3-n} provide syn selectivity, again irrespective of the ene geometry.

Scheme 42



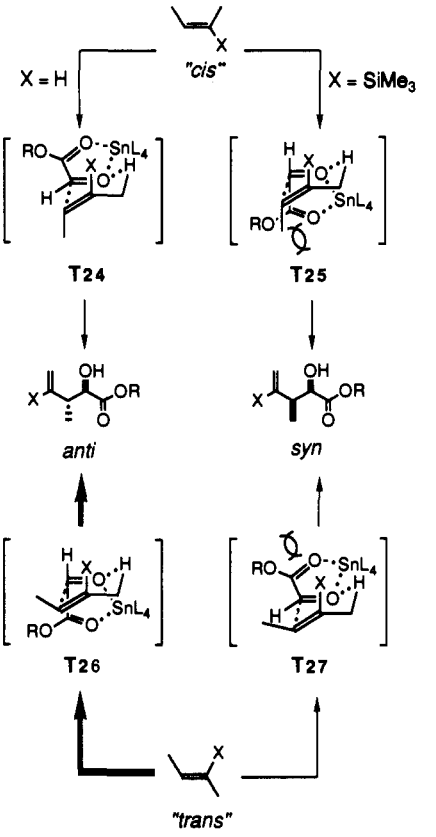
Particularly notable are the relatively high anti selectivity obtained with *trans*-2-butene and the relatively high syn selectivity obtained with *cis*-2-butene.[138]

The changeover in diastereoselectivity can be visualized by the chairlike model. Thus, the syn selectivity can be rationalized in terms of the reasonable postulate that aluminum reagent is complexed to the glyoxylate in a monodentate fashion (A). Thus, the trans to syn and cis to syn selectivities are exemplified by the trans-ax (T_{23}) and the cis-eq (T_{21}) transition states, respectively (Scheme 42).

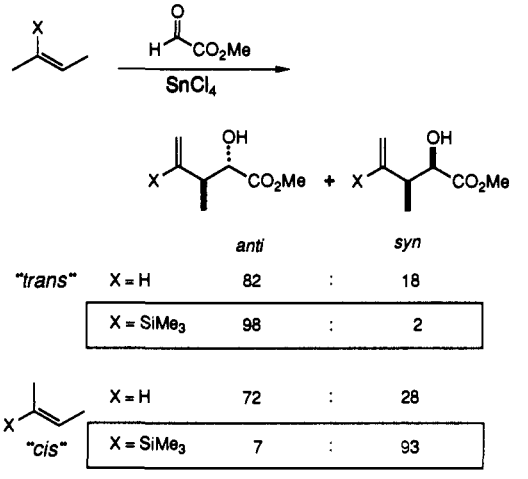
On the other hand, the anti selectivity could be rationalized in terms of the reasonable postulate that stannic chloride is complexed to the glyoxylate in a bidentate fashion (B). Thus, the trans to anti and cis to anti selectivities are visualized by the trans-eq (T_{26}) and cis-ax (T_{24}) transition states, respectively (Scheme 43).

On the basis of our model, the use of "*trans*"-vinylsilane would result in an increase in anti selectivity, because of the greatly increased 1,3-repulsion in the trans-ax transition state (T_{27}) leading to syn product. On the other hand, the use of "*cis*"-vinylsilane might be predicted to provide an enhanced syn selectivity in view of the increased 1,3-repulsion in the cis-ax transition state (T_{24}). As expected, the reaction with "*trans*"-vinylsilane did proceed regioselectively to give the anti

Scheme 43



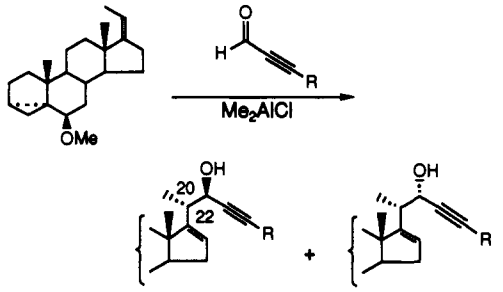
Scheme 44



product with remarkably enhanced selectivity (Scheme 44). Similarly, the reaction of "*cis*"-vinylsilane gave the high syn selectivity. Thus, the chairlike model would provide a guiding principle for analyzing and predicting the stereochemistry of the Lewis acid-promoted ene reactions.

The authors are also interested in developing a new type of ene reactions using propynals as carbonyl enophiles, which may provide an efficient method for the concurrent stereocontrol over steroidal C-20 and -22. Based on the argument that the monodentate complexation of a glyoxylate with a Lewis acid results in syn diastereoselectivity, the use of propynal as enophile would lead to the formation of the syn product via an monodentate complexation (see A). As expected, all the ene reactions, except for propynal itself, afford the desired carbonyl–ene products rather than the "ole-

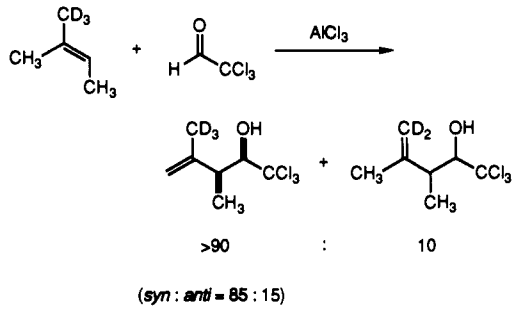
Scheme 45



R	%Yield	20(*S*)-*syn*	:	20(*S*)-*anti*
Me	90	90	:	10
i-Pr	quant	90 (78%)*	:	10
$SiMe_3$	quant	>95	:	<5

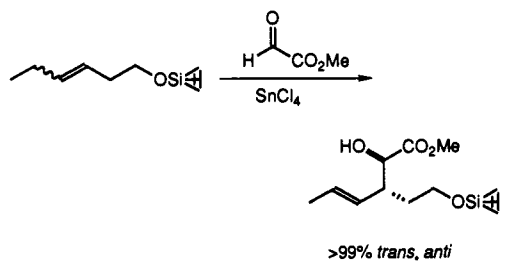
* Isolated yield by silica gel chromatography.

Scheme 46



(*syn* : *anti* = 85 : 15)

Scheme 47



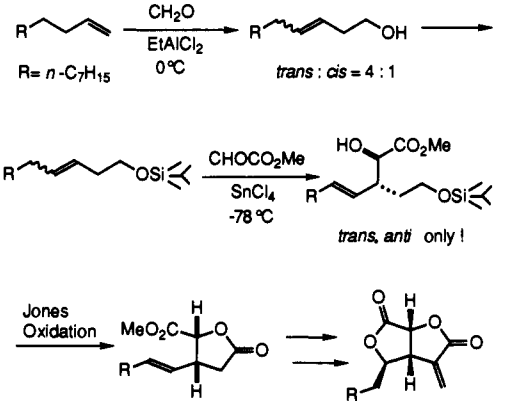
>99% *trans, anti*

fin–ene" product in the presence of Me_2AlCl with high (20*S*,22*R*)-syn selectivity without decomposition of the acid-labile cyclopropylcarbinyl ether (Scheme 45).[38]

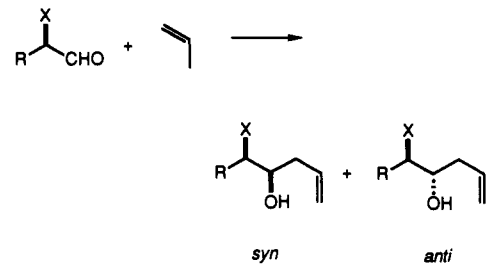
$AlCl_3$-catalyzed chloral–ene reaction with trisubstituted alkenes are more complex since the hydrogen can be transferred from two different sites. 2-Methyl-2-butene gives an 85:15 mixture of diastereomers with the major syn isomer apparently formed via the cis-eq transition state (Scheme 46; also see Scheme 42).[25] The results show a high preference for the operation of the "cis effect",[139] namely preference for the alkyl group trans to the alkenyl hydrogen (see T_{21}).

The introduction of an alkoxy group into the ene component also leads to a high level of diastereocontrol (Scheme 47).[126] Significantly, the reaction with a (homo)allylic ether also provides the trans,anti ester as a single isomer, *irrespective of the ene geometry*. Taking advantage of this highly regio- and stereoselective glyoxylate–ene reaction, the authors carried out a formal synthesis of avenaciolide.[140,141] Thus, the double carbonyl–ene reactions, namely the formaldehyde–ene/glyoxylate–ene sequence starting from 1-undecene followed by highly chemoselective oxidation under Jones' conditions furnished directly the key intermediate, *trans,cis*-lactone,[141b] as a single isomer (Scheme 48).

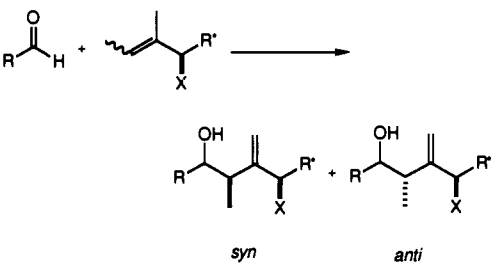
Scheme 48



Scheme 49



Scheme 50



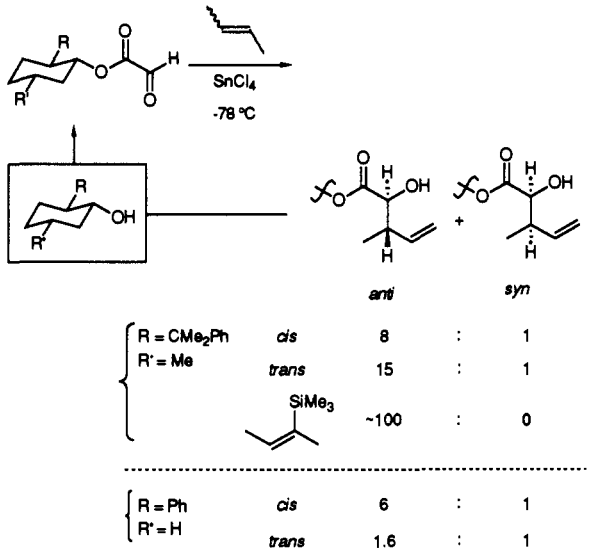
With trans-1,2-di- and trisubstituted alkenes, the ene reaction of α-haloacrylates controls the 1,3-internal asymmetric induction (see Scheme 34). Transfer of a hydrogen occurs predominantly (90–100%) from the alkyl group cis to the alkenyl hydrogen because of the steric interaction. This interaction retards the ene reaction with cis-1,2-di- and tetrasubstituted alkenes.

E. Relative Asymmetric Induction

Two types of diastereofacial selection are involved in the induction of stereogenic centers relative to preexisting ones (relative asymmetric induction). One is the Cram/anti-Cram problem in the reactions of chiral aldehydes (Scheme 49). However, the chelation vs nonchelation problem, which arises in the reaction of chiral alkoxy, amino, or halo aldehyde has remained totally unexplored for a long time. The other is the relative asymmetric induction in the reaction of achiral aldehyde with a chiral ene component (Scheme 50).

A moderate level of Cram (syn) selectivity has been reported for the Me_2AlCl-promoted ene reaction with 2-phenylpropanal.[30] The ene reactions, when applied

Scheme 51

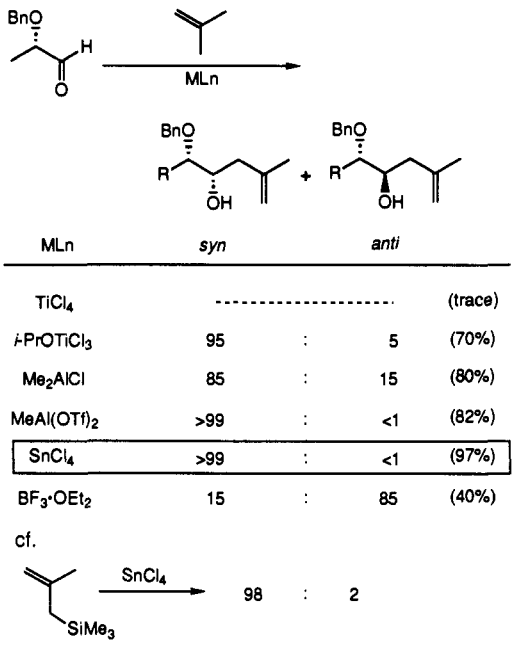


to chiral carbonyl compounds having a chiral auxiliary should constitute a "conservative" asymmetric synthesis with a certain level of diastereofacial selection. The chiral auxiliary can be recovered nondestructively. Ene reactions of (−)-menthyl glyoxylate with 1-pentene have been reported to show a modest level (5–30% de) of asymmetric induction.[142] Interestingly, the absolute configuration of the newly created chiral center in the ene products was *S* with $SnCl_4$ and $TiCl_4$ and, by contrast, *R* with $AlCl_3$ (see A and B in Scheme 42). Recently, Whitesell has reported that excellent levels of relative asymmetric induction are attained with 8-phenylmenthyl and *trans*-2-phenylcyclohexyl glyoxylates (Scheme 51).[131,143] Reaction with *trans*-2-butene proceeds with a high level of internal asymmetric induction to give a 93:7 mixture of diastereomers at C-3 in 85% yield. The authors have recently found that the introduction of trimethylsilyl group into *trans*-2-butene increases the anti diastereoselectivity up to ~100%.[144]

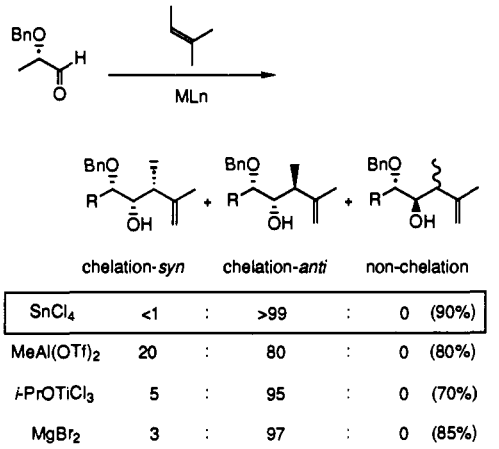
The authors have exploited the reaction of hydroxy or amino aldehyde–ene reactions to provide a new efficient method for asymmetric synthesis of diols[31] and amino alcohols[32] which occur in biologically active natural products. The reactions of chiral α-benzyloxy aldehyde with isobutylene are shown to give syn diastereofacial selectivity in the presence of various Lewis acids except for $TiCl_4$ and BF_3·OEt_2 (Scheme 52). Significantly, the syn product was obtained quantitatively with ~100% of selectivity in the $SnCl_4$-promoted reactions. The observed diastereofacial selectivity is slightly higher than that of a similar reaction with methallylsilane.[145] The $SnCl_4$-promoted ene reaction apparently proceeds under the chelation control.[146]

In view of the anti diastereoselectivity observed with the $SnCl_4$-promoted glyoxylate–ene reaction, the alkoxy-aldehyde–ene reaction would also exhibit anti diastereoselectivity via bidentate complexation (see B). As expected, $SnCl_4$ provides chelation (syn)–anti selectivity (>99%) (Scheme 53). The observed anti diastereoselectivity strongly suggests a synclinal, namely 6-membered, transition state (T_{28}), which is stereocomplementary to the antiperiplanar transition state (T_{29}) for the crotyltin or -silane reaction leading to chelation

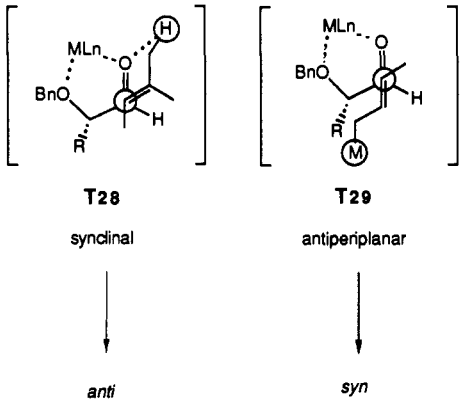
Scheme 52



Scheme 53



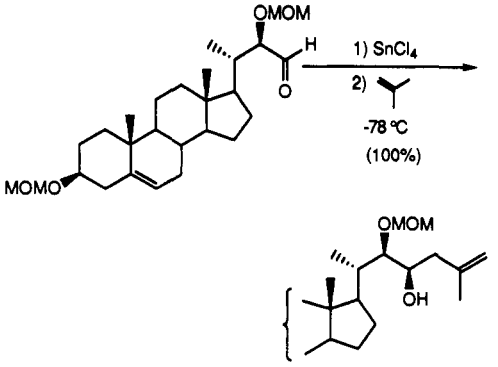
Scheme 54



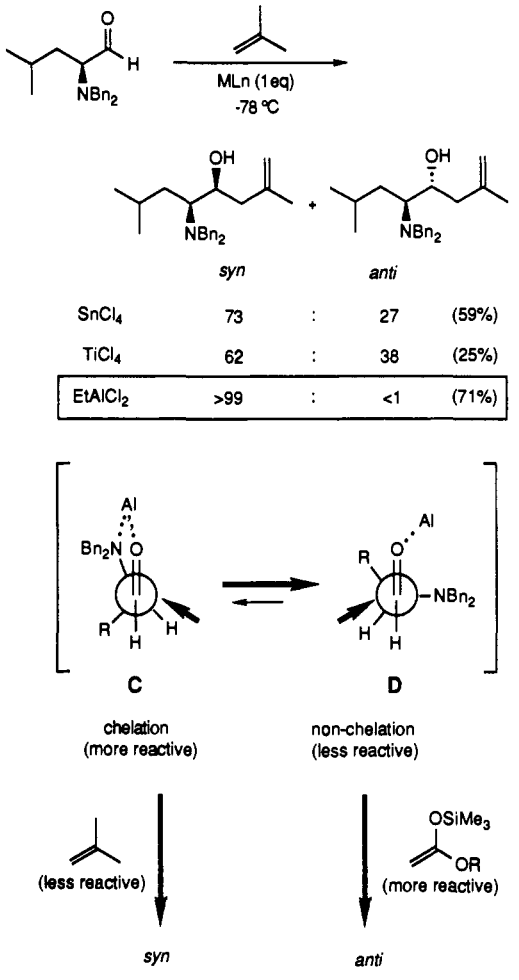
(syn)–syn selection (Scheme 54).[10b,147-148] Thus, the stereocontrol over three contiguous chiral centers could be attained by the combination of chelation (syn) diastereofacial and syn diastereocontrols.[31]

The alkoxy aldehyde–ene reaction can be applied to the side chain synthesis of brassinolides.[136] Thus, the 22(*R*)-(methoxymethyl)oxy aldehyde, which can be obtained via glyoxylate–ene reaction, reacts with isobutylene in the presence of $SnCl_4$ to give a quantitative

Scheme 55



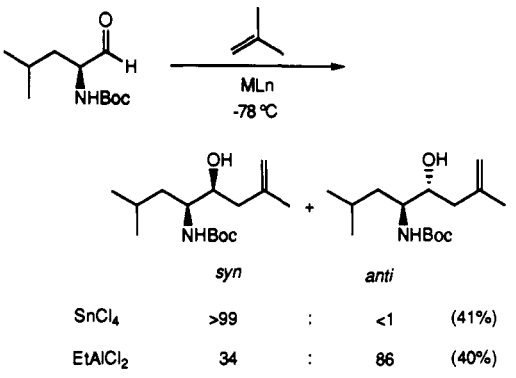
Scheme 56



yield of the syn product as a single isomer (Scheme 55).[31]

Chiral β-amino alcohols such as hydroxyethylene dipeptide isosteres, statine, and its analogues are biologically and pharmacologically important compounds.[149] The ene reaction using an amino aldehyde as an enophile should constitute one of the simplest entries to chiral β-amino alcohol units. The authors recently reported that chiral α-dibenzylamino aldehydes give the ene products (Scheme 56). All the reactions preferentially afforded syn products.[32] Of special value is the $EtAlCl_2$-promoted reaction which provides syn products exclusively. The syn selectivity observed with $EtAlCl_2$ is rather surprising and may be explicable in term of the Curtin–Hammett principle,[150] and the order of the nucleophile reactivity is alkenes (ene) < allylic silanes < enol silanes. $EtAlCl_2$ should be favorable for monodentate complexation. Indeed,

Scheme 57



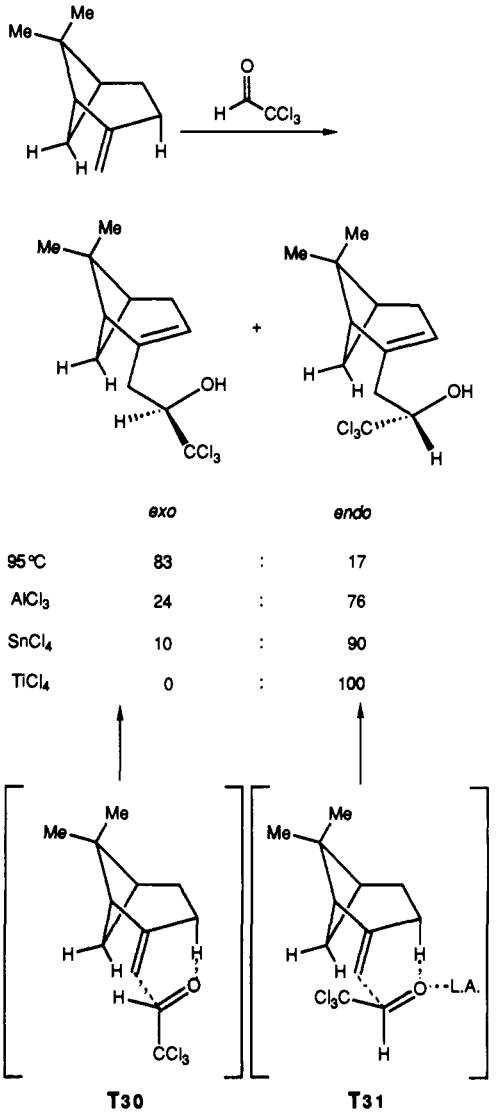
the highly reactive enol silanes could react to give the anti (nonchelation) product with high selectivity. On the contrary, the less reactive alkenes would be incapable of reacting with the less reactive nonchelation complex. Thus, the ene reaction would proceed via the minor but more reactive bidentate complex to give the syn (chelation) product with high selectivity. By contrast, the ene reaction with chiral *N*-Boc-amino aldehyde in the presence of $SnCl_4$ but not $EtAlCl_2$ provides the syn product with high selectivity (Scheme 57). These results clearly show the importance of fine tuning of the amino-protecting group and the Lewis acid employed to constitute the stereoselective ene route to β-amino alcohols.

The other type of diastereofacial selection (see Scheme 50) was first examined with β-pinene. The endo/exo selectivity in the thermal chloral–ene reactions has been examined (Scheme 58). A hydrogen is abstracted selectively from the face opposite to the *gem*-dimethyl bridge. Exo/endo selectivity (83:17) appears to be determined by steric interactions rather than electronic effects. The major product is formed via transition state with the trichloromethyl group exo (T_{30}). By contrast, Lewis acid-catalyzed reactions provide the endo isomer preferentially. Particularly, $TiCl_4$ gives the endo product exclusively. The Lewis acid complexes to the carbonyl group anti to the trichloromethyl group. Reaction occurs selectively from transition state with trichloromethyl group endo and the $TiCl_4$ exo (T_{31}), which minimizes steric intractions of the bulky Lewis acid with β-pinene.

Formaldehyde–ene reactions also occur with high diastereofacial selectivity from the less hindered β-face of *cis*-2-methylethylidenecyclopentane to give a 86:10:4 mixture of products (Scheme 59).[151] Formaldehyde shows a preference for transfer of a hydrogen from the alkyl group cis to the alkenyl hydrogen of the ethylidenecyclopentane. The major product was converted to the Prelog–Djerassi lactonic acid (PDLA).[152] The regioselectivity is due to steric interaction between the formaldehyde–BF_3 complex and the olefinic methyl group in the transition state for proton abstraction from the carbon trans to the alkenyl hydrogen.

These diastereofacial selective ene reactions are applied to the synthesis of steroid side chains with the natural (or unnatural) stereochemistry at C-20 from *cis*-(or *trans*-)-17(20)-pregnenes. $EtAlCl_2$-mediated ene reactions with methyl propiolate and acrylate proceed selectively from the α-face to give a 25-hydroxycholesterol precursor (Scheme 60).[153,154] Lewis acid-accelerated ene reactions of methyl propiolate with

Scheme 58



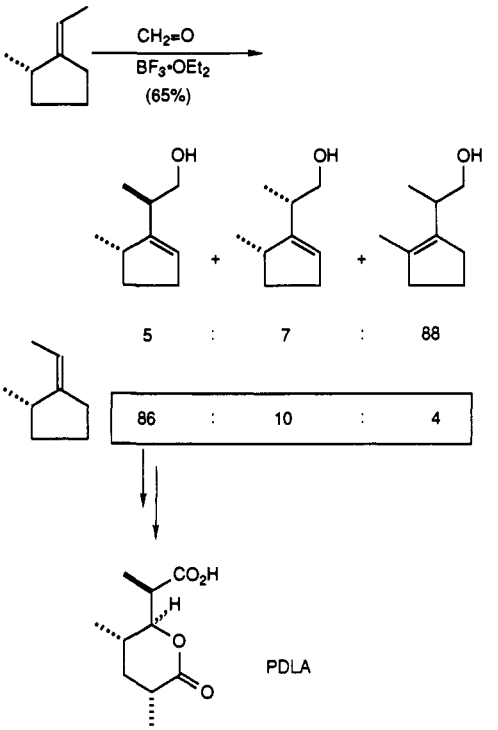
trans-17(20)-pregnenes produces the unnatural stereochemistry at C-20.[155] An additional equivalent of $EtAlCl_2$ must be used to complex basic functional groups on the steroid nucleus.[156] BF_3·OEt_2-promoted formaldehyde–ene reactions with *cis*-17(20)-pregnenes can be used to introduce the natural stereochemistry at C-20.[130,157] $EtAlCl_2$-mediated reaction with α-haloacrylates are applied to the synthesis of functionalized side chains with internal asymmetric induction over C-20 and -23 (6:1).[157,158] 24-Oxocholesteryl acetate has been synthesized from *cis*-5,17(20)-pregnadienyl 3β-acetate by reaction with isopropyl vinyl ketone and 2 equiv of Me_2AlCl at 25 °C to give the olefin–ene product in 46% yield.[38]

The authors have recently exploited a unified strategy based on the alkoxy aldehyde–ene reaction for the concurrent stereocontrol over not only C-20 but -22 (Scheme 61). Either (22*S*)- or (22*R*)-23-dihydroxy steroid side chain with natural C-20 stereochemistry can be synthesized with a high degree of anti and syn diastereoselectivity, by the judicious choice of the protecting groups of the α-hydroxy acetaldehyde.[159,160]

F. Remote Asymmetric Induction

Although several methods have been devised for stereocontrol over adjacent stereogenic centers with high relative asymmetric induction, approaches to control remote asymmeric relationships by efficient 1,>3-asymmetric induction are rare.

Scheme 59



With the successful regio- and stereocontrol in the ene reaction with (homo)allylic ethers (see Schemes 31, 32, 36, and 47), the authors have examined the bishomoallylic ether systems. Surprising however, the opposite regioisomer was obtained exclusively with high trans,anti selectivity (Scheme 62). Dramatic changeover of the regioselectivity can be rationalized in terms of an O-5 interaction in the glyoxylate–ene reaction which now proceeds via the tricyclic transition state (T_{32}).

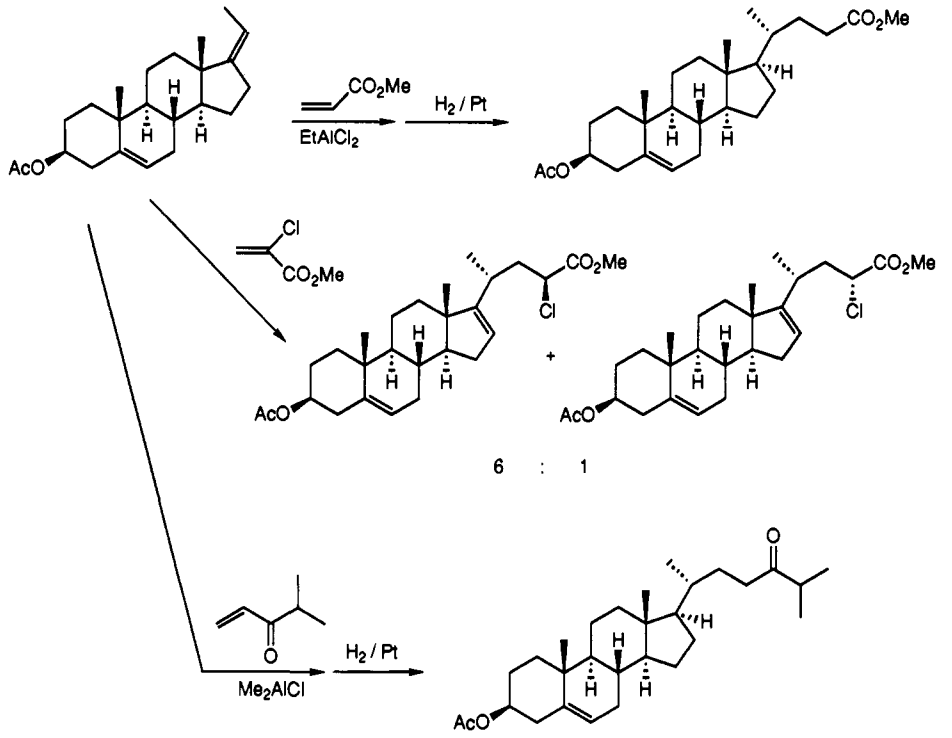
Thus, 1,4-remote stereocontrol is predictable (Scheme 63). In the reaction of chiral bishomoallylic ether, the axial conformer (T_{34}) would be less favorable because of the 1,3-diaxial repulsion. Thus, the 1,4-anti isomer would be formed via the equatorial conformer (T_{33}). As expected, the reaction of the chiral ether provides the 1,4-anti diastereomer with 94% stereoselectivity.[161] The 1,4-relative stereochemistry is confirmed after transformation to the known diol which has been obtained via cyclic hydroboration.[162] The 1,6-diol thus obtained can be transformed to 13,16-*anti*-dimethyloctacosane-1,28-diol, isolated from Messel shale kerogen.[163]

Furthermore, without the terminal methyl group, the 1,5-remote stereochemistry of methyl and hydroxy groups can be controlled in a syn fashion with 94% selectivity (Scheme 64). Thus, the authors have developed an efficient method for 1,4- and 1,5-remote stereocontrol, which is otherwise difficult to establish.[164]

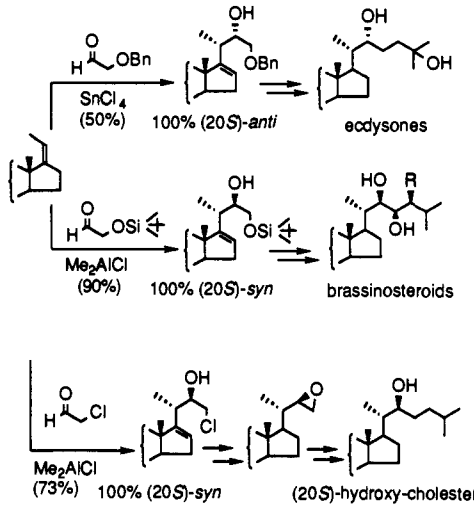
G. Asymmetric Transfer

The chirality transfer (Scheme 65) from a chiral ene to a prochiral enophile has thus far been investigated mainly from the mechanistic viewpoint. This type of asymmetric ene reaction destroys the original chiral center in the ene component, while simultaneously creating a new one and hence is referred to as a "self-immolative" asymmetric synthesis.[165]

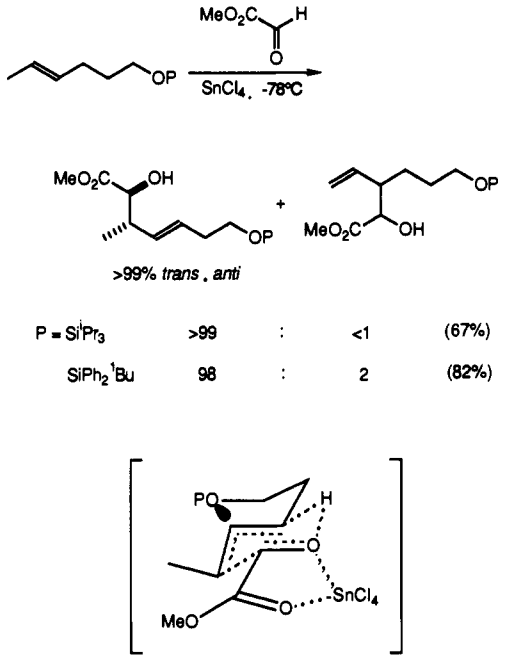
Scheme 60



Scheme 61



Scheme 62

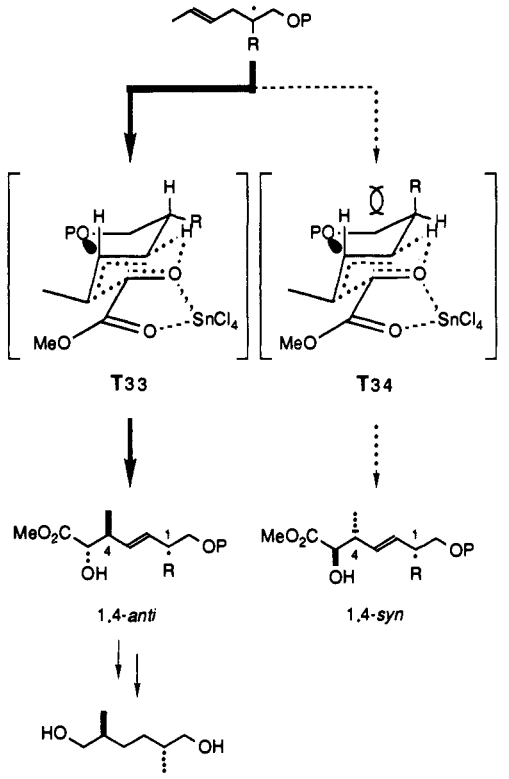


The ene reaction is a pericyclic process proceeding through a 6-membered transition state, unless prohibited by steric or some other factors. This is supported by the observation of "cis addition" and by the fact that optically active products are formed in reactions. The reaction of maleic anhydride with an optically active alkene has already been shown to give an optically active product. However, it is unknown to what extent chirality is precisely transferred through the reaction.[166] Asymmetric transfer in the ene reaction of dimethyl azodicarboxylate has been examined quantitatively (Scheme 66).[167] The abstraction from the chiral benzylic center occurs with an isotope effect (k_H/k_D = 3.3 ± 0.7). Since this ratio well matches the ratio of enantiomers (S/R = 3.1 ± 0.3) in the formation of the new C—N bond, the reaction has been reported to proceed via concerted mechanism with 94% transfer of chirality [$(S/R)/(k_H/k_D)$].

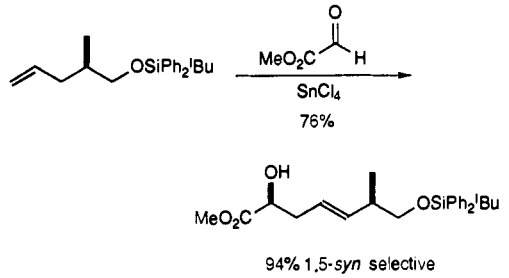
A photo ene reaction has been reported for 2,6-dimethyl-7-octen-3-one, which on irradiation with ultraviolet light forms terpinen-4-ol in 2.5% yield with complete transfer of chirality. The result is suggestive of a concerted transformation of the excited ketone into the product.[168] Microscopic reversibility requires that the reverse reaction is also completely stereospecific. Indeed, the reverse reaction proceeds thermally with complete induction of chirality.[169]

Quite recently, Kuwajima et al. have exploited a high level of asymmetric transfer in the ene reaction of an aldehyde with (*S*)-2-(ethylthio)-3-siloxy-1-butene derived from lactate (Scheme 67).[170] They found a remarkably high level of chirality transfer (99%) by the proper choice of enophile and employed the product for anthracycline synthesis.[171]

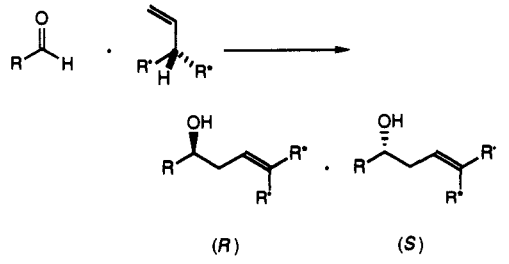
Scheme 63



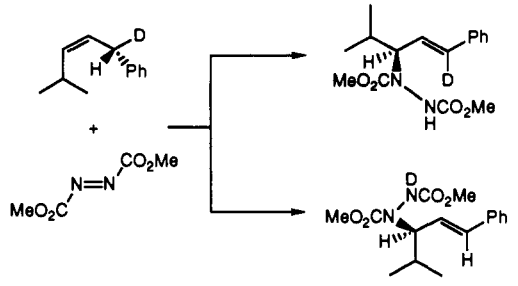
Scheme 64



Scheme 65



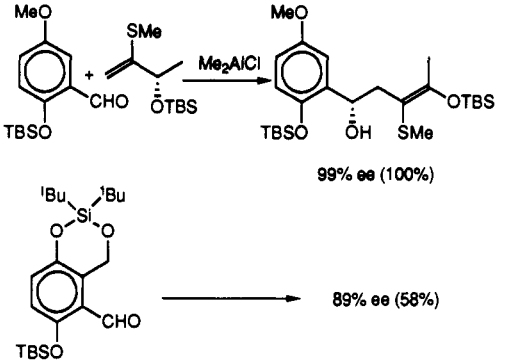
Scheme 66



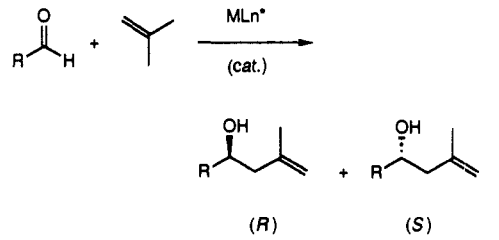
H. Asymmetric Catalysis

Catalyst-based enantiofacial control, in the reactions of achiral ene and enophile components, maximizes the synthetic efficiency for asymmetric synthesis but is difficult to realize, because Lewis acid seems to be relatively far from the site of the formation of the new chiral center (Scheme 68).[172] Here, the selection of the central metals and the design of the chiral ligands are particularly important.

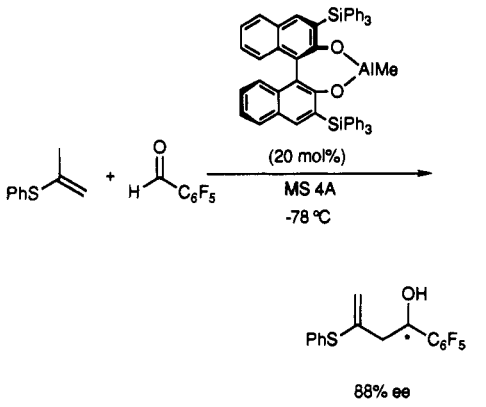
Scheme 67



Scheme 68



Scheme 69

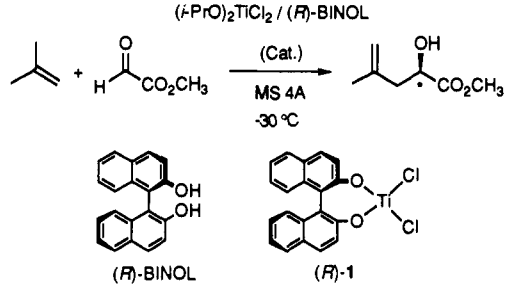


Yamamoto et al. have recently reported an example of a catalytic ene reaction with halogenated aldehydes by using the modified binaphthol-derived aluminum reagent (Scheme 69).[173] However, the asymmetric catalysis for carbonyl–ene reaction particularly with prochiral glyoxylate remained unexplored, despite its potential for the asymmetric synthesis for α-hydroxy esters of biological and synthetic importance.[174]

The authors have recently developed the extremely efficient asymmetric catalysis of the glyoxylate–ene reaction (Scheme 70).[175] The key to the success is the use of early transition metal titanium complex of type (*R*)-1, prepared in situ from diisopropoxytitanium dihalide and optically pure binaphthol (BINOL) in the presence of molecular sieves (MS 4A).

The present asymmetric catalysis is applicable to a variety of 1,1-disubstituted alkenes to provide the ene products in extremely high enantiomeric purities by the judicious choice of the dichloro or dibromo chiral catalyst (Table 2). The remarkable selectivity for the trans isomer with these chiral titanium catalysts (entry

Scheme 70



(*R*)-BINOL / (i-PrO)$_2$TiCl$_2$	(10 mol%)	95% ee (*R*)	(72%)
(*R*)-BINOL / (i-PrO)$_2$TiCl$_2$	(1 mol%)	93% ee (*R*)	(78%)
(*S*)-BINOL / (i-PrO)$_2$TiCl$_2$	(10 mol%)	95% ee (*S*)	(68%)

C) contrasts sharply with the lower level of selectivity (64–67%) obtained with achiral titanium catalysts such as titanium tetrachloride or diisopropoxytitanium dichloride.

The authors have furthermore found that the glyoxylate–ene reaction with vinyl sulfides exhibits an extremely high degree of enantiofacial selection (>99% ee!) along with high anti diastereoselectivity (Scheme 71).[176]

I. Asymmetric Desymmetrization

Desymmetrization of an achiral bifunctional molecule at symmetrically, and therefore, functionally equivalent sites is a potentially powerful but relatively unexplored basic concept for asymmetric synthesis (Scheme 72).[177] When a plane of symmetry is present in a molecule the two halves are enantiotopic and can therefore be differentiated only by reagents or catalysts capable of chiral recognition. While the ability of enzymes to differentiate between enantiotopic functional groups is well known, the utility of nonenzymatic catalysts is less recognized for C—C bond formations, in particular. From the standpoint of desymmetrization, the kinetic optical resolution[178] of a racemic mixture of chiral ene substrate can be recognized as an intermolecular desymmetrization. Furthermore, an efficient kinetic resolution can be understood in terms of a remarkable rate difference in the double asymmetric induction[179] between "matched" and "mismatched" reactions.

In the desymmetrization by enantiofacial selective C—C bond formations, at least two new chiral centers are generated. Thus, the enantiofacial selective carbonyl–ene reaction of prochiral ene substrates with planar symmetry could provide an efficient access to remote internal asymmetric induction which is otherwise difficult to attain.

1. Asymmetric Desymmetrization

The authors have found that the desymmetrization is efficiently carried out in the ene reaction of prochiral bis-allylic silyl ethers catalyzed by the chiral titanium complex (*R*)-1 (Scheme 73).[180] The (2*R*,5*S*)-syn product is obtained in >99% ee with more than 99% diastereoselectivity. The importance of desymmetrization is exemplified by the synthesis of isocarbacycline intermediate (Scheme 74). Reaction with the bicyclic ene substrate proceeds with high diastereo- (96%) and enantioselectivities (99% ee). Thus, these examples represent the rarely precedented asymmetric synthesis based on asymmetric catalytic desymmetrization in C—C bond formation.

Similarly, *diastereofacial* selective glyoxylate–ene reaction using a chiral glyoxylate and a stoichiometric amount of stannic chloride has been reported to convert a symmetrical bicyclic ene component to diastereomeric products (Scheme 75).[181] The (+)-hydroxy ester has been converted to (−)-specionin.[182]

2. Kinetic Optical Resolution and Double Asymmetric Induction

Diastereofacial selective glyoxylate–ene reaction of a chiral glyoxylate has also been reported to discriminate between the enantiomeric pairs of a bicyclic racemate in the kinetic resolution (Scheme 76).[183] The (+)-hydroxy ester has been obtained in a ratio of 8:1. The major diastereomer has been converted to (−)-xylomollin.

Kinetic resolution in the asymmetric catalytic glyoxylate–ene reaction with a racemic allylic ether (Scheme 77) can also provide an efficient procedure for remote asymmetric induction.[180] Catalyst (*R*)-1 provides the (2*R*,5*S*)-syn product with 99% diastereoselectivity with 99.6% enantiomeric excess. The high diastereoselectivity, coupled with the high % ee, strongly suggests that the chiral catalyst efficiently discriminates between the two enantiomeric reactants to accomplish an effective kinetic resolution. In fact, the relative rate between the enantiomeric ethers reaches up to 700. The authors show indeed that the reaction of (*R*)-2 using the catalyst (*S*)-1 ("matched" catalytic system) provides the complete (>99%) 1,4-syn diastereoselectivity in high chemical yield (71%), whereas the reaction of (*R*)-2 using (*R*)-1 ("mismatched" catalytic system) affords the diastereomeric mixture in quite low yield (33%) (Scheme 78). It should be noted here that the alkoxy-group acts as a controlling element not only for regiocontrol but also for diastereofacial control.[126]

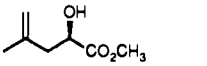
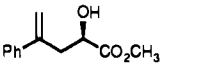
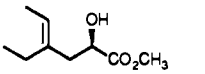
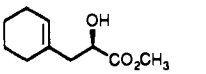
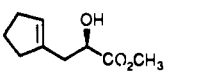
A similar reaction with racemic homoallylic ethers using (*R*)-1 provides a lower level of diastereoselection (syn/anti = 2:1), however, with remarkably high enantiomeric excess (>95% ee) for both diastereomers (Scheme 79).[184] That means that the enantiocontrol over the prochiral glyoxylate would be achieved essentially independent of the reactant chirality in these reactions. Indeed, the reaction of (*R*)-3 using (*R*)-1 or (*S*)-1 provides the syn and anti diastereomers, respectively, in virtually complete diastereoselectivity (>95%) (Scheme 80). Now, one can synthesize the four possible diastereomers in a highly scalemic[185] form at will by the proper combination of the chiral catalyst and the ene substrate.

J. Asymmetric Amplification: Positive Nonlinear Effect

Chiral recognition by a chiral titanium catalyst between enantiomeric ene components results in the efficient asymmetric desymmetrization. By contrast, chiral self-recognition, namely diastereomeric self-assembly of asymmetric catalyst, leads to chiral amplification or chiral evolution.[186] Such a nonclassical phenomena has been observed in the asymmetric catalysis of our carbonyl–ene reactions.

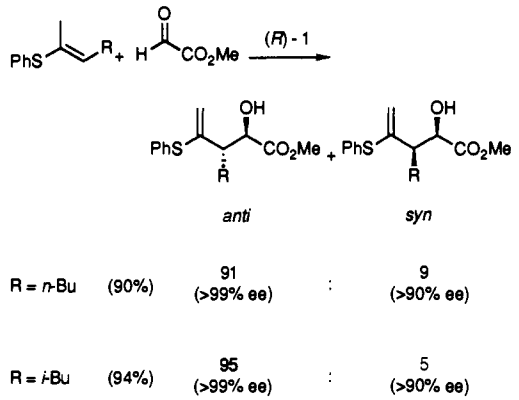
In 1986 Kagan reported the so-called nonlinear effect in the Sharpless epoxidation of geraniol by the stoi-

Table 2. Asymmetric Catalytic Glyoxylate-ene Reactions with 1,1-Disubstituted Olefins

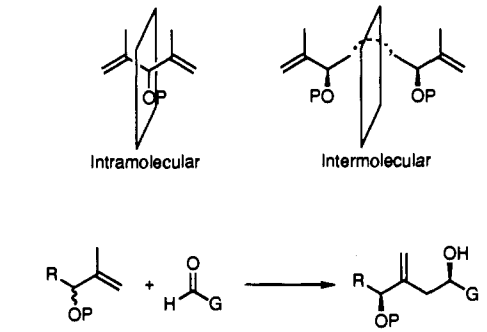
entry	olefin	$(i\text{-PrO})_2TiX_2$ (X)	catalyst, mol %	time, h	product	% yield	% (ee)
A		Cl	10	8		72	95 (*R*)
						68	95 (*S*)[a]
		Br	10	3		87	94 (*R*)
B		Cl	1.0	8		97	97 (*R*)
		Br	1.0	3		98	94 (*R*)
C		Cl	10	8		68[b]	94[c] (*R*)
		Br	5	3		73[d]	98[c] (*R*)
D		Cl	10	8		82	97 (*R*)
		Br	5	3		89	98 (*R*)
E		Cl	10	8		93	88 (*R*)
		Br	5	3		92	89 (*R*)

[a] (*S*)-BINOL was used instead of the (*R*) counterpart. [b] The combined yield of the (*E*) and (*Z*) isomer (*E*/*Z* = 89:11). [c] Refers to the optical purity of the major (*E*) product. [d] The combined yield of the (*E*) and (*Z*) isomer (*E*/*Z* = 91:9).

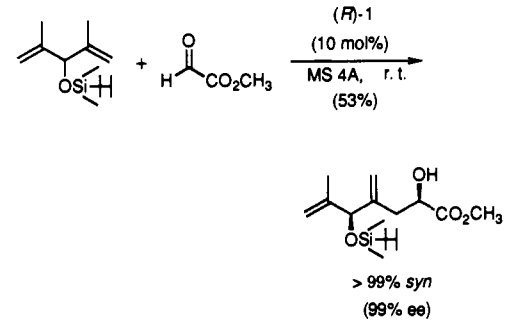
Scheme 71



Scheme 72



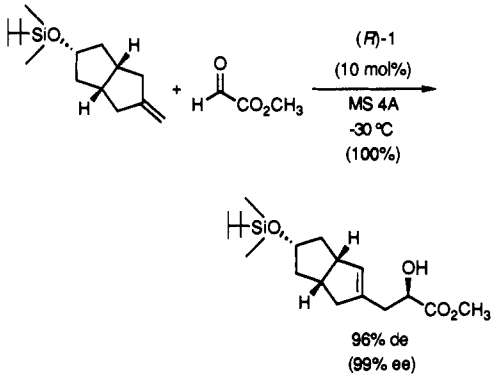
Scheme 73



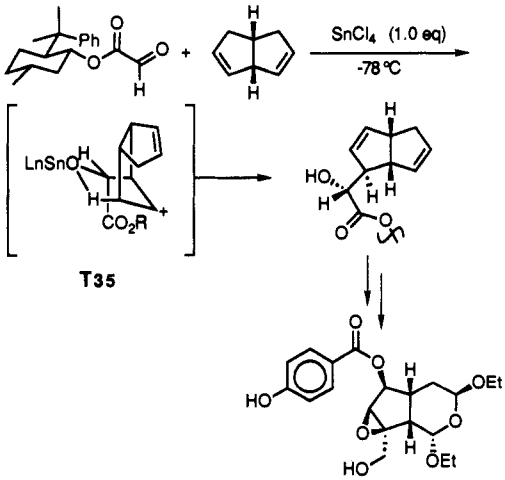
chiometric use of tartrate-derived chiral titanium complex.[187] Since then considerable attention has been focused on the, let us say, "positive" nonlinear effect ((+)-NLE) in the asymmetric catalysis of C—C bond formations in particular, from a practical and/or mechanistic point of view.[188,189] The authors have found the remarkable (+)-NLE in an enatioselective glyoxylate–ene reaction, wherein the optical yield of the ene product (Y% ee) significantly exceeds the enantiomeric purity (X% ee) of chiral BINOL ligand (Figure 3).[190] For instance, the glyoxylate–ene reaction catalyzed by chiral titanium complex derived from a slightly scalemic[185] BINOL of 33.0% ee provides the ene product with 91.4% ee which is close to 94.6% ee obtained with enantiomerically pure BINOL.

In view of the dinuclear chelate structure determined by X-ray crystal analysis for diphenoxytitanium dichloride,[191] it appears likely that the remarkable NLE is a result of a marked difference in the catalytic activity between the diastereomeric dimers, namely homochiral C_2 symmetric (*R*)(*R*)-1_2 (E) with distorted Ti_2O_2 4-membered ring and heterochiral, namely meso (C_i

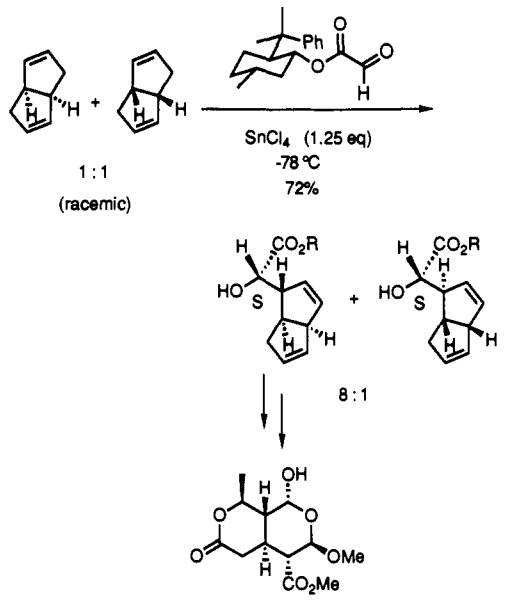
Scheme 74



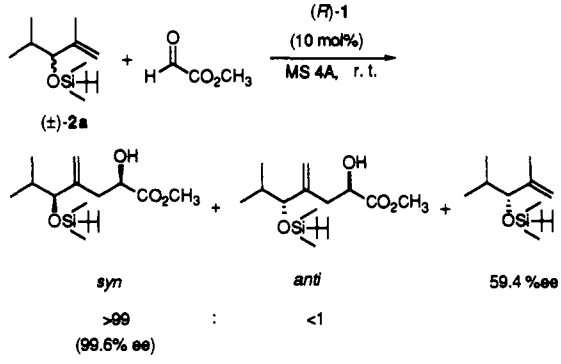
Scheme 75



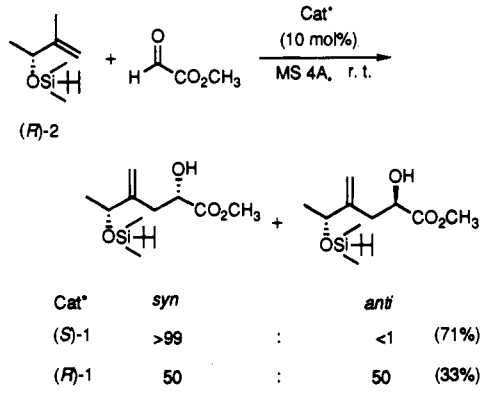
Scheme 76



Scheme 77



Scheme 78



symmetric) dimer $(S)(R)$-1_2 (F) possessing coplanar Ti_2O_2 4-membered ring (Figure 4).[192]

The dimeric nature of the titanium complex was proven by the molecular weight (MW) measurement in dichloromethane. The MW of $(R)(R)$ dimer prepared from optically pure BINOL is, however, concentration-dependent ranging from 864 in 37 mM solution to 762 in dilute (9.2 mM) solution, indicating its lability to dissociate to the monomer. In sharp contrast, the MW of the heterochiral dimer $(R)(S)$ is not concentration dependent, 872 in 37 mM and 874 in 9.2 mM, clearly indicating the stability of the heterochiral dimer. Thus, the origin of our (+)-NLE is due to the stability of the readily formed heterochiral dimer and to the lability of the homochiral dimer to dissociate to the monomer-

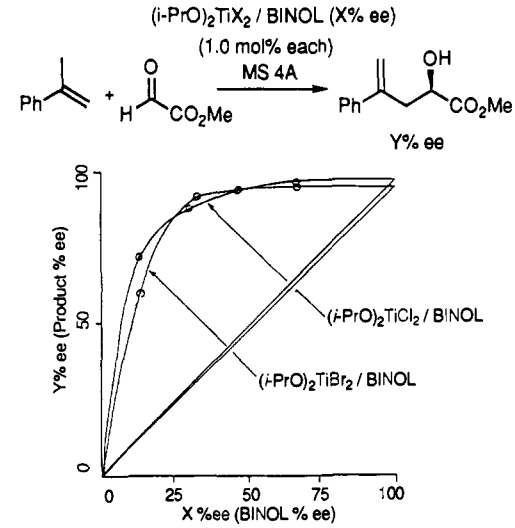
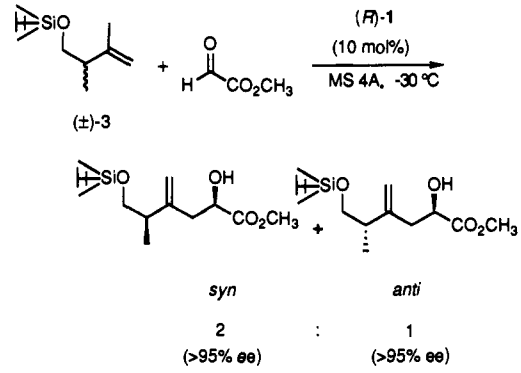
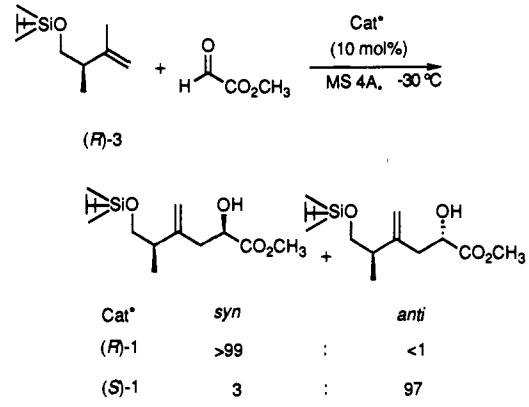


Figure 3. Positive NLE in asymmetric catalytic glyoxylate-ene reaction.

Scheme 79



Scheme 80



ic complex of chiral titanium eventually with glyoxylate which is responsible for the ene reaction to give an equally high optical yield to that obtained with optically pure BINOL.

V. Ene Cyclizations

Intramolecular ene reactions (ene cyclizations) are much more facile than their intermolecular counterparts.[193] Therefore, even simple olefins and acetylenes can be used as enophiles in thermal ene cyclizations. Conceptually, ene cyclizations can be classified into six different modes of cyclizations (Scheme 81)[35] by modifying Ziegler's notation originally proposed for the cyclic Claisen sigmatropic shifts.[194] In the ene cyclizations, the carbons, to which the tether connecting the

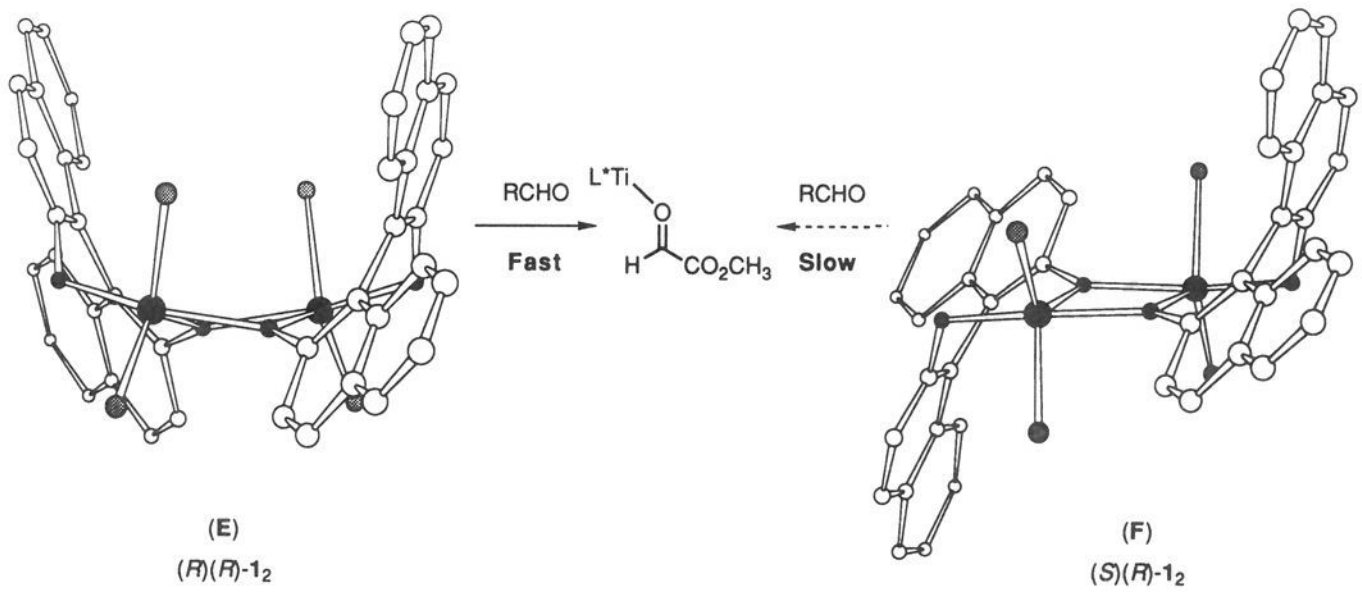
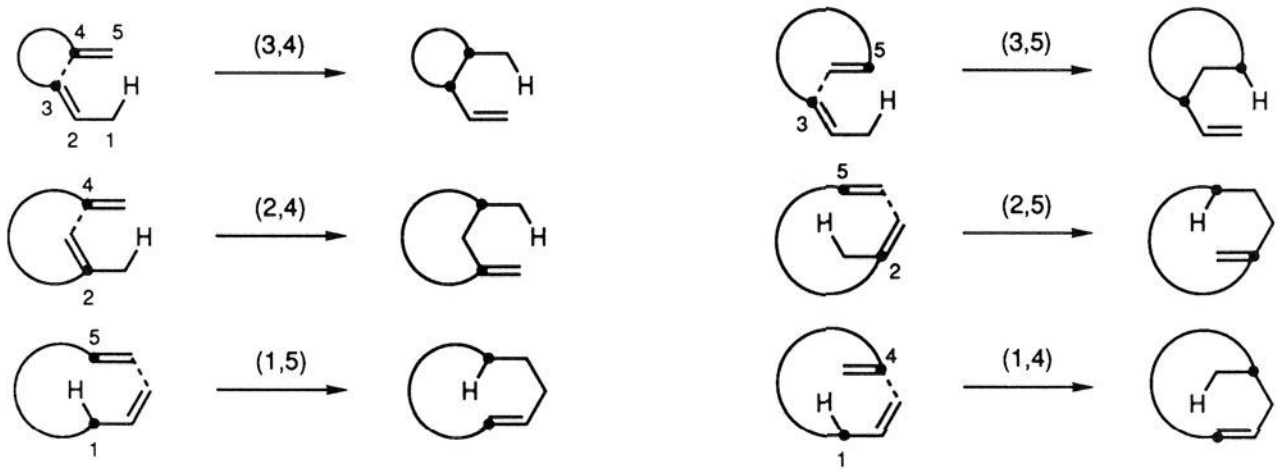


Figure 4. 3D representation of BINOL–Ti complex.

Scheme 81



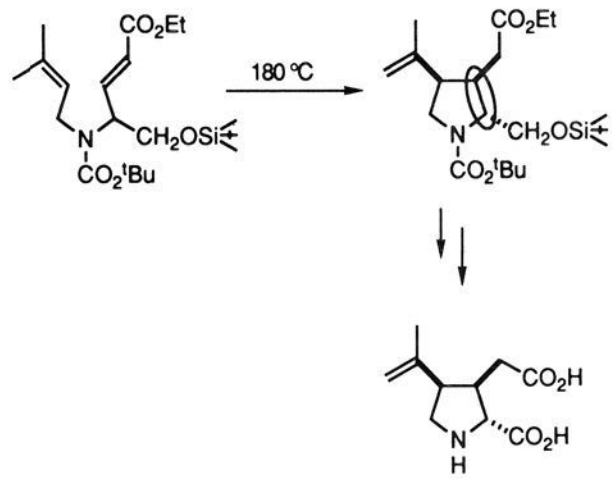
[1,5]-hydrogen shift system is attached, are exemplified in (m,n) fashion.[195] The ring size may be designated by a numerical prefix l-. (3,4) ene cyclizations are restricted to the formation of 5-, 6- ≫ 7-membered rings. Five-membered ring formation is a facile process for olefinic enophiles. A similar 6-(3,4) ene cyclization is less facile. The order is reversed for carbonyl enophiles. The formation of larger rings by (3,4) ene cyclizations is rare. (2,4) ene cyclizations are restricted to the formation of 7- and 6-membered rings.[196] (1,5) ene cyclizations provide only medium-sized rings.[197–200] Oppolzer referred to these three modes of ene cyclizations as types I–III.[193b] However, type (3,5) has occasionally been found. Introduction of an electron-withdrawing group on the interior adjacent carbon to the enophile favors the 6-(3,5) ene cyclizations rather than the type 5-(3,4).[201–203] Quite recently, a (1,4) ene cyclization has been found in the $EtAlCl_2$-induced cyclization of reactive trifluoromethyl ketones to give cyclohexenol and cycloheptenol in good yields.[204,205] Such an ene cyclization has recently been recognized as an efficient method for stereocontrolled cyclization with C–C bond formation ("carbocyclization").

A. Diastereofacial Selection

Asymmetric ene cyclizations reported thus far have been mainly based on the diastereofacial selections (see "Relative Asymmetric Induction") employing chiral internal enophiles.[206] The most impressive example is the asymmetric synthesis of α-kainic acid via 5-(3,4) ene cyclization where a high trans diastereofacial selectivity (83%) is attained (Scheme 82).[206e]

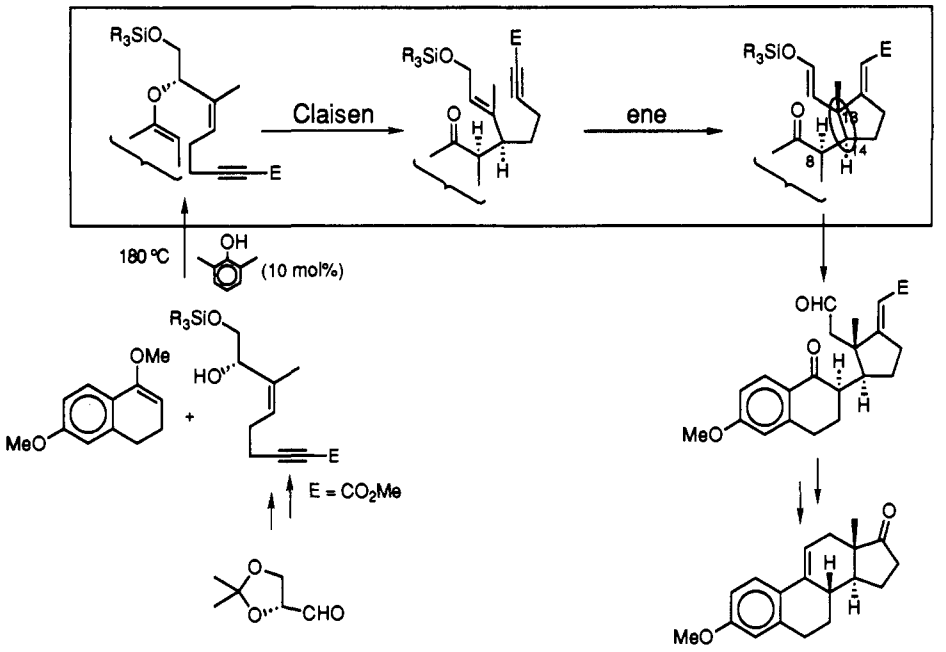
In a series of studies on the use of chiral ene components, the authors have reported an asymmetric tandem Claisen–ene[207] strategy for steroid total synthesis (Scheme 83).[208] Thus, (+)-9(11)-dehydroestrone methyl ether, a key intermediate for estrogens[209] can be obtained in enantiopure from (R)-glyceraldehyde acetonide via 11 steps in 17% overall yield. The S-cis chirality of allylic alcohol is completely transmitted to the 14S chirality via the cyclic enol ether Claisen rearrangement[210] for asymmetric introduction of the acyclic side chain onto the α-position of cyclic ketones. The subsequent (3,4) ene cyclization proceeds to establish the 13,14-trans diastereofacial selection in the steroidal D ring by virtue of the 14S chirality in the ene component, along with the formation of the silyl enol ether.

Scheme 82

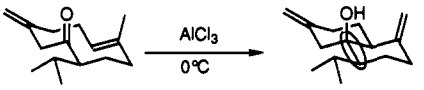


6-(2,4) ene cyclization of preisocalamendiol affords a trans-bicyclic system with high cis diastereofacial selectivity (Scheme 84)[211] via a transannular ene cyclization.[212–216] Snider et al. have also reported that Me_2AlCl-promoted 6-(2,4) ene cyclization affords a high level of cis-diastereofacial stereocontrol (Scheme 85).[217] However, Yamamoto et al. have recently reported that

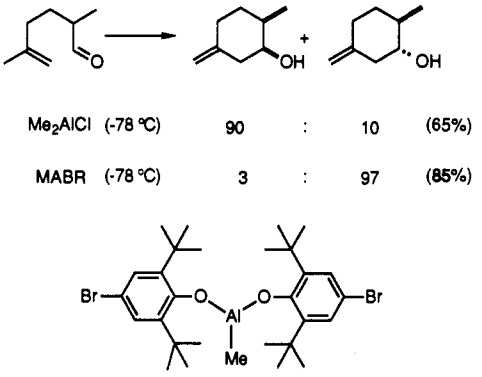
Scheme 83



Scheme 84



Scheme 85



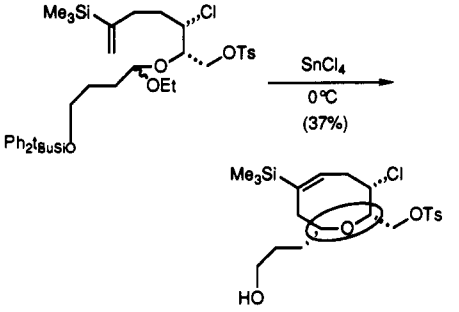
the use of a bulky aluminum reagent MABR can alter the diastereofacial selectivity (Scheme 85).[218]

An acetal, hemiacetal, or enol ether can be converted to an oxonium ion which cyclizes in different modes, depending on the substitution pattern of the ene component. In the synthesis of laurenyne, Overman et al. have shown that 8- and 9-membered cyclic ethers can be prepared via (1,5) ene cyclizations of oxonium ion with high diastereofacial selectivity (Scheme 86).[219] $SnCl_4$-promoted cyclization of acetal using vinylsilanes as a selective ene component provides oxocene in 37% yield as the sole cyclic ether.[220,221]

B. Intraannular Diastereoselection

(3,4) ene cyclizations exhibit high level of diastereoselection over two new ring stereogenic centers, which we will refer to as intraannular diastereoselection. In general, steric, rather than electronic effects, determine the cis/trans diastereoselection (see "Internal Asymmetric Induction") of newly formed 1,2-disubstituted

Scheme 86



cycloalkanes. Cis diastereomers are obtained predominantly or exclusively in 5-membered ring formation particularly in thermal processes as shown in the recent example (Scheme 87),[222,223] while 6-membered ring formation results in mainly trans diastereomers.

However, Tietze et al. have reported that $ZnBr_2$-mediated 5-(3,4) ene cyclizations of malonates at 25 °C exhibit high selectivity but for trans diastereomer (Scheme 88).[206d,224,225] The effects of electron-withdrawing groups and geminal substituents in a similar system have been examined on the intraannular diastereoselectivities and rates of the thermal ene reactions.[226]

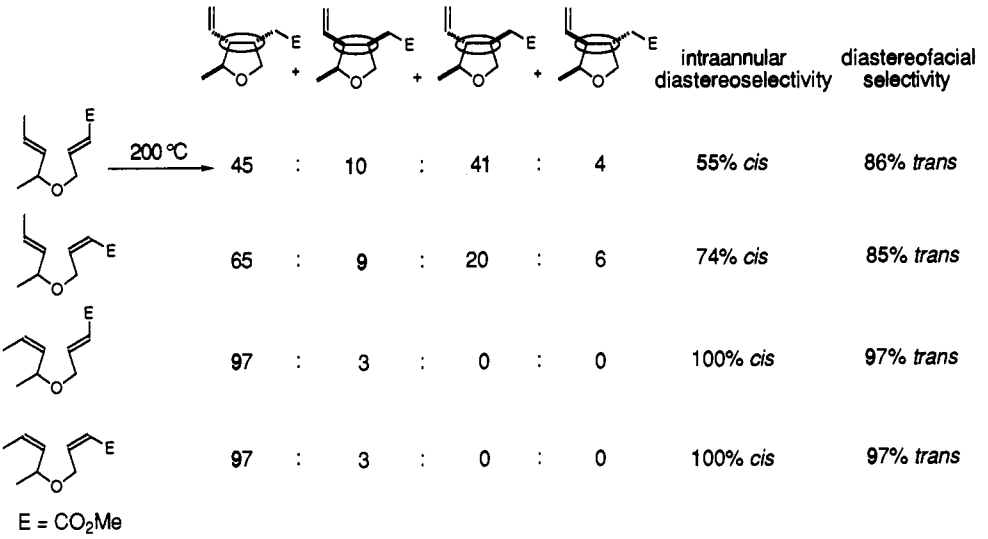
Snider et al. have exploited 6-(3,4) ene cyclizations of enals (Scheme 89).[227] The *trans*-aldehyde gives mainly the *trans*-cyclohexanol.[228] By contrast, the *cis*-aldehyde affords exclusively the cis diastereomer.

Quite recently, 6-(2,4) ene cyclizations of a stereochemically defined ene component have been reported to show a high level of intraannular diastereoselectivity (Scheme 90).[218] The "*cis*"-ene gives the *trans*-methylenecyclohexanol, while the "*trans*"-ene affords the cis diastereomer.

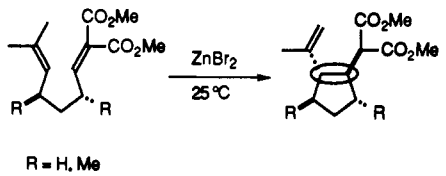
C. Extraannular Diastereoselection

"Cis addition" of an ene component onto the geometrically defined double bond of enophile results in diastereocontrol over two stereogenic centers at the side chain, which we will refer to as extraannular diaste-

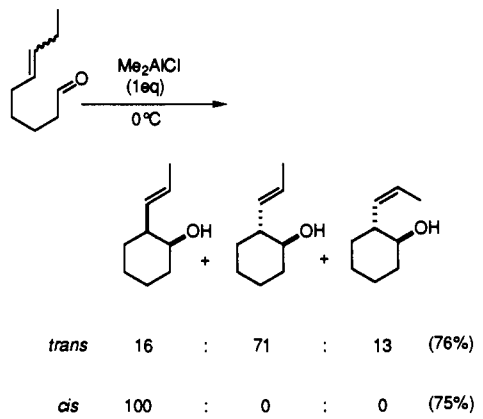
Scheme 87



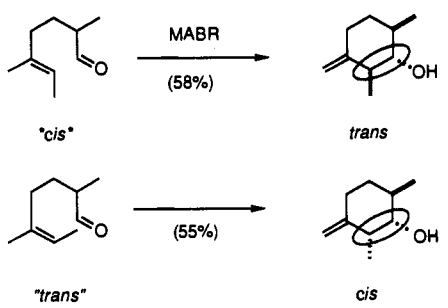
Scheme 88



Scheme 89

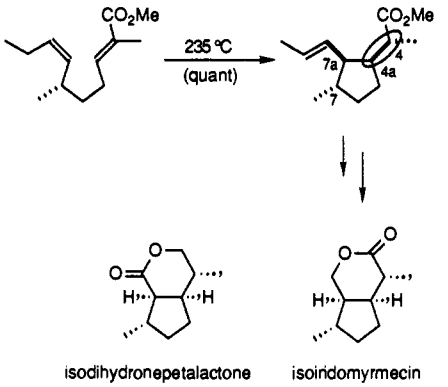


Scheme 90

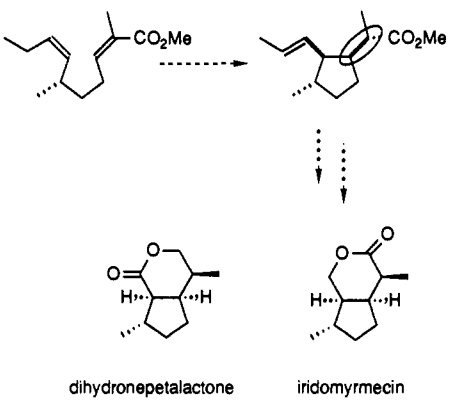


reoselection (Scheme 91).[229] The ene reaction of *trans,cis*-dienoate at 235 °C in heptane affords the cyclopentane in quantitative yield. The relative stereochemistry over four contiguous chiral centers has been determined by further transformation to iridoids, isodihydronepetalactone, and isoiridomyrmecin. Thus, the ene–carbocyclization provides an efficient method for stereocontrol over four contiguous chiral centers, by the convergent combination of diastereofacial control over C-7 and C-7a, intraannular diastereocontrol over

Scheme 91



Scheme 92

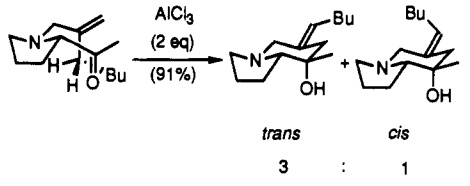


C-7a and C-4a, and extraannular diastereocontrol over C-4a and C-4. Similarly, the ene cyclization of *cis,cis*-dienoate should proceed with opposite sense of extraannular diastereoselection to provide a route to the 4-epimers dihydronepetalactone and iridomyrmecin, respectively (Scheme 92).

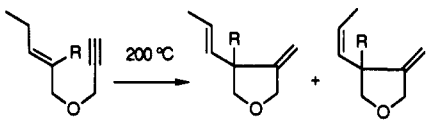
D. Olefinic Diastereoselection

In the context of the synthesis of pumiliotoxin A,[230] Overman et al. have reported that a "trans/cis"-exocyclic trisubstituted double bond is produced in a ratio of 3:1 via the 6-(2,4) ene cyclization of ketone with 2 equiv of $AlCl_3$ (Scheme 93).[231] The effect of the amine is notable. In a similar system but without an amino group, the opposite olefinic diastereomer is formed predominantly.[217,218]

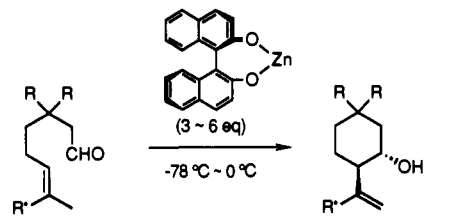
Scheme 93



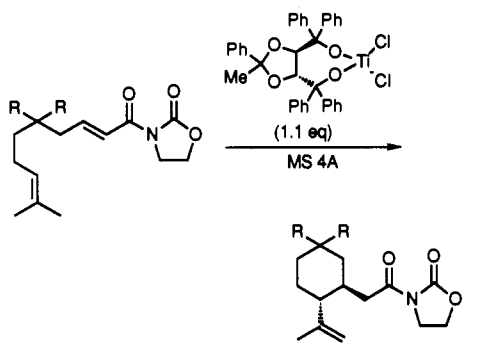
Scheme 94



Scheme 95



Scheme 96



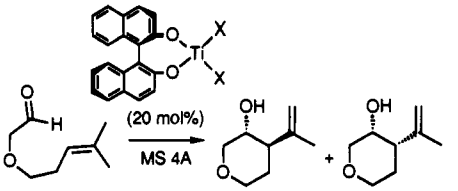
In 5-(3,4) ene cyclizations of allyl propargyl ethers,[232] the authors have reported that an excellent trans olefinic stereoselectivity can be attained by maximizing the allylic 1,3-strain (Scheme 94).[233]

E. Asymmetric Catalysis

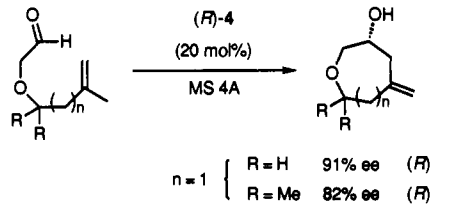
Asymmetric catalysis was initially investigated in the more facile intramolecular reactions. Such a trial of asymmetric (3,4) ene cyclization of prochiral aldehyde with geminal dimethyl groups has been made with the use of a binaphthol-derived zinc reagent (at least 3 equiv) (Scheme 95).[234] Quite recently, an asymmetric olefin–ene cyclization was reported using tartrate-derived chiral titanium complex (Scheme 96).[235] It is still, however, a stoichiometric asymmetric transfer even in the presence of MS 4A.

The authors have recently reported the *enantioselective catalysis* of ene cyclization not only of type (3,4) (Scheme 97) but also of type (2,4) (Scheme 98) which

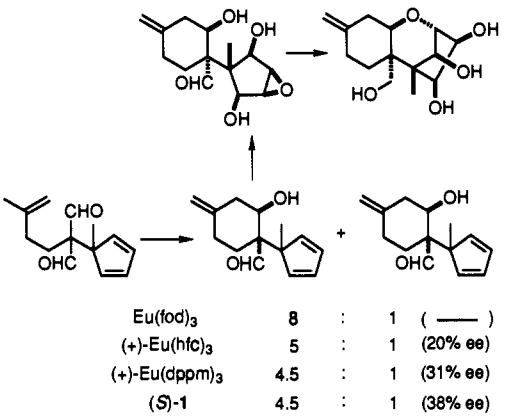
Scheme 97



Scheme 98



Scheme 99



are catalyzed by a BINOL-derived titanium complex (*R*)-4, modified by the perchlorate ligand.[35,236]

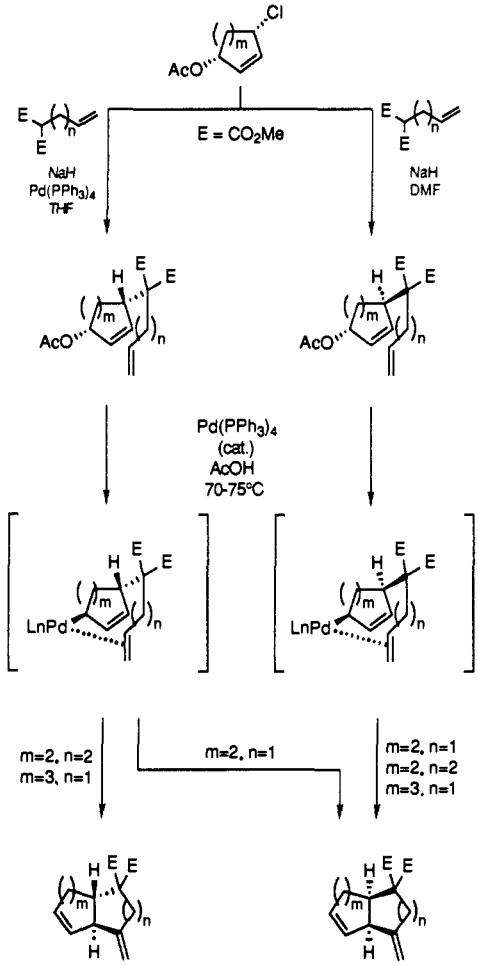
F. Asymmetric Desymmetrization

Quite recently, Ziegler and Sobolov reported the symmetry-assisted approach to the synthesis of the trichothecene, anguidine, via an ene cyclization (Scheme 99).[237] The (2,4) ene cyclization of the prochiral aldehyde on silica gel gives a 1:1 mixture. Cyclization with purified $Eu(fod)_3$ as Lewis acid catalyst for 1 week gives an 8:1 mixture. The major isomer is a potential intermediate for the synthesis of anguidine. However, use of (+)-$Eu(hfc)_3$, (+)-$Eu(dppm)_3$, or (*S*)-1 as chiral Lewis acid affords only 20–38% ee.

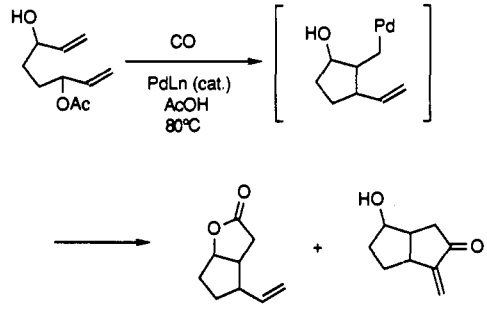
G. Metallo–Ene Reaction

Metallo–ene reactions[238–240] have been successfully applied in an intramolecular systems.[241,242] Efficient regio- and stereoselective magnesium–ene cyclizations have been applied to the syntheses of a variety of natural products.[242] Palladium-, platinum-, and nickel-catalyzed versions reveal great potential in terms of functional group compatibility. Oppolzer et al. have found that solvent employed dramatically influences the Pd–ene process; the rate and yield are significantly increased on going from THF to methanol to acetic

Scheme 100



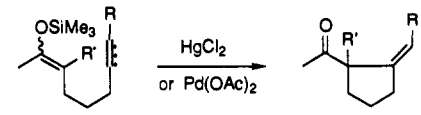
Scheme 101



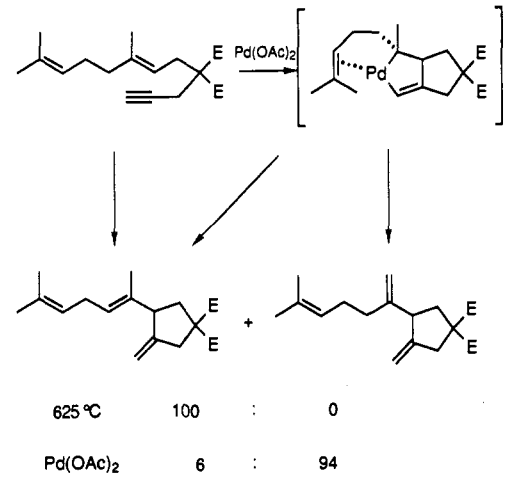
acid. An almost 100% stereospecific C–O → C–Pd → C–C chirality transfer permits simple and selective, cis- or trans-annelation processes (Scheme 100). The authors have recently reported the carbon monoxide insertions of the cyclized σ-Pd intermediates (Scheme 101).[243] The ease of metallo–ene cyclizations decreases in the following order, which is slightly different from those in the thermal and Lewis acid-promoted cyclizations: type (3,4), 5 > 6 ≫ 7; type (2,4), 6 > 5 ≃ 7 ≫ 8.

Conia-type ene cyclizations[193a] can be carried out using silyl enol ethers of alkynones under mild conditions (Scheme 102).[244-248] Treatment of silyl enol ethers with $HgCl_2$ in CH_2Cl_2 in the presence of hexamethyldisilazene for 30 min gives the vinylmercurial in quantitative yield. Functionalization (R = CO_2Me, COMe, or Br) of the C–Hg bond can be carried out. Similar cyclizations of silyl enol ethers of alkenones

Scheme 102



Scheme 103



with $Pd(OAc)_2$ can be regarded as the "Pd Conia" cyclization (Scheme 102).[249,250]

Trost et al. have recently discovered that $Pd(OAc)_2$ and other Pd(II) compounds catalyze the cyclization of terminal 1,6-enynes to give ene-type products (Scheme 103).[251] Treatment with 5 mol % $Pd(OAc)_2$ at 60–66 °C gives palladacyclopentene which reacts further to give a 6:94 regioisomeric mixture in 80% yield.

These metallo–ene reactions not only occur under much milder conditions but sometime give different isomeric products. In some cases, the metallo–ene reaction gives products which are not available from a thermal ene reaction.[252] A further advance will be the asymmetric catalysis of these metallo–ene reactions.

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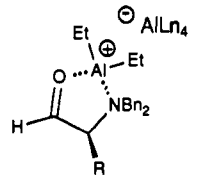

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