Substrate-Directable Chemical Reactions

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Contents

I. Introduction

Control of the regio- and stereochemical aspects of reaction selectivity[1] is a continuing challenge to organic chemists. *Nonbonding interactions* contributed by substrate substituents generally provide the dominant stereochemical control element in the preferential attack of a reagent onto the more accessible face of a prostereogenic carbon center. Such interactions between reacting partners which are repulsive in nature are modulated by *stereoelectronic effects*,[2] which either enhance, diminish, or override the "steric bias" in the vicinity of a given reaction site. In certain instances,

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Amir Hoveyda received his undergraduate degree at Columbia, where he was introduced to organic chemistry by Tom Katz and Nick Turro. He received his graduate education with Stuart Schreiber at Yale, where he examined the mechanism and synthetic applications of furancarbonyl photocycloaddition. After postdoctoral work with David Evans at Harvard as an American Cancer Society Postdoctoral Fellow, he assumed the position of Assistant Professor of Chemistry at Boston College in 1990. His research interests include development of new methods in synthesis and study of metal-catalyzed carbon–carbon bond-forming transformations with particular attention to reaction mechanism and asymmetric catalysis. He is an NSF National Young Investigator, an Eli Lilly Grantee, and the recipient of an American Cancer Society Junior Faculty Award.

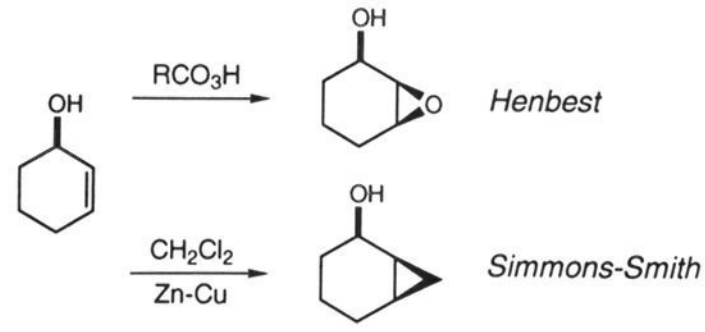
David Evans was born in Washington, DC, in 1941. He received his A.B. degree from Oberlin College in 1963 and his Ph.D. from the California Institute of Technology in 1967 under the supervision of Robert Ireland. In that year he joined the faculty at the University of California, Los Angeles. In 1973 he was promoted to the rank of Full Professor, and shortly thereafter returned to Caltech where he remained until 1983. In 1983 he moved to his present position at Harvard University where he is currently the Abbott and James Lawrence Professor of Chemistry. His interests are focused in the area of organic synthesis. His laboratory is engaged both in the development of new stereoselective reactions and asymmetric synthesis methodology as well as the application of these concepts to the synthesis of a range of targets of biological significance.

reagents have been documented to preassociate with polar functional groups in the vicinity of the reaction center and to influence the sterochemical outcome of the process. Such interactions between substrate and reagent, which are attractive rather than repulsive in nature, frequently provide a stereochemical outcome that is opposite to that predicted on the basis of an analysis of steric effects alone. Those cases wherein such contrasteric selectivity has been observed invariably involve substrates that carry polar, oxygen-containing functional groups and metal-based reagents. Preassociation of the reacting partners either through hydrogen bonding, covalent, or Lewis acid–base union is followed by the maintainance of this interaction

Greg Fu was born in Ohio in 1963. He received his S.B. degree in chemistry in 1985 from M.I.T., where he worked in the laboratory of K. Barry Sharpless. In 1991, he earned a Ph.D. in organic chemistry from Harvard University under the guidance of David A. Evans. His thesis dealt with the scope and the mechanism of the transition metal-catalyzed hydroboration reaction. He is currently a National Science Foundation postdoctoral fellow with Robert H. Grubbs at Caltech and will join the faculty at MIT this summer.

during the ensuing chemical transformation. Such reactions characteristically proceed through highly ordered transition states, frequently with exceptional levels of stereoselection.

Two of the earliest examples of such *directed reactions* are the Henbest epoxidation of 2-cyclohexen-1-ol and the Simmons–Smith cyclopropanation of the same substrate. In these stereoselective processes, hydroxyl participation results in the delivery of the reagent to the sterically more congested olefin diastereoface, syn to the allylic heteroatom. As a class, such transformations afford the opportunity for overriding steric factors in stereoselective bond constructions. Accordingly, these reactions are of great importance in stereoselective synthesis.



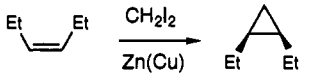
The principal aim of this article is to present a general overview of heteroatom-directed organic reactions, a topic which has not previously been reviewed. Processes that are covered in the following discussion are those which have explicitly been demonstrated to involve *transient* interaction of a substrate functional group with the incoming reagent, or those reactions where the most plausible explanation for their regio- and stereochemical outcome would invoke such an interplay. That is, reactions where the delivered reagent is covalently bound to the starting material are not discussed. In addition, this review is limited to those reactions where the directing functionality itself does not undergo a transformation and is recovered intact in the final product.[3] Finally, we have only included processes where the delivery of the reagent[4] and the

determination of the stereochemical identity of the products transpires in a unimolecular step.

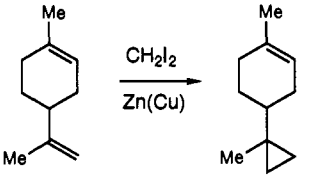
II. Directed Cyclopropanation Reactions

A. Introduction

In 1958, Simmons and Smith reported that treatment of simple alkenes with a mixture of methylene iodide and zinc–copper couple results in the high yield formation of cyclopropanes.[5] Several important features of this process were later presented in a more detailed account.[6] The reaction of alkenes with the "zinc reagent" is stereospecific with regard to the correlation of olefin geometry and product stereochemistry (eq 1) and is influenced by both steric and electronic factors.[7] The transformation is kinetically first order in both the organometallic reagent and the olefin.



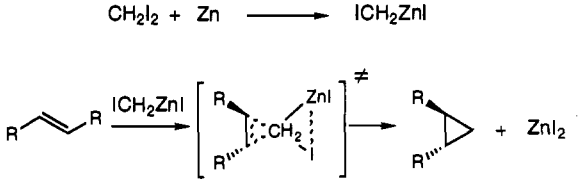
(1)



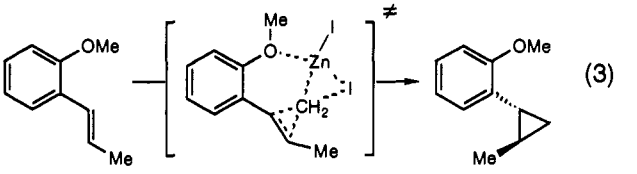
(2)

Simmons and Smith subsequently outlined a mechanism, where (iodomethyl)zinc iodide, the product of the initial reaction of methylene iodide and zinc metal, was proposed to be the active cyclopropanation reagent (Scheme 1).[8] Accordingly, the organometallic entity "could be considered as a relatively strongly bonded complex of methylene and zinc iodide, the carbon atom of which is electrophilic in character". A three-centered transition structure was proposed to account for the observed stereoselectivities. The preference of the cyclopropanation reagent for the less encumbered alkenes (eq 2) was attributed to the sterically demanding nature of the organometallic reagent.

Scheme 1

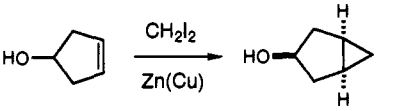


The initial indications that the cyclopropanation reaction may be affected by resident heteroatoms surfaced when it was discovered that the influence of steric factors can be somewhat unpredictable.[6] For example, the more hindered *o*-methoxyphenylpropene gives a higher yield of the cyclopropane adduct than either the meta or para isomers.[9] This unanticipated behavior was attributed to initial coordination of the Lewis basic ether oxygen with the Lewis acidic (iodomethyl)zinc iodide, thereby stabilizing the transition structure for the ortho-substituted anisole derivative (eq 3). Simmons and Smith thus made the important observation that internal functional groups can "assist and direct addition" in the zinc-mediated cyclopropanation.



(3)

The notion of utilizing a "steering" interaction between a suitably disposed heteroatom and the incoming zinc reagent was first exploited in 1961.[10] Winstein and co-workers reported that treatment of 3-cyclopenten-1-ol with methylene iodide and zinc–copper couple afforded the syn cyclopropyl carbinol as a single stereoisomer in 75% yield (eq 4). Cyclopropanation of the cyclopentenyl acetate and cyclopentadiene proved to be considerably more sluggish (3% conversion). Winstein surmised that *in the reaction of 3-cyclopenten-1-ol, prior coordination of the zinc reagent with the hydroxy group both directs the addition of methylene to the neighboring alkene and enhances the rate of the overall transformation.*[11]

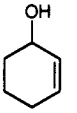
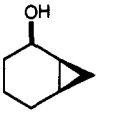
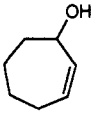
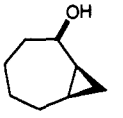
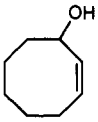
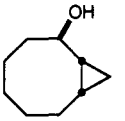


(4)

B. Cyclopropanation of Allylic Alcohols

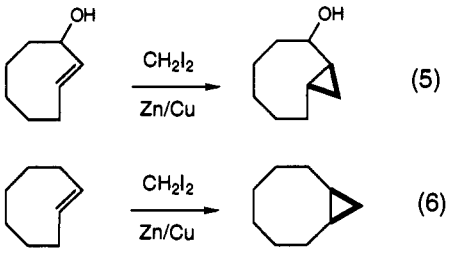
The utility of hydroxyl-directed cyclopropanation reactions has been demonstrated in a number of cyclic systems (Table 1) and incorporated in several natural product syntheses. 2-Cyclohexen-1-ol and its derived methyl ether are reported to undergo cyclopropanation to afford the *syn*-cyclopropyl alcohol product exclusively.[12] Winstein and co-workers performed a comprehensive study of the addition reaction of cyclic allylic alcohols and confirmed earlier reports[13] that syn addition is predominant in the reaction of 2-cyclohepten-1-ol.[14] In contrast, 2-cycloocten-1-ol and 2-cyclononen-1-ol yield anti bicyclic carbinols stereoselectively (entry 3).

Table 1. Stereoselective Cyclopropanation of Cyclic Allylic Alcohols

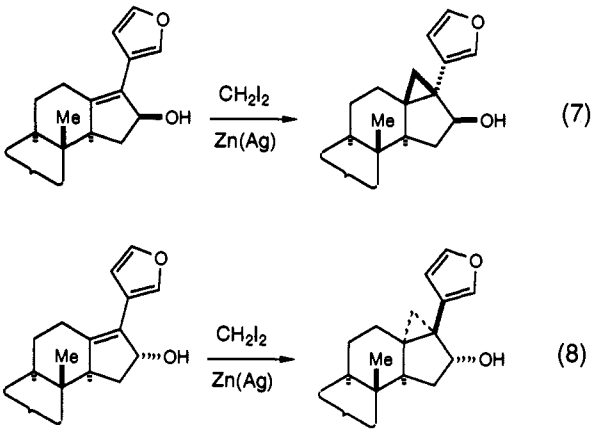
Entry	Substrate	Major Product	Selectivity
1			>99 : 1
2			9 : 1
3			>99 : 1

Rate enhancement by a neighboring hydroxy group is such that *trans*-2-cycloocten-1-ol affords the *anti*-cyclopropyl alcohol (eq 5), whereas the reaction of the

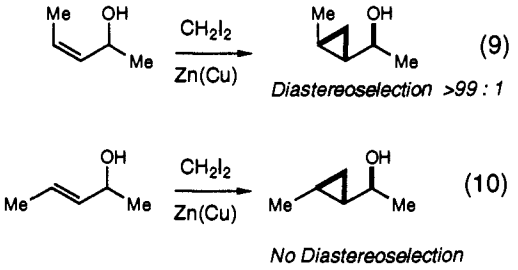
parent hydrocarbon is impaired by an intervening trans-to-cis isomerization (eq 6).[15]



Use of a zinc–silver couple instead of the original zinc–copper mixture is advantageous in several regards.[16] Cyclopropanations of enamines,[17] enol ethers, enol esters, and α,β-unsaturated aldehydes and ketones,[18] which often proceed in low yield under the Simmons–Smith conditions, can be effected satisfactorily with zinc–silver couple. Moreover, the usual hydrolytic workup is replaced by the simple addition of an amine (e.g., pyridine) and filtration of the resulting zinc salts. In studies on synthetic routes to the limonoid system, Conia's modifications facilitated the preparation of both the α- and the β-cyclopropyl isomers in ~90% yield (eqs 7 and 8).[19] Through subsequent oxidation and lithium–ammonia reduction of the resultant ketones, the difficult task of introducing the C/D angular methyl group was accomplished.

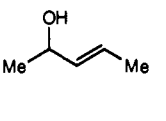
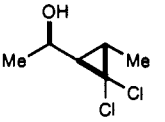
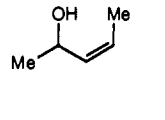
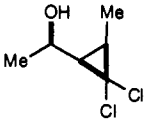
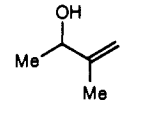
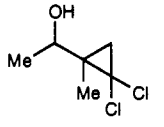
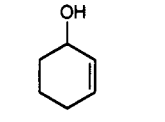
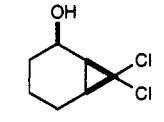


The stereochemical outcome of the Simmons–Smith reaction on acyclic allylic alcohols has been examined. Addition reactions of cis-disubstituted substrates are highly stereoselective, whereas the related trans isomers exhibit only modest levels of stereocontrol (eqs 9 and 10).[20]



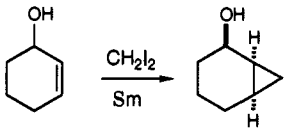
In a stereochemically related reaction, dichlorocarbene ($CHCl_3$, NaOH, $BnNEt_3Cl$) was also found to selectively react with allylic alcohols to give syn cyclopropyl carbinols (Table 2).[21] The last entry of Table 2 indicates that the dichloromethylene group is introduced predominantly syn to the neighboring

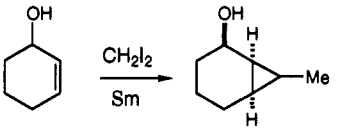
Table 2. Stereoselective Cyclopropanation of Allylic Alcohols with Dichlorocarbene

Entry	Substrate	Major Product	Selectivity
1			8 : 1
2			51 : 1
3			1 : 1
4			10 : 1

hydroxyl group. (The *tert*-butyldiphenylsilyl ether of *trans*-pent-3-en-2-ol reacts in a stereorandom manner.) Association of dichlorocarbene and the olefinic substrate through a hydrogen bond, in conjunction with restriction of conformational mobility to minimize allylic strain, accounts for the observed stereoselectivities.[22]

Samarium-derived carbenoids are also effective agents for the cyclopropanation of allylic alcohols.[23] The reaction often occurs at –60 °C, in contrast to the Simmons–Smith conditions which require above-ambient temperatures. When samarium is used, 2-cyclohexen-1-ol affords the syn cyclopropyl carbinol as a single isomer (eq 11, 92%). As illustrated in eq 12, ethylene iodide may be used in the samarium-mediated cyclopropanations: contrary to the Simmons–Smith conditions, higher levels of exo/endo stereoselectivity are observed.



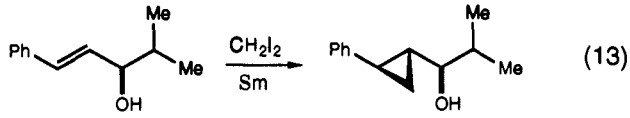


	Exo : Endo
Sm / CH_3CHI_2	5 : 1
Et_2Zn / CH_3CHI_2	1.6 : 1

Samarium carbenoids react with acyclic allylic alcohols to afford cyclopropyl carbinols with diastereocontrol (eqs 13–15). The samarium-promoted, directed cyclopropanation reaction is highly site selective. In the cyclopropanation of geraniol, reaction of the olefin adjacent to the hydroxyl group occurs with >95% selectivity.

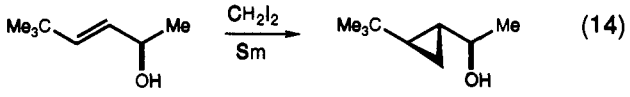
Nonracemic cyclopropyl ketones may be obtained through methylenation of the corresponding β-hydroxysulfoximine.[24] As shown in eq 16, this technology has

been employed in the preparation of (−)- and (+)-thujospene (eq 16).



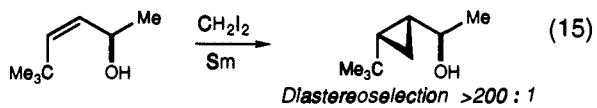
(13)

Diastereoselection >200 : 1



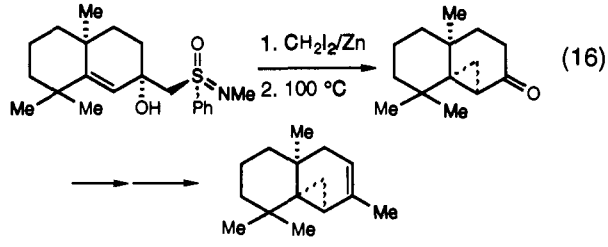
(14)

Diastereoselection >200 : 1



(15)

Diastereoselection >200 : 1



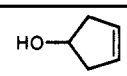
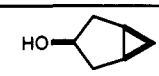
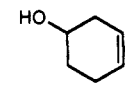
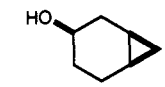
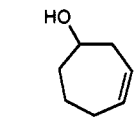
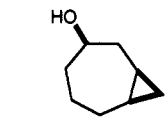
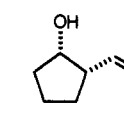
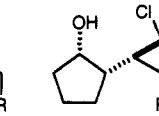
(16)

(-)- m-ospene

C. Cyclopropanation of Homoallylic Alcohols

Cyclopropanation of homoallylic alcohols is subject to directivity by a resident heteroatom. 3-Cyclopenten-1-ol,[11] 3-cyclohexen-1-ol,[25] and 3-cycloheptan-1-ol[25] afford the corresponding syn cyclopropyl carbinols with equally high levels of stereochemical control (Table 3). As illustrated in entry 4 of Table 3, cyclopropanation of a homoallylic alcohol with dichlorocarbene may also proceed with high levels of stereochemical control.[26]

Table 3. Stereoselective Cyclopropanation of Homoallylic Alcohols

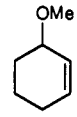
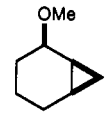
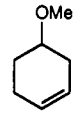
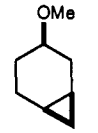
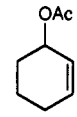
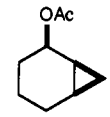
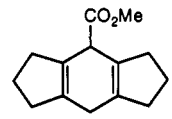
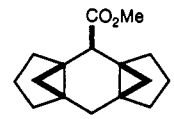
Entry	Substrate	Major Product	Selectivity
1			>20:1
2			>20:1
3			>20:1
4			>20:1

R = $(CH_2)_3$-OTBS

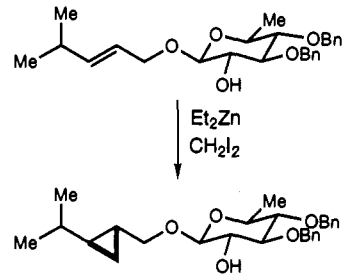
D. Cyclopropanation of Olefinic Ethers and Esters

Table 4 illustrates a number of cases where the stereochemical course of the cyclopropanation process is influenced by functionality other than a hydroxyl group. The methyl ethers derived from both 2-cyclohexen-1-ol[27] and 3-cyclohexen-1-ol[28] afford syn cyclopropyl carbinols exclusively. In apparent contrast to Winstein's early reports,[10] carboxylic esters, even from the homoallylic position, direct the stereochemical course of the cyclopropanation reaction, as illustrated by entries 3 and 4 of Table 4.[29]

Table 4. Stereoselective Cyclopropanation of Unsaturated Ethers and Esters

Entry	Substrate	Major Product	Selectivity
1			>99 : 1
2			>99 : 1
3			4 : 1
4			>99 : 1

Recently, carbohydrate-derived allylic acetals have been employed in diastereoselective cyclopropanation (eq 17). Presumably both the allylic ether and the neighboring hydroxyl are responsible for the delivery of the methylenation reagent: protection of the alcohol or removal of the ether functionality leads to significant diminution in stereocontrol (~2:1).[30]



(17)

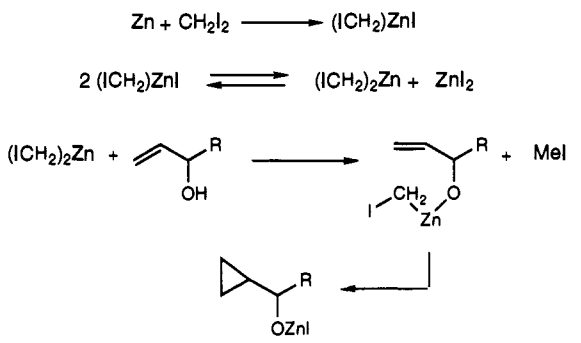
Diastereoselection >50 : 1

E. Mechanistic Considerations

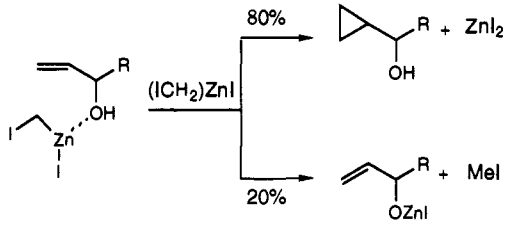
In 1964, Simmons proposed that the reaction of unsaturated alcohols involves the formation of an intermediate zinc alkoxide, since in the cyclopropanation of 3-cyclopenten-1-ol, 1 mol of iodomethane is formed for each mole of the desired bicyclic alcohol.[31] It was suggested that upon formation of (iodomethyl)-zinc iodide, a Schlenk equilibrium is established, resulting in the formation of bis(iodomethyl)zinc (Scheme 2). Reaction of the latter species with the allylic alcohol yields equimolar amounts of the corresponding zinc alkoxide and iodomethane; intramolecular methylene transfer would then afford the final product.[32]

Dauben later showed that an iodometrically equivalent amount of (iodomethyl)zinc iodide and 2-cyclopentene-1-ol gives the cyclopropane product in 80%

Scheme 2



Scheme 3



yield.[12] This observation is in contrast to Simmons' postulate where 2 equiv of the zinc reagent are required for completion of the reaction. Dauben therefore suggested that the first step in the methylenation process is the formation of a *dative* complex between the zinc reagent and the hydroxy group (Scheme 3). Generation of iodomethane as a side product would be the result of competitive decomposition of (iodomethyl)-zinc iodide by the alcohol moiety.

The exact nature of the reacting complex in the cyclopropanation reactions of allylic alcohols remains an unresolved issue. It is likely that initial complexation is followed by formation of a zinc alkoxide and that both types of species, covalent and dative, are capable of directing the methylenation process. A transient dative oxygen–zinc complex has been proposed to account for the stereochemical preferences in reactions of allylic ethers and esters (Table 3).[33] Although these data indicate that directivity by certain oxygen-containing functional groups occurs without formation of a covalent oxygen–zinc bond, there is no conclusive evidence that dative complexes are exclusively involved in the reaction of allylic alcohols.

Homoallylic alcohols react more slowly than the corresponding allylic systems, but immeasurably faster than simple alkenes. It appears that the practical limit of heteroatom directivity is at the homoallylic position, since the bishomoallylic alcohol in entry 3 of Table 5 exhibits a reaction rate comparable to that of cyclohexene (however, compare with entries 3 and 4 of Table 4).

The influence of substrate structure on both the rate and the stereochemical outcome of the cyclopropanation of various cyclohexenols can offer insight into the mechanism and conformational preferences involved in the cyclopropanation reaction (Table 6).[7] 2-Cyclohexen-1-ol reacts only twice as fast as its derived methyl ether (entries 1 and 2). It was suggested that if the reaction of the parent alcohol did proceed through a covalently bound zinc alkoxide intermediate, as opposed to the cyclopropanation of the methyl ether which must involve a dative complex, it is likely that a larger difference in rate would have been observed. As entries 3 and 4 of Table 6 show, both *syn*- and *anti*-5-methyl-2-cyclohexen-1-ol afford a single cyclopropane adduct, with the anti isomer reacting about 3 times faster.

Table 5. Relative Rates and Stereoselectivity in Cyclopropanation of Cyclic Unsaturated Alcohols

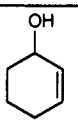
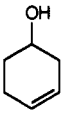
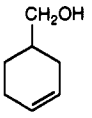
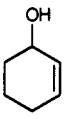
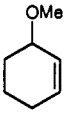
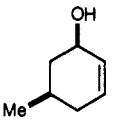
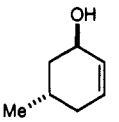
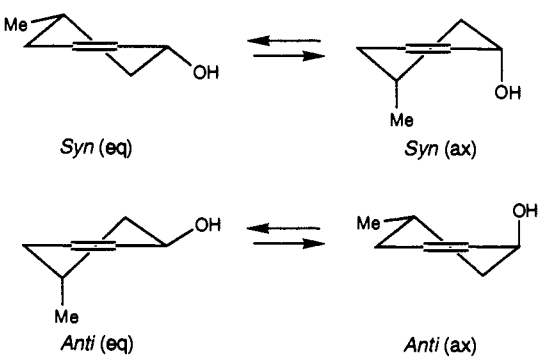
Entry	Substrate	Relative Rate (k)	Selectivity *Syn : Anti*
1		1.00	>99 : 1
2		0.091 ± 0.012	>99 : 1
3		Very slow	1 : 1

Table 6. Relative Rates and Stereoselectivity in Cyclopropanation of Cyclic Allylic Alcohols

Entry	Substrate	Relative Rate (k)	Selectivity *Syn : Anti*
1		1.00	>99 : 1
2		0.50 ± 0.05	>99 : 1
3		1.54 ± 0.10	>99 : 1
4		0.46 ± 0.05	>99 : 1

To account for these data, Rickborn considered four half-chair conformers, two each for the axial and equatorial alcohols (Scheme 4). If the reaction proceeds through the pseudoaxial hydroxyl–zinc complex, the anti isomer should react faster, as it contains a pseudoequatorial rather than an energetically unfavorable pseudoaxial methyl substituent. Nonetheless, the opposite trend was observed: the syn isomer exhibits

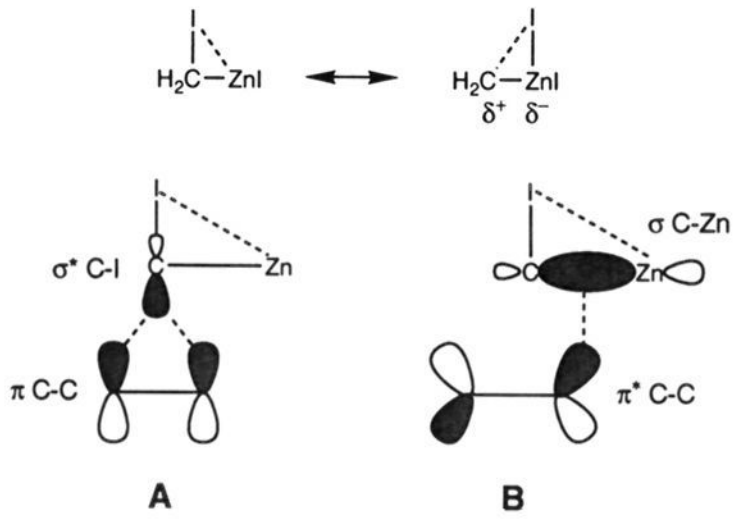
Scheme 4



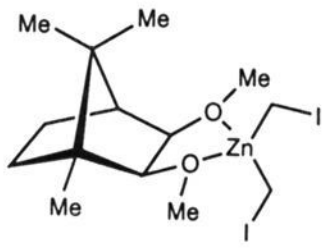
greater reactivity. It is therefore proposed that cyclopropanation occurs through the pseudoequatorial metal alkoxide.

The geometric and stereoelectronic requirements of the methylenation reaction may offer insights into the structure of the most reactive transition structure involved in this process. It is plausible that formation of the carbon–carbon bonds of the cyclopropane is triggered by two interactions: (1) The overlap of the π_{C-C} and the σ^*_{C-I} orbitals (Scheme 5, A), and (2) The overlap of the σ_{C-Zn} and the π^*_{C-C} orbitals (Scheme 5, B). Additionally, the incipient Zn–I bond should lower the energy level of σ^*_{C-I}, thereby accommodating the mixing of π_{C-C} with σ^*_{C-I}.

Scheme 5

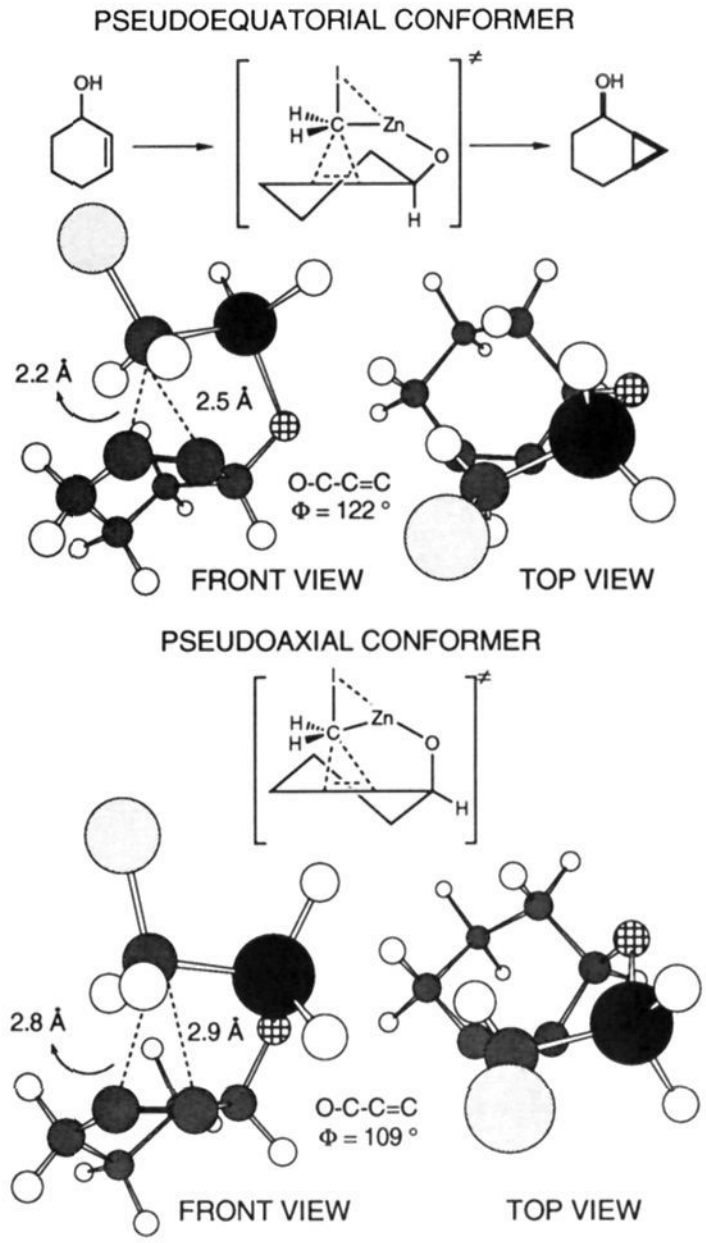


Recently, a solid-state structure of the cyclopropanation reagent has been reported (see below). The exo iodomethyl groups possess particularly smaller Zn–C–I angles and shorter Zn–I distances. It is claimed that "this close contact is reminiscent of the internal activation proposed by Simmons in the methylene transfer step".[34]



The model illustrated in Scheme 5 agrees with the original Simmons' supposition that the carbon atom in the zinc reagent is electrophilic in character but reserves a significant role for the C–Zn bond in the mechanism of the cyclopropanation reaction. In the case of cyclohexenyl allylic alcohols, analysis of molecular models reveals that both the pseudoaxial and the pseudoequatorial complexes of the half-chair conformers can orient for maximum overlap of the π_{C-C} and the σ^*_{C-I} orbitals or σ_{C-Zn}, π^*_{C-C} overlap (Scheme 6; available ligation site on Zn may be occupied by solvent molecules).[35] However, in the axial conformer, with the smaller O—C—C=C dihedral angle of 109°, the organometallic agent and the alkene center are unable to achieve the distance that is requisite for formation of carbon–carbon bonds.[36] It is noteworthy that the proposed interaction between the σ_{C-Zn} and the π^*_{C-C} orbitals closely parallels the interaction of a peracid lone pair with the π^*_{C-C} in directed peracid epoxidation reactions (section III).

Scheme 6



An additional stereoelectronic effect, which may also provide a bias for preferential reaction through the pseudoequatorial conformer, involves the overlap of the low-lying hydroxyl σ^*_{C-O} and the alkene π_{C-C}. This interaction, which is present to a larger degree in the pseudoaxial hydroxyl orientation, attenuates the nucleophilic character of the olefin and should thereby render the pseudoaxial conformer less reactive (Figure 1).[37] Within this context, measurement of the relative rates and levels of stereoinduction in cyclopropanation reactions of *cis*- and *trans*-5-*tert*-butyl-2-cyclohexen-1-ols may prove enlightening.

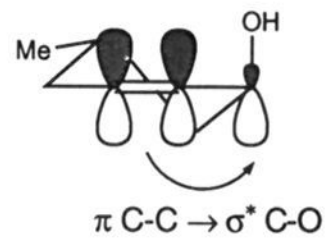
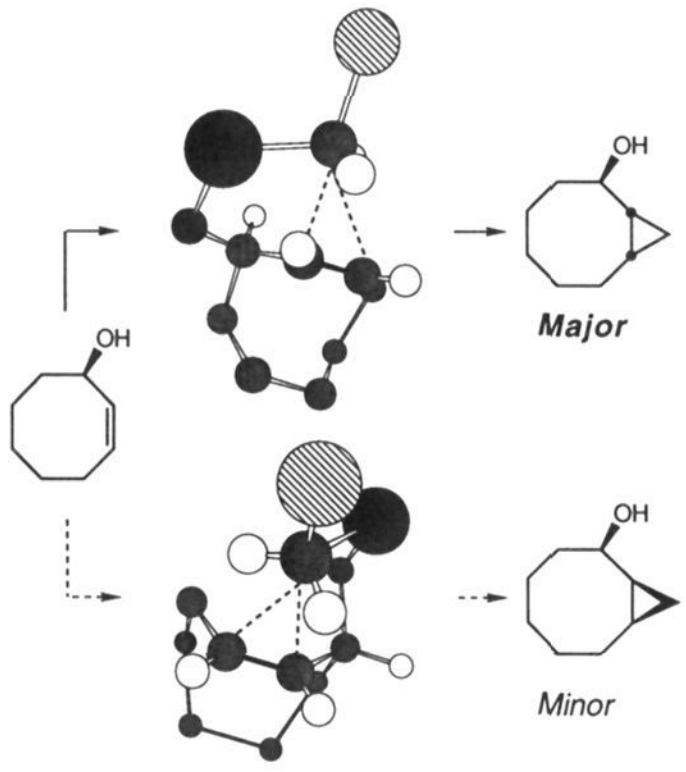


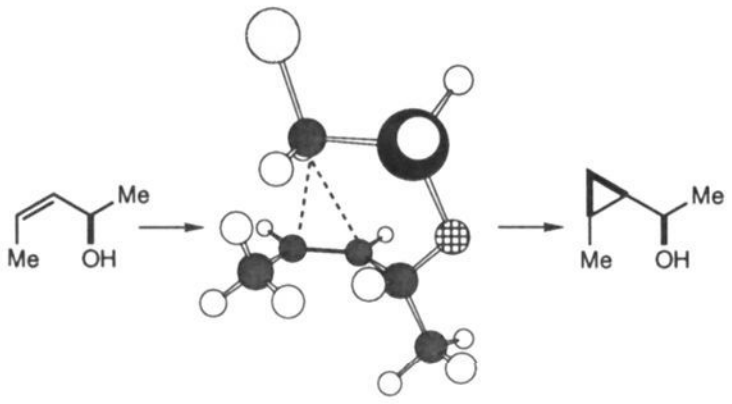
Figure 1. Overlap of π_{C-C} and σ^*_{C-O} in the allylic system leads to attenuation of the nucleophilic character of the olefin.

The stereoelectronic requirements delineated above account for the trend in the stereochemical outcome of the cyclopropanation reactions of 2-cyclohepten-1-ol (syn cyclopropyl carbinol; Table 1, entry 2) and 2-cycloocten-1-ol (anti cyclopropyl carbinol; Table 1, entry 3). Both the pseudoaxial and pseudoequatorial zinc alkoxides may afford the major product diastereomer. However, as is illustrated in Scheme 7, in the cyclopropanation of 2-cycloocten-1-ol the pseudoequatorial conformer is favored on simple steric grounds,

Scheme 7



Scheme 8



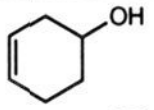
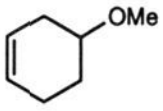
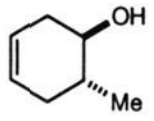
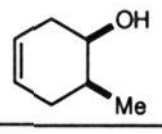
and as a result of the larger O—C—C=C dihedral angle, offers a more desirable alignment of the interacting orbitals, leading to the predominant formation of the anti diastereomer.[38]

The observed stereochemical preferences in the cyclopropanation of acyclic allylic alcohols (eqs 9–10 and 13–15 and Table 2) may be rationalized in a similar fashion. For *cis*-alkenes, A(1,3) allylic strain[22] favors the transition state conformation shown in Scheme 8; formation of the erythro product is thus preferred. As this destabilizing interaction is absent in trans-disubstituted alkenes, the cyclopropanation occurs nonstereoselectively.

It is noteworthy that the staggered model offers a plausible representation of the more reactive transition state. On the one hand, the aforementioned deactivating overlap of the π_{C-C} with the σ^*_{C-O} is attenuated, and on the other, this orientation allows for the hyperconjugative interaction between the σ_{C-C} and the π^*_{C-C} orbitals, which should in turn enhance the nucleophilicity of the olefin. These effects require a O—C—C=C dihedral angle of ~130°, which closely resembles the values predicted for the more reactive conformers of six-, seven-, and eight-membered cyclic allylic systems. Similar arguments apply to samarium-mediated cyclopropanation reactions.

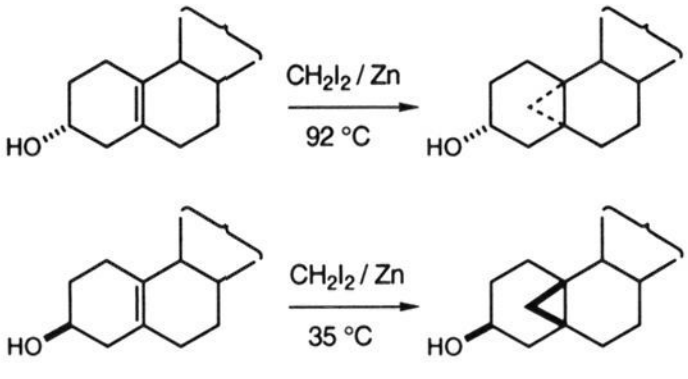
Studies on the conformational aspects of the directive effect in the cyclopropanation of cyclic homoallylic alcohols[7] indicate that these compounds mainly react through conformers with an axial hydroxy group (Table 7), in contrast to the corresponding allylic systems. This

Table 7. Relative Rates and Stereoselectivity in Reactions of Homoallylic Alcohols

Entry	Substrate	Relative Rate (k)	Selectivity *Syn : Anti*
1		1.00	>99 : 1
2		0.18 ± 0.2	>99 : 1
3		2.6 ± 0.2	>99 : 1
4		5.2 ± 0.4	>99 : 1

is perhaps to be expected, since when the directing group adopts the pseudoaxial position, the alkene is more accessible to the hydroxy-organometallic complex. The deactivating interaction between the π_{C-C} and σ^*_{C-O}, proposed to exert an influence in the allylic systems (Figure 1), is no longer operative and therefore does not disfavor the pseudoaxial zinc hydroxy conformer. Entries 3 and 4 of Table 7 show that substituents which enforce the axial hydroxy conformer effect an increase in the rate of cyclopropanation.

In the case of the homoallylic substrates, the difference in rate between the cyclopropanation of the parent alcohol and the derived methyl ether is larger than that observed for the corresponding allylic substrates (see entries 1 and 2, Tables 6 and 7). However, as has been suggested by Rickborn, such differences in reaction rates are too small to support different mechanisms for alcohol and ether substrates.[26] A related observation is that the highly stereoselective cyclopropanation of 5-α-hydroxy steroidal substrates requires unusually elevated temperatures (92 °C), whereas the related β isomers undergo cyclopropanation smoothly at 35 °C (eqs 18 and 19).[39] It has been demonstrated that the preferred half-chair conformation of the A ring in these compounds favors a pseudoequatorial orientation for the α-hydroxy and a pseudoaxial disposition for the β-hydroxy isomers.[40] The aforementioned data serve as further evidence that reactions of homoallylic alcohols preferentially occur through conformers which possess a pseudoaxial heteroatom. Furthermore, in support of Simmons' mechanistic paradigm, formation of the zinc alkoxide takes place prior to cyclopropanation in the case of the α-hydroxy isomer.[41]

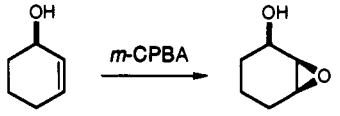


III. Directed Peracid Epoxidation Reactions

A. Introduction

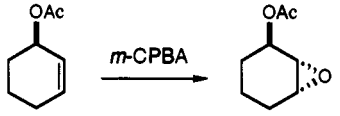
In 1959, Henbest and Wilson observed that upon treatment with perbenzoic acid "formation of epoxides

from cyclic allylic alcohols occurs on the side cis to the hydroxyl group".[42] Whereas oxidation of 2-cyclohexen-1-ol results in the predominant formation of the syn epoxy alcohol, the derived acetate or methyl ether affords the anti isomer as the major product (eqs 20 and 21; *m*-CPBA = *m*-chloroperbenzoic acid).



(20)

Diastereoselection 10 : 1

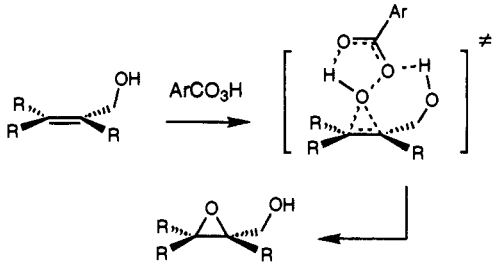


(21)

Diastereoselection 4 : 1

The difference in the stereochemical outcome of the above transformations was rationalized through a transition structure largely based on the "butterfly" mechanism of Bartlett, involving the interaction of the *nucleophilic* alkene with the *electrophilic* peracid.[43] It was postulated that a hydrogen bond formed between the hydroxy group and one of the peracid oxygens leads to delivery of the reagent to the olefin face syn to the hydroxy group (Scheme 9). Subsequently, the concept of heteroatom-directed peracid epoxidations was demonstrated in a number of cyclic and acyclic systems. In addition, the question of the mechanism of the "Henbest effect" formed the basis of several studies.[44]

Scheme 9



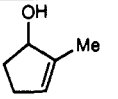
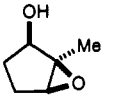
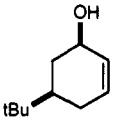
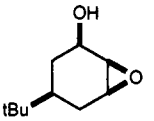
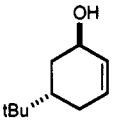
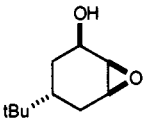
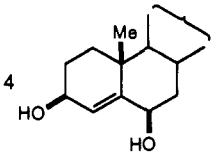
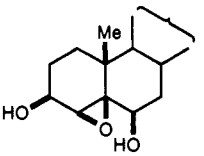
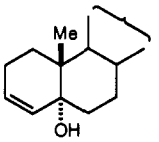
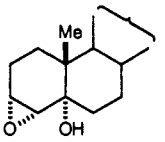
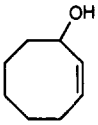
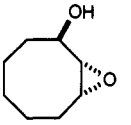
B. Peracid Epoxidation of Cyclic Olefins with Allylic Directing Groups

Table 8 illustrates cases where the stereochemical course of the peracid epoxidation of a cyclopentenol is controlled by a hydroxyl group.[45] Whereas oxidation (perlauric acid) of 2-cyclopenten-1-ol in cyclopentane produces the syn epoxy carbinol predominantly, under identical conditions the reaction of the derived methyl ether affords the anti isomer as the major product (11.5:1).[46] 2-Cyclopenten-1-ol is stereorandomly oxidized when methanol is used as solvent, as protic media preempt the formation of the necessary hydrogen bond.

A comparison of the outcome of the reactions shown in entries 2 and 3 (Table 8) suggests that a hydroxyl group is more efficient in directing epoxidation from a pseudoequatorial than a pseudoaxial position.[47] Entries 4 and 5 illustrate two bicyclic allylic alcohols which are oxidized stereoselectively regardless of the position of the directing group.[42,48] Peracid epoxidation of 2-cycloocten-1-ol affords the anti product isomer with high selectivity (entry 6).

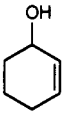
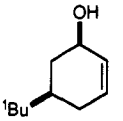
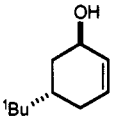
Epoxidation of allylic alcohols with trifluoroperacetic acid offers significantly higher levels of stereocontrol

Table 8. Stereoselective Epoxidation of Cyclic Allylic Alcohols[a]

Entry	Substrate	Major Product	Selectivity
1			>20:1
2			24:1
3			5:1
4			"highly selective"
5			"highly selective"
6			"highly selective"

[a] Conditions: Perbenzoic acid, perlauric acid, or *m*-chlorobenzoic acid in benzene.

Table 9. Stereoselective Epoxidation of Cyclic Allylic Alcohols with CF_3CO_3H

Entry	Substrate	*Syn* : *Anti* (*m*-CPBA)	*Syn* : *Anti* (CF_3CO_3H)
1		24:1	50:1
2		24:1	100:1
3		5:1	100:1

than perbenzoic acids.[49] Comparison of the stereochemical outcomes in entries 2 and 3 of Table 9 implies that the heteroatom functionality directs the oxidation reaction more effectively from the pseudoequatorial orientation (O—C—C=C dihedral angle of 140°).

With *m*-chloroperbenzoic acid (*m*-CPBA) as the oxidant, epoxidation reactions of unsaturated cyclic silyl ethers are not subject to heteroatom directivity; however, when trifluoroperacetic acid is employed, syn epoxy silyl ethers are formed selectively (Table 10). The ability of silyl ethers to direct the epoxidation process when trifluoroperacetic acid is used may be

Table 10. Stereoselective Epoxidation of Silyl Ethers with CF_3CO_3H

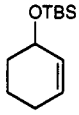
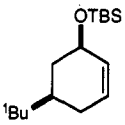
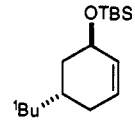
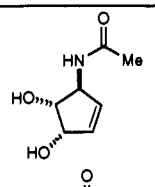
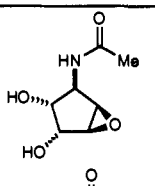
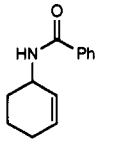
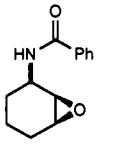
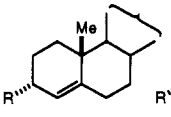
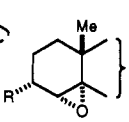
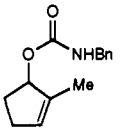
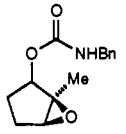
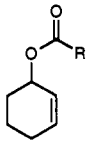
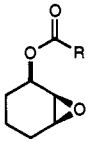
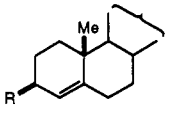
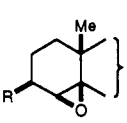
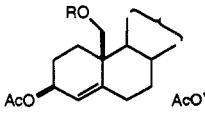
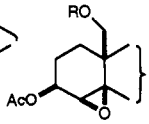
Entry	Substrate	*Syn* : *Anti* (*m*-CPBA)	*Syn* : *Anti* (CF_3CO_3H)
1		1 : 7	5 : 1
2		1 : 8	12 : 1
3		1 : 4	1 : 6

Table 11. Epoxidation of Cyclic Olefins with Amide-, Urea-, and Urethane-Directing Groups[a]

Entry	Substrate	Major Product		Selectivity
1				"highly selective"
2				"highly selective"
3			a. R = NHCONHAc b. R = $NHCONH_2$ c. R = NHCOMe	2 : 1 "highly selective" "highly selective"
4				>20 : 1
5			a. R = NH_2 b. R = NHBn c. R = NMe_2	3 : 1 5 : 1 10 : 1
6			a. R = OCONHBn b. R = $OCONMe_2$	>20 : 1 >20 : 1
7			a. R = $CONH_2$ b. R = CONHBn c. R = $CONMe_2$	6 : 1 >10 : 1 2 : 1

[a] Conditions: Perbenzoic acid or *m*-chlorobenzoic acid in benzene.

attributed to the higher acidity of this reagent compared to *m*-CPBA.

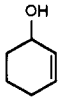
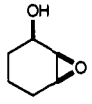
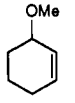
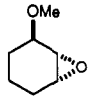
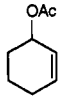
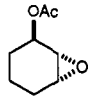
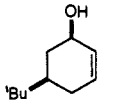
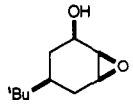
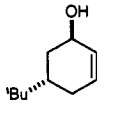
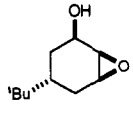
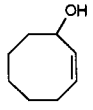
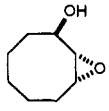
Table 11 illustrates cases where amide, urea, and urethane groups direct the stereochemical course of the epoxidation. The examples in entries 1[50] and 2[51] indicate that a carboxamide group effectively delivers the peracid reagent onto the syn face of the adjacent alkene. Moreover, the stereochemical outcome shown in entry 1 implies that amides may effectively direct the oxidation reaction in the presence of a competing hydroxyl group. Entries 3 and 4[52] of Table 11 offer instances where urethanes, ureas, and amides control the stereochemical course of the epoxidation process. Reaction of the acylurea shown in entry 3a proceeds with little selectivity, since *intramolecular* hydrogen bonding of the allylic NH preempts *intermolecular* association with the peracid.[45a] With regard to the substrates shown in entries 5–7, it has been proposed that the Lewis basic carbonyl, through its interaction with the peracid proton, plays the role of the proton *acceptor*. The case illustrated in entry 6b attests to the ability of the carbonyl group of a carbamate to direct the course of the epoxidation.

C. Mechanistic Considerations

Henbest and Chamberlain reported the relative rates of peracid oxidation of a number of olefinic substrates; these data are summarized in Table 12.[46,47] Entries 1–4 illustrate that 2-cyclohexen-1-ol reacts *slower* than cyclohexene, but significantly *faster* than its nondirecting methyl ether and ester derivatives. The higher rate of epoxidation of *cis*-5-*tert*-butyl-2-cyclohexen-1-ol (entry 5) relative to that of its trans isomer (entry 6) is consistent with differences in the levels of stereochemical induction reported for these substrates (24:1 vs 5:1, respectively). The *cis*-*tert*-butyl derivative is oxidized faster and more selectively than 2-cyclohexen-1-ol; this observation supports the proposal that the adjacent hydroxyl functionality is a more effective directing group when oriented pseudoequatorially.

2-Cyclooctene-1-ol is oxidized slower than cyclooctene (relative rate = 2.16), but 15 times faster than the

Table 12. Relative Rates of Epoxidation of Representative Cyclic Olefins[a]

Entry	Substrate	Major Product	Relative Rate (k)
1			1.00
2			0.55
3			0.067
4			0.046
5			0.75
6			0.10
7			1.80

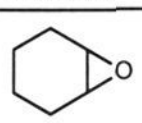
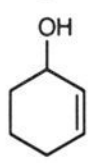
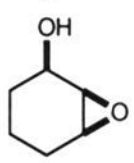
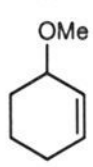
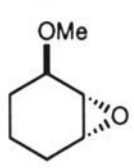
[a] Conditions: Perbenzoic acid, benzene, 5 °C.

derived methyl ether (relative rate = 0.12). It is significant that both the cyclopropanation and the peracid epoxidation of 2-cycloocten-1-ol result in the anti functionalization of the allylic alcohol. The rationale for the anti selectivity in the epoxidation of 2-cycloocten-1-ol closely parallels that which was presented for the cyclopropanation of this compound (see above).

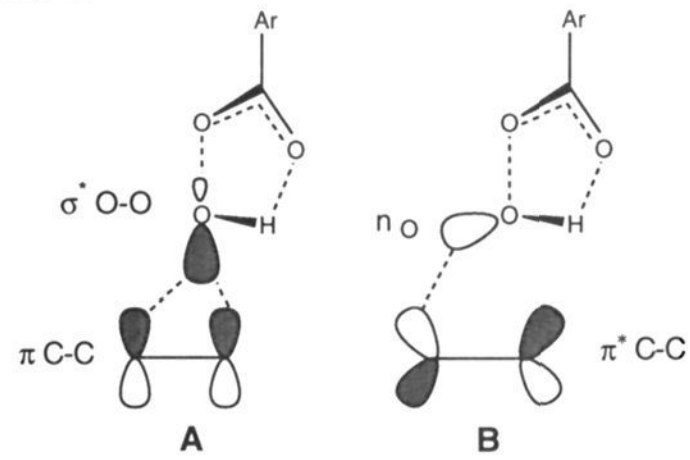
The values for the enthalpies and entropies of activation ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) in the epoxidation reactions of three of the aforementioned substrates are shown in Table 13. The enthalpy of activation ($\Delta H^{\ddagger}$) for the allylic alcohol is ~2 kcal/mol lower than that of the parent cycloalkene. This value is probably the net effect of two opposing factors: (1) stabilization of the transition structure as a result of hydrogen bonding between the hydroxyl group and the peracid reagent and (2) reduction in the nucleophilic character of the alkene, stemming from the electron-withdrawing ability of the adjacent heteroatom and the larger steric bulk of a methoxy versus a hydrogen group. Comparison of the activation parameters for epoxidations of cyclohexene and 2-cyclohexen-1-ol reveals that in the reaction of the latter substrate the diminution in $\Delta H^{\ddagger}$ is countered by a decrease in $\Delta S^{\ddagger}$, which results in an overall increase in the free energy of activation. Therefore, it is largely the variation in the activation entropy that leads to the reduction of the reaction rate in the epoxidation of the alcohol substrate. The values reported for the entropies of activation suggest a more organized transition structure for the peracid oxidations of the hydroxylic versus nonhydroxylic alkenes and thus support the directing influence of the resident alcohol moiety. With regard to the epoxidation of the allylic ether, in the absence of the steering influence of a hydroxy group, the entropy of activation is nearly identical to that of cyclohexene. The deactivating inductive effect of the ether functionality, in addition to the larger steric bulk of a methoxy, result in a higher enthalpy of activation.

For the peracid epoxidation of allylic alcohols, the interactions between the olefin π-system and the peracid shown in Scheme 10 can be suggested. A number of experimental data and theoretical considerations support this proposal. The role of the alkene as the nucleophile and that of the peracid as the electrophile[53] implies backside displacement of the peroxide bond and requires proper alignment of the π_{C-C} and σ^*_{O-O} orbitals (A).[54] The intramolecular hydrogen bonding in the oxidant facilitates the epoxidation process, as the carboxylic acid and not the corresponding carboxylate anion will be the leaving group.

Table 13. Activation Energy Parameters for Epoxidation of Representative Cyclohexenes

Substrate	Major Product	$\Delta H^{\neq}$ (kcal/mol)	$\Delta S^{\neq}$ (cal/deg/mol)
		10.42	-32.9
		8.35	-41.0
		12.36	-30.7

Scheme 10



Hanzlik and Shearer observed small peracid isotope effects in epoxidations of a number of simple olefins (e.g., stilbene), and thus proposed that "the peracid hydrogen remains hydrogen-bonded, or at least is not being transferred in the transition state".[55] This paradigm is supported by two independent observations: added acids do not catalyze the epoxidation reaction of simple olefins,[50] and basic solvents inhibit oxidation since the internally hydrogen-bonded structure of the peracid monomer is disrupted.[56] Transition structures with O—C—C=C dihedral angles of ~140° are preferred (equatorial OH), so that the deactivating effect of the adjacent heteroatom on the nucleophilic character of the π-cloud is minimized (see Figure 1). It is worthy of mention that, with regard to the favored O—C—C=C dihedral angle, similar arguments were presented in the case of Simmons–Smith cyclopropanation reactions of allylic alcohols.

Sharpless has proposed that a dihedral angle of ~60° between the planes defined by the two molecules orients one of the nonbonding electron pairs for donation into the π^*_{C-C} orbital, thus initiating formation of the second C–O bond of the incipient epoxide (Scheme 10, B).[57] Such association of the peroxide oxygen nonbonding pair and the π^*_{C-C} is reminiscent of the interaction between σ_{C-Zn} and π^*_{C-C} in the Simmons–Smith cyclopropanation. Moreover, it has been suggested that such an orientation properly disposes the second lone pair of the terminal peracid oxygen for hydrogen bonding with the adjacent hydroxyl group.[58]

The unsymmetrical transition structure illustrated in Figure 2 is based on the theoretical and mechanistic work of Hanzlik and Shearer.[52] Examination of the kinetic isotope effects of several peracid epoxidations indicates that extensive bond formation occurs at the site adjacent to the heteroatom such that the developing partial positive charge resides at the carbon more distant from the electron-withdrawing oxygen substituent. Molecular models imply that in the case of pseudoequatorial alcohol (O—C—C=C dihedral angle of ~140°), with the commonly depicted symmetrical transition structures, the hydroxyl proton and the peracid oxygen are too distant for effective hydrogen bonding (~2.6 Å).[59] However, in an unsymmetrical structure, where the peracid has slipped closer to the directing group, these atoms may lie easily within an acceptable distance for formation of a hydrogen bond (~1.9 Å).[60] Hanzlik and Shearer suggest that the developing carbocationic character of the β-carbon is in turn ameliorated through electron donation by the

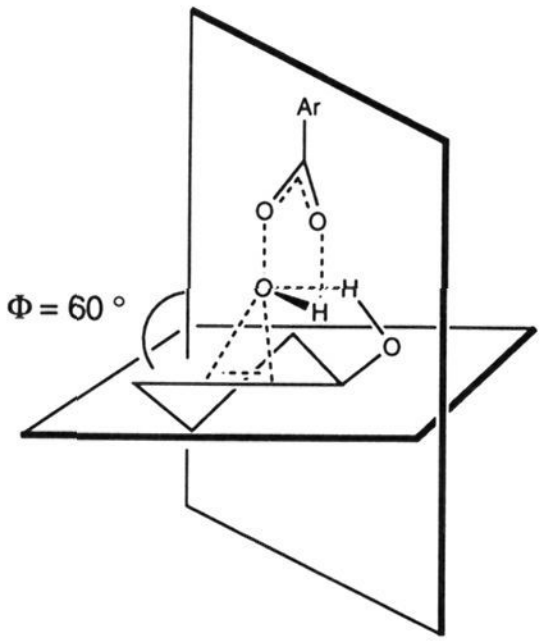


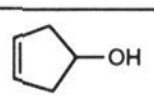
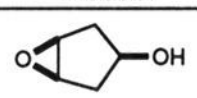
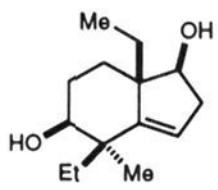
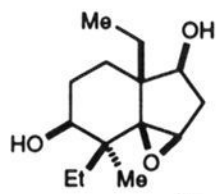
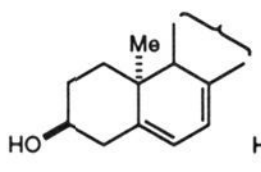
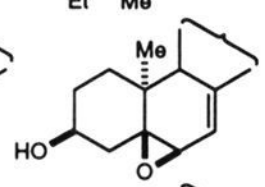
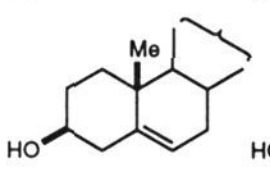
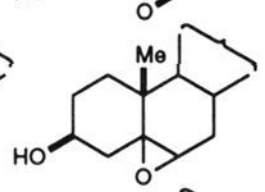
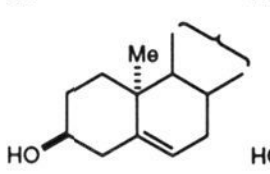
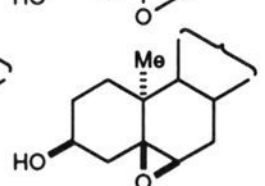
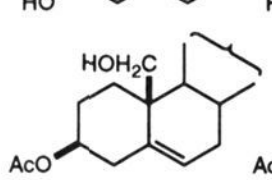
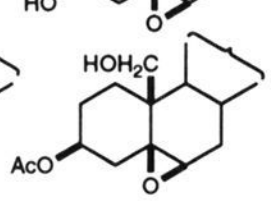
Figure 2. Transition structure for the peracid epoxidation of cyclic alcohols.

nonbonding electrons of the peracid oxygen; this interaction is illustrated in Scheme 10, B. As mentioned previously, Sharpless has proposed that this latter overlap eventually leads to the formation of the second epoxide C–O bond. With allylic amides and urethanes (Table 11), a transition structure involving formation of a hydrogen bond between the terminal peracid oxygen and the amide NH, similar to that proposed for the oxidation of allylic alcohols, readily accounts for the observed stereoselectivities.

D. Peracid Epoxidation of Cyclic Olefins with Homoallylic Directing Groups

Table 14 illustrates instances where a homoallylic hydroxyl group directs the course of the peracid epoxidation reaction.[61] Entries 1[62] and 2[63] show cases where a cyclopentenyl alkene is oxidized with stereochemical control. 3-Cyclopenten-1-ol is epoxidized stereoselectively in cyclopentane but stereorandomly in methanol. Regardless of the solvent employed, the reaction of the derived methyl ether affords the anti isomer as the major product (4:1).[46] Entry 3[64] illustrates a regio- and stereoselective peracid oxidation; the derived acetate reacts less selectively (7:1) and with a rate 4 times slower. With the substrate in entry 4, where the alcohol function is disposed pseudoequatorially, epoxidation proceeds nonselectively; in contrast the corresponding axial isomer affords the expected epoxide with excellent selectivity (entry 5).[65] Thus, with homoallylic alcohols directivity is more efficient with a pseudoaxially disposed hydroxyl group. The example in entry 6 indicates that the more flexible primary carbinols may not direct epoxidation reactions as efficiently as the secondary or tertiary derivatives.[66] Hydroxy groups in bishomoallylic cyclic alcohols exert little or no influence on the course of peracid epoxidation reactions.[67]

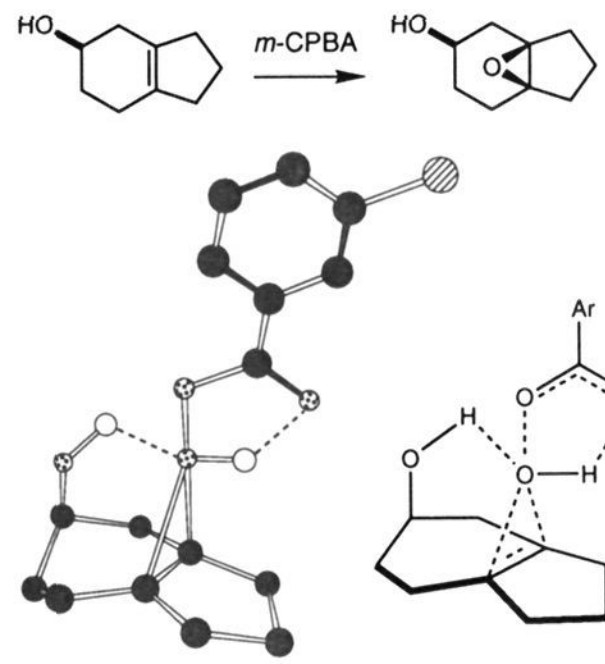
Table 14. Epoxidation of Cyclic Homoallylic Alcohols[a]

Entry	Substrate	Major Product	Selectivity
1			9 : 1
2			"highly selective"
3			16 : 1
4			1 : 1
5			21 : 1
6			5 : 1

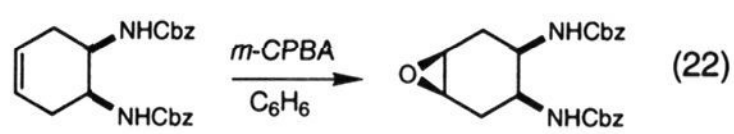
[a] Conditions: Perbenzoic acid, or *m*-chloroperbenzoic acid in benzene or cyclopentane.

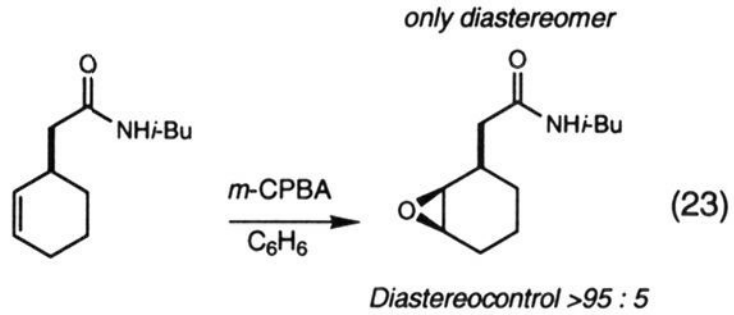
A transition structure for the epoxidation of homoallylic alcohols is proposed on the basis of the same principles described for the reaction of allylic systems (vide supra). The transition structure depicted in Scheme 11 may serve as an example.

Scheme 11



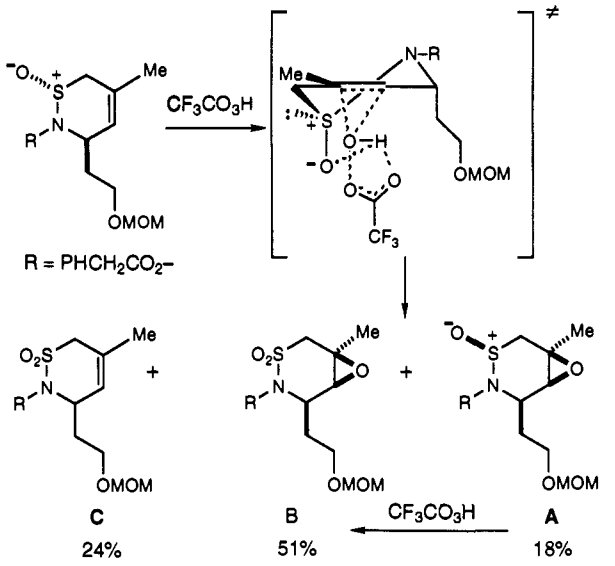
Equations 22[68] and 23[69] illustrate cases where a homoallylic carbamate and a homoallylic amide may affect the stereochemical course of the epoxidation.





With trifluoroperacetic acid as oxidant, sulfoxides may direct the epoxidation process (Scheme 12).[70] The *cis*-3,6-dihydrothiazine 1-oxide shown below is oxidized

Scheme 12



stereoselectively to afford the β-epoxy thiazineoxide (A) and the β-epoxy sultam (B) in 18% and 51% yield, respectively. The corresponding unsaturated sultam (C) was isolated as a side product (24%); this compound was shown not to be an intermediate in the formation of aforementioned epoxides, since treatment of this material with trifluoroperacetic acid affords the α-epoxide exclusively. It was proposed that the relevant transition structure contains a sidechain disposed in the pseudoaxial position, so that the unfavorable A(1,3) allylic strain[22] that would otherwise develop between this group and the neighboring carbamate functionality is avoided.

E. Peracid Epoxidation of Acyclic Olefins

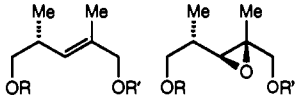
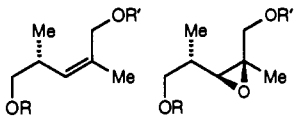
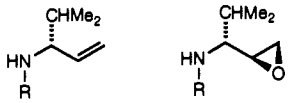
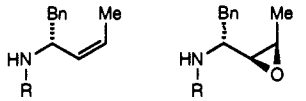
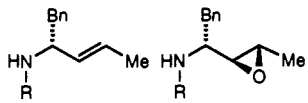
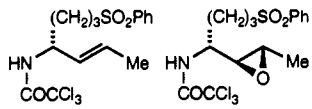
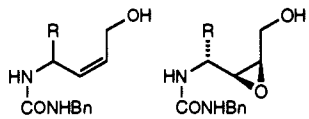
The trisubstituted alkenes shown in entries 1 and 2 of Table 15, upon treatment with *m*-chloroperbenzoic acid at 5 °C, are oxidized with varying levels of stereoselectivity, depending on whether the allylic or the homoallylic hydroxyl group is protected.[71] To account for the observed stereoselectivities, two cooperative hydrogen bonding interactions between the peracid and the olefinic substrate were proposed.

Figure 3 illustrates plausible transition structures where simultaneous association of the peracid with allylic and homoallylic hydroxyl or alkoxy groups leads to diastereoselective epoxidations. These transition states are based on the same steric and stereoelectronic principles that were discussed in detail previously (Figure 2 and Scheme 10). However, as the hydrogen bonding network involves substituents on both of the olefinic carbons, the transition-state structure is expected to be more symmetrical. Therefore, to achieve the proper interatomic distances for effective formation of hydrogen bonds, one of the heteroatom substituents must adopt the "inside" position (~30° O—C—C=C dihedral angle). It is the *allylic* hydroxyl group which projects inside and adopts the smaller O—C—C=C dihedral angle in order to avoid the destabilizing A(1,3) allylic strain. With regard to the dibenzyl ethers in entries 1d and 2d, in the absence of the directing influence of a hydroxy group, epoxidation is nonselective and proceeds at a much slower rate.

Entries 3–7[72] of Table 15 illustrate cases where the epoxidation process is directed by an amide or a urethane functionality. The observed selectivities may be explained through similar mechanisms that were discussed before for cyclic unsaturated carbamates. The transition structure for entry 4a in Table 15 is illustrative (Figure 4).

The improvement in stereoselectivity in entry 6 (Table 15) as compared to that of entry 5b may be ascribed to the additional hydrogen bonding between the peracid and the sulfone oxygens. The trends shown in entries 3–5 of Table 7 are, in general, puzzling and difficult to explain, and any plausible rationalization must await further experimental data. The stereoselectivities illustrated in entry 7 can be accounted for through similar arguments to those that were described for the reaction shown in entry 4a. In fact, the example

Table 15. Stereoselective Epoxidations of Acyclic Olefins[a]

Entry	Substrate	Major Product		Selectivity
1			a. R = H, R' = H	>25 : 1
			b. R = H, R' = Bn	6 : 1
			c. R = Bn, R' = H	>25 : 1
			d. R = Bn, R' = Bn	1 : 1
2			a. R = H, R' = H	4 : 1
			b. R = H, R' = Bn	7 : 1
			c. R = Bn, R' = H	15 : 1
			d. R = Bn, R' = Bn	1 : 1
3			a. R = CO_2t-Bu	15 : 1
			b. R = Phth	4 : 1
4			a. R = CONHPh	>19 : 1
			b. R = $COCCl_3$	3 : 1
5			a. R = CONHPh	1 : 1
			b. R = $COCCl_3$	3 : 1
6				"highly selective"
7			a. R = Me	10 : 1
			b. R = *i*-Pr	28 : 1

[a] Conditions: *m*-Chloroperbenzoic acid in benzene or CH_2Cl_2.

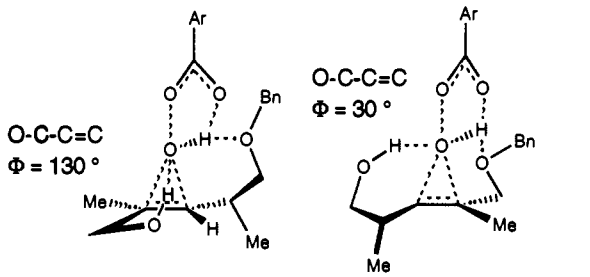


Figure 3. Transition structures for directed epoxidation of acyclic olefins containing both allylic and homoalyllic oxygen heteroatoms.

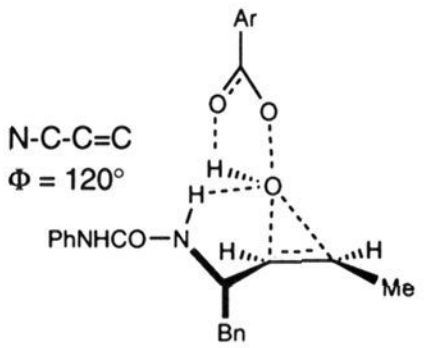


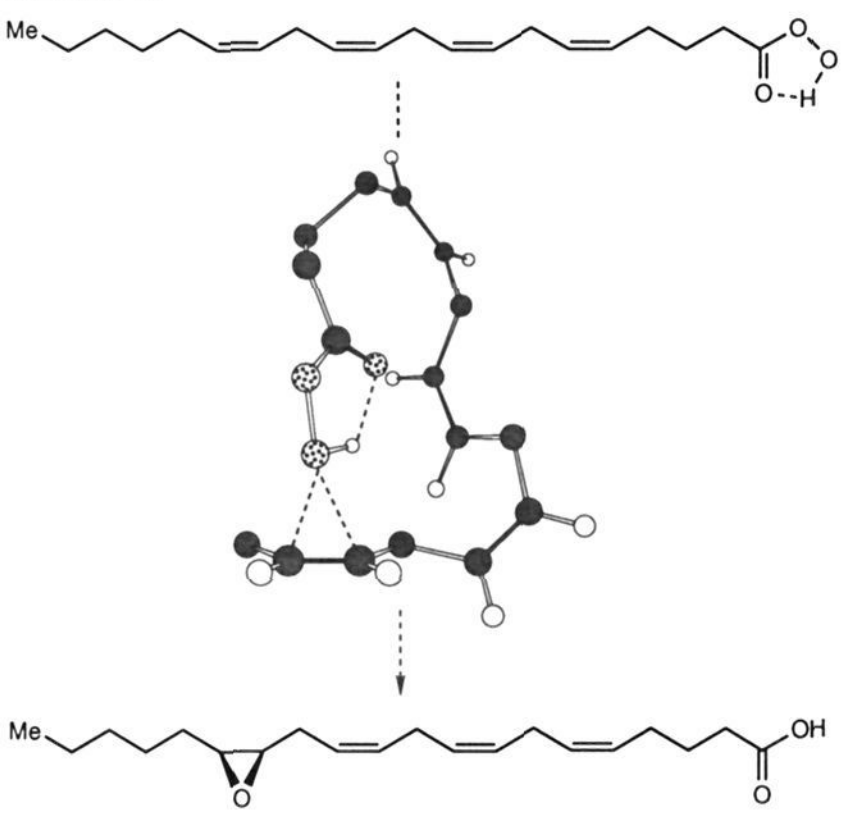
Figure 4. Transition structure for directed epoxidation of acyclic urethane shown in Table 15, entry 4a.

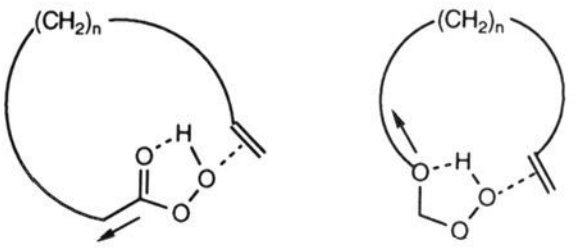
shown in entry 4a serves as a control experiment, indicating that in the oxidation of substrates in entry 7 cooperative hydrogen bonding of the primary alcohol may not be required for high stereoselectivity.

Another class of directed epoxidations are those reactions where a resident peracid or peroxy moiety is generated in situ from a suitable precursor. A remarkable example of this type of epoxidation is shown in Scheme 13.[73] Arachidonic (*cis*-5,8,11,14-tetraenoic) peracid (generated in situ from the corresponding acid), upon standing at 20 °C is epoxidized site selectively to afford a single epoxy ester in near quantitative yield (after esterification with diazomethane). In a control experiment, oxidation of arachidonic acid or the corresponding ester with *m*-CPBA is nonselective and yields a mixture of all possible epoxides. According to Corey, this unprecedented selectivity is an indication that "the 15-membered cyclic structure is energetically quite favorable compared with alternative geometries involving more proximate double bonds and smaller rings". The observed selectivity indicates that "the favored transition state for oxygen transfer may be an (S_N2 like) arrangement with...the C=C π cloud attacking oxygen back side to and collinear with the O–O bond being broken". That is, proper positioning of the alkene and the peracid moiety, as is illustrated in Figure 2, may only be geometrically possible when a certain number of atoms separate the two reacting groups (the peracid and the olefin).

The geometric requirements for intramolecular epoxidation by an internal peracid or peroxide were later investigated.[74] This study was based on the principle that analogous α-hydroperoxy ethers are expected to be highly conducive to intramolecular delivery of oxygen onto a neighboring olefin. As is illustrated below, "the direction of the first bond away from the peroxy carbon permits the geometry required for intramolecular epoxidation to be achieved with fewer connective atoms".

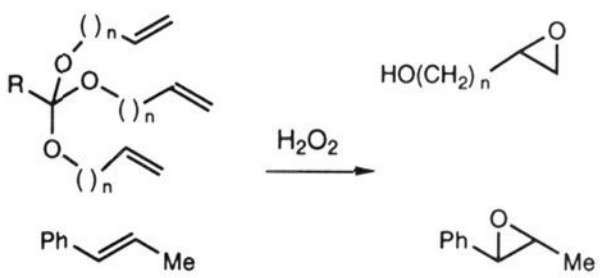
Scheme 13





The relative facility of intramolecular epoxidation of hydroperoxy substrates with variable chain lengths was examined through competition experiments, with β-methylstyrene serving as reference. The outcome of some of these experiments is shown in Table 16. With 90% H_2O_2 (α-hydroperoxy ethers are generated in situ), oxidation of the substrate in entry 1 is slower than β-methylstyrene, whereas the longer chain acetal in entry 3 reacts ~40 times faster. Furthermore, as the reaction solution is made more dilute, the ratio of the acetal oxide to the styrene oxide *decreases* for the substrate in entry 1, but *increases* for the substrate in entry 2 and significantly more so for the compound shown in entry 3. These data indicate that for the allylic substrate (Table 16, entry 1) the intramolecular component for epoxidation is relatively insignificant. The homoallylic (entry 2) and bishomoallylic (entry 3) cases, however, offer strong evidence in support of the intramolecular pathway.

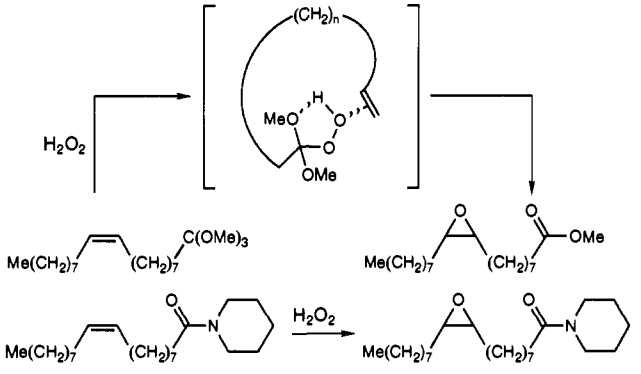
Table 16. Facility of Intramolecular Epoxidations as a Function of Chain Length



Entry	Substrate	k_{intra} / $k_{styrene}$
1	HC[-O-CH_2-C=CH_2]$_3$	<1 M
2	MeC[-O-$(CH_2)_2$-C=CH_2]$_3$	7 M
3	HC[-O-$(CH_2)_3$-C=CH_2]$_3$	40 M

Epoxidations of a structurally analogous class of α-hydroperoxy ethers, where the hydrocarbon tether is attached to the acetal *carbon* (as opposed to former cases where it is attached to the acetal *oxygen*), corroborate the above-mentioned hypotheses. Upon repeated dilutions of a 90% H_2O_2 solution of equimolar amounts of the ortho ester and the related cyclohexyl amide, the ester product/amide product ratio rises steadily (Scheme 14). It was therefore concluded that in the above reactions transient hydroperoxy ethers are generated (shown in Scheme 14), and if the resident alkene is accessible, intramolecular oxidation occurs readily.

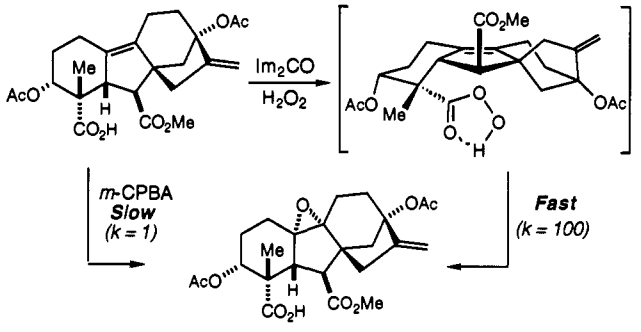
Scheme 14



[*ortho* ester] = [Amide], M	[Ester Prod.] / [Amide Prod.]
1	7
0.5	12
0.25	27

A recent report adds an interesting note to the aforementioned mechanistic proposals: treatment of the carboxylic acid shown in Scheme 15 with *m*-CPBA leads to selective formation of the α-epoxide.[75] The corresponding peracid (prepared in situ from the acid by treatment with Im_2CO and H_2O_2) also affords a single diastereomeric product but at a rate ~100 times faster than the parent carboxylic acid. It was suggested that intramolecular oxidation of the tetrasubstituted olefin by the transient peracid accounts for the above observation. Examination of molecular models clearly indicates that with an internally hydrogen-bonded peracid, alignment of the π_{C-C} and σ^*_{O-O} orbitals is impossible. However, if the peracid is *not* internally hydrogen bonded, proper association of these orbitals is feasible. Accordingly, this transformation should be further catalyzed by added acids. Nonetheless, it is intriguing that in spite of the absence of an internal hydrogen bond, prior generation of the bound peracid results in a noticeable rate acceleration.

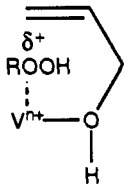
Scheme 15



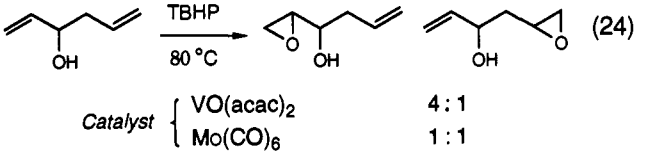
IV. Directed Metal-Catalyzed Epoxidation Reactions

A. Introduction

Interest in catalytic epoxidation increased markedly in the late 1960s following the discovery of transition metal-catalyzed *tert*-butyl hydroperoxide (TBHP)[76,77] epoxidation[78] by Indictor and Brill.[79] Soon afterward, it was established that the reactivity of an olefin typically correlates with its nucleophilicity,[80] and that the epoxidation of allylic alcohols with vanadium catalysts is anomalously rapid.[80,81] Whereas $Mo(CO)_6$ is generally a more active catalyst than $VO(acac)_2$, for allylic alcohols the reverse is true.[80] There had been earlier indications that strong inhibition by *tert*-butyl alcohol of $VO(acac)_2$-catalyzed TBHP epoxidation.[82] To account for these observations, Sheng and Zajacek postulated that the vanadium-catalyzed reaction proceeds through the ternary complex shown.[83]

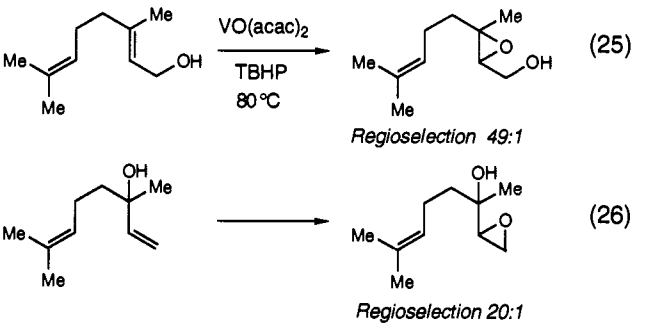


Later reports indicated that the diastereoselective epoxidation of an allylic and a homoallylic alcohol by $VO(acac)_2$/TBHP, as well as the regioselective epoxidation of 1,5-hexadien-3-ol (eq 24).[84,85]



(24)

Olefinic alcohols are epoxidized with regio- and stereocontrol by TBHP in the presence of either $Mo(CO)_6$ or $VO(acac)_2$.[86] The site-selective epoxidation of geraniol and linalool (eqs 25 and 26) illustrates that hydroxyl groups are able to deliver the oxidant regioselectively to the less electron-rich alkene of a diene.



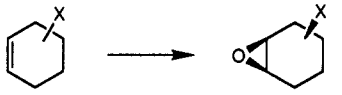
(25)

(26)

Sharpless and co-workers quantified the enhanced reactivity observed as a result of a directing functionality (Table 17).[87] In contrast to directed peracid epoxidation (Table 12),[88] where introduction of a hydroxyl group has a net *deactivating* impact on olefin reactivity, the metal-catalyzed reaction shows a dramatic overall *rate enhancement*.[89] Allylic, homoallylic, and even bishomoallylic alcohols are substantially more reactive toward epoxidation by $VO(acac)_2$/TBHP than are the analogues lacking an OH. In cyclic systems, high levels of syn stereoselectivity are observed (Table 17), consistent with oxygen atom transfer within an intramolecular complex.

Although a detailed mechanistic pathway for these metal-catalyzed epoxidations has not been elucidated, based on the available data, Sharpless has proposed that the vanadium-catalyzed reaction proceeds through the cycle depicted in Scheme 16.[57] The lower-valent $VO(acac)_2$ complex is oxidized by TBHP to a catalyt-

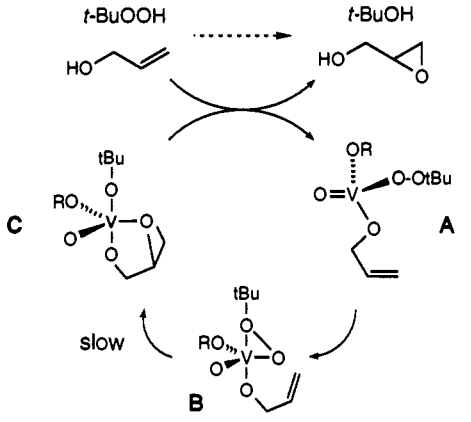
Table 17. Relative Rates (Diastereoselectivities) for the Epoxidation of Cyclohexene Derivatives



Substrate	k_{rel}[a,b] (diastereoselectivity[c])		
	peracid	$Mo(CO)_6$	$VO(acac)_2$
	1.00	1.00	1.00
	0.55 (92 : 8)	4.5 (98 : 2)	>200 (98 : 2)
	0.046 (37 : 63)	0.07 (40 : 60)	--
	0.42 (60 : 40)	11.0 (98 : 2)	10.0 (98 : 2)

[a] The relative rate data apply only to a given column. [b] The peracid relative rates are reported in ref 87. [c] The values in parentheses refer to the ratio of syn:anti epoxide.

Scheme 16



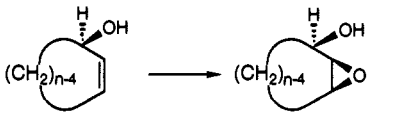
ically active d^0 vanadate ester ($VO(OR)_3$),[90-92] which undergoes rapid ligand exchange[93] to provide A. Following activation of the alkylperoxide by bidentate coordination (B),[94] nucleophilic attack by the alkene in the rate- and stereochemistry-determining step yields the epoxy alcohol complex C.

Applications of hydroxyl-directed,[95,96] metal-catalyzed epoxidation in organic synthesis are discussed below.[97-99] As the issue of diastereoselectivity constitutes the primary focus, where possible, working transition state models based on the Sharpless mechanism are provided.

B. Metal-Catalyzed Epoxidation of Cyclic Olefins

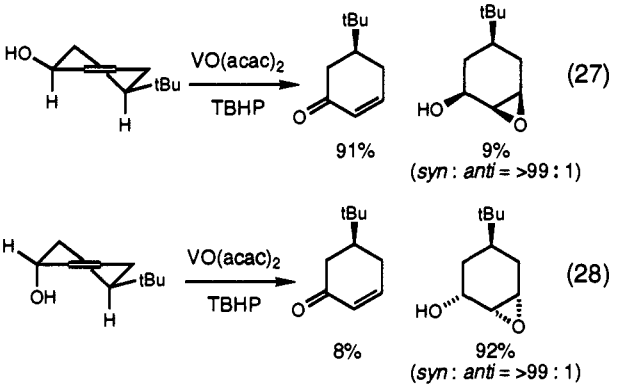
Sharpless demonstrated that directed epoxidation of cyclohexenols occurs syn to the hydroxyl group.[86] Subsequent reports provided a more comprehensive examination of reactions of cyclic olefinic alcohols.[100,101] In contrast to epoxidations with *m*-CPBA or $MoO_2(acac)_2$, for which formation of the anti epoxy alcohol is favored for medium (eight- and nine-) membered rings, $VO(acac)_2$-catalyzed reactions display a preference for the syn product for all ring sizes from five to nine (Table 18).[102] Oxidation of the allylic alcohol to the enone[103] can be a significant side reaction, particularly for substrates in which the hydroxyl group is strongly disposed to lie in a pseudoequatorial position.

Table 18. Percent Syn Isomer in the Epoxidation of Cyclic Allylic Alcohols



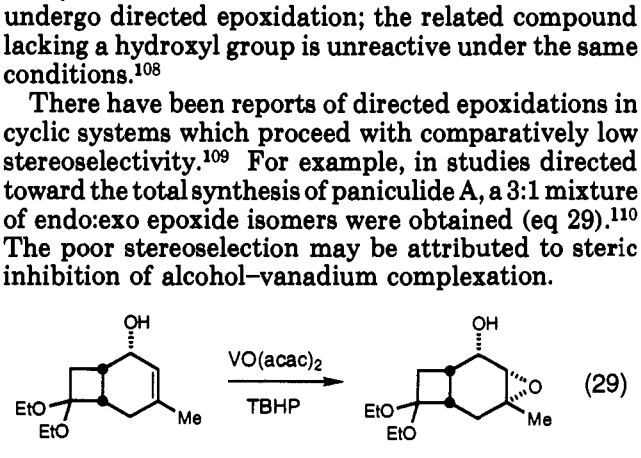
n	$VO(acac)_2$	$MoO_2(acac)_2$	*m*-CPBA
5	99.2	--	84
6	99.7	98	95
7	99.6	95	61
8	97	42	0.2
9	91	3	0.2

In the reaction of 5-*tert*-butyl-2-cyclohexenol, the pseudoaxial alcohol undergoes epoxidation 34 times faster than the pseudoequatorial diastereomer, whereas the latter alcohol is oxidized to the enone about three times faster than the former (eqs 27 and 28).[104,105] These data suggest a preferred epoxidation geometry wherein the hydroxyl group is oriented well above the nodal plane of the alkene π system.



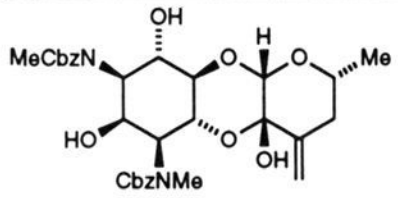
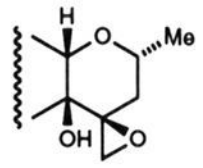
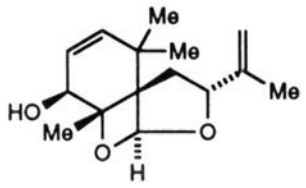
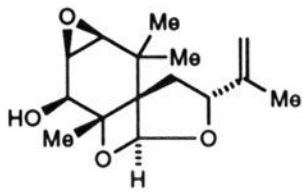
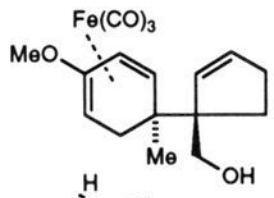
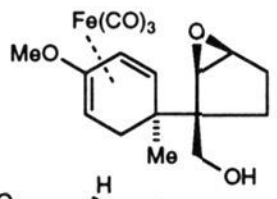
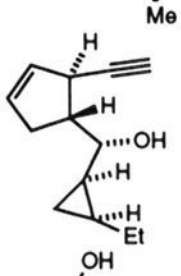
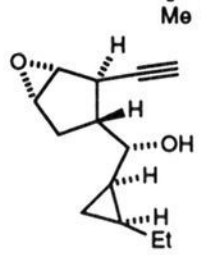
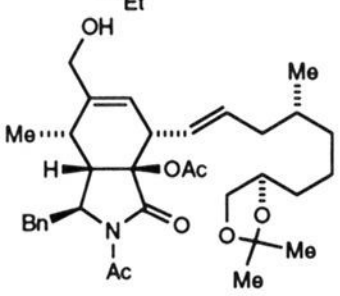
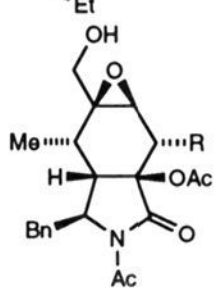
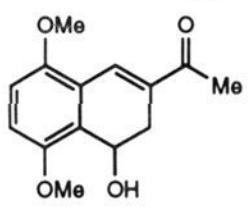
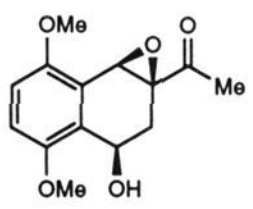
Allylic, homoallylic, and bishomoallylic alcohols direct epoxidations effectively and a range of functional groups are compatible with the reaction conditions (Table 19).[106] In the example shown in entry 5, the hydroxyl group provides regioselectivity while the topography of the substrate dictates facial selectivity.[107] Entry 6 demonstrates that electron-deficient olefins undergo directed epoxidation; the related compound lacking a hydroxyl group is unreactive under the same conditions.[108]

There have been reports of directed epoxidations in cyclic systems which proceed with comparatively low stereoselectivity.[109] For example, in studies directed toward the total synthesis of paniculide A, a 3:1 mixture of endo:exo epoxide isomers were obtained (eq 29).[110] The poor stereoselection may be attributed to steric inhibition of alcohol–vanadium complexation.



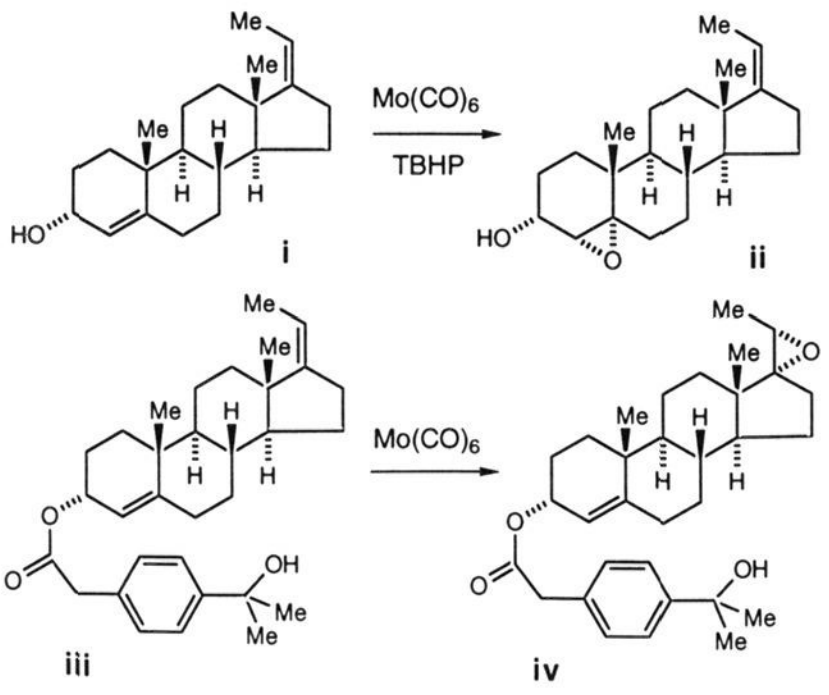
Scheme 17 illustrates an epoxidation method that involves incorporation of a removable functionality bearing a hydroxyl group positioned for delivering an

Table 19. Mo-Catalyzed Epoxidation of Cyclic Olefinic Alcohols

Entry	Substrate	Product	Yield (%)
1			78
2			94
3			90
4			87
5[a]			95
6			--

[a] Catalyst: $Mo(CO)_6$.

Scheme 17



oxidant to a nearby alkene.[111] Site-selective directed epoxidation of remote olefins was achieved, and the geometrical requirements for reaction were shown to be stringent. Whereas epoxidation of i provides ii as the only product, reaction of the derived hydroxy ester iii produces only iv. Interestingly, attempted epoxidation of the meta isomer of iii results in no detectable reaction under these conditions.

There have been numerous reports on the stereoselective directed epoxidation of complex macrocycles (Table 20).[112] The requirement of hydroxyl delivery for reaction permits regioselective epoxidation of polyene systems. Analogous regioselectivity is not observed with *m*-CPBA. For example, in the epoxidation illustrated in entry 2, reaction with peracid occurs preferentially at the *trans*-olefin. As is indicated in entry 5, treatment with *m*-CPBA produces a mixture of products resulting from competitive epoxidation of all three olefins.

C. Metal-Catalyzed Epoxidation of Acyclic Olefins

1. Allylic Alcohols

High levels of organization in the transition state of a reaction often result in high levels of acyclic stereocontrol. A systematic study of diastereocontrol in epoxidation reactions of acyclic allylic alcohols was performed by Sharpless;[113] a representative set of the data reported in this study are illustrated in Table 21.

A three-dimensional depiction of a reasonable transition structure,[114] essentially identical to the model suggested by Sharpless, is shown in Figure 5.[57] The O—C—C=C dihedral angle in the allylic alcohol is about 40°.[115] The salient interactions are (1) A(1,2) strain[22] between R_{gem} and R_1,[116] favoring the erythro isomer; (2) A(1,3) strain between R_2 and R_{cis}, favoring the threo isomer; (3) 1,3-interaction between L and R_1, favoring the erythro isomer; (4) hyperconjugative donation (σ_{C-R_2} to $\pi^*_{C=C}$), which increases the nucleophilicity of the olefin, favoring the erythro isomer.

Careful analysis of experimental data leads to the conclusion that minimization of A(1,2) or A(1,3) strain typically dictates the observed sense of epoxidation. For terminal or trans olefins, where these interactions are comparatively weak, otherwise subordinate steric and electronic effects become important (Scheme 18).

The patterns of erythro selectivity illustrated in Table 22 are consistent with the trends predicted by the above model.[117] Comparison of entry pairs (1, 2), (3, 4), and (5, 6) reveals a modest sensitivity to the steric bulk of R_α, whereas entries 1, 3, and 7 show a substantial dependence on the size of R_{gem}.

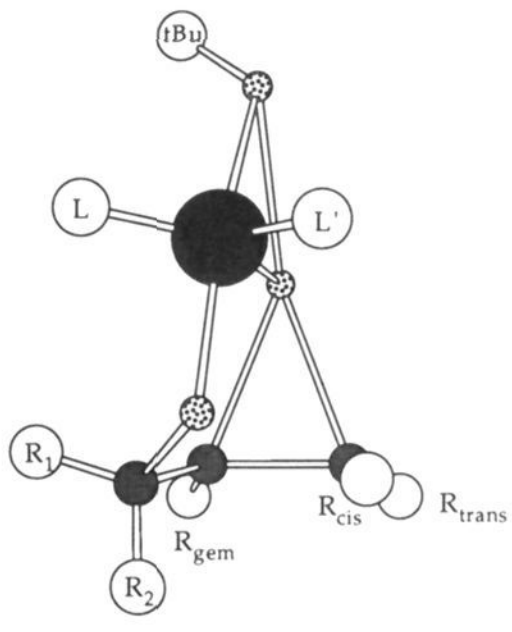
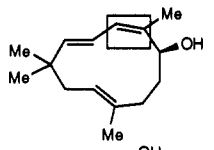
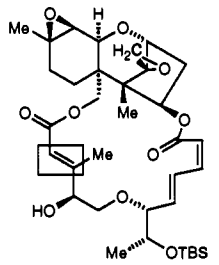
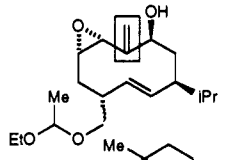
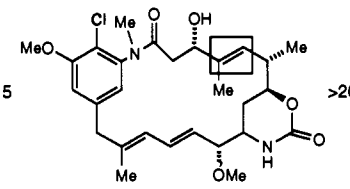
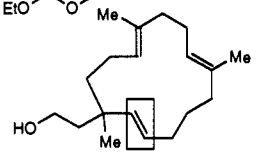


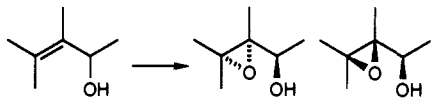
Figure 5. Transition structure for metal-catalyzed allylic alcohol epoxidation.

Table 20. Epoxidation of Macrocyclic Olefinic Alcohols[a]

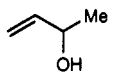
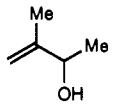
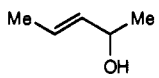
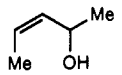
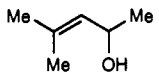
Entry	Substrate	Selectivity	Entry	Substrate	Selectivity
1		9 : 1 (α)	4		single epoxide (α)
2		single epoxide (β)	5		>200 : 1 (β)
3		1 : 1			

[a] Site of epoxidation indicated with a box.

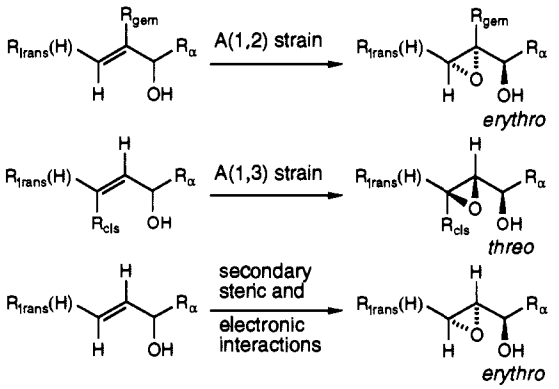
Table 21. Epoxidation Selectivity of Allylic Alcohols



erythro : *threo*

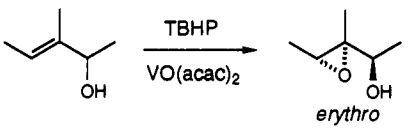
Entry	Substrate	$VO(acac)_2$	$Mo(CO)_6$	*m*-CPBA
1		4 : 1	1 : 1	1 : 1.5
2		19 : 1	5 : 1	1 : 1
3		2.5 : 1	1 : 1.5	1 : 1.7
4		1 : 2.4	1 : 5	1 : 19
5		1 : 5	1 : 19	1 : 19

Scheme 18



This sensitivity of reaction diastereoselection to the bulk of R_{gem} has been exploited in a number of applications in synthesis.[118] Thus, use of a trimethylsilyl group as a dummy substituent[119,120] affords a route to diastereomerically pure erythro epoxy alcohols (diastereoselection >25:1, eq 30).[121]

Table 22. Erythro-Selective Epoxidation of Allylic Alcohols



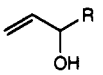
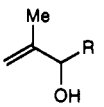
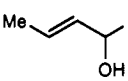
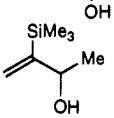
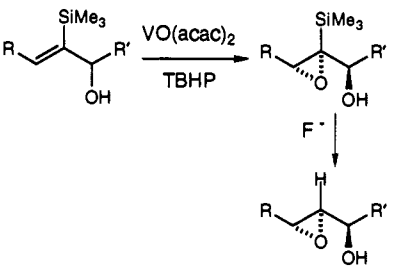
Substrate	Entry	R	*Erythro*:*Threo*
	1	Me	4 : 1
	2	*i*-Pr	5.6 : 1
	3	Me	19 : 1
	4	Bu	49 : 1
	5	Me	2.4 : 1
	6	*t*-Bu	3.7 : 1
	7		>99 : 1

Table 23[122] presents examples of epoxidations of more highly functionalized acyclic systems.[123] The level of erythro selectivity is comparable to that observed with

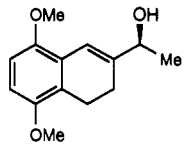
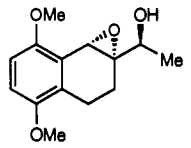
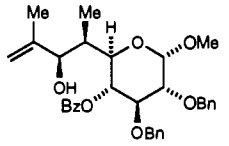
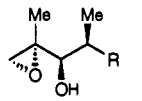
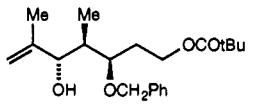
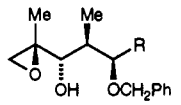
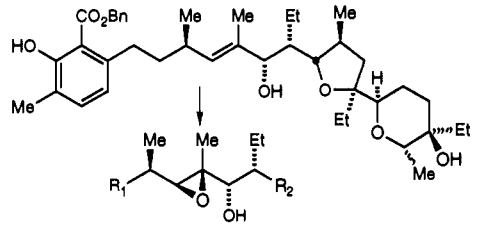


(30)

the simpler substrates.[124] Entries 2 and 3 indicate that the α-stereocenter is the dominant stereocontrol element.[125]

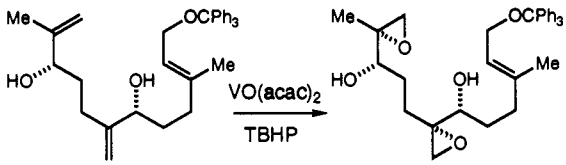
The erythro-selective epoxidation of two allylic alcohols shown in eq 31, key step in the synthesis of *dl*-C_{18} *Cecropia* juvenile hormone, has been performed by a one-pot operation.[126,127]

Table 23. Erythro-Selective Epoxidation of Allylic Alcohols: Applications

Entry	Substrate	Product	Selectivity[a]
1			24 : 1
2			only (8 : 1)
3			only
4			10 : 1 (7 : 3)

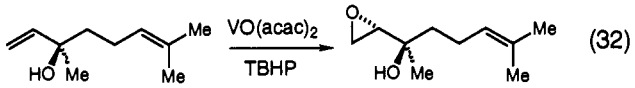
[a] Values in parentheses refer to selectivity observed with *m*-CPBA.

Equations 32 and 33 provide examples of stereoselective epoxidations of tertiary allylic alcohols.[128,129] In



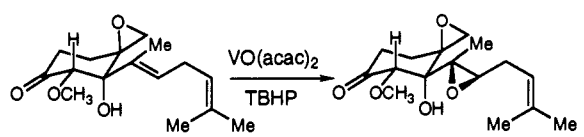
(31)

general, the reaction proceeds with low levels of selectivity, as one would predict from the A(1,2) strain-based model discussed earlier. However, the Corey synthesis of (±)-ovalicin, which employs directed epoxidation as the ultimate step (eq 33), affords a rare example of a highly stereoselective epoxidation of a tertiary allylic alcohol.[128d]



(32)

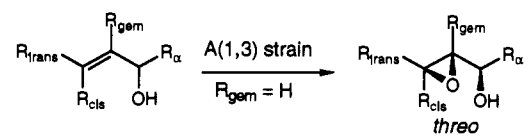
Diastereoselection 2:1



(33)

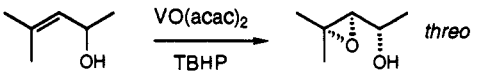
Diastereoselection >20:1

As noted above, allylic alcohols bearing R_{cis} but no R_{gem} undergo a threo-selective epoxidation. Table 24[130] shows that as the bulk of R_{cis} (entries 1 and 2) or R_{anti} (entries 2 and 3) increases, the diastereoselectivity increases, in accord with the prediction of the A(1,3)-

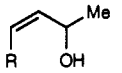
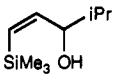
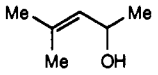


threo

Table 24. Threo-Selective Epoxidation of Allylic Alcohols

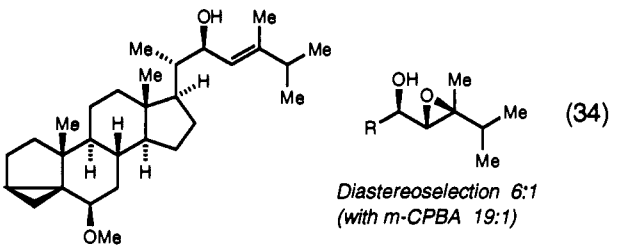


threo

Substrate	Entry	R	*Threo* : *Erythro*
	1	Me	3 : 1
	2	$SiMe_3$	24 : 1
	3		>99 : 1
	4		6 : 1

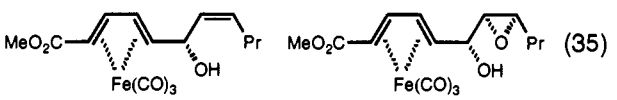
strain[22] model. A sufficiently bulky R_{cis} substituent may override the normal erythro preference of allylic alcohols which bear R_{gem}.[118]

Equations 34–36 are examples of threo-selective epoxidation in more complex systems.[131] The reaction in eq 35 demonstrates that a diene complexed to iron tricarbonyl is stable to the reaction conditions. In studies directed toward the total synthesis of tirandamycin A, a directed epoxidation of the diol shown in eq 36 was realized; no rationale was offered for the observed stereoselectivity.[131c]



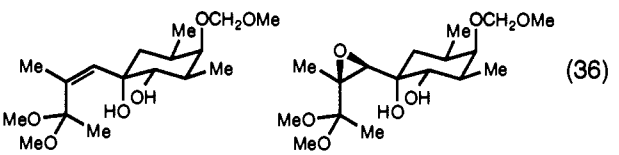
(34)

Diastereoselection 6:1 (with m-CPBA 19:1)



(35)

Diastereoselection 1.5:1



(36)

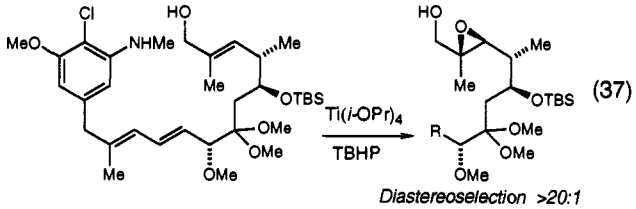
Diastereoselection >20:1 (with m-CPBA 9:1)

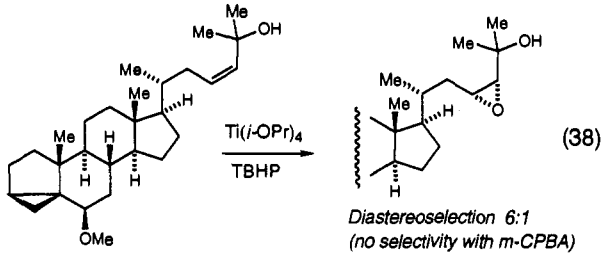
Diastereoselective epoxidation of allylic alcohols where the hydroxyl-bearing carbon is not a stereogenic center has been achieved (Table 25).[132] In these reactions, the role of the hydroxyl group is to enhance the reactivity of the olefin, while the allylic stereocenter dictates the facial selectivity. First-order models for electrophilic addition to olefins do not properly rationalize these results (entries 1 vs 2; 3 vs 5, Table 25).[133]

Entries 3–5 of Table 25 illustrate cases of stereoselective Ti(O*i*-Pr)$_4$-catalyzed epoxidation of allylic alcohols. Equation 37 depicts the selective oxidation performed in the synthesis of racemic maysine.[132b] Equation 38 illustrates a case of epoxidations of allylic alcohols where a remote *homoallylic* stereocenter controls the diastereoselection; no rationale was provided for these results (eq 38).[134]

Table 25. Epoxidation Diastereocontrol by Other Stereocenters

Entry	Substrate	Product	Reagent	Selectivity
1	R = H		$VO(OEt)_3$	5 : 1
2	R = CH_2OBn		$VO(OEt)_3$	1 : 3.5
3	R = $(CH_2)_4OTBS$		$Ti(O\text{-}i\text{-}Pr)_4$ $VO(acac)_2$ *m*-CPBA	10 : 1 1.5 : 1 1 : 99
4	R = CH_2CH_2Ph		$Ti(O\text{-}i\text{-}Pr)_4$ $VO(acac)_2$ *m*-CPBA	2.3 : 1 2.5 : 1 >25 : 1
5	R = CH_2CH_2Ph		$Ti(O\text{-}i\text{-}Pr)_4$	5.7 : 1





2. Homoallylic Alcohols

In 1981, Mihelich reported the first systematic study of the diastereoselective epoxidation of acyclic homoallylic alcohols.[135] Substrates bearing a stereocenter either α or β to the alkene were found to undergo epoxidation with high levels of stereocontrol (entries 1 and 2). It is worthy of note that the diastereoselection observed for (*Z*)-2-methyl-3-penten-1-ol (entry 1) is higher than that observed for its allylic homologue (Table 26, entry 4). With an α- and a β-stereocenter present, the former appears to be the dominant stereocontrolling element (entries 3 and 4).

Other classes of alkenes have not been studied as systematically, but there are indications that, in general, oxidations proceed with somewhat lower levels of selectivity (Table 27, entries 1–3, 5, and 6).[136] As with allylic alcohols, use of a removable trimethylsilyl group at the R_{gem} position to control diastereoselection can be effective (entry 5 vs 7). This strategy was used in a synthesis of the C(1)–C(7) segment of 6-deoxyerythronolide B.[136d] The approach fails with the corresponding anti isomer (entry 8).

Mihelich has proposed that both the sense and the magnitude of asymmetric induction may be predicted through comparison of two diastereomeric chairlike transition states.[137] According to this model (Figure 6,

Table 26. Epoxidation of Cis Homoallylic Alcohols[a]

Entry	Substrate	Product		Selectivity
1				>400 : 1
2				12 : 1
3			a. R = Me b. R = $CH(CH_3)_2$	104 : 1 >400 : 1
4			a. R = Me b. R = $CH(CH_3)_2$	70 : 1 2.1 : 1

[a] Conditions: TBHP, $VO(acac)_2$.

Table 27. Epoxidation of Homoallylic Alcohols[a]

Entry	Substrate	Product	Selectivity
1			2 : 1
2			4.6 : 1
3	R = $(CH_2)_7CO_2Me$		1.4 : 1
4			"only"
5			1.5 : 1
6			8 : 1
7			>99 : 1
8			2 : 1

[a] Conditions: TBHP, $VO(acac)_2$.

box), the sense of stereoselection is governed by the minimization of A(1,3) strain between R_4 and R_7, and better selectivity is generally obtained when the substituent α to the alcohol is oriented in the less encumbered pseudoequatorial orientation. Our analysis (Figure 6) largely echoes that of Mihelich. Only geometries i and ii, which afford diastereomeric products, obey the constraints suggested by molecular models. For *cis*-olefins, i, which corresponds to the transition structure in Figure 6, is greatly preferred over ii due to the highly unfavorable R_1–R_7 interaction present in the latter. However, for substrates with R_7 = H (Table 27), low levels of diastereoselection are

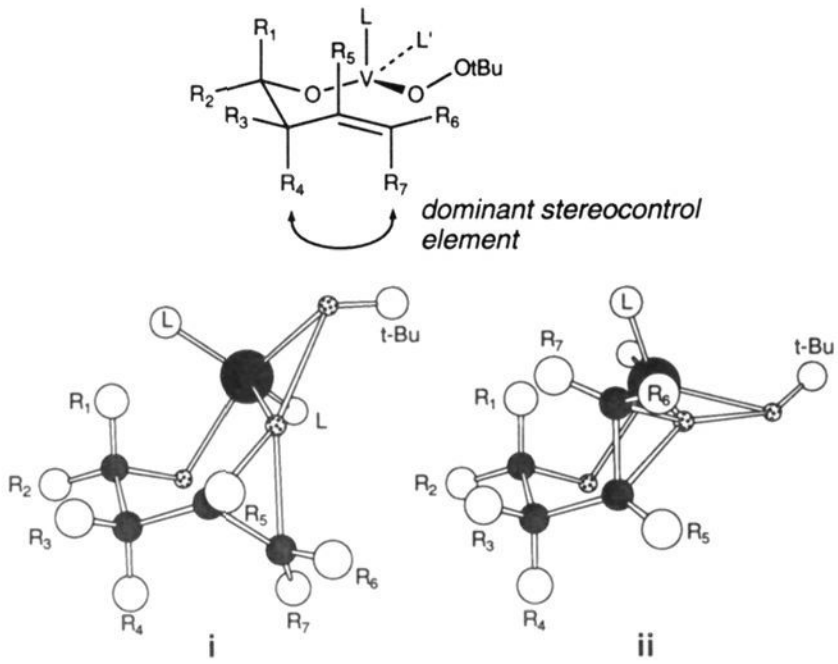
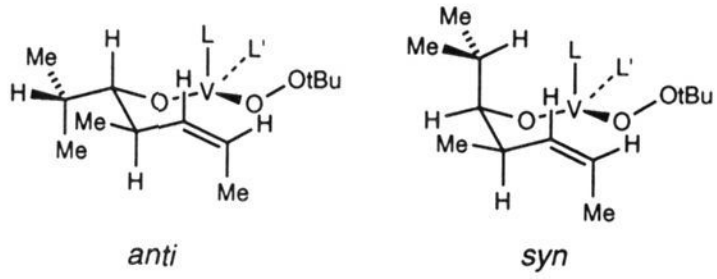


Figure 6. Transition structure for metal-catalyzed homoallylic alcohol epoxidation.

observed since structure ii is now of comparable energy to i (Figure 6).

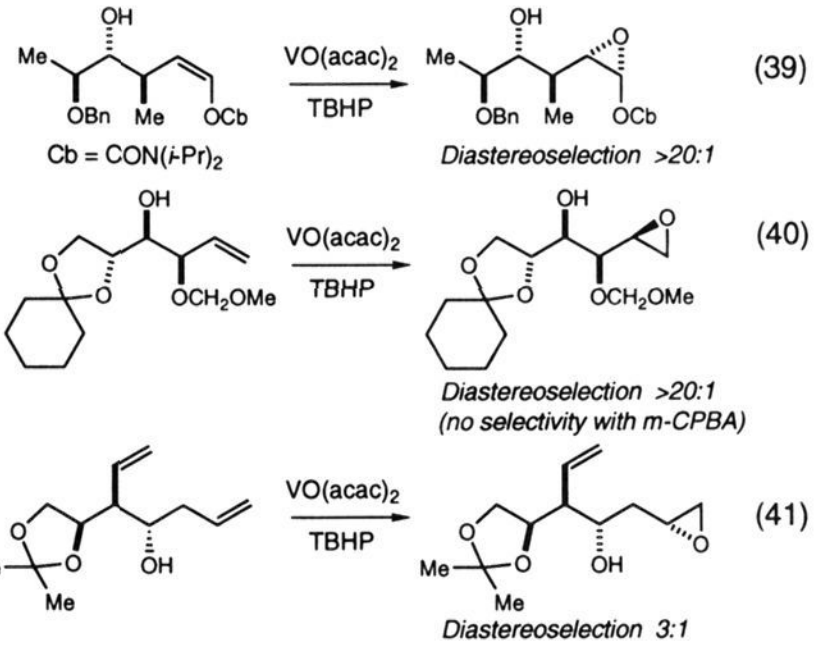
The seemingly anomalous result shown in entry 4b of Table 26 is accommodated within this analysis.[138] Structure i suggests that the anti isomer should provide slightly higher diastereoselection than the syn compound, since both substituents occupy pseudoequatorial positions in the transition state (R_2 and R_3). The relative selectivities displayed in entries 3a and 4a are consistent with this paradigm. The dramatic difference in stereoselection observed for entries 3b and 4b may at first appear puzzling. However, closer inspection of the transition structure reveals the key role played by the isopropyl group: whereas for the anti compound this group may adopt a conformation devoid of destabilizing interactions, for the syn isomer avoiding an unfavorable *syn*-pentane relationship is not feasible.



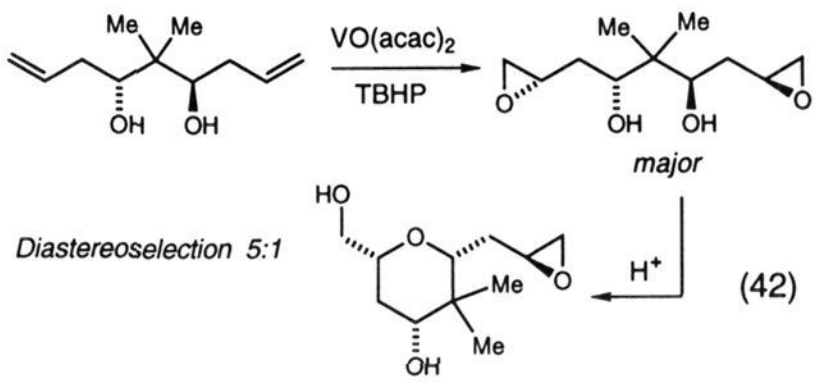
Equations 39–41 present several diastereoselective epoxidations of more highly functionalized homoallylic alcohols.[139] Enol carbamates are epoxidized with high selectivity; for the case shown in eq 39, the stereochemistry of the γ-carbon plays no appreciable role in the stereodifferentiation. The transformation shown in eq 40 offers a rare example of a highly stereoselective epoxidation of a homoallylic alcohol bearing no cis substituent.[140] The diastereoselectivity obtained in the course of a synthesis of the C_{14}–C_{20} unit of amphotericin B is more typical (eq 41). The site specificity of this reaction has been attributed to the presence of an additional 1,3-interaction in the transition state of the less reactive alkene.[141]

Epoxidation of alkenes in the symmetrical diene shown in eq 42, followed by acid-catalyzed cyclization results in the formation of a 5:1 mixture of pyran diastereomers.[142]

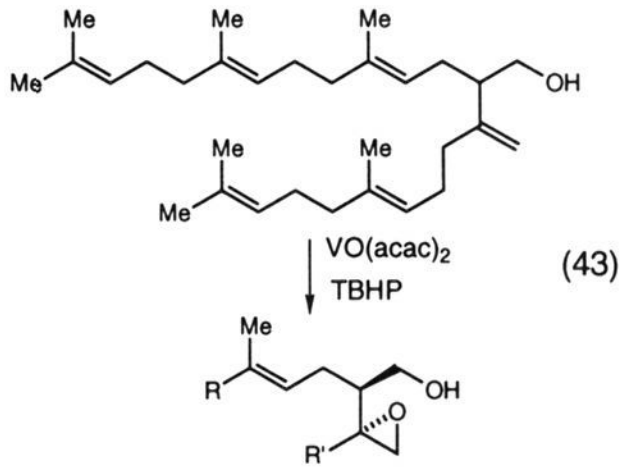
The stereo- and regiospecific epoxidation of a polyene on route to a synthesis of (±)-bifarnesol (eq 43) affords



yet another example of hydroxyl-mediated regio- and stereocontrol. Oxidation through the intermediacy of

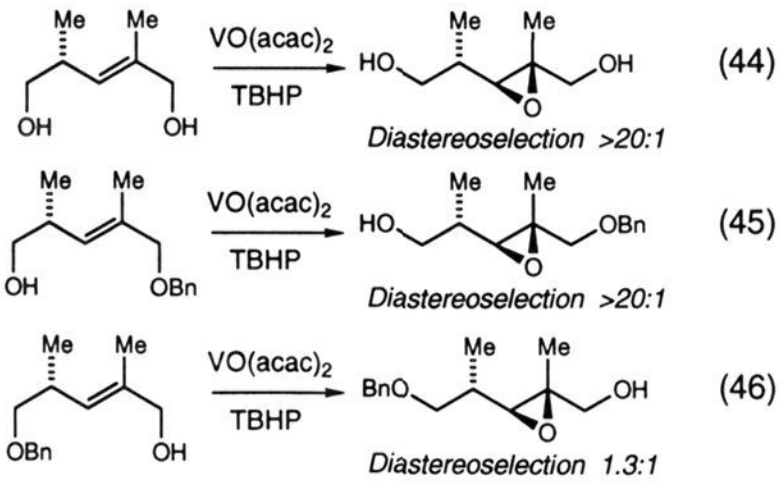


transition structure i (Figure 7), where the triene unit occupies R_4 to minimize A(1,2) strain, offers a plausible rationale for the observed selectivity.[143]

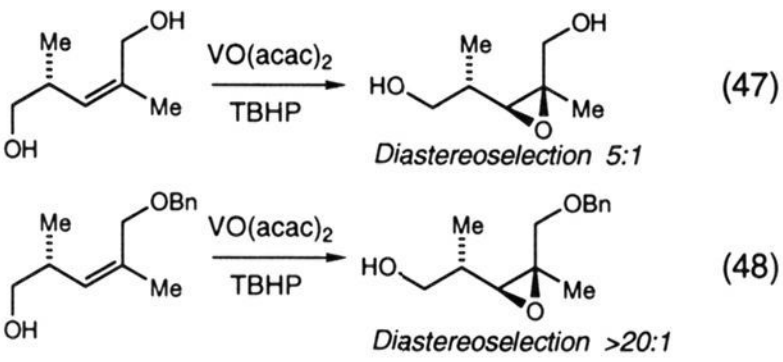


Equations 44–46 illustrate three epoxidations where either an allylic or a homoallylic heteroatom may direct the course of the reaction.[71,144] For the *trans*-olefin, epoxidation of the allylic benzyl ether affords the same sense and level of stereoselectivity as that of the diol (eq 44 and 45). In contrast, when the homoallylic alcohol is protected, epoxidation proceeds essentially stereorandomly (eq 46); this is consistent with exclusive binding of the allylic alcohol to the metal center as the source of diastereoselectivity in eq 44. These data require a transition state that involves participation of the homoallylic hydroxyl, but neither preclude nor demand the simultaneous involvement of the allylic hydroxyl group.

For the *cis*-alkene, the data suggest a role in diastereoselection for the allylic (eqs 47 and 48), as well as for the homoallylic, hydroxyl group; whether these groups interact independently or simultaneously (or



both) with vanadium is unclear. Comparison of the relative rates of epoxidation within each set of substrates might provide additional insight with regard to the nature of the vanadium-alcohol interactions responsible for the observed diastereoselectivity.[145]

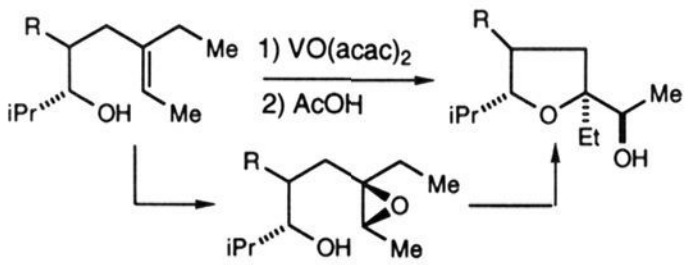


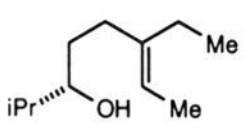
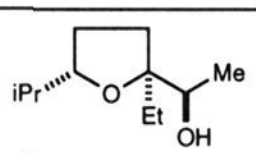
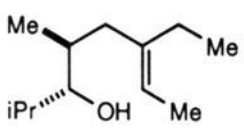
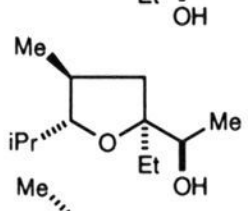
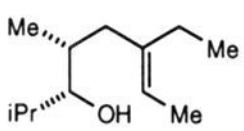
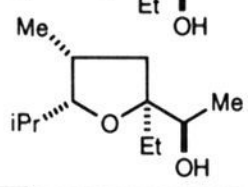
3. Bishomoallylic and Trishomoallylic Alcohols

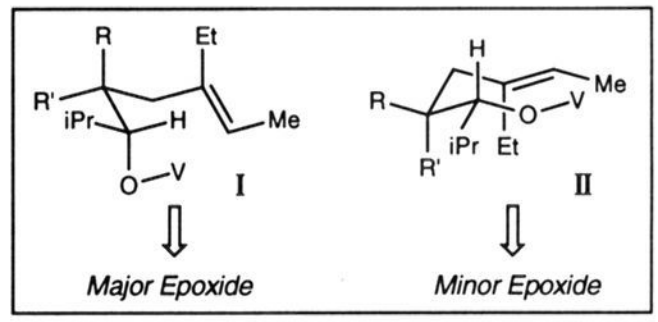
In connection with the synthesis of lasalocid A, the first diastereoselective directed epoxidations of bishomoallylic alcohols was realized (Table 28).[146] Efficient 1,4-asymmetric induction was achieved; the stereocenter α to the alcohol appears to play a dominant role over the β-site in determining the sense of observed induction.

The two distinct transition structures illustrated in Figure 7 (box) were proposed by Kishi. Models indicate that structure I (Figure 7) best fulfills the steric, stereoelectronic, and geometrical constraints for epoxidation. To avoid a destabilizing transannular interaction, the substituent α to the hydroxyl group

Table 28. Epoxidation of Bishomoallylic Alcohols



Entry	Substrate	Product	Selectivity
1			9 : 1
2			6 : 1
3			>20 : 1



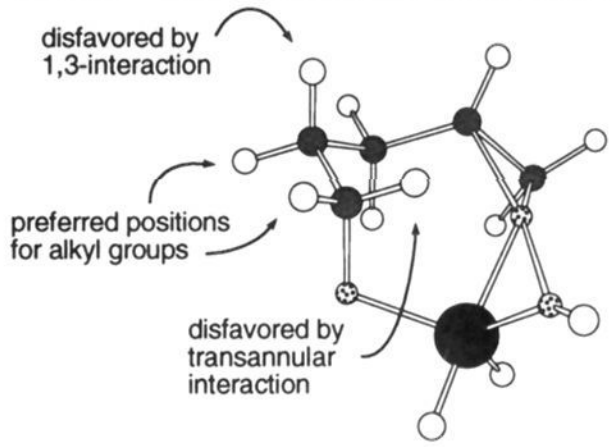
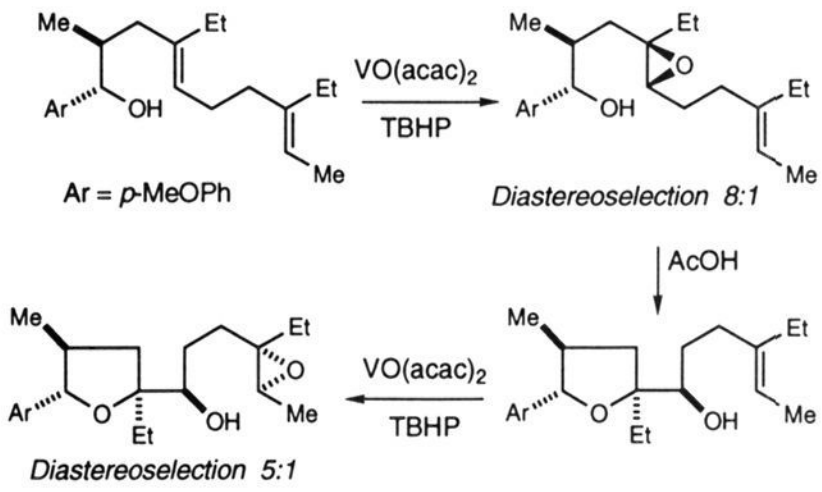


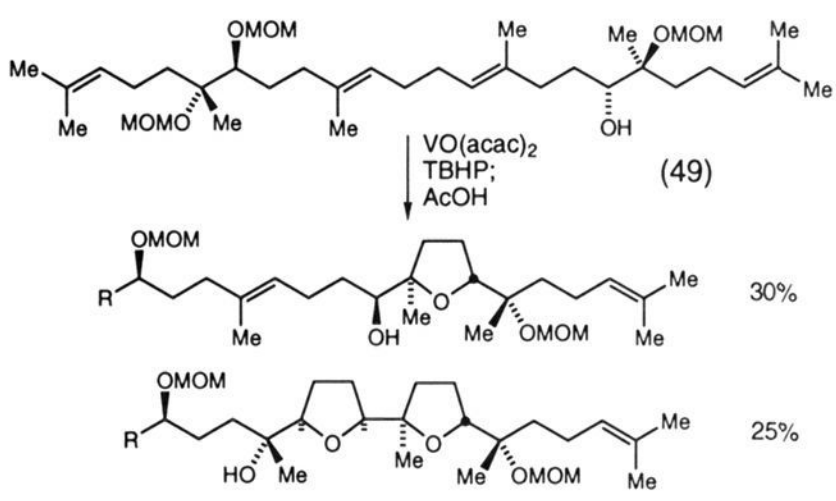
Figure 7. Transition structure for metal-catalyzed bishomoallylic alcohol epoxidation.

Scheme 19



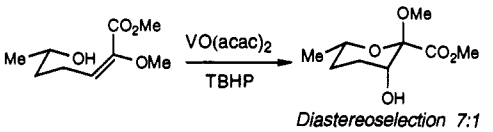
occupies the "outside" position in I; this accounts for the sense of stereoselection shown in entry 1 (Table 28).[147] Kishi's model offers a tenable rationale for the trends indicated in entries 2 and 3. Replacement of hydrogen with alkyl at R destabilizes I more than it does II (by an additional 1,3-interaction), leading to decreased stereoselectivity (entry 1 vs 2). Similarly, replacement of hydrogen with alkyl at R′ results in higher stereoselectivity (entry 1 vs 3).

Iterative epoxidation has been utilized as a key sequence in a number of synthesis plans; Kishi's lasalocid A synthesis is illustrative (Scheme 19).[148] Other syntheses of polyether antibiotics have helped to define further the scope of the diastereoselective epoxidation of bishomoallylic alcohols.[149]



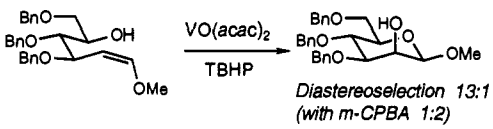
Directed epoxidation has been used for the construction of a bis(tetrahydrofuran) intermediate in the synthesis of teurilene (eq 49).[150] Despite the low yield, the reaction is worthy of note, as it represents the first report of a successful propagating epoxidation–cyclization.

The epoxidation of bishomoallylic alcohols has also found use in the synthesis of glycosides (eqs 50 and 51).[151] The first example of a stereoselective hydroxyl-directed epoxidation of a trishomoallylic alcohol is illustrated in eq 52.[152]



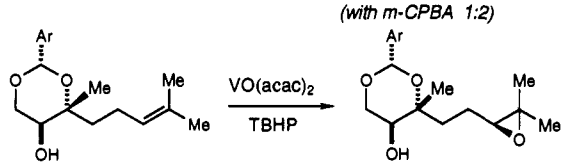
(50)

Diastereoselection 7:1
(no selectivity with m-CPBA)



(51)

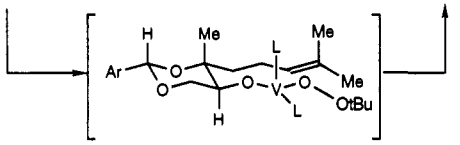
Diastereoselection 13:1
(with m-CPBA 1:2)



(52)

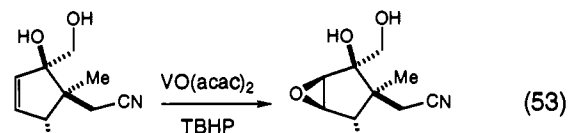
Ar = 3,4-dimethoxyphenyl

Diastereoselection 6.5:1



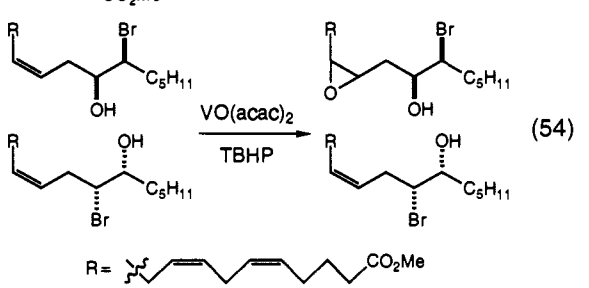
D. Relative Reactivity of Homologous Olefinic Alcohols

In general, the reactivity of an olefinic alcohol depends on the proximity of the hydroxyl group to the alkene.[80,86] In studies directed toward the synthesis of vitamin B-12, the superior directing ability of an allylic to a homoallylic hydroxyl group was demonstrated (eq 53).[153] Furthermore, as is illustrated in eq 54, the differential reactivity of homoallylic and bishomoallylic alcohols has been exploited in the separation of a mixture of bromohydrins formed in route to the synthesis of a family of eicosanoids.[154]



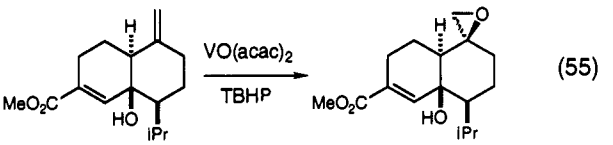
(53)

Diastereoselection >20:1

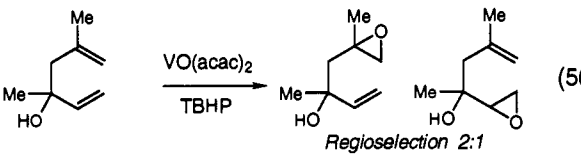


(54)

There have been several accounts of preferential epoxidations of a homoallylic alcohol in the presence of an allylic system (eqs 55–58).[155] The low nucleophilicity of an enoate π-system provides an explanation for the $Mo(CO)_6$-catalyzed epoxidation shown in eq 55;[106p] in contrast, the outcome shown in eq 56 is somewhat surprising.[155b] Equation 57 illustrates an epoxidation where either diastereomer of the diol shown affords the derived α-epoxide as a single isomer.[106f] Only the homoallylic alcohol dictates the facial selectivity, overriding the high erythro preference observed when this hydroxyl is either protected or removed (Table 23, entry 1); reaction by way of a chelated substrate–metal complex is not geometrically feasible. The transformation depicted in eq 58 is consistent with direction by a homoallylic hydroxyl in preference to an allylic hydroxyl group. Competition experiments both within each class of olefinic alcohols and among homologues would provide insight into the factors determining the relative rates of directed epoxidations.

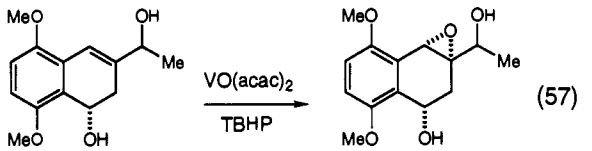


(55)

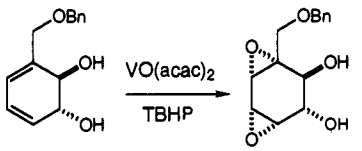


(56)

Regioselection 2:1



(57)



(58)

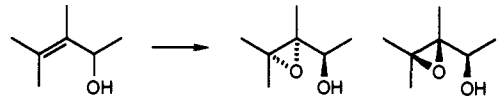
E. Other Metal Catalysts for Directed Epoxidation

A variety of reagents other than vanadium[91] and molybdenum[92] complexes selectively epoxidize allylic alcohols in the presence of isolated olefins, but most of these systems have not been examined extensively. Niobium, zirconium, tantalum, hafnium, titanium, and a number of lanthanide alkoxides effect the regioselective epoxidation of geraniol with TBHP,[156] but only $Ti(Oi\text{-}Pr)_4$ has found use in the synthesis of complex molecules.[157] Treatment of geraniol with oxo(tetraphenylporphyrinato)titanium(IV) and TBHP regiospecifically produces the 2,3-epoxy alcohol,[158] an observation which is not accommodated by a Sharpless-type mechanism, where three coordination sites on the same side of the porphyrin are required. Arenearsonic acids ($ArAsO(OH)_2$) in combination with aqueous H_2O_2 effect site-selective epoxidation of geraniol (22:1), as well as syn epoxidation of 2-cyclohexen-1-ol (20:1).[159] The reaction is postulated to occur via the allyl arsonate.

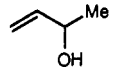
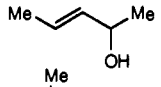
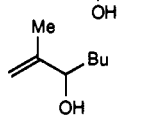
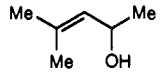
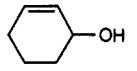
Three directed epoxidation systems have been studied in some detail: H_2WO_4/H_2O_2,[160] $Al(Ot\text{-}Bu)_3$/TBHP,[161] and Bu_2SnO/TBHP.[153c] For each, epoxidation of geraniol provides the 2,3-epoxy alcohol exclu-

sively. The erythro/threo selectivity of these catalysts for typical allylic alcohols is shown in Table 29.[162] The tungstic acid diastereoselection resembles that of VO(acac)$_2$; the aluminum *tert*-butoxide, Mo(CO)$_6$. Tin-catalyzed epoxidation is responsive both to the nucleophilicity of the olefin and to the proximity of the hydroxyl group.[153c]

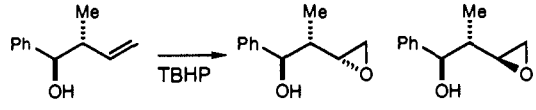
Table 29. Epoxidation Selectivity of Various Metal Catalysts



erythro : *threo*

Substrate	V	W	Mo	Al	Sn
	80 : 20	85 : 15	56 : 44	58 : 42	--
	71 : 29	60 : 40	38 : 62	36 : 84	--
	98 : 2	95 : 5	84 : 16	87 : 13	90 : 10
	14 : 86	10 : 90	5 : 95	<0.5 : >99.5	5 : 95
	98 : 2	95 : 5	98 : 2	>99.5 : <0.5	--

The only reported example of an epoxidation of a homoallylic alcohol by Al(O*t*-Bu)$_3$/TBHP (eq 59) is promising,[163] since the reaction affords the opposite sense of diastereoselection to VO(acac)$_2$. The tungstic acid system delivers low levels of selectivity with this class of substrates, whereas epoxidation with Bu$_2$SnO is too sluggish to be useful in synthesis. More recently, a variety of lanthanide alkoxides were reported to be effective epoxidation catalysts; for example, Yb(O*i*-Pr)$_3$ (10 mol %) effects the site-selective oxidation of the allylic alcohol of geraniol (23:1).[164] The full scope and utility of these catalysts for the epoxidation of allylic and homoallylic alcohols has yet to be explored fully.



(59)

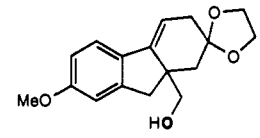
Al(O*t*-Bu)$_3$ *Diastereoselection 4 : 1*

VO(acac)$_2$ *Diastereoselection 1 : 3*

V. Directed Heterogeneous Hydrogenation Reactions

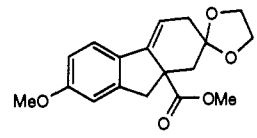
The stereochemical course of heterogeneous hydrogenation reactions may be influenced by a neighboring heteroatom.[165] Association of an internal polar group with the metal surface can lead to the delivery of hydrogen to the unsaturation site in a syn fashion. This catalyst–substrate interaction may be largely preempted or facilitated, depending on the nature of the metal, the support, or the solvent employed.

For example, catalytic hydrogenation of the tricyclic alcohol shown below affords the syn isomer as the major product (eq 60, 5% Pd/C, 15 psi H$_2$, EtOH).[166] The stereochemical outcome implies that the substrate is bound to the catalyst surface on the same side as the hydroxy group and that this affinity results in the addition of hydrogen syn to the coordinating moiety. Reduction of the corresponding ester derivative under identical conditions leads to the predominant formation of the anti system (eq 61).



(60)

Diastereoselection 95:5



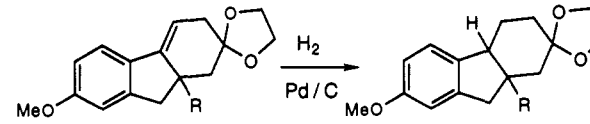
(61)

Diastereoselection 86:14

As is illustrated in Table 30, for this olefinic substrate the level and sense of asymmetric induction is greatly dependent on the nature of the heteroatom.[167] Although the primary alcohol and the aldehyde functionalities can perform well as directing groups, with an amide or a ketone the stereochemical course of the reduction is largely influenced by steric factors: the anti isomer is isolated as the major product. The stereoselectivity trends that are illustrated in Table 30 cannot be correlated with the directing group's physical properties such as its Brönsted basicity (pK_a) or its electronegativity.[168] However, solvent polarity has a more predictable influence on the course of heterogeneous reductions. That is, highly polar solvents (DMF) which compete for metal binding sites afford the anti adduct preferentially, whereas nonpolar media (hexane) enforce heteroatom–catalyst association and thereby favor formation of the syn isomer. Nonetheless, the effect of solvents on the stereochemical outcome of heterogeneous hydrogenations is not always predictable: Thompson's stereoselective reduction of the tricyclic alcohol was performed in ethanol (eq 60).

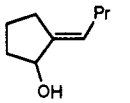
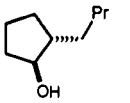
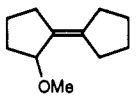
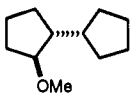
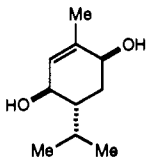
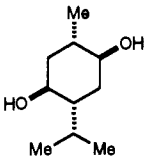
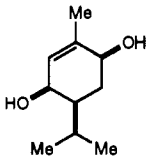
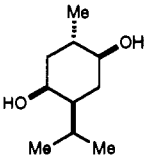
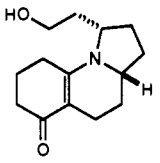
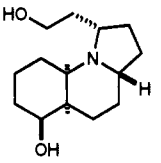
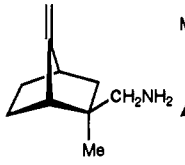
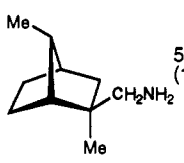
Table 31 illustrates additional examples of directed heterogeneous hydrogenation processes. 2-Butylidene-1-cyclopentanol is reduced with Raney nickel to afford the anti product preferentially (entry 1).[169] Hydrogenation of the cyclopentylidene allylic methyl ether

Table 30. Directivity by Various Functional Groups in Heterogeneous Hydrogenation



R	*Cis* : *Trans*	pK_a	Electronegativity
CH_2OH	19 : 1	-2	3.65
CHO	13 : 1	-8	2.90
CO_2Na	1 : 1	+5	2.95
CO_2H	1 : 4	-6	2.85
CO_2Me	1 : 6	-6	2.75
COMe	1 : 6	-7	2.70
$CONH_2$	1 : 9	-1	2.95

Table 31. Directed Heterogeneous Hydrogenation

Entry	Substrate	Major Product	Catalyst (H_2 Pressure)	Selectivity
1			Raney-Ni (1000 psi)	24:1
2			Raney-Ni (1000 psi)	12:1
3			Raney-Ni (30 psi)	9:1
4			Raney-Ni (30 psi)	2:1
5			5% Pt / Al_2O_3 (60 psi)	12:1
6			5% Pd / C (15 psi)	>99:1

(entry 2) indicates that, although less effectively than parent alcohols, alkyl ethers can also direct the addition reaction. Hydrogenation of the cyclohexenediol in entry 3 proceeds stereoselectively in the presence of Raney nickel, but minor modifications in substrate structure result in diminished stereodifferentation.[170] As is shown in entry 4, if hydrogen delivery is to occur from the same face as the sizeable isopropyl group, the reduction proceeds with significantly lower levels of stereocontrol. Hydrogenation of the vinylogous amide shown in entry 5 proceeds smoothly to yield the amino alcohol.[171] The directing effect of the primary alcohol was ascertained by control experiments; under identical conditions, the corresponding acetate, silyl ether, or deoxy derivatives give no reduction products. As the example in entry 6 indicates, a primary amine may also direct the course of the reduction process.[172]

Although heteroatom functional groups can influence the stereochemical course of heterogeneous reductions, a number of variables, such as the nature of the directing group, solvent, catalyst, support, and hydrogen pressure are important and often must be optimized to achieve useful levels of selectivity. These changes in reaction conditions cannot be effected predictably; poisoning is often a problem, and different catalyst batches seldom show identical reactivity. It is for these reasons that heterogeneous catalysis does not offer a general and reliable solution to the notion of heteroatom-directed hydrogenation reactions.

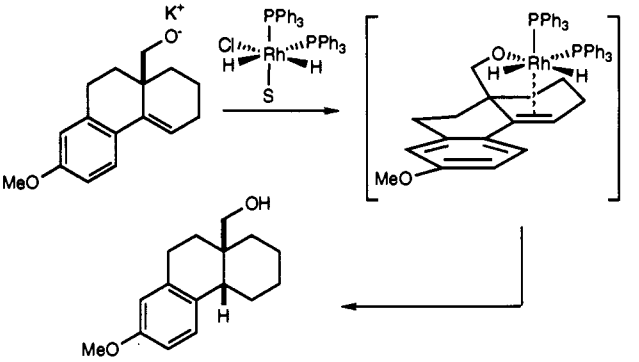
VI. Directed Homogeneous Hydrogenation Reactions

A. Introduction

Homogeneous hydrogenation catalysts were first introduced in 1961 by Halpern; a number of simple alkenes, such as maleic, fumaric, and acrylic acids, can be reduced efficiently with chlororuthenate(II) complexes.[173] Subsequently, other significant advances were made in this area, chiefly by Wilkinson and coworkers, who developed an array of effective rhodium and ruthenium catalysts.[174] Perhaps the most notable of such complexes, $RhCl(PPh_3)_3$ (Wilkinson's complex), was shown to effect hydrogenation reactions with site and diastereoselectivity.[175]

The first systematic studies of directed homogeneous hydrogenation reactions were reported in 1974.[176] The tricyclic alcohol shown in Scheme 20 is resistant to reduction by hydrogen and $RhCl(PPh_3)_3$, even at 100 psi and 50 °C. However, when the corresponding potassium alkoxide is subjected to the above conditions (100 psi H_2, 50 °C, 0.04 mol % catalyst), the syn isomer is produced exclusively. It was proposed that the reaction involves a rhodium–dihydride complex where both the solvent molecule (S; e.g., THF) and the chloride ion are replaced by the olefinic alkoxide, which in turn delivers hydrogen to the unsaturation site. In these experiments prior formation of the potassium alkoxide and subsequent displacement of the chloride ligand are *required* for efficient delivery of hydrogen. Hydrogenation reactions of this alcohol substrate and its various salts with heterogeneous palladium and platinum catalysts provide significant amounts of the anti isomer.[168]

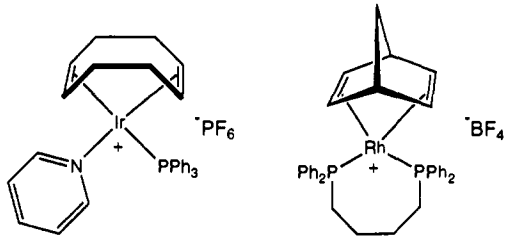
Scheme 20



Heteroatom directivity requires binding of H_2, the alkene, and the directing group to the transition metal; three ligation sites on the metal center of the catalyst are necessary. With $RhCl(PPh_3)_3$, the active 14-electron species $RhCl(PPh_3)_2$ cannot accommodate the three groups, as this would result in the formation of an unfavorable 20-electron complex (an additional ligand (Cl) must be lost). To effect a directed reaction with a hydroxy or another polar heteroatom group which is not capable of initiating ligand displacement, an active catalyst with a 12-electron structure is required. A number of hydrogenation catalysts satisfy this criterion. Chiral cationic rhodium catalysts (e.g., [Rh(nbd)(*S,S*-chiraphos)]BF_4) have been employed successfully in enantioselective reductions of dehydroamino acids,[177] where association of both the olefin and the *N*-acyl

carbonyl group plays a crucial role in efficient transfer of chirality. More recently, hydrogenation of a variety of allylic and homoallylic alcohols, under the agency of chiral ruthenium complexes (e.g., Ru(*S*-binap)($OCOCH_3$)$_2$), has been shown to occur with high enantioface differentiation (~98%).[178] In this instance as well, two-point binding between the catalyst and the substrate is crucial for achieving high selectivity.

This section of the article will be primarily concerned with *diastereoselective*, directed hydrogenation processes. Among the various catalysts, [Ir(cod)py(PCy_3)]PF_6[179] and [Rh(nbd)(diphos-4)]BF_4[180] have emerged as the most commonly used, and their role in directed hydrogenation reactions with be emphasized.[181]



[Ir(cod)py(PCy_3)]PF_6 (Ir^+) [Rh(nbd)(diphos-4)]BF_4 (Rh^+)

B. General Mechanistic Considerations

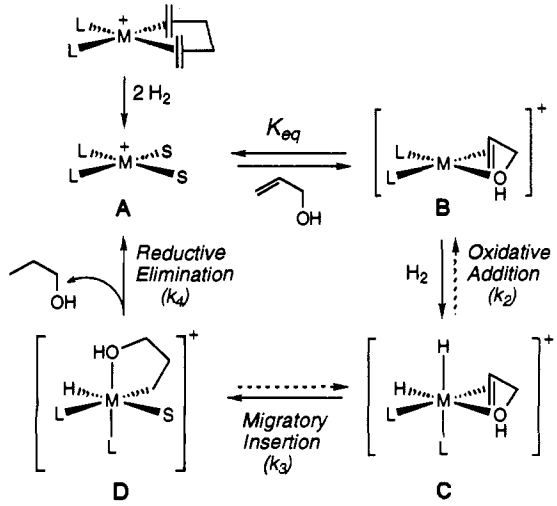
Upon treatment with H_2, the cyclooctadiene (cod) and norbornadiene (nbd) ligands of [Ir(cod)py(PCy_3)]PF_6 and [Rh(nbd)(diphos-4)]BF_4 are promptly reduced, and the 12-electron "IrR_2^+" and "RhL_2^+" systems are formed (A, Scheme 21). The course of the reduction process illustrated below and the intermediates involved can be inferred from Halpern's mechanistic studies on the rhodium-catalyzed hydrogenation of dehydroamino acids.[182] The heteroatom and its neighboring alkene readily bind to the coordinatively unsaturated metal complex. Coordination of the substrate is followed by oxidative addition of hydrogen and subsequent migratory insertion to afford the alkyl metal complex (D). Reductive elimination then yields the desired product and regenerates the active hydrogenation catalyst.

Whether any of the steps presented in the catalytic cycle are reversible is largely a function of the catalyst and the reaction conditions (e.g., temperature and pressure). Halpern's studies have demonstrated that in the cationic rhodium-catalyzed hydrogenation of dehydroamino acids, at 15 psi (1 atm) H_2 the oxidative addition step (B → C) is rate determining, whereas at elevated hydrogen pressure reductive elimination is the slow step (D → A).[182] In contrast, Crabtree's mechanistic work on *iridium*-catalyzed hydrogenation indicates that, at least in certain instances, formation of the alkyliridium complex is rate limiting (C → D).[179]

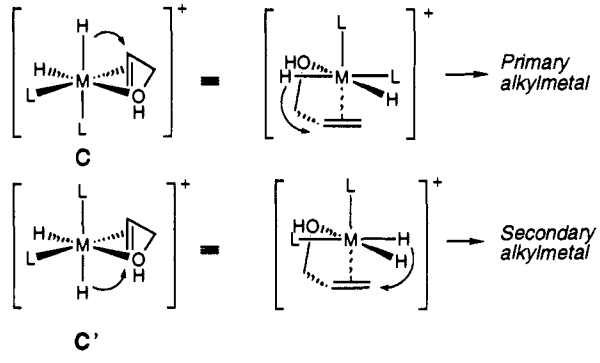
As is indicated in Scheme 21, formation of the hydridoalkyl complex, D, could occur via the metal dihydride species (B → C → D). Although iridium dihydrides have been detected spectroscopically, the analogous rhodium complexes have not yet been observed. In the proposed catalytic cycle for the rhodium-catalyzed reduction of dehydroamino acids, the dihydride complex, (C), remains the only intermediate that has not thus far been intercepted and characterized, due to the rapid rate of the migratory insertion step ($k_3 \gg k_2$). However, the well-recognized oxidative addition reactions of hydrogen with a number of d^8 complexes, and the similarity of the related activation parameters (k_2) to those of the dehydroamino acid asymmetric reductions, render the involvement of metal dihydrides (such as C) likely.[183] The intermediacy of these complexes is therefore invoked in the ensuing discussions.

Complex C contains two diastereotopic hydrides, initial transfer of one of which is predicted to be favored. As is illustrated in Scheme 22, the parallel metal hydride (H—M—C=C dihedral angle of ~0°) is properly aligned to overlap with the olefin σ^*_{C-C} and should therefore be transferred first. The perpendicular hydride is orthogonal to the C–C π cloud (H—M—C=C dihedral angle of ~90°), and its insertion is predicted to be energetically unfavorable. Scheme 22 also demonstrates that there are two possible modes of hydride insertion wherein the above stereoelectronic effects are satisfied. In the case of a monosubstituted allylic alcohol, C′ affords a *secondary* alkylmetal complex whereas C generates the more (thermodynamically) favorable *primary* product. In the case of a 1,2-disubstituted olefin, where a secondary alkylrhodium is generated regardless of the mode of hydride transfer, steric factors may also prove to be significant (e.g., preferences for certain metallacycle ring sizes).

Scheme 21



Scheme 22



C. Hydrogenation of Cyclic Olefins

In 1983, Crabtree[184] and Stork[185] demonstrated that the cationic iridium catalyst ([Ir(cod)py(PCy_3)]PF_6, Ir^+)

Table 32. Hydrogenation of Cyclic Homo- and Bishomoallylic Alcohols with [Ir(cod)py(PCy$_3$)]PF$_6$

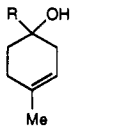
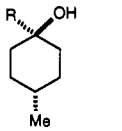
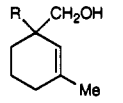
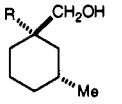
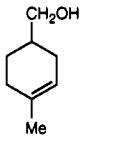
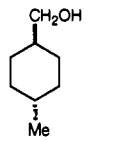
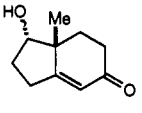
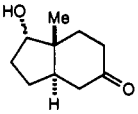
Entry	Substrate	Major Product	Mol % Ir catalyst		Selectivity
1			20	a. R = H	>99 : 1
			20	b. R = Me	33 : 1
2			20	a. R = H	6 : 1
			20	b. R = Me	9 : 1
3			2		>99 : 1
4			20		24 : 1

Table 33. Hydrogenation of Cyclic Allylic Alcohols with [Ir(cod)py(PCy$_3$)]PF$_6$

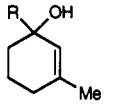
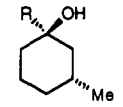
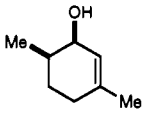
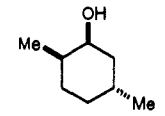
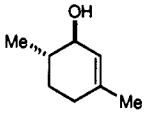
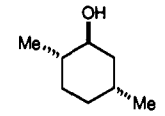
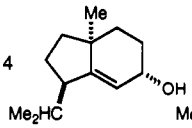
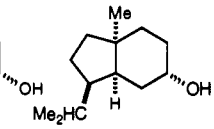
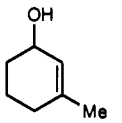
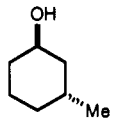
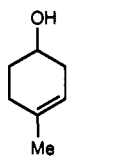
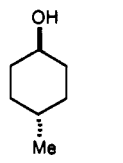
Entry	Substrate	Major Product	Mol % Ir catalyst		Selectivity
1			20	a. R = H	74 : 1
			20	b. R = Me	>100 : 1
2			2		65 : 1
3			2		36 : 1
4			20		"highly selective"

Table 34. Stereoselectivity as a Function of [Ir(cod)py(PCy$_3$)]PF$_6$ Concentration

Substrate	Major Product	Mol % Ir catalyst	Selectivity
		20.0	50 : 1
		2.5	150 : 1
		20.0	33 : 1
		2.5	52 : 1

is effective in the directed reduction of a diverse selection of cyclic olefinic alcohols. As shown in Table 32, endocyclic homoallylic carbinols are generally hydrogenated with good to excellent selectivity; the major product corresponds to addition of hydrogen syn to the hydroxy group. As is indicated in entry 2 of Table 32, homoallylic alcohols which bear a primary hydroxy group may undergo directed hydrogenation reactions with relatively lower levels of stereocontrol. Comparison of entries 2 and 3 implies that levels of diastereoselection are dependent on catalyst concentration. As will be discussed later in more detail, higher concentrations of the iridium catalyst result in significantly lower levels of stereoinduction.[186] The reaction of the enone system shown in entry 5 is significantly slower than that of unconjugated olefins, yet the desired *trans*-indanone is produced as the major product.

Table 33 illustrates several examples of stereoselective hydrogenation reactions of cyclic allylic alcohols catalyzed by [Ir(cod)py(PCy$_3$)]PF$_6$. Entries 2 and 3 of Table 33 demonstrate that the level of stereocontrol is not greatly affected by the relative stereochemistry of substituents proximal to the directing functionality.[187] Hydrogenation of the bicyclic alcohol shown in entry 4 gives the cis-fused system as the sole product.[188]

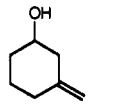
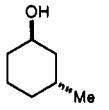
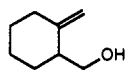
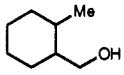
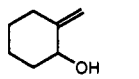
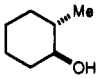
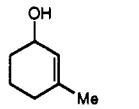
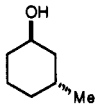
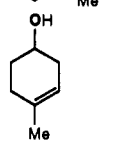
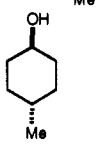
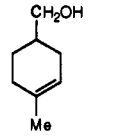
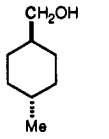
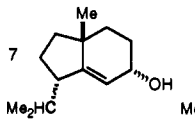
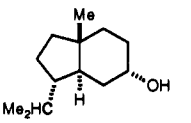
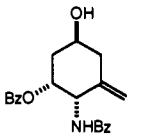
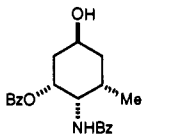
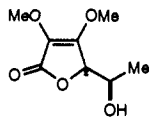
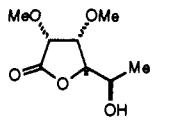
In the initial studies on iridium-catalyzed directed hydrogenations, 20 mol % of the catalyst was employed;[185] these conditions were later determined not to be optimal for achieving high levels of stereoselection.[186] For example, reductions of 3-methyl-2-cyclohexen-1-ol and 4-methyl-3-cyclohexen-1-ol with [Ir(cod)py(PCy$_3$)]PF$_6$ were shown to be more selective at lower catalyst loadings (Table 34). It is possible that at higher catalyst concentrations more than one metal complex is present. Some of these species, such as the trinuclear bridged hydride system examined by Crabtree,[189] is inactive, whereas others, although active, might not be constrained to the same directivity effects as the mononuclear complex.

The cationic rhodium complex, [Rh(nbd)(diphos-4)]-BF$_4$ (Rh$^+$), has also proved to be a useful catalyst for directed hydrogenation of cyclic alkenes (Table 35). Upon treatment of 3-methylenecyclohexan-1-ol with 2 mol % of the rhodium catalyst (15 psi H$_2$), *trans*-3-methylcyclohexan-1-ol is obtained stereoselectively (>98%, entry 1).[190] In contrast, reduction of 2-methylenecyclohexanemethanol proceeds in a stereorandom fashion (entry 2). Subjection of 2-methylenecyclohexan-1-ol to the above conditions leads to the formation of hydrogenation products with low selectivity (entry 3). This transformation is plagued with olefin isomerization; 2-methylcyclohexan-1-one is produced as the major product.[191]

Alkene isomerization in rhodium-catalyzed hydrogenation processes is largely circumvented if reactions are carried out at elevated hydrogen pressures.[191] Although reduction of 2-methylenecyclohexan-1-ol at 500 and 1000 psi H$_2$ does not result in improvement of stereoselectivity (3:1; Table 35, entry 3), generation of the undesired ketone is diminished to 20% and 13%, respectively. Hydrogenation of 3-methyl-2-cyclohexen-1-ol at 375 psi H$_2$ affords *trans*-3-methylcyclohexan-1-ol in a >200:1 ratio (entry 4, 200:1 at 15 psi).[191] As entries 5, 6, and 8 of Table 35 show, homoallylic and bishomoallylic cyclic olefins are reduced stereoselectively with the cationic rhodium catalyst at high H$_2$ pressure.[192]

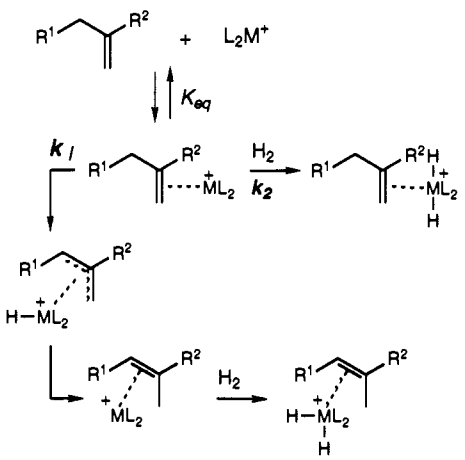
Thus, in rhodium-catalyzed hydrogenations an increase in hydrogen pressure results in diminished olefin isomerization and higher selectivity (Scheme 23, M =

Table 35. Hydrogenation of Cyclic Alcohols with [Rh(nbd)(diphos-4)]BF_4

Entry	Substrate	Major Product	Mol %, Catalyst[a] (H_2 Pressure)	Selectivity
1			2, Rh^+ (15 psi)	>49 : 1
2			2, Rh^+ (15 psi)	1 : 1
3			3.5, Rh^+ (500 psi)	3 : 1
4			3.5, Rh^+ (375 psi) 2.5, Ir^+ (15 psi)	>200 : 1 150 : 1
5			10, Rh^+ (1000 psi) 2.5, Ir^+ (15 psi)	64 : 1 52 : 1
6			10, Rh^+ (1000 psi) 20, Ir^+ (15 psi)	19 : 1 6 : 1
7			10, Rh^+ (800 psi)	70 : 1
8			35, Rh^+ (15 psi) 17.5, Ir^+ (15 psi)	>19 : 1 2 : 1
9			20, Rh^+ (1850 psi)	"highly selective"

[a] Catalysts: [Rh(nbd)(diphos-4)]BF_4 (Rh^+); [Ir(cod)py(PCY_3)]PF_6 (Ir^+).

Scheme 23



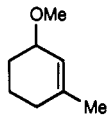
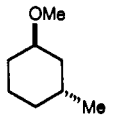
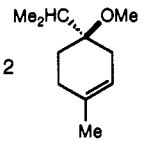
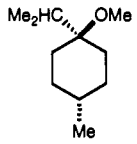
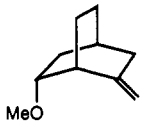
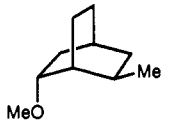
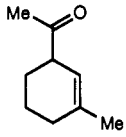
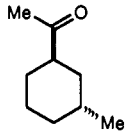
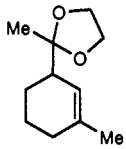
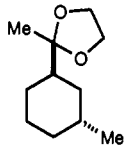
Rh). In direct analogy with the asymmetric hydrogenation of dehydroamino acids by closely related rhodium complexes,[193] in reactions of allylic alcohols at 15 psi H_2 oxidative addition of hydrogen is probably the rate-determining step. As a result, the substrate–catalyst adduct may competitively undergo alkene isomerization through a route involving the corresponding π-allyl hydride ($k_2[H_2] \cong k_1$). When pressures above 15 psi (1 atm) are employed, olefin isomerization is attenuated ($k_2[H_2] > k_1$), and formation of the putative π-allyl hydride no longer competes with the desired pathway. Another plausible explanation points to competition between a β-elimination pathway (resulting in alkene isomerization) and a reductive elimination route (affording hydrogenation product) of the intermediate alkyl hydride. It may be that H_2 at high pressures acts as a ligand which induces reductive elimination and thus favors hydrogenation of the unrearranged alkene. In the iridium-catalyzed processes (M = Ir) variations in hydrogen pressure are of little consequence.[191]

Table 35 illustrates several instances where the directed, rhodium-catalyzed hydrogenation has been employed in a synthesis strategy. In the case of the bicyclic system shown in entry 7, in spite of an exceptional level of steric congestion which is disposed to override hydroxyl directivity, the trans-fused adduct is formed as the major product.[191] Due to the instability of this substrate toward the Lewis acidic rhodium, satisfactory results are achieved only when reduction is performed in tetrahydrofuran. (Unlike dichloromethane, tetrahydrofuran effectively buffers the catalyst Lewis acidity.[194]) This transformation fails at low hydrogen pressure or with the cationic iridium complex.[188]

Rhodium-catalyzed hydrogenation of the substrate shown in entry 8 (Table 35) proceeds with high levels of stereochemical control.[195] With [Ir(cod)py(PCy_3)]PF_6 only a 2:1 ratio is obtained; the lack of stereoselectivity could be attributed to competitive binding and directivity by the amide group (vide infra). Entry 9 of Table 35 indicates that a directing group positioned on an exocyclic group can effectively control the stereochemical outcome of the reaction.[196]

Other heteroatom-containing functional groups, such as ethers, carboxylic esters, and amides, efficiently bind to cationic rhodium and iridium complexes and direct the hydrogenation reactions of cyclic substrates.[197] As the first three entries of Table 36 demonstrate, methyl ethers are effective directing groups. The bicyclic ether of entry 3 is reduced with lower selectivity but faster than the parent alcohol, even when the more discriminating iridium complex is employed.[198] This relationship between rate and selectivity (that faster transformations are less selective) is not general and appears to depend on the nature of the directing group, at least with regard to the iridium-catalyzed reactions. For instance, with [Ir(cod)py(PCy_3)]PF_6, hydrogenation of the unsaturated ketone in entry 4 is faster and more selective than that of the carbinol derivative (>99:1 vs 6:1). Somewhat surprisingly, reduction of the ethylidene ketal shown in entry 5 occurs with low stereoselectivity and with <50% conversion.[184]

Table 36. Hydrogenation of Cyclic Olefinic Ethers and Ketones[a]

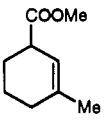
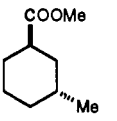
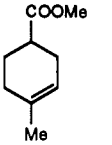
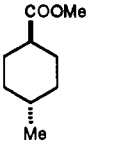
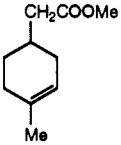
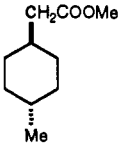
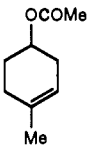
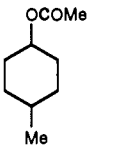
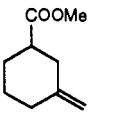
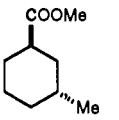
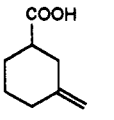
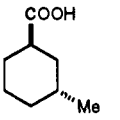
Entry	Substrate	Major Product	Mol %, Cat[a]	Selectivity
1			2, Ir^+	>99 : 1
2			2, Ir^+	>99 : 1
3			2, Ir^+ 2, Rh^+	32 : 1 7 : 1
4			2, Ir^+	>99 : 1
5			2, Ir^+	1.6 : 1

[a] Catalysts: [Rh(nbd)(diphos-4)]BF_4(Rh^+); [Ir(cod)py-(PCY_3)]PF_6(Ir^+). Reactions were run at 15 psi H_2.

Table 37 illustrates a number of stereoselective hydrogenations where an ester functionality acts as the directing group. The β,γ-unsaturated ester in entry 1 is reduced with high selectively with both iridium and rhodium catalysts.[190] Reduction of the more distant alkene of the γ,δ-unsaturated ester in entry 2 is slower and less stereoselective. The resident heteroatom functionality in the δ,ϵ-unsaturated ester of entry 3 is too distant from the olefin for effective differentiation of its syn and anti faces; the same argument holds for the structurally analogous acetate in entry 4 which is also reduced in a stereorandom fashion.[185] Table 37 includes the case of an unsaturated carboxylic acid (entry 6) which is reduced selectively in presence of the iridium complex (7:1), albeit not as rapidly as the related ester (entry 5).

The carboxamide group serves admirably as a directing agent in hydrogenations with the cationic iridium catalyst.[199] Entries in Table 38 clearly indicate that delivery by an amide group is more efficient than by an ester functionality. An increase in distance between the amide carbonyl and the alkene results in little erosion of stereoselectivity, as might be expected for this more Lewis basic functional group (this is in contrast to the less Lewis basic esters). In contrast to the corresponding methyl ester which is hydrogenated stereorandomly (entry 3, Table 37), the δ,ϵ-unsaturated amide in entry 3 (Table 38) is reduced with >100:1 selectivity. Particularly impressive is the highly selective reduction of the Lewis-acid sensitive enol ether of entry 2b. As illustrated in entry 4, this technology has found an important application in connection with the total syntheses of pumiliotoxins.

Table 37. Hydrogenation of Cyclic Olefinic Ethers and Acids

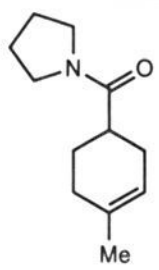
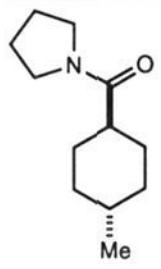
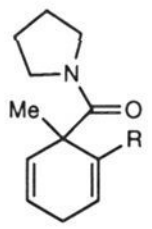
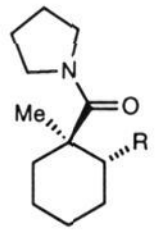
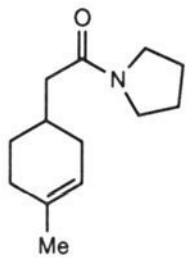
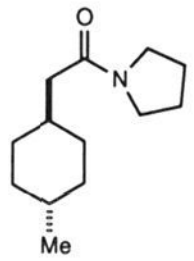
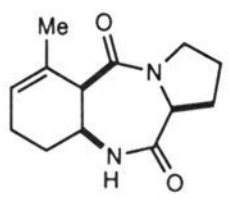
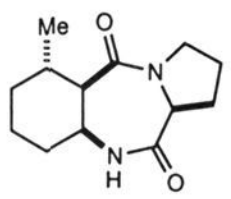
Entry	Substrate	Major Product	Mol %, Cat[a]	Selectivity
1			2, Ir^+ 2, Rh^+	>99 : 1 32 : 1
2			2, Ir^+ 2, Rh^+	41 : 1 7 : 1
3			5, Ir^+	1 : 1
4			5, Ir^+	1 : 1
5			2, Ir^+ 2, Rh^+	10 : 1 4 : 1
6			2, Ir^+ 2, Rh^+	7 : 1 1 : 1

[a] Catalysts: [Rh(nbd)(diphos-4)]BF_4(Rh^+); [Ir(cod)py-(PCY_3)]PF_6(Ir^+). Reactions were run at 15 psi H_2.

With regard to the preferred geometry in reductions of cyclic homoallylic substrates, similar to the directed cyclopropanation reaction (vide supra), it appears plausible that the internal alkene is within reach only when the hydroxy–metal complex is in the pseudoaxial orientation (Figure 8, box). Substrates which are reduced with higher degrees of stereochemical control are those which are more strongly favored to be axially disposed. Comparison of entries 1–3 in Table 33 suggests that, unlike the directed methylenation processes, hydrogenation reactions of allylic substrates proceed through the pseudoaxial hydroxy conformer (Figure 8, parts a and b). As was discussed previously in detail (Scheme 22), one of the two diastereomeric hydrides is properly aligned with the alkene π-system and is consequently transferred first (H_A; H—M—C=C dihedral angle of 0°). There are two possible modes of hydride insertion wherein the metal hydride and π^*_{C-C} are properly aligned. From illustrations in Figure 8, it is not obvious whether one mode should be preferred over the other.

In contrast to Simmons–Smith cyclopropanations and metal-catalyzed epoxidations, the presence of a hydroxy group has been shown to *decrease* the overall efficiency of iridium-catalyzed hydrogenations. Whereas in the reaction of 1-methylcyclohexene ~4000 mol of H_2 per mole of iridium [Ir(cod)py(PCy_3)]PF_6 is consumed, with terpinen-4-ol this value is diminished to ~30 mol of H_2 per mole of the catalyst.[187] This observation implies

Table 38. Hydrogenation of Cyclic Olefinic Amides

Entry	Substrate	Major Product	Mol %, Cat[a]	Selectivity
1			5, Ir^+	130 : 1
2			a. R = Me 5, Ir^+ b. R = OMe 5, Ir^+	170 : 1 170 : 1
3			5, Ir^+	>100 : 1
4			5, Ir^+	>99 : 1

[a] Catalyst: $[Ir(cod)py(PCY_3)]PF_6(Ir^+)$.

that coordination of the catalyst to the hydroxyl group results in attenuation of the catalytic activity of the iridium system. Moreover, unless larger amounts of the iridium complex are used, hydrogenation of non-hydroxylic olefins usually occurs in much lower yields than hydroxylic analogues. Such reactivity patterns have been attributed to catalyst deactivation (e.g., trimerization), which is largely inhibited when the complex is bound to a heteroatom.[200] Collectively, these data imply that the resident hydroxy group rapidly binds to the metal,[179a] protects the catalyst from decomposition and directs the H_2 delivery, but at the expense of catalyst deactivation and reduction of the reaction rates.

D. Hydrogenation of Acyclic Olefins

Hydrogenation of the 1,1-disubstituted allylic alcohol shown in entry 1 of Table 39 proceeds stereoselectively with 2 mol % $[Rh(nbd)(diphos\text{-}4)]BF_4$.[201] Under these conditions ~20% of the corresponding methyl ketone is produced due to olefin isomerization. When the iridium catalyst (Ir^+) is employed, 60% of the reaction mixture consists of the ketone side product, and the reduction occurs with lower selectivity (15:1). It is noteworthy that either the syn or the anti stereochemical relationship can be generated, depending on the substitution pattern of the starting alkene. This complementarity in diastereoselective hydrogenation of di- and trisubstituted olefins, and the general stereochemical outcome in reductions of allylic systems, may be rationalized on the basis of a number of conformational preferences.

Two-point binding of the transition metal with the olefin and its neighboring heteroatom occurs in such a fashion so that the A(1,2) allylic strain between R_1 and CH_2R_2 or Me substituents is avoided (~3.0 kcal/mol; Scheme 24).[202] In this manner, simultaneous coordination of the metal with the alkene and hydroxy groups results in effective differentiation of the two diastereotopic faces.

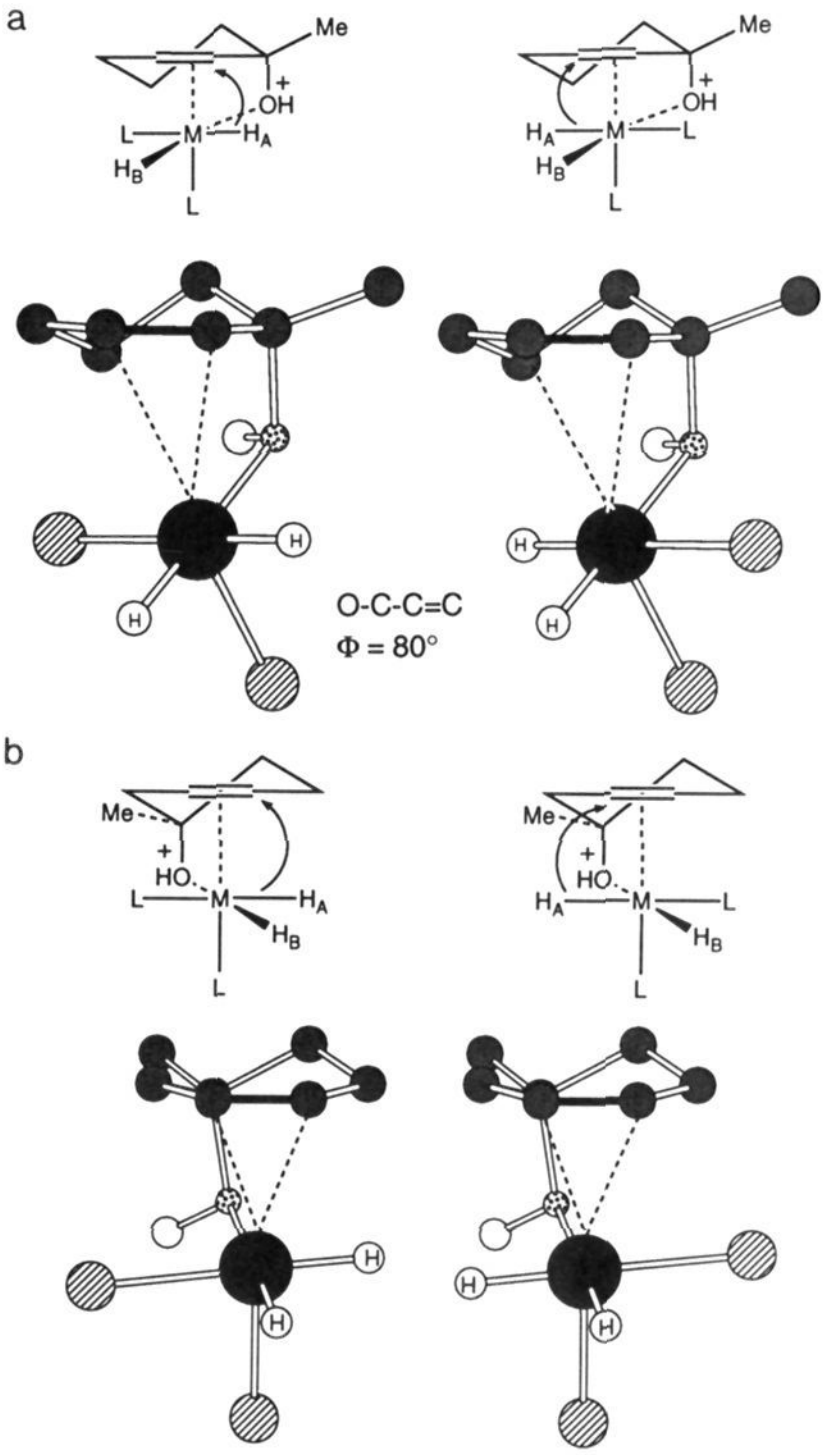
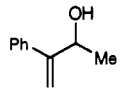
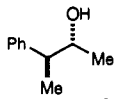
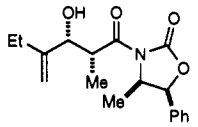
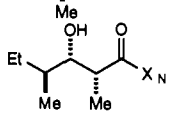
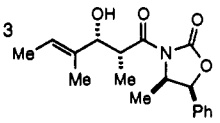
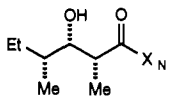
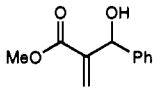
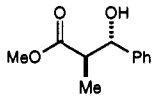
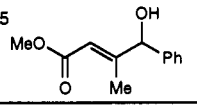
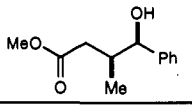


Figure 8. Preferred orientations of catalyst–olefin complexes of cyclic allylic (a) and cyclic homoallylic (b) alcohols.

The cationic rhodium complex is a uniquely effective catalyst for the stereoselective reduction of hydroxyacrylate esters (see entries 4 and 5 in Table 39). The iridium-mediated reactions are nonselective, and reductions catalyzed by Wilkinson's complex or common heterogeneous systems are slow and occur stereorandomly.[203] It is remarkable that hydrogenation of the disubstituted alkene in entry 4 proceeds with such high levels of stereocontrol at 15 psi H_2, since isomerization and formation of the β-keto ester should be prevalent under these conditions.

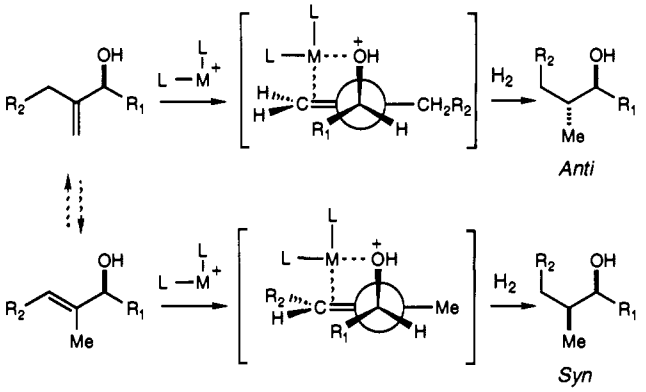
That hydrogenation of di- and trisubstituted alkenes leads to the formation of *opposite* stereo relationships has significant implications (entries 2 and 3, Table 39). If olefin isomerization occurs prior to hydrogenation, diminished overall stereoselectivities will be observed even though the individual transformations could be inherently discriminating. This complication, often inconsequential in cyclic systems, can be detrimental with acyclic substrates. At 15 psi H_2, when olefin

Table 39. Hydrogenation of Acyclic Allylic Alcohols

Entry	Substrate	Major Product	Mol %, Cat[a] (H_2 Press)	Selectivity
1			2, Rh^+ (15 psi)	32 : 1
2			17.5, Rh^+ (640 psi) 2.5, Ir^+ (15 psi)	13 : 1 6 : 1
3			17.5, Rh^+ (640 psi) 2.5, Ir^+ (15 psi)	10 : 1 3 : 1
4			0.5, Rh^+ (15 psi)	99 : 1
5			10, Rh^+ (15 psi)	32 : 1

[a] Catalysts: [Rh(nbd)(diphos-4)]BF_4(Rh^+); [Ir(cod)py(PCY_3)]PF_6(Ir^+).

Scheme 24

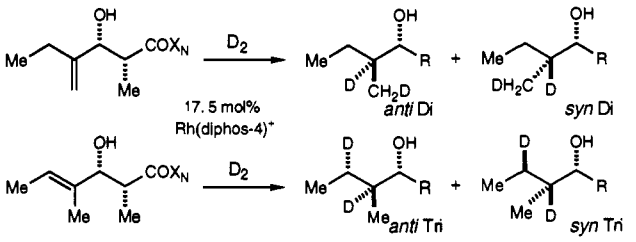


isomerization is most rampant, reduction of the disubstituted alkene affords predominantly the syn product, the product expected from hydrogenation of the trisubstituted isomer.

Studies with D_2 indicate that olefin isomerization takes place and low stereoselectivities are obtained unless elevated pressures are employed. Table 40 shows that this is especially true with disubstituted olefins; whereas at 515 psi D_2 addition occurs exclusively at the original unsaturation site, at 15 psi 75% of the product mixture corresponds to deuteration of the trisubstituted system.

As entries 2 and 3 in Table 39 illustrate, the cationic iridium catalyst is less effective than the cationic rhodium complex in mediating stereoselective reductions of acyclic allylic alcohols. The observed levels of stereoselectivity could be due to competitive binding and directivity by the amide carbonyl. However, control experiments that rigorously address this possibility have not yet been performed. With the cationic iridium complex, changes in hydrogen pressure do not affect the observed levels of stereodifferentiation, as was also the case with the cyclic compounds. In the iridium-

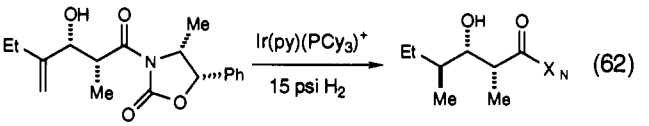
Table 40. Effects of Variations in D_2 Pressure in Stereoselective Hydrogenations of Allylic Alcohols[a]



Substrate	D_2 Pressure (psi)	Ratio *anti* : *syn*	{ *anti* Di / *syn* Di : *anti* Tri : *syn* Tri
Disubstituted alkene	15	1 : 2	25 : 8 : 67
Disubstituted alkene	515	9 : 1	100 : 0 : 0
Trisubstituted alkene	15	1 : 6	10 : 10 : 80
Trisubstituted alkene	515	1 : 9	0 : 10 : 90

[a] Abbreviations: X_N = norephedrine oxazolidone chiral auxiliary.

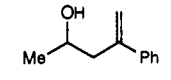
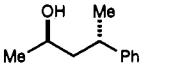
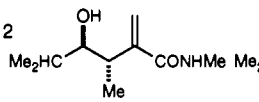
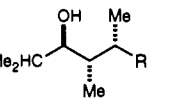
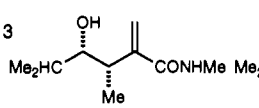
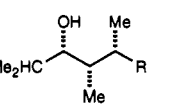
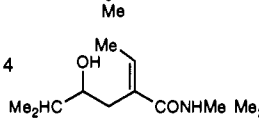
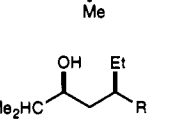
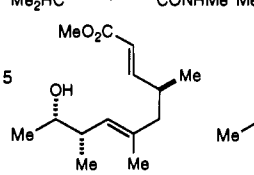
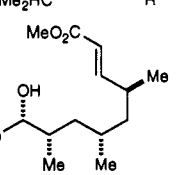
catalyzed hydrogenation reactions, adventitious olefin isomerization may largely be responsible for the diminished levels of stereocontrol. In further contrast to the cationic rhodium system, in iridium-catalyzed hydrogenations variations in the catalyst concentration influenced the stereoselective outcome of the reduction (eq 62).



1.3 mol% catalyst, Diastereoselection 7:1
5.0 mol% catalyst, Diastereoselection 3: 1
20.0 mol% catalyst, No Diastereoselection

Entry 1 of Table 41 illustrates that, with [Rh(nbd)(diphos-4)]BF_4 as catalyst, a homoallylic carbinol center of a 1,1-disubstituted olefin can exert modest levels of

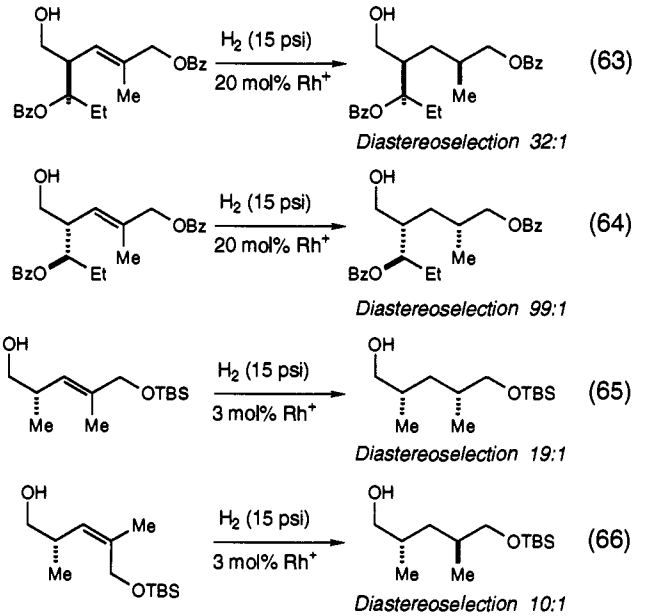
Table 41. Hydrogenations of Acyclic Homoallylic Alcohols

Entry	Substrate	Major Product	Mol %, Cat[a] (H_2 Pres)	Selectivity
1			2, Rh^+ (15 psi)	7 : 1
2			5, Rh^+ (15 psi) *b*	10 : 1
3			5, Rh^+ (15 psi) *b*	2 : 1
4			5, Rh^+ (15 psi) *b*	8 : 1
5			5, Rh^+ (15 psi)	16 : 1

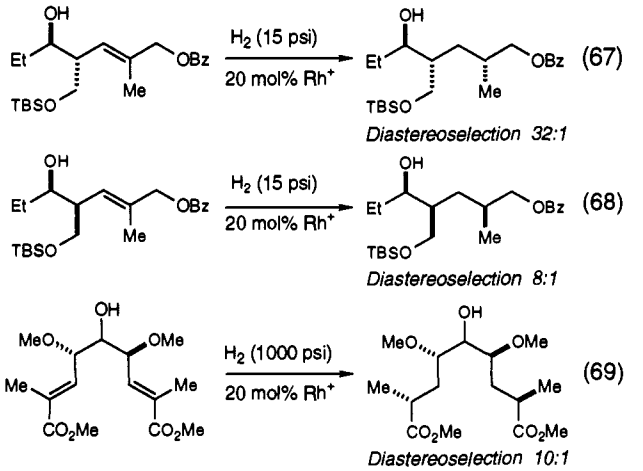
[a] Catalyst: [Rh(nbd)(diphos-4)]BF_4 or [Rh(nbd)(diphos-4)]-OSO_2CF_3.

asymmetric induction in the hydrogenation process;[201] however, with a protic solvent (e.g., MeOH) the reduction proceeds nonselectively. As entries 2–3 illustrate, the level of stereodifferentiation is greatly dependent on the substitution pattern of the starting material.[204] Directed hydrogenation of trisubstituted alkenes proceeds efficiently with useful levels of diastereocontrol (entries 4 and 5, Table 41).

In hydrogenations of trisubstituted olefins, the steric requirements of the allylic substituent and the olefin geometry have a small but marked effect on the reaction diastereoselection (eqs 63–66, Rh^+ = [Rh(nbd)(diphos-4)]BF_4).[186b] Since homoallylic hydroxyl groups perform well as directing groups, alkene geometry, along with the relative stereochemistry of the homoallylic hydroxy functionality, can be manipulated for effective control of the sense of asymmetric induction.

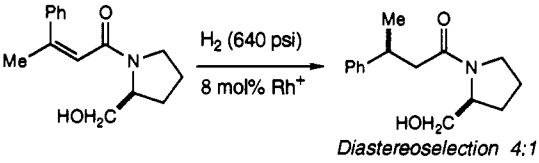


In cases where allylic and homoallylic stereogenic centers are present, alkene rearrangement is not observed at 15 psi H_2, and the cationic rhodium and the cationic iridium catalysts afford high levels of diastereoselection (eqs 67–69).[186b] Once again, it is the allylic center, not the stereogenic homoallylic carbinol site, that determines which diastereoface will be preferentially hydrogenated. Moreover, comparison of eqs 67 and 68 indicates that the anti relative stereochemistry



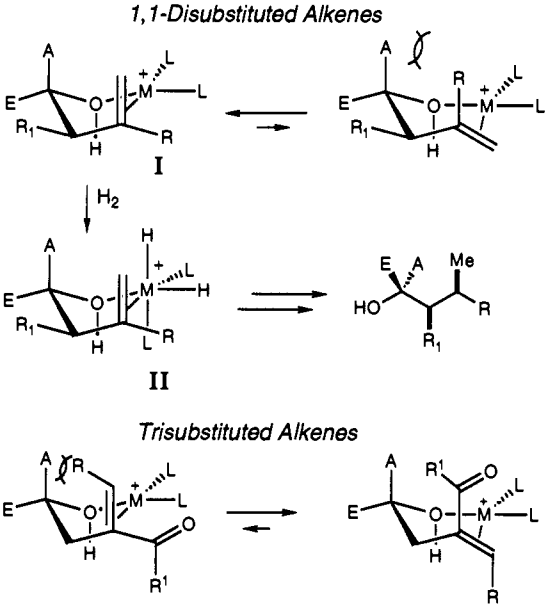
between the hydroxy and allylic centers leads to greater levels of stereodifferentiation. Equation 69 depicts a directed hydrogenation reaction used in efforts toward the total synthesis of the immunosuppressant FK-506.[205]

The stereoselective hydrogenation of the amide in eq 70 provides a rare example of 1,5-asymmetric induction.



The observed stereoselectivity in the hydrogenation of the 1,1-disubstituted homoallylic alcohols can be rationalized through complexes I and II, shown in Scheme 25. Alkene conformation I is preferred; unfavorable A(1,2) interactions are minimized in this conformation. In instances where there is no allylic substituent (R_1 = H), the homoallylic group adopts the pseudoequatorial orientation. In cases with an allylic stereogenic center ($R_1 \neq H$), this group will also prefer the pseudoequatorial disposition so that the destabilizing A(1,2) strain between R and R_1 groups is avoided (~3.0 kcal/mol). Inspection of the data presented in eqs 63 and 64 clearly indicates that in cases where there is both an allylic and a homoallylic substituent, the sense of asymmetric induction is primarily dictated by the *allylic* stereogenic center.[206]

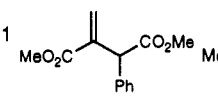
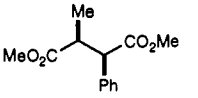
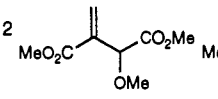
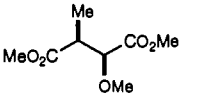
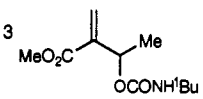
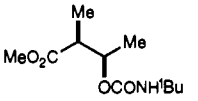
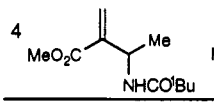
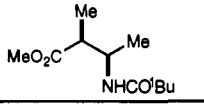
Scheme 25



The above hypotheses readily account for the lack of stereocontrol observed for the syn substrate in entry 3 of Table 41, since either the allylic or the homoallylic group would have to occupy the unfavorable pseudoaxial position. The trisubstituted olefins do not react through the same type of intermediates, as the resulting A(1,3) allylic strain[202] between R and A groups would be rather costly (~3.9 kcal/mol). Similar arguments pertain to reactions of trisubstituted alkenes that possess other substitution patterns.

In the asymmetric hydrogenation of dehydroamino acids by chiral cationic rhodium catalysts, the less

Table 42. Directed Hydrogenation of Nonhydroxylic Acyclic Alkenes

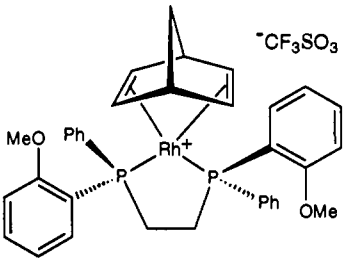
Entry	Substrate	Major Product	Mol %, Cat[a] (Solvent)	Selectivity
1			2, Rh^+ (MeOH)	200 : 1
2			2, Rh^+ (MeOH)	49 : 1
3			?, Rh^+	17 : 1
4			5, Rh^+ (CH_2Cl_2)	99 : 1

[a] Catalyst: [Rh(nbd)(diphos-4)]BF *or* [Rh(nbd)(diphos-4)]-OSO_2CF_3.

stable, *minor* metal–substrate complex reacts with H_2 far more rapidly (~500 times faster) than the major complex and thereby dictates the eventual stereochemical outcome of the reaction.[182] Therefore, in connection to the rhodium-catalyzed directed hydrogenations, if the rate-limiting step in the sequence of events is the oxidative addition process (B → C, Scheme 21), it is perhaps warranted that we base our rationalization on the relative rates of formation of the diastereomeric *dihydrides* (the oxidative insertion step) and not of the metal substrate complexes (the initial equilibrium). In the rhodium-catalyzed hydrogenations of hydroxylic olefins, unlike the asymmetric dehydroamino acid reductions, the more stable metal–catalyst complexes consistently predict the predominant product diastereomers. In the hydrogenation of these substrates, if the second step is in fact the rate-determining step, the complex with the higher thermodynamic concentration either undergoes oxidative addition faster than, or with the same rate as, the minor system. Oxidative addition of the major system could even be somewhat slower than that of the minor complex; however, this rate difference may not be large enough to overcome the initial binding preferences. Moreover, hydrogenation of dehydroamino acids proceeds less selectively under conditions which lower the effective concentration of the minor complex, namely, at lower reaction temperatures or under increased hydrogen pressure.[182] In contrast, unsaturated alcohols are reduced with higher stereochemical control when reactions are performed at high pressure or low temperature, implying that with these substrates it is primarily the *major* rhodium–hydroxy alkene complex that determines the stereochemical course of the reduction.

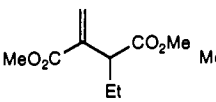
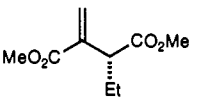
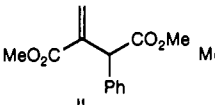
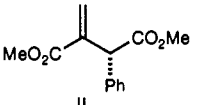
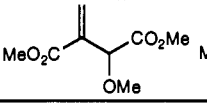
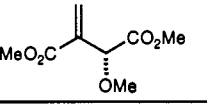
The selective hydrogenation of the 3-methyl itaconate ester shown in entry 1 of Table 42 suggests that, with [Rh(nbd)(diphos-4)]BF_4 as catalyst, methyl carboxylates can effectively direct reductions of acyclic substrates.[207] Entries 1 and 2 indicate a noticeable effect by the ether functionality on the sense of asymmetric induction in these hydrogenation reactions. The amide in entry 4 is reduced stereoselectively, but hydrogenations of the derived amine and that of the corresponding trifluoroacetate salt were nonselective.

The levels of stereocontrol observed in the hydrogenation of unsaturated alcohols is largely due to efficient substrate–metal binding, which leads to the formation of highly organized reactive complexes and results in effective diastereotopic face differentiation. Such high levels of structural organization indicate that the influence by *chiral* ligands on the *absolute* face selectivity in these reductions may be significant. Hydrogenation of a number of itaconate esters with Rh(*R*,*R*-dipamp)$^+$ leads to the recovery of >80% optically pure starting material after ~60% conversion (Table 43).[208] As is illustrated in entry 1, an increase in the reaction temperature results in lower asymmetric induction. This trend is opposite to that observed forthe reductions of dehydroamino acids catalyzed by the same metal complex.[209]



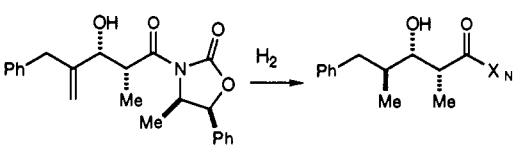
[Rh(nbd)(R,R-dipamp)]CF_3SO_3

Table 43. Kinetic Resolution in Hydrogenation of Itaconate Esters with Rh(dipamp)$^+$

Entry	Substrate	Recovered Enantiomer[a]	Temp., °C (% Reaction)	ee, %[b]
1			0 (65)	≥96
			50 (55)	64
2			20 (62)	82
3			20 (62)	93

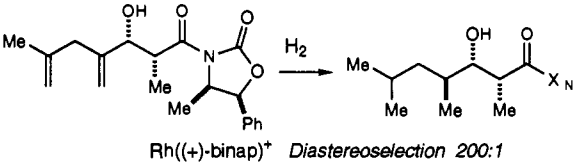
[a] All reactions were performed in MeOH at 15 psi H_2. [b] Indicates ee of the recovered starting material.

Reaction diastereoselectivity in the reductions of enantiopure allylic and homoallylic alcohols may be influenced by chiral catalysts. Two of the more dramatic examples of this phenomenon are shown in eqs 71 and 72. Noteworthy is the allylic diene of eq



(71)

Rh((+)-binap)$^+$ *Diastereoselection 15:1*
Rh((-)-binap)$^+$ *Diastereoselection 3:1*



(72)

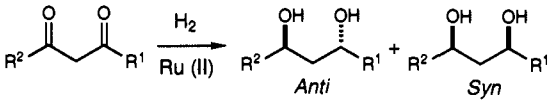
Rh((+)-binap)$^+$ *Diastereoselection 200:1*
Rh((-)-binap)$^+$ *Diastereoselection 1:3*

71: the hydrogenation reaction affords different diastereomeric products, depending on the catalyst antipode employed.

E. Hydrogenation of Acyclic Hydroxylic Ketones

In contrast to the directed catalytic hydrogenation reactions of alkenes, there is a paucity of instances where a ketone group is reduced stereoselectively through metal catalysis. A variety of simple 1,3-diketones can be hydrogenated to afford *trans*-1,3-diols with high diastereo- and enantioselectivity (700 psi H_2, 0.2 mol % $Ru_2Cl_4[(R)\text{-binap}]_2(NEt_3)$; Table 44.[210] In the sluggish hydrogenation of phenyl ketones, the major product is the related β-hydroxy phenyl ketone. This observation is consistent with the hypothesis that β-hydroxy ketones are intermediates in these reductions.

Table 44. Directed Hydrogenation of 1,3-Diketones



R^1	R^2	*Anti* : *Syn*	Yield
Me	Me	99 : 1	98 %
Me	Et	16 : 1	89 %
Me	*i*-Pr	32 : 1	92 %
Et	Et	49 : 1	84 %

Since simple ketones, such as pentan-2-one, are resistant to hydrogenation under the above conditions, coordination of the two carbonyl units with the ruthenium metal is believed to play an important role in the initial reduction process.[211] Association of the resulting hydroxyl group with the metal catalyst subsequently delivers the *anti*-diol selectively. Similar transition-state arguments as was put forth for the hydrogenation of the corresponding olefins (see Scheme 25) can be used to account for these cases.

More recently, Noyori and co-workers have employed RuX_2(binap) (X = Cl or Br) as a catalyst that effects stereoselective hydrogenation of a variety of ketones with neighboring nitrogen-, sulfur-, and oxygen-containing directing groups (e.g., hydroxyl, dialkylamino, alkoxy, keto, and alkylthiocarbonyl groups).[212] The sense of asymmetric induction, which is identical to that illustrated in Table 44, suggests that once again the critical factor in the stereodifferentiation is the simultaneous coordination of the carbonyl and the neighboring heteroatom-containing functionality. Nonetheless, both the Saburi and the Noyori methods reduce 1,2-diketones with only low levels of stereocontrol (~3:1).

VII. Directed Nucleophilic Addition Reactions

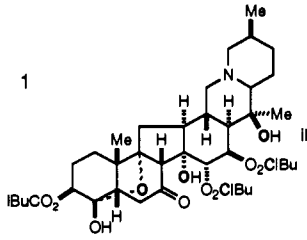
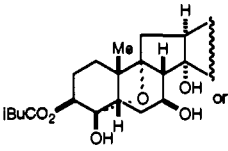
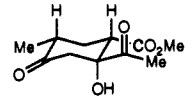
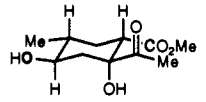
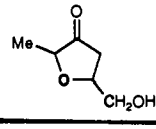
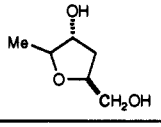
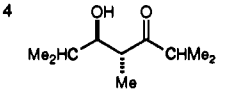
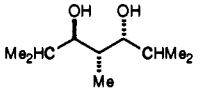
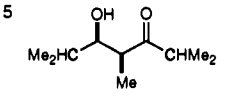
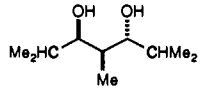
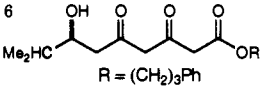
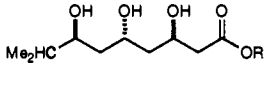
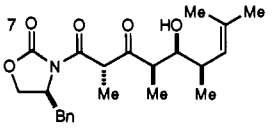
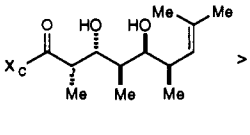
A. Reduction of C=O and C=N

The following discussion consists of two parts. The first deals with directed reductions involving tetravalent metal hydride reagents. Reductions by these species frequently involve initial reaction with an acidic substrate functional group to form a *covalent* metal hydride complex, from which H^- is subsequently delivered. The second section focuses on reductions by trivalent hydrides, which generally are bound to the substrate in a *dative* fashion prior to hydride transfer.

1. Reduction by Tetravalent Hydride Reagents

The stability of ketones, but not aldehydes, to reduction by $NaBH(OAc)_3$ was established in 1975.[213] In 1983, it was discovered that the reagent can effect the reduction of ketones bearing hydroxyl groups suitably positioned for interaction with the borohydride (for example, Table 45, entry 1).[214] To explain the observed selectivity and reactivity, a sequence involving a ligand exchange reaction at boron by the substrate (ROH) to form $NaBH(OAc)_2(OR)$, followed by intramolecular delivery of hydride to the carbonyl carbon, was proposed. Entry 2 of Table 45 provides an example of a highly regioselective reduction by $NaBH(OAc)_3$. More recently it has been demonstrated that a γ-hydroxyl group can deliver hydride onto a carbonyl site as well (entry 3).

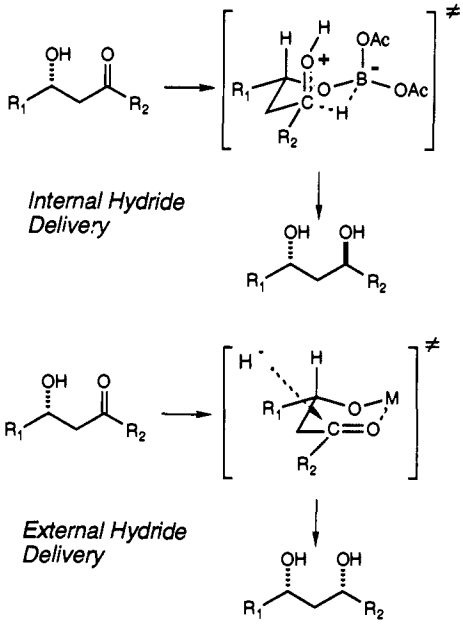
Table 45. Directed Ketone Reduction by Triacetoxyborohydride

Entry	Substrate	Product	Selectivity
1			one isomer
2			one isomer
3			"stereospecific"
4			50 : 1
5			50 : 1
6			6 : 1[a]
7			> 30 : 1

[a] Ratio of *anti,anti*-triol to all other diastereomers.

A study of the mechanism and diastereoselectivity of the directed reduction of acyclic β-hydroxy ketones by $Me_4NBH(OAc)_3$ has appeared recently; ketones, β-keto esters, and simple β-diketones which lack a suitably disposed hydroxyl group are not reduced under the standard conditions.[214e] Entries 4 and 5 (Table 45) illustrate the high anti selectivity of the reaction, regardless of the substitution at the α-carbon.[215] Consideration of chairlike transition structures provides a plausible rationale for the observed diastereoselection (Scheme 26).[216] It is noteworthy that the weak response of the stereoselectivity to the substitution at the α-carbon is well accommodated by this model. Entry 6 provides an example of sequential diastereoselective directed reductions. The potential utility of this directed reduction in the synthesis of polyketide-derived natural products is clear.

Scheme 26

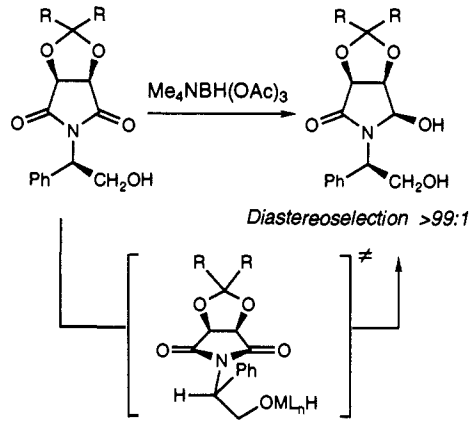


Intramolecular delivery of hydride in $Me_4NBH(OAc)_3$ reductions is supported not only by the stereochemical outcome of the reaction of cyclic substrates, but of acyclic systems as well. A general pattern holds with regard to stereoselectivity in the reduction of acyclic β-hydroxy ketones: Chelate-controlled additions of hydride reagents (external delivery) to α-unsubstituted substrates preferentially generate the *syn*-1,3-diol (Scheme 26),[217] whereas reductions proceeding through intramolecular delivery selectively produce the *anti*-1,3-diol.[218]

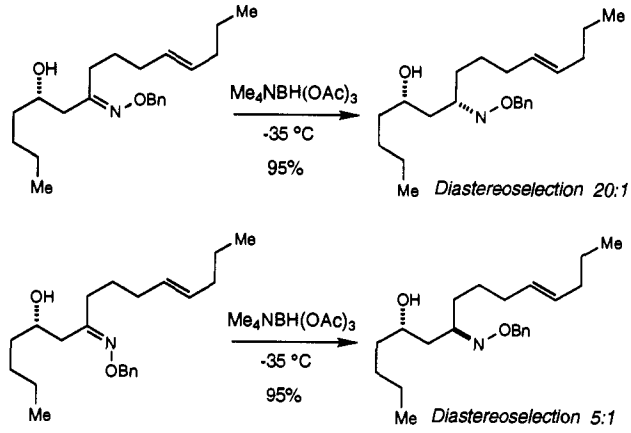
Imides (Scheme 27) and oximino ethers (Scheme 28) can also serve as substrates for hydroxyl-directed triacetoxyborohydride reduction.[219] The tartaric acid derivative shown below undergoes highly selective addition to one of the diastereotopic carbonyl groups when treated with $Me_4NBH(OAc)_3$, whereas the corresponding TBS ether is inert to the same conditions. Reduction through the reactive conformer shown is plausible; nucleophilic attack occurs from the convex face of the bicyclic system, where A(1,3) strain[22] is minimized leading to the positioning of the hydrogen in the amide plane.

Most recently, it has been reported that a β-hydroxy group may effectively control the reduction of an

Scheme 27

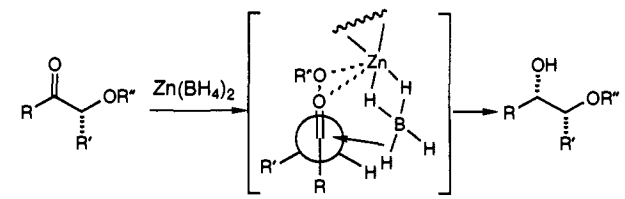


Scheme 28



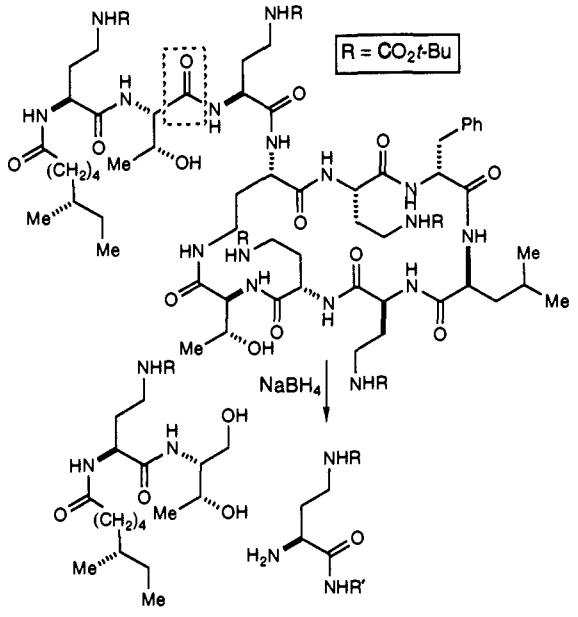
oxime.[219] As is illustrated in Scheme 28, reduction by $Me_4NBH(OAc)_3$ affords either the syn or the anti product with stereocontrol. The rationale behind such reversal of stereochemistry will undoubtedly be the subject of future reports.

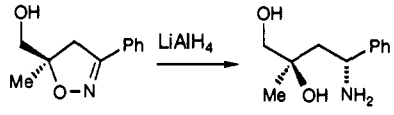
A number of reports have implicated internal delivery when rationalizing stereoselective reactions which involve other borohydrides.[220] For example, intramolecular reduction has been invoked in $Zn(BH_4)_2$ reactions of ketones bearing α- or β-heteroatoms,[221] although metal ion chelation followed by intermolecular attack by hydride would also rationalize the sense of stereoselection obtained. Scheme 29 illustrates a remarkable reductive cleavage by $NaBH_4$ of one of two threonine peptide bonds of a polymyxin antibiotic; the alcohol and amine shown were the principal isolated products.[222] A reaction directed by the less encumbered hydroxyl group is postulated; when the threonine hydroxyls are protected (OTHP), no transformation takes place.

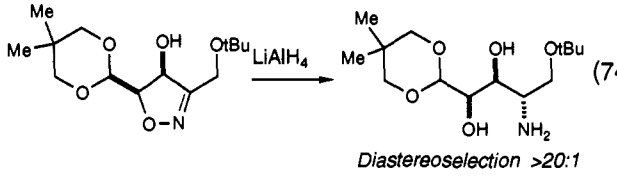


Aluminum hydrides may also participate in directed reduction processes.[223] As eqs 73 and 74 demonstrate, hydroxyl groups direct the addition of $LiAlH_4$ to isoxazolines.[224]

Scheme 29

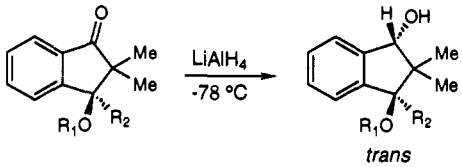






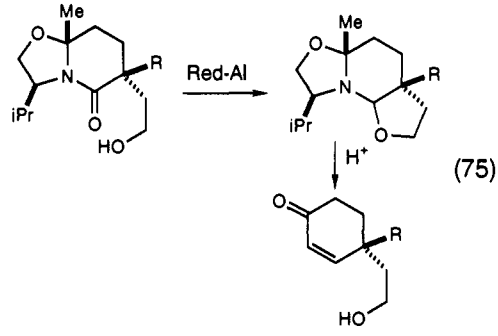
Cawley and Petrocine have reported the reduction of a series of cyclic hydroxy and alkoxy ketones with $LiAlH_4$ (Table 46).[225] The overall stereoselectivity of the reaction is proposed to depend on a competition between oxygen-delivered reduction, which provides the trans isomer exclusively, and intermolecular reduction, which yields a mixture of products. The trends observed with variation in the ratio of substrate to hydride are consistent with this postulate, if the undirected reaction involves a kinetic scheme which is higher order in $LiAlH_4$ than the directed process. Comparison of entry 2 with entry 4 indicates that the presence of an alkyl group α to the methyl ether may hinder dative complexation of the oxygen to the aluminum, thereby retarding the rate of intramolecular reduction. It is not clear a priori why ethers afford higher trans selectivity than do the corresponding alcohols (entry 1 vs 2 and 3 vs 4).

Table 46. Stereoselective Reduction of Cyclic Ketones by $LiAlH_4$

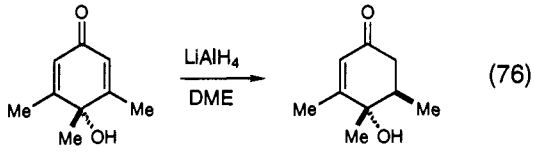


Entry	R_1	R_2	Substrate : Hydride 0.5	1.0	2.0
1	H	H	3	12	56
2	Me	H	100	100	100
3	H	Me	20	22	31
4	Me	Me	19	52	83

The ability of an internal hydroxyl group to facilitate reduction by $NaAlH_2(OCH_2CH_2OMe)_2$ (Red-Al) has been exploited in the design of a chiral auxiliary for the synthesis of 4,4-disubstituted cyclohexenones (eq 75).[226] Whereas attempted cleavage of a valine-derived auxiliary with this reagent furnishes a host of undesired products, in the presence of an appropriately situated hydroxyethyl or aminoethyl substituent, smooth reduction of the lactam occurs. The precise mechanism by which the hydroxyl group accelerates the reduction (internal delivery of hydride versus metal ion binding site for carbonyl activation) has not yet been established.

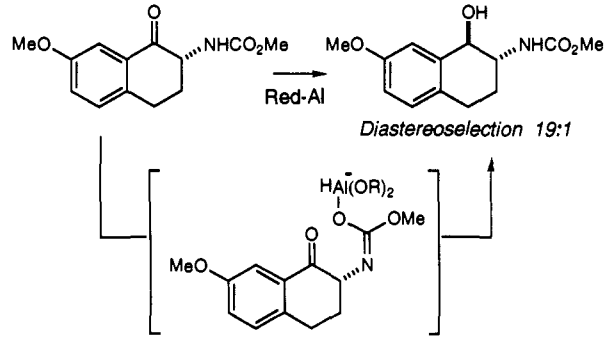


Recent reports demonstrate that a γ-hydroxyl group can deliver hydride from $LiAlH_4$ to the β-carbon of a cyclic enone (eq 76).[227] The regio- and stereochemical outcome of the reaction are consistent with intramolecular transfer of hydride from an alkoxyaluminum hydride complex.



In the course of studies directed toward the synthesis of a nonracemic dopamine agonist, an example of an amide-directed Red-Al reduction was realized (Scheme 30).[228] If the hydride reagent is added to the tetralone, racemization and incomplete reduction result. These data are consistent with the reaction proceeding through rapid formation of the monohydric aluminate intermediate, followed by intramolecular ketone reduction, which occurs in preference to both ketone deprotonation and intermolecular reduction. With excess tetralone, a tetrakisalkoxyaluminate may form. This species is

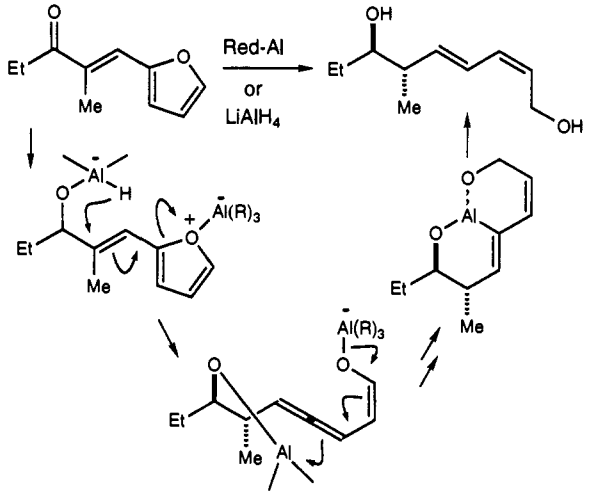
Scheme 30



unable to undergo intramolecular reduction without prior disproportionation with aluminum hydride, a process which is apparently sluggish.

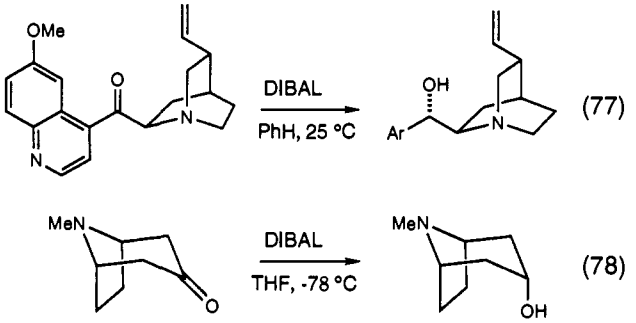
More recently, it has been shown that $LiAlH_4$ or Red-Al can effect the reductive fragmentation of a number of β-furanyl systems.[229] As is shown in Scheme 31, it is suggested that the hydroxyl group, formed from initial reduction of the corresponding ketone, directs delivery of the hydride.

Scheme 31



2. Reduction by Trivalent Hydride Reagents

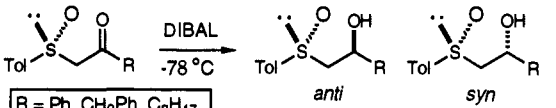
The stereochemical outcome of a variety of carbonyl reductions by DIBAL (diisobutylaluminum hydride) has been rationalized on the basis of a directed reaction.[230] DIBAL stereoselectively reduces quinidinone to quinidine (eq 77), whereas $NaBH_4$ affords the opposite (Felkin–Anh) sense of stereoselection. Amine complexation to DIBAL, followed by intramolecular delivery, has been proposed.[231] The sense of stereoselection observed in the reduction of tropinone is dependent on the nature of the reducing agent; whereas DIBAL preferentially furnishes tropine (eq 78),[232] tetravalent metal hydride reagents such as lithium aluminum hydride and sodium borohydride preferentially produce the diastereomeric alcohol.



Diastereoselection 32:1

In the reduction of β-keto sulfoxides, the presence or absence of a Lewis acid plays a decisive role in determining the sense of diastereoselection (eq 79).[233] It was subsequently reported that similar results can be obtained with cyclic substrates (eq 80).[234]

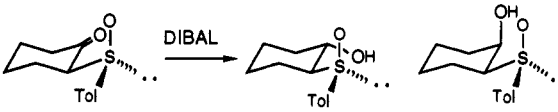
It has been postulated that in the presence of $ZnCl_2$, chelate i undergoes reduction, whereas in its absence, conformer ii is the reactive species "because of dipolar



R = Ph, CH_2Ph, C_8H_{17}, (*E*)-CHCHPh

No $ZnCl_2$; Diastereoselection ≥13:1

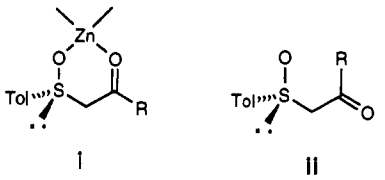
with 1.0 equiv $ZnCl_2$; Diastereoselection <1:20



No $ZnCl_2$; Diastereoselection >20:1

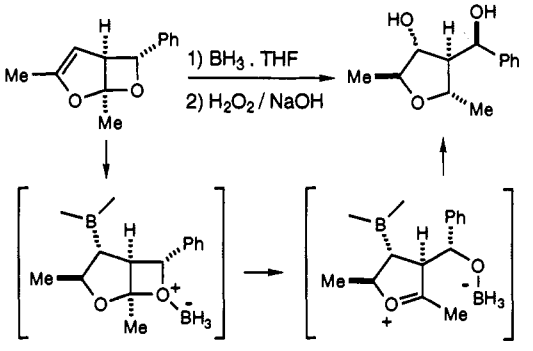
with $ZnCl_2$; Diastereoselection 1:9

interactions"; in both cases, attack of external hydride occurs on the less hindered (β) face.[235]



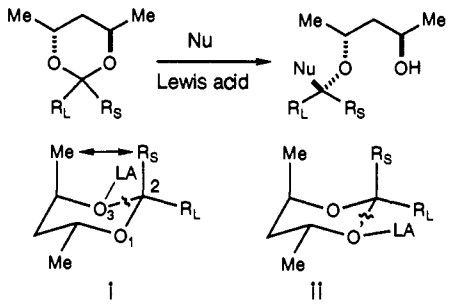
Another class of directed reductions by trivalent metal hydrides includes the cleavage of cyclic ketals by boranes and alanes. The proposed mechanism for this reaction involves (1) coordination by the Lewis acidic metal to a ketal oxygen (2) cleavage of the ring into an oxonium ion and an alkoxy metal hydride, and (3) intramolecular delivery of hydride to the oxonium ion. The reduction of the carbon–oxygen bond in the bicyclic ketal shown in Scheme 32 proceeds stereoselectively with retention of configuration, consistent with the postulate of intramolecular delivery.[236] The choice of which ketal C–O bond is cleaved in these reactions may be rationalized by consideration of steric inhibition to complexation to the metal, chelation by substrate heteroatoms to the metal, and relief of strain.

Scheme 32



Chiral ketals derived from 2,4-pentanediol have been cleaved by a wide range of nucleophiles with high diastereoselectivity (Scheme 33).[237] A preference for relieving the more severe 1,3-diaxial interaction (M ↔ R_S) offers a plausible rationale for the sense of induction observed in these reactions. Thus, binding of the Lewis acid to O_3 (i) should be preferred to O_1 (ii), since this complexation simultaneously increases the strength of the $n_{O1} \rightarrow \sigma^*_{C2-O3}$ stabilization and decreases the ability of O3 to donate to σ^*_{C2-O1}. Both effects serve to lengthen the O3–C2 (and shorten the O1–C2) bond relative to the uncomplexed ketal, thereby relieving the more

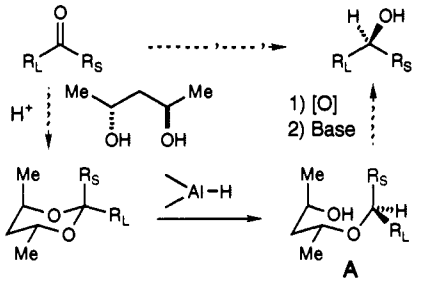
Scheme 33



destabilizing diaxial interaction (Me ↔ R_S); similarly, complexation of O1 (ii) would worsen this interaction by shortening the O3–C2 bond.[238] Identical stereoelectronic and steric effects are also expressed along the pathway to formation of the oxonium ion.

For most nucleophiles, acetal cleavage occurs with inversion of configuration at the carbon undergoing substitution, consistent with either nucleophilic attack on a tightly ion-paired oxonium intermediate or direct S_N2 displacement. However, it has been established that trivalent aluminum hydrides diverge from this stereochemical regularity by providing the product with retention of configuration.[239] This observation is consistent with the notion of rapid intramolecular hydride delivery within the ion-paired intermediate. A sequence which involves this reaction as a key step affords the equivalent of an enantioselective ketone reduction (Table 47). Low temperatures, high concentrations of aluminum hydride, and solvents of low to moderate Lewis basicity are required for high selectivity. The stereochemistry of the products of reduction by binary hydride–Lewis acid reagents suggests attack by external hydride (entry 1).[240]

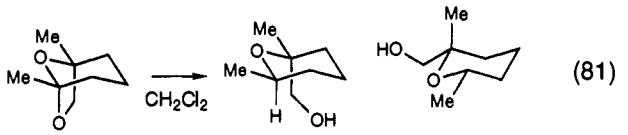
Table 47. Reduction of Acetals by DIBAL



Entry	R_L	R_S	Reagent (equiv)	% de of A
1	C_6H_{11}	Me	DIBAL (5.0)	88
			Cl_2AlH (6.0)	92
			Br_2AlH (6.0)	95
			Et_3SiH (1.0) /BF_3·OEt_2 (1.0)	14[a]
			Et_3SiH (1.2) /$TiCl_4$ (1.2)	4[b]
2	Hex	Me	Br_2AlH (20.0)	78
3	Ph	Me	Br_2AlH (6.0)	96
4	Me	C≡CBu	Br_2AlH (2.0)	0
			Br_2AlH (4.0)	36
			Br_2AlH (6.0)	86

[a] Other isomer formed with 86% selectivity. [b] Other isomer formed with 96% selectivity.

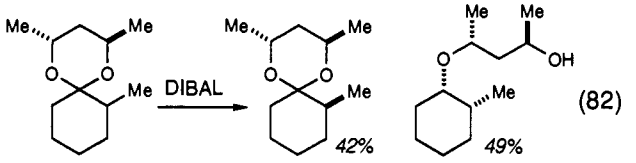
Recently, the stereoselective reduction of a series of bicyclic ketals has been reported (eq 81).[241] Most noteworthy is that in selected instances satisfactory levels of kinetic resolution of diastereomeric ketals has been achieved (eq 82).[242]



(81)

with DIBAL (25°C); Diastereoselection 32:1

with Et_3SiH, $TiCl_4$ (-78 °C); Diastereoselection 1:99



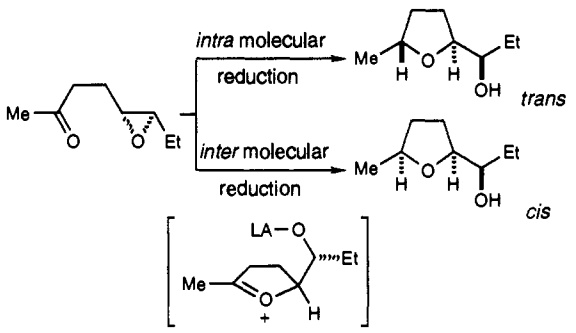
(82)

42% *Diastereoselection >99:1*

49% *Diastereoselection 19:1*

A related cyclization, directed reduction sequence has been utilized for the synthesis of a trans-2,5-disubstituted tetrahydrofuran from an epoxy ketone.[243] Nucleophilic attack by the carbonyl oxygen on the epoxide, induced by a Lewis or Brönsted acid, generates the oxonium ion. Intramolecular delivery of hydride to this intermediate furnishes the trans isomer, whereas intermolecular reaction should favor the cis. Silane–acid reagents provide the cis tetrahydrofuran, albeit with low selectivity, whereas BH_3·SMe_2 and thexylborane afford the trans isomer predominantly (Table 48). The concentration effect observed with BH_3·SMe_2 is consistent with the postulate that the overall reaction diastereoselectivity reflects competition between internal and external hydride for the oxonium ion. Cyclization–reduction of the corresponding cis epoxide proceeds with comparable levels of stereocontrol.

Table 48. Reduction of Oxonium Ions by Boranes

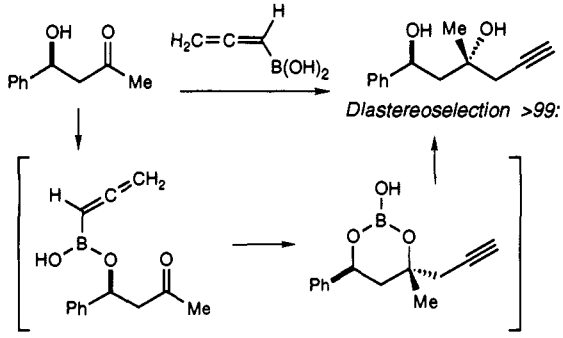


Conditions	*Cis : Trans*
Et_3SiH, TFA	2 : 1
Ph_3SiH, BF_3·OEt_2	5 : 1
BH_3·SMe_2 (0.005 M)	1 : 24
BH_3·SMe_2 (0.012 M)	1 : 11
thexylborane (0.030 M)	1 : 9

B. Nucleophilic Addition to C=O and C=N

Several reports suggest that directed addition of main group organometallics to polarized double bonds is possible.[244,245] As illustrated in Scheme 34, treatment of β-hydroxy ketones with allenylboronic acid furnishes homopropargylic alcohols with high diastereoselectivity (>99:1).[246] The reaction is proposed to proceed in-

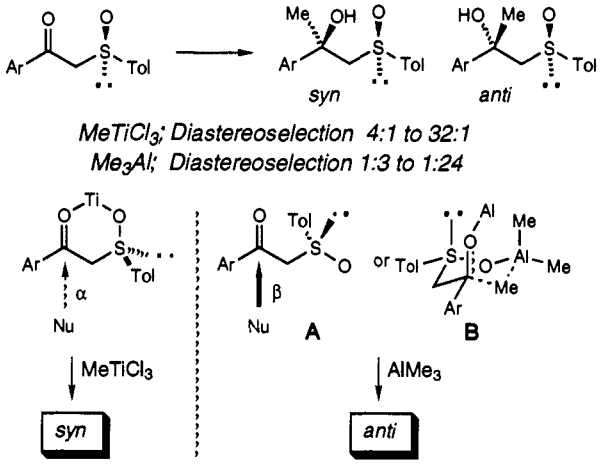
Scheme 34



tramolecularly, as indicated. Control experiments establish that a hydroxyl group accelerates the addition, but the precise mechanism by which this is effected (internal delivery versus chelation–activation) is unclear. It has been suggested that the diastereoselectivity of the allenylboronic acid reaction (>99:1) in comparison with that of propargylmagnesium bromide (<3:1) provides support for a highly organized transition state involving delivery rather than a less rigid transition state involving chelation.

The sense of stereoselection observed in the addition of methyl organometallics to β-keto sulfoxides is reagent dependent:[247] external attack at the less hindered face of a chelated intermediate rationalizes the syn selectivity of the $MeTiCl_3$ reaction (Scheme 35). It has been suggested that the intermolecular alkylation of the less encumbered face of a dipole-minimized β-keto sulfoxide conformer (A) leads to the complementary diastereoselection obtained upon reaction with $AlMe_3$. In analogy to tetravalent borohydride reduction of β-hydroxy ketones, we suggest an alternate transition-state model which invokes intramolecular delivery of the nucleophile by the sulfoxide oxygen (B; see Scheme 26 for comparison).

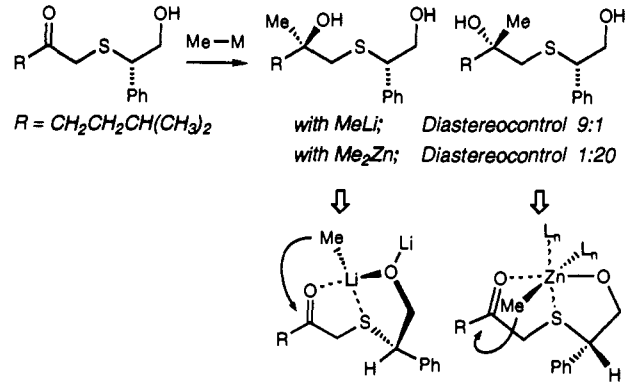
Scheme 35



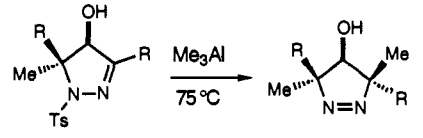
Nucleophilic addition of alkylmetals to chiral thiomethyl ketones has been shown to be diastereoselective and stereochemically complementary, depending on the alkylmetal employed.[248] Two examples are shown in Scheme 36; the opposite stereochemical outcomes with alkyllithium and alkylzinc reagents have been rationalized by the transition structures shown.

With $AlMe_3$, hydroxypyrazolines undergo addition exclusively syn to the hydroxyl group (eq 83).[249]

Scheme 36



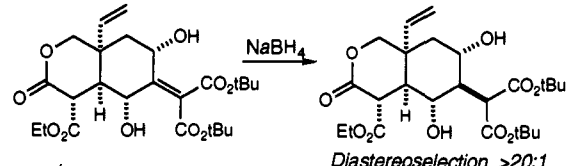
Thecorresponding methyl ethers are unreactive toward trimethylaluminum even at higher temperatures (110 °C),



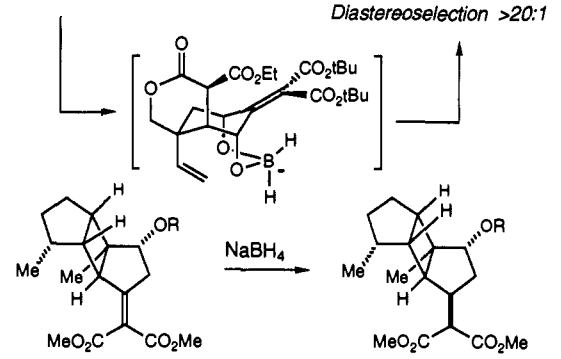
(83)

C. Conjugate Addition Reactions

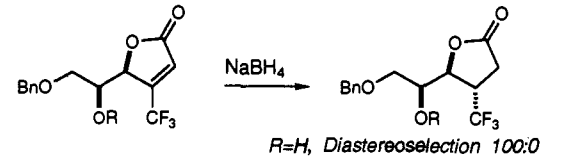
A range of nucleophiles (hydrides, organometallics, and peroxides) can be delivered in a 1,4-fashion to conjugated alkenes. There have been several reports of diastereoselective reductions of α,β-unsaturated carbonyl systems by $NaBH_4$ where the sense of addition is consistent with internal delivery by a hydroxyl group (eqs 84–86).[250] The reaction shown in eq 84 is believed to proceed via the chelated dialkoxyborohydride. Hydride delivery by the homoallylic alcohols in eqs 85–86 is effective; protection of these directing groups, however, leads to a diminution in stereoselectivity.



(84)

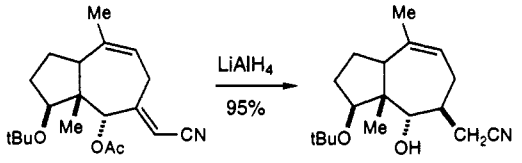


(85)

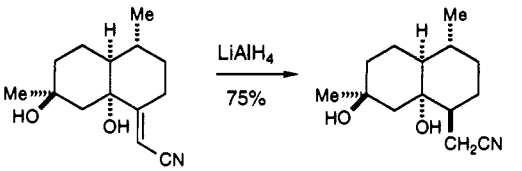


(86)

Lansbury has developed a general route to *trans*-γ-lactones through a sequence involving highly diastereoselective hydroxyl-directed reduction of α,β-unsaturated nitriles with $LiBH_4$ or $LiAlH_4$, followed by hydrolysis. Isolated α,β-unsaturated nitriles are unreactive toward $LiBH_4$ under the same conditions, whereas $LiAlH_4$ preferentially reduces the C–N π-system. Two examples are illustrated in eqs 87 and 88.[251]

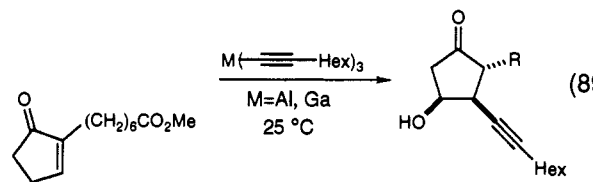


(87)

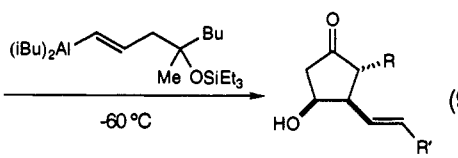


(88)

Although alanes do not generally add in a 1,4-fashion to enones that are constrained to lie in an s-trans conformation,[252] treatment of the hydroxycyclopentenone shown below with alkynyl- and alkenylalanes results in conjugate addition exclusively syn to the hydroxyl group (eqs 89 and 90).[253] The corresponding THP ether and the des(hydroxy) enone are unreactive; these data indicate delivery of the alane by the hydroxyl group.

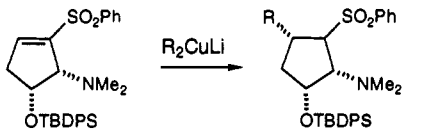


(89)



(90)

It appears that amines can direct the conjugate addition of dialkylcuprates to a cyclopentenyl sulfone.[254] In contrast to alkyllithiums, which add only to the less hindered face of the olefin, cuprates add exclusively to the more sterically encumbered face (eq 91).

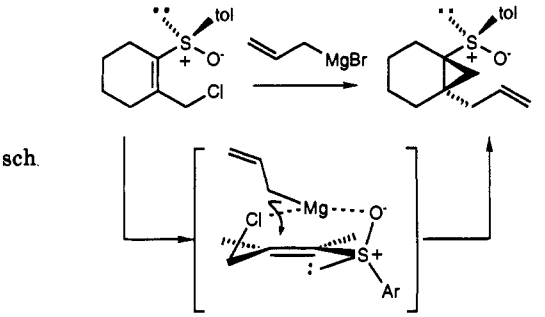


(91)

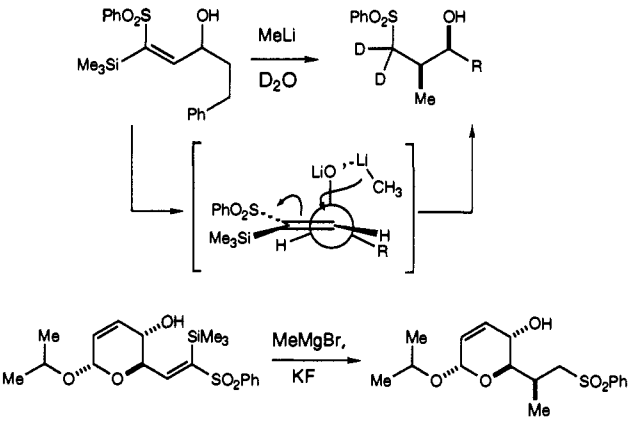
R = Me, Ph, $CHCH_2$

Recently, it was reported that reaction of allylmagnesium chloride with the unsaturated sulfoxide shown in Scheme 37 results in the stereoselective formation of the corresponding cyclopropane.[255] The proposed transition structure, where unfavorable allylic interactions (A(1,3)) are minimized,[202] is illustrated; association of the alkylmagnesium with the pendant chloride and sulfoxide groups is believed to lead to high levels of diastereocontrol.

Scheme 37

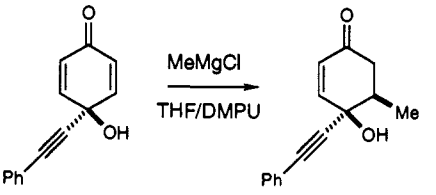


Scheme 38



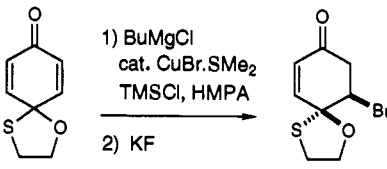
An interesting case of directed conjugate addition is shown in Scheme 38.[256] Association of the alkyllithium with the Lewis basic lithium alkoxide results in the stereoselective formation of the carbon–carbon bond. Also presented in Scheme 38 is a step in the synthesis of okadaic acid where this type of addition process is employed.[256e]

Addition of MeMgCl to quinol alkoxides proceeds with high levels of diastereocontrol; these reactions are believed to be directed ("ligand-assisted") by the internal hydroxyl group.[257] The example shown in eq 92 is illustrative. The transformation shown in eq 93 indicates that the directing ability of the alkoxy group is superior to that of the sulfide.[258]



(92)

Diastereoselection 13:1

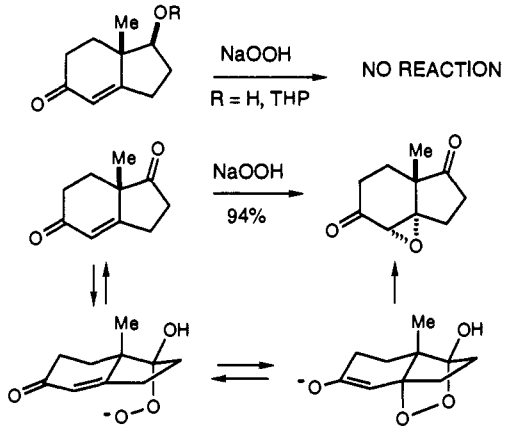


(93)

Diastereoselection 13:1

A remote carbonyl group has been reported to deliver an oxygen nucleophile, a peroxide, in an enone epoxidation reaction.[259] Whereas treatment of the alcohol or ether with NaOOH leads to no reaction, the derived ketone affords the α-epoxide as a single diastereomer in 94% yield (Scheme 39). It was proposed that initial

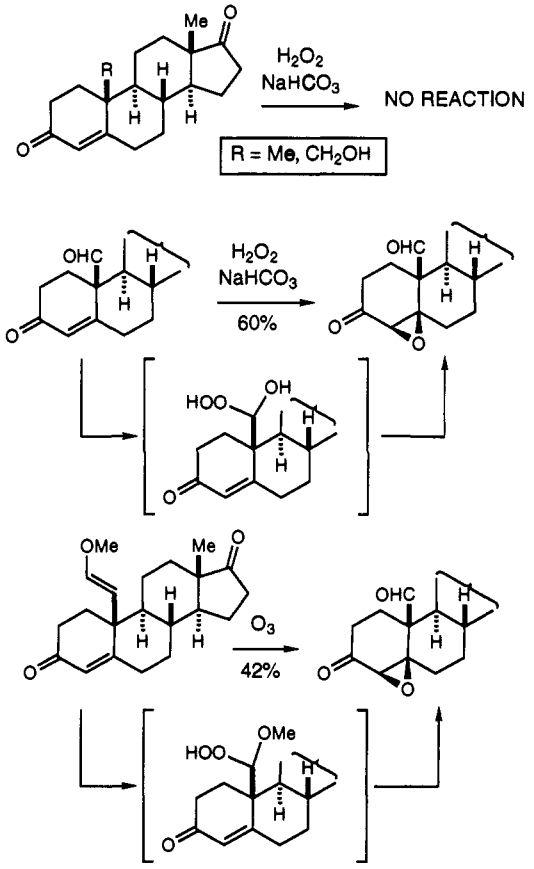
Scheme 39



addition of hydrogen peroxide to the nonconjugated ketone results in the formation of an alkyl hydroperoxide adduct, which then effects epoxidation intramolecularly. The Wieland–Miescher ketone also affords exclusively the trans-fused ring system under these conditions.

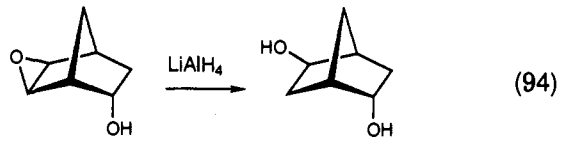
Similar observations were subsequently reported in connection to an androgen system (Scheme 40):[260] *tert*-butyl hydroperoxide does not effect epoxidation under these conditions, consistent with the mechanism illustrated in Scheme 39. Generation of the alkyl hydroperoxide intermediate through other pathways can also result in stereoselective epoxidation.[261] Thus, treatment of the illustrated enol ether with ozone furnishes only the *syn*-epoxy aldehyde.

Scheme 40

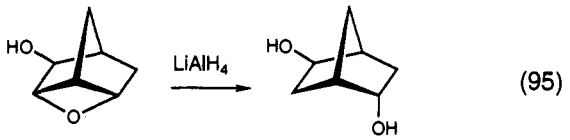


D. Nucleophilic Substitution Reactions

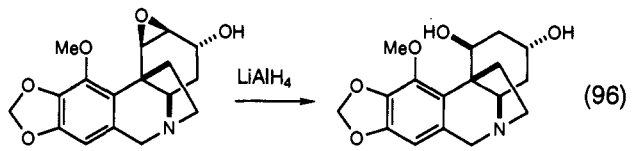
The hydroxyl-directed, regioselective ring cleavage of epoxy alcohols and related compounds by a variety of nucleophiles (hydride, alkoxide, and organometallic) has been achieved.[262] The first example of directed cleavage involved opening with hydride, and this reaction remains the most widely used in this class. Early work in this area involved $LiAlH_4$ as the reducing agent; examples shown in eqs 94–96 are illustrative.[263] The reaction is believed to proceed through ligation of the hydroxyl group to the reagent, followed by intramolecular hydride delivery from the resulting aluminate complex. Lithium aluminum hydride reduction of the methyl or THP ether of the alcohol in eq 94 preferentially affords the 1,2-diol (>10:1).



(94)



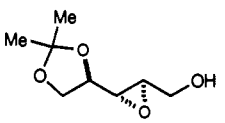
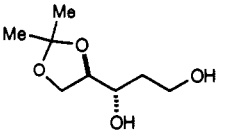
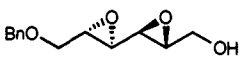
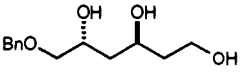
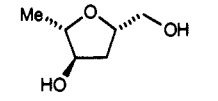
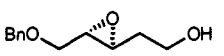
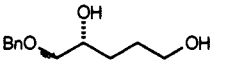
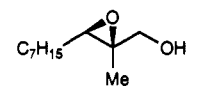
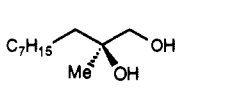
(95)



(96)

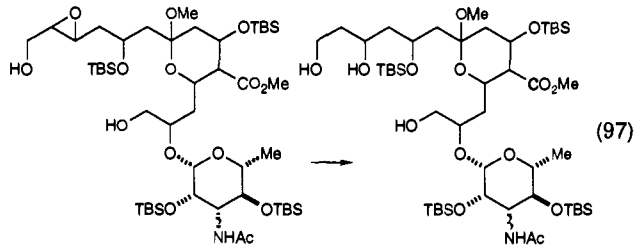
Recently, $NaAlH_2(OCH_2CH_2OMe)_2$ (Red-Al) has supplanted $LiAlH_4$ as the reagent of choice for hydroxyl-directed epoxide opening.[264] In 1982, several reports indicated that this reagent regioselectively reduces acyclic 2,3-epoxy alcohols to 1,3-diols at or below ambient temperature (Table 49, entries 1 and 2).[265] Under identical conditions, no reaction is observed if the alcohol is protected. Propagating reductive cleavage of bis-epoxides (entry 2),[266] available from asymmetric epoxidation, furnishes access to the *syn*- and the *anti*-1,3-diol pattern found in many polyacetate-derived

Table 49. Cleavage of Epoxy Alcohols by $NaAlH_2(OCH_2CH_2OMe)_2$

Entry	Substrate	Product	Selectivity
1			only
2			only
3			12 : 1
4			only
5			100 : 1

natural products. Entry 3 illustrates a successful cleavage of a cyclic homoallylic epoxy alcohol.[267] Intramolecular delivery of hydride can be effected from the homoallylic position (entry 4), but not when opposed by strong steric hindrance to attack at C2 (entry 5).[268]

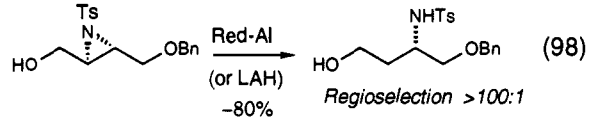
In the short interval since its discovery, the hydroxyl-delivered cleavage of epoxy alcohols by Red-Al has found widespread application in synthesis.[269] Equation 97 provides an application of regioselective reductive opening to a highly functionalized molecule.[270]



(97)

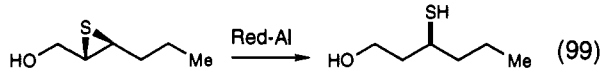
Regioselection 8:1

The available data suggest that the corresponding sulfur and nitrogen heterocycles react analogously. Reduction of the aziridino alcohol shown in eq 98 with either Red-Al or $LiAlH_4$ proceeds with high regioselectivity; reaction with DIBAL (THF) is equally selective, although the yield is 30%.[271] Exposure of a hydroxy thiirane to Red-Al also affords a product consistent with internal delivery of hydride (eq 99).[272]



(98)

Regioselection >100:1

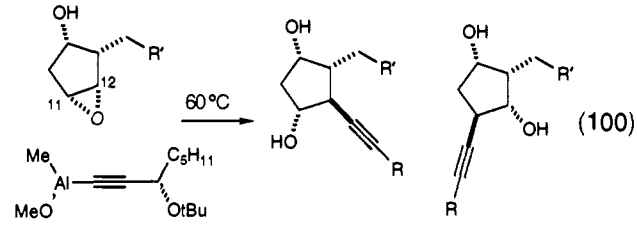


(99)

Regioselection 13:1

Treatment of a variety of steroidal *anti*-2,3-epoxy alcohols with $NaBH_4$/methanol results in the efficient cleavage of the epoxide (Scheme 41).[273] The corresponding α-alcohol is unreactive toward these conditions, as were all *syn*-epoxy alcohols examined. As is shown in Scheme 41, an *anti*-3,4-epoxy alcohol can undergo directed cleavage as well; under identical conditions the corresponding α-epoxide is recovered untouched.

The hydroxyl-directed cleavage of an epoxy alcohol by an organometallic has also been reported; whereas treatment of the acetal illustrated below with the alkynylalane provides the opening products with poor selectivity, reaction of the derived alcohol results in epoxide cleavage exclusively at the position proximal to the primary hydroxyl group (eq 100).[274] The corresponding dimethylalkynylalane affords the product of attack at C12 with much lower selectivity (1–4:1), indicating that the reaction is highly sensitive to the nature of the alkylating reagent.[275] Other workers have demonstrated that additions of alkyl- and alkynylaluminum species to cyclic and acyclic 2,3-epoxy alcohols[276,277] typically are not subject to internal delivery.[278]



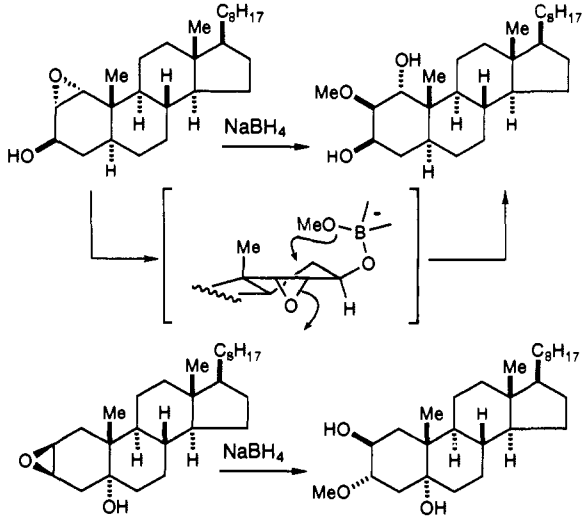
(100)

with R' =  *No Regioselection*

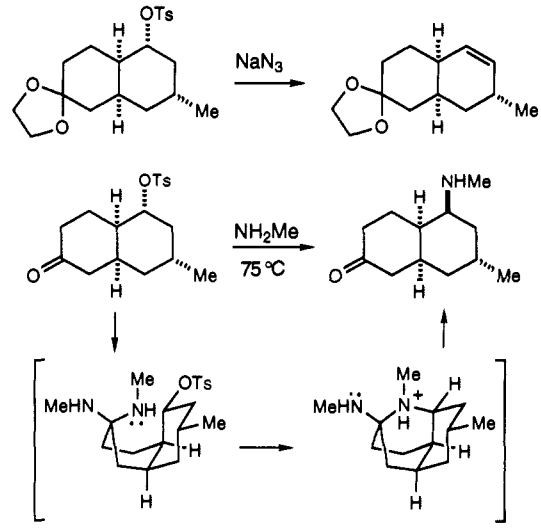
with = -CH_2OH *Regioselection >20:1*

Carbonyl groups have been reported to direct the displacement reaction of a secondary tosylate from the concave face of a *cis*-decalin system.[279] Treatment of the acetal shown in Scheme 42 with sodium azide results in elimination primarily (70%), as well as some substitution (30%).[280] However, reaction of the corresponding ketone with NH_2Me furnishes the desired secondary amine in excellent yield as the only product. To explain the difference in reactivity, it was postulated that the latter transformation proceeds in an intramolecular fashion through a transient aminal.

Scheme 41



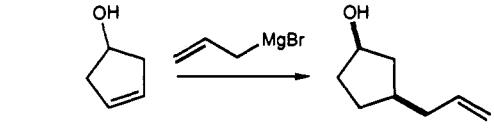
Scheme 42



VIII. Directed Carbometalation and Hydrometalation Reactions

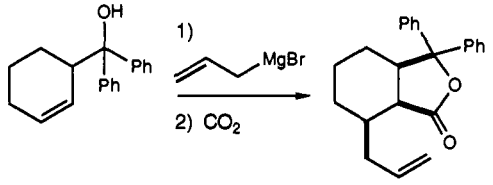
A. Alkylmagnesium Additions

Although alkylmagnesium halides normally do not react with unactivated alkenes, in certain instances the presence of a hydroxyl group can lead to the addition of the alkylmagnesium halide to the alkene. For example, treatment of allylmagnesium bromide to alkenes shown below (eqs 101 and 102, in refluxing ether) results in the stereoselective formation of carbon–carbon bonds.[281,282]



(101)

Diastereoselection 4:1



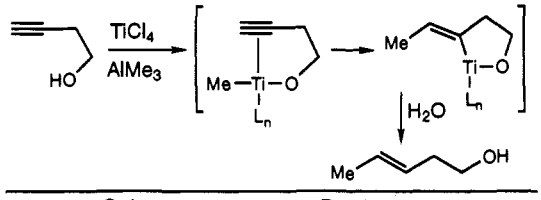
(102)

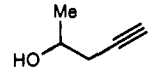
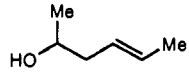
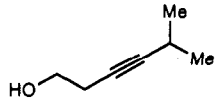
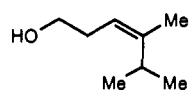
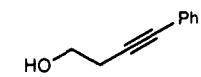
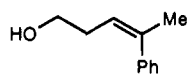
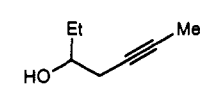
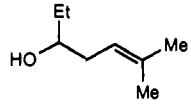
Diastereoselection >20:1

B. Alkyltitanium Additions

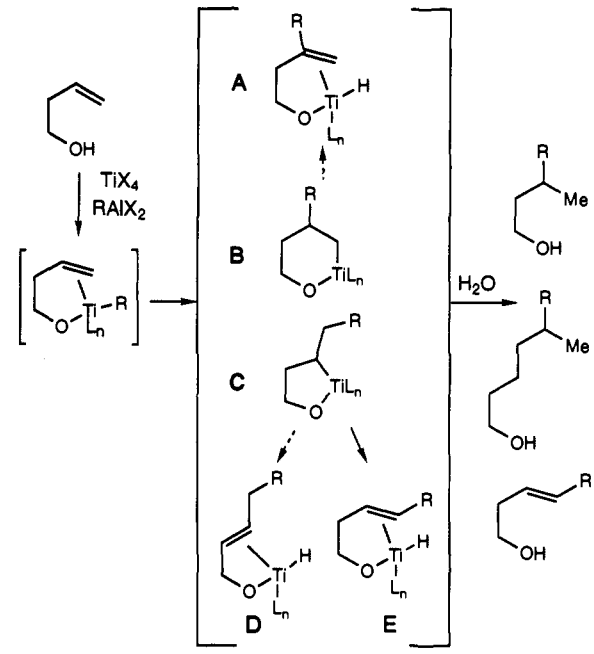
A number of transition metal-mediated, hydroxyl-delivered carbometalations of multiple bonds have been reported. Whereas 1-octyne forms dimers and higher oligomers upon treatment with $TiCl_4/AlMe_3$, under the same conditions homopropargylic alcohols undergo regioselective methylmetalation (Table 50).[283] Quenching with D_2O results in deuterium incorporation cis to the newly introduced methyl group. The mechanism shown below, involving delivery by the hydroxyl, accommodates these results. Ethylmetalation of terminal homopropargylic alcohols can be effected with $TiCl_4/ClAlEt_2$; however, reaction of the corresponding internal alkynes affords none of the desired addition

Table 50. Methyltitanium Addition to Homopropargylic Alcohols



Entry	Substrate	Product	Yield (%)
1			80
2			67
3			76
4			66

Scheme 43

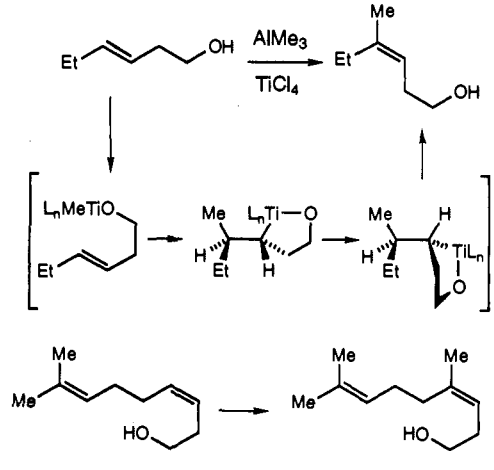


product.[284] Hydroxyl-delivered carbometalation of bishomopropargylic alcohols is also possible.

Carbometalation of homoallylic alcohols with Ti/Al reagents provides a number of products (Scheme 43).[285] Although this reduces the reaction's utility in synthesis, the presence of only one olefin product suggests that delivery of the metalalkyl by the hydroxyl group is occurring. Addition to the alkene can furnish either of two alkyltitanium species (B or C). These intermediates may react further by β-hydride elimination. β-Elimination of exocyclic hydrogens is known to be favored relative to endocyclic.[286] Therefore, if chelation is operative, it would be reasonable that formation of only one of the three possible β-hydride elimination products (E) is observed. In the absence of chelation, one would expect to see production of A and D as well.

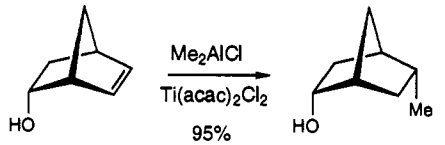
The facility with which these β-hydride eliminations occur is highly solvent dependent, pentane/Me_2O being the medium of choice for a more rapid reaction.[287] Homoallylic alcohols react site selectively and regio- and stereoselectively with $AlMe_3/TiCl_4$ in pentane/Me_2O to afford the methylated olefins (Scheme 44). The hydroxyl-delivered olefin carbometalation–β-hy-

Scheme 44



dride elimination mechanism shown in Scheme 44 has been proposed to account for these observations.

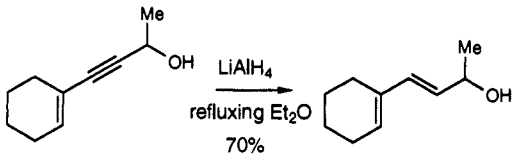
Recent studies indicate that treatment of rigid bicyclic alkenes bearing a heteroatom with $AlMe_2Cl$ and $AlEt_2Cl$ in the presence of small amounts of Ti(IV) complexes (e.g., Cp_2TiCl_2 or $Ti(acac)_2Cl_2$) results in the attachment of the alkyl group to the face of the alkene syn to the directing group.[288] The example shown in eq 103 is illustrative; the corresponding exo isomer affords no product.



(103)

C. Hydroaluminations of Alkynes

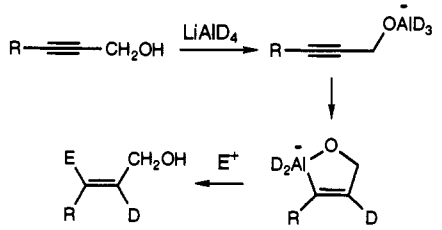
The hydroalumination of isolated alkynes by $LiAlH_4$ can be directed by properly situated heteroatoms, but requires vigorous conditions.[289] Reduction of the enynol shown in eq 104 with lithium aluminum hydride proceeds under mild conditions.[290] This reaction has been shown to be general for propargylic alcohols.[291]



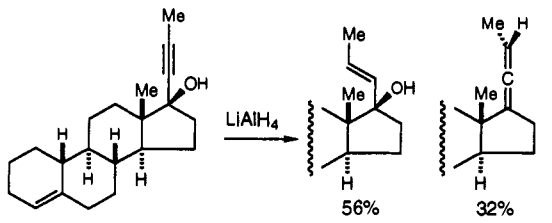
(104)

The reaction mechanism most probably involves coordination of the substrate hydroxyl to aluminum, then intramolecular delivery of hydride to the proximal carbon of the acetylene (Scheme 45).[292,293] The intermediate vinyl alanates can be derivatized with I_2 stereoselectivity to afford trisubstituted alkenes.[294]

Scheme 45

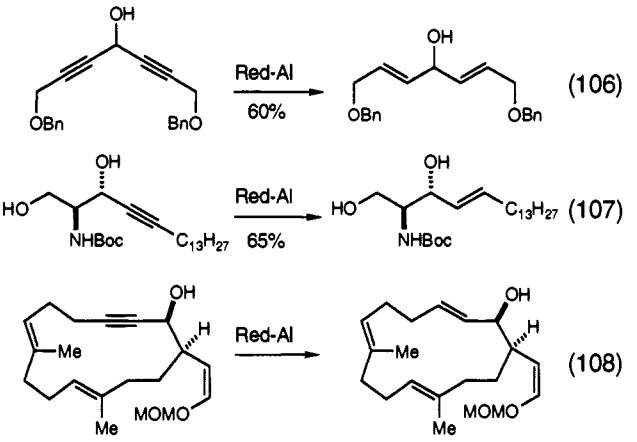


Formation of allenes, presumably a result of delivery of hydride to the distal carbon, can be a significant reaction pathway in these reductions (eq 105).[295] Other common side products are the cis allylic alcohol and the fully saturated alcohol.

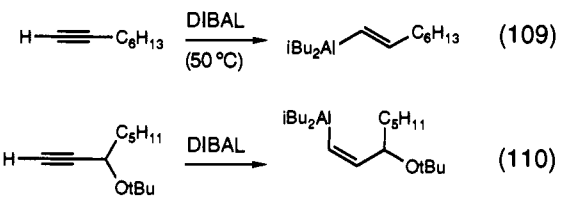


(105)

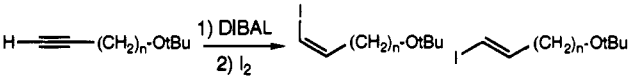
Recent reports indicate that $NaAlH_2(OCH_2CH_2OMe)_2$ (Red-Al) effects trans hydroalumination of propargylic alcohols more selectively than does $LiAlH_4$.[296] This complex, which provides the fastest, highest yielding, and most stereoselective reduction among the metal hydrides examined, is the reagent of choice for accomplishing this transformation (eqs 106–108).[297]



Ether oxygens are capable of delivering hydride to alkynes. Whereas treatment of unfunctionalized acetylenes with DIBAL furnishes the product of cis addition, a propargylic *tert*-butyl ether undergoes selective trans hydroalumination (eqs 109 and 110).[298] Since the derived trityl ether reacts in a normal fashion, it was suggested that dative coordination of oxygen to the trivalent metal might be responsible for the altered mode of addition.



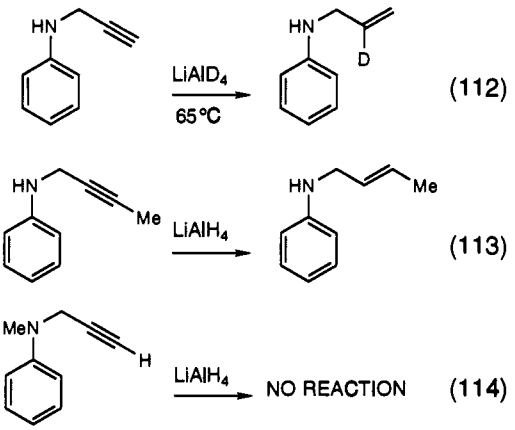
Hydroalumination of *ω-tert*-butoxyalkynes by DIBAL demonstrates that trans addition only prevails for acetylenes in which a chelate is favored (n = 1, 2, eq 111).[299] These data are consistent with oxygen-delivered hydroalumination of propargylic and homopropargylic *tert*-butyl ethers.



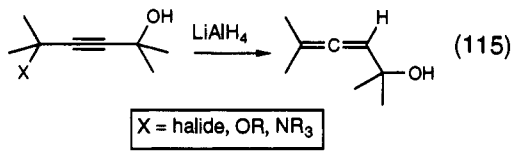
with n=1, 2	*>99:1*	(111)
with n=3	*1:24*	
with n=4, 6, 8, 10	*<1:99*	

As with alcohols, propargylic amines may be reduced to the corresponding alkene upon treatment with lithium aluminum hydride.[300] Thus, exposure of *N*-(2-propynyl)aniline to $LiAlD_4$ in refluxing THF, followed by aqueous workup, affords the allylic amine shown in eq 112 in 84% yield. Hydroalumination of an internal acetylene selectively provides the *trans*-olefin product (eq 113). The observation that *N*-methyl-*N*-(2-propynyl)aniline does not react under these conditions suggests that internal delivery of hydride proceeds by way of an aluminum amide (eq 114).[301]

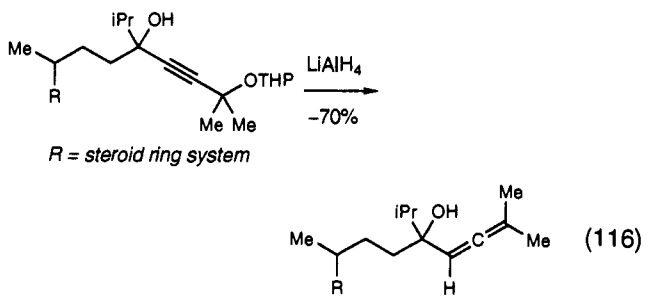
Treatment of 4-hydroxy-,[302] 4-halo-,[303] 4-(trialkylammonio)-,[304] and 4-alkoxy-2-butyn-1-ols[305] with Li-



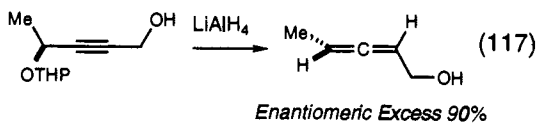
AlH_4 efficiently affords α-allenic alcohols (eq 115).[306] Reduction of the corresponding homopropargylic substrates furnishes β-allenic alcohols.[307] Again, the available data are consistent with intramolecular delivery of hydride to the alkyne.



This type of reduction has been used in a synthesis of an allenic analogue of desmosterol, an intermediate in sterol biosynthesis (eq 116). A related compound lacking a hydroxyl substituent is unreactive toward $LiAlH_4$.[295d]



As is illustrated in eq 117, reduction of optically active substrates can provide a route to nonracemic α- and β-allenic alcohols.[308]

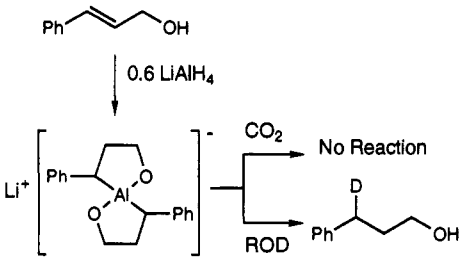


D. Hydroaluminations of Olefins

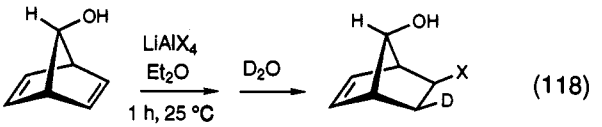
A variety of olefinic alcohols and amines are converted to their saturated derivatives when treated with lithium aluminum hydride; generally the alkene is activated toward hydroalumination either by ring strain or by an anion-stabilizing group. Reduction of cinnamyl alcohol to 3-phenyl-1-propanol serves as an example (Scheme 46).[309] On the basis of reactivity and deuterium labeling studies, it was surmised that the product of the reaction (prior to hydrolysis) is a chelated alkylaluminum species.[310]

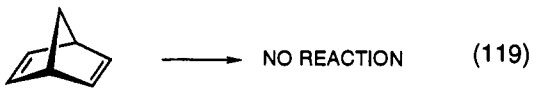
7-Hydroxynorbornadiene selectively undergoes exo,-cis addition to the alkene syn to the homoallylic

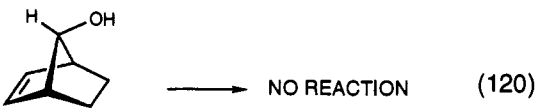
Scheme 46



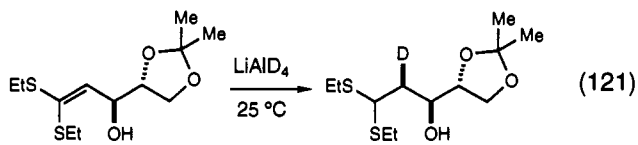
hydroxyl under conditions toward which norbornadiene and 7-*tert*-butoxynorbornadiene are unreactive (eqs 118 and 119).[311,312] This observation supports the postulate of intramolecular delivery in these alkene hydroaluminations. *syn*-7-Norbornenol is reduced by $LiAlH_4$ to 7-norbornanol, whereas the olefins of the anti isomer and of *syn*-7-formylnorbornene are unreactive under the same conditions (eq 120). Together, these results demonstrate the viability of directed hydroalumination of olefins which bear appropriately situated directing groups.[313]

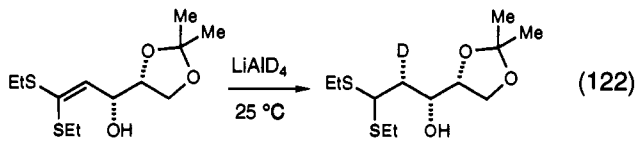






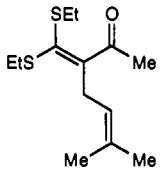
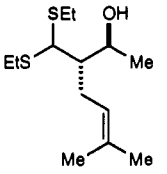
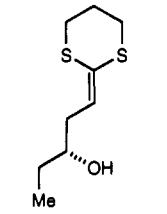
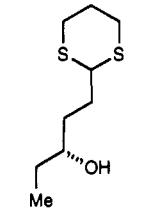
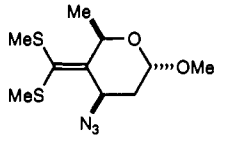
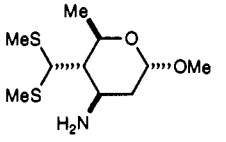
Reduction of ketene dithioacetals with $LiAlH_4$ can be directed by an internal hydroxyl group (eqs 121 and 122);[314] in contrast, the corresponding methyl ether is unreactive. Labeling studies demonstrate that hydride addition occurs at the alkene carbon proximal to the hydroxyl group and that the reaction is stereospecific. The sense of induction is consistent with intramolecular hydroalumination occurring out of a conformer which minimizes A(1,3) strain.[202]





Similarly, the reduction of α-oxo ketene dithioacetals is subject to delivery by a resident heteroatom.[315] Hydride addition to the carbonyl precedes alkene hydroalumination, which occurs at 25 °C for trisubstituted olefins and at 50–65 °C for tetrasubstituted alkenes. Reduction affords a single diastereomer for

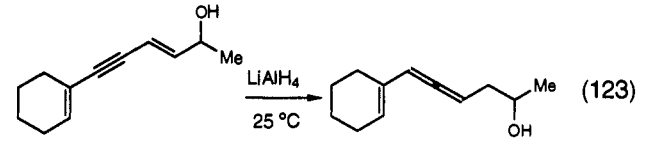
Table 51. Hydroalumination of Ketene Dithioacetals with $LiAlH_4$

Entry	Substrate	Product	Yield
1			71
2			--
3			84

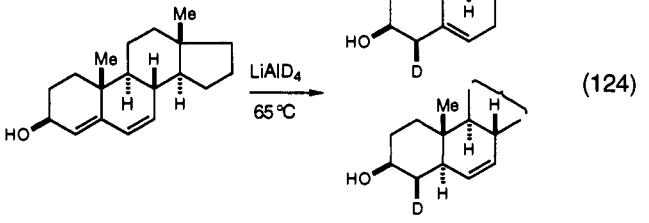
a range of substrates, providing the same sense of stereoselection regardless of the nature of the C_2 substituent (Table 51).[316]

Delivery of hydride to an alkene in an S_N2' fashion is possible under specified conditions. For example, $LiAlH_4$ effects the reductive rearrangement of 2,3-unsaturated methyl pyranosides to 3-deoxyglycals (Scheme 47).[317] The reactivity and stereochemical data are consistent with a requirement of syn S_N2' delivery of hydride.

An yne–diene may be converted to the corresponding β-allenic alcohol upon treatment with $LiAlH_4$ (eq 123).[318] Chiral lithium aluminum hydride complexes afford nonracemic β-allenic alcohols, albeit in low optical purity.[319] The directed reduction of dienols to olefinic alcohols can also be effected (eq 124).[320]



(123)



(124)

A number of other olefinic alcohols and amines, some of which are shown in Table 52,[321] are also reduced to their saturated derivatives by lithium aluminum hydride. Cyclopropenes undergo stereospecific hydroxyl-directed hydroalumination when treated with $LiAlH_4$ (entry 1);[322] the product stereochemistry and deuterium labeling studies are consistent with a delivered reaction.[323] In connection to the example provided in entry 2, the observation that *N*-allyl-*N*,*N*-dimethylamine does not react under identical conditions suggests a role for the remote amine in directing this process. The alkene of *N*-methyl-7-aza-2,3-benzobicyclo[2.2.1]heptadiene is reduced by $LiAlH_4$ at room temperature (entry 3); the unexpected reactivity has been attributed to intramolecular delivery of alane, presumed to be accessible under the reaction conditions, by the amine to the strained olefin.[324]

Although a few synthetically useful delivered $LiAlH_4$ hydroaluminations of alkenes have been discovered, as yet there are no broadly applicable methods for effecting this reaction.

Scheme 47

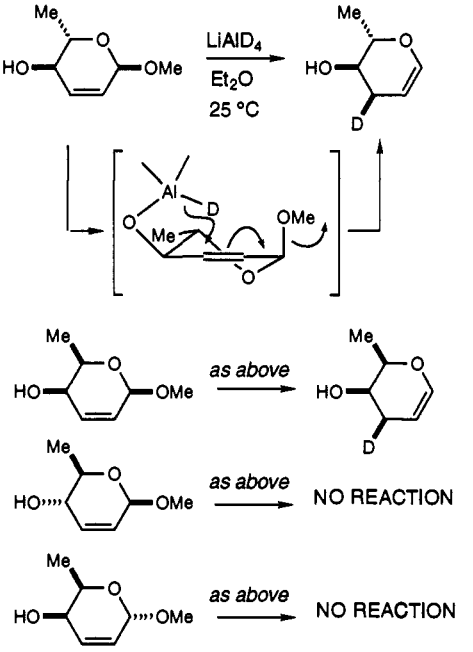
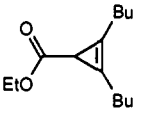
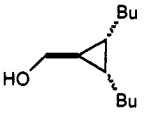
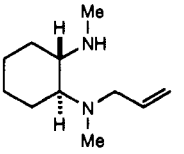
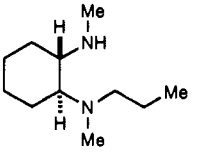
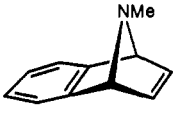
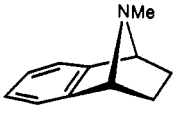


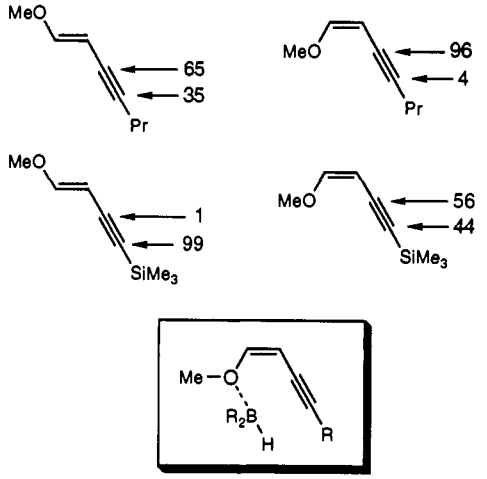
Table 52. Hydroalumination of Alkenes with $LiAlH_4$

Entry	Substrate	Product
1		
2		
3		

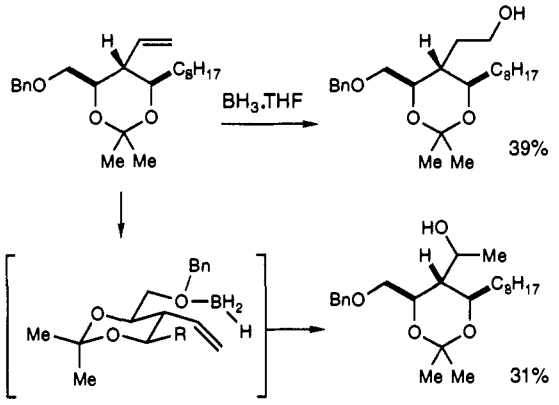
E. Hydroborations

Alkyne addition reactions of dialkylboranes to cis and trans 4-substituted-1-methoxybut-1-en-3-ynes afford different regioselectivities (Scheme 48), the cis isomer displaying a greater preference for placement of boron at the internal acetylenic carbon of the enyne.[325] Coordination of the cis ether oxygen to the borane prior to hydroboration is proposed as a rationale (see below), since the two isomers are electronically similar and steric considerations would predict the opposite trend. It is

Scheme 48



Scheme 49

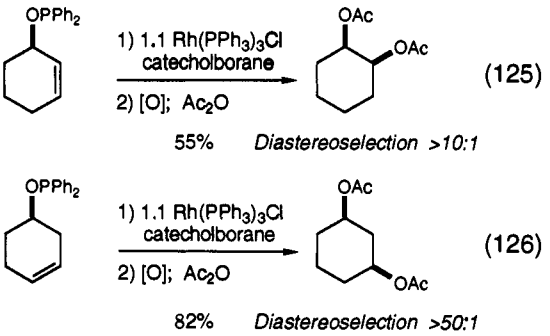


worthy of note that backside displacement of the Lewis base by the multiple bond, a step postulated to occur in hydroboration with borane–Lewis base complexes, is not possible in this geometry.[326]

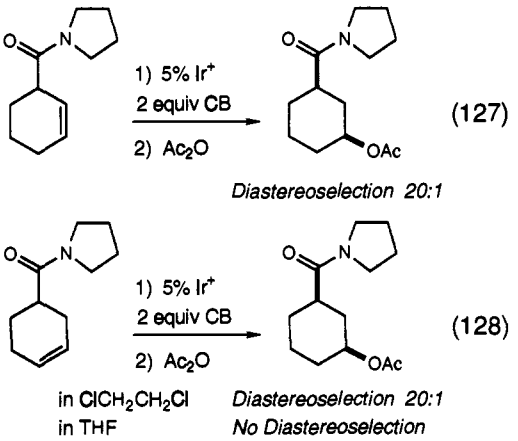
The directed hydroboration of alkenes has been the subject of several recent reports.[327] Intramolecular delivery by an ether has been suggested as an explanation for the surprisingly poor regioselectivity observed in the BH_3·THF hydroboration of the terminal olefin illustrated in Scheme 49.[328] Reaction with dicyclohexylborane, a bulkier reagent for which complexation to the ether oxygen is less favorable, provides the desired primary alcohol in 86% yield.

More recently, phosphinites have proved to be effective directing groups in rhodium-mediated alkene hydroboration (eq 125).[329] Reaction of the phosphinite derived from 2-cyclohexen-1-ol provides the syn-1,2 product, in contrast to hydroboration of the corresponding silyl ether, which affords the anti-1,3 isomer preferentially. A homoallylic phosphinite effectively directs hydroboration to the syn face (eq 126), in contrast to the TBS ether, which affords an approximately statistical mixture of products.

Directed, transition metal-catalyzed hydroboration reactions may be performed in a catalytic manner. Hydroxyl groups are not suitable directing groups, as the derived boronic ester, formed before the hydroboration process begins, is a poor ligand for both rhodium and iridium complexes.[330] However, amides efficiently direct the hydroboration process, with catecholborane (CB) and 5 mol % of [Ir(cod)(PCy_3)(py)]-

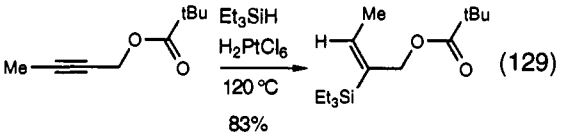


PF_6 (Ir^+). The examples in eqs 127 and 128 are illustrative; as shown, solvent effects provide further evidence that association of the Lewis basic amide group and the transition metal is responsible for the regio- and stereochemical outcome of these reactions.



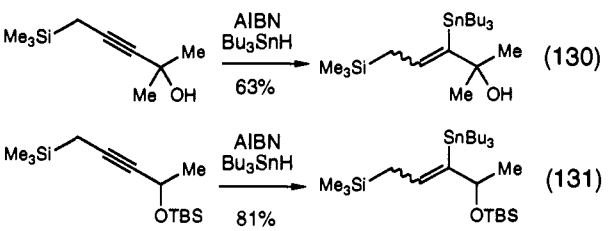
F. Hydrosilylations

Hydrosilylation of the alkyne shown in eq 129 provides a single vinylsilane, whereas reaction of the corresponding propargylic alcohol preferentially furnishes the regioisomeric product.[331] Chelation of the ester group to platinum is proposed as an explanation for the selectivity.



G. Hydrostannylations

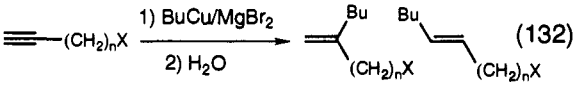
Hydrostannylation reactions of propargylic alcohol derivatives proceed with high levels of regiocontrol; internal delivery by the oxygen functionality has been suggested as an explanation for these observations.[332] Addition of Bu_3SnH to alkynes typically affords a mixture of isomers, but for propargylic alcohols, acetates, and ethers only the regioisomer derived from addition of the tributyltin radical to the carbon proximal to the oxygen is produced (eqs 130–131). Homopro



pargylic hydroxyl groups are not effective in these processes. Coordination of oxygen to the tin radical prior to its addition to the π-system is proposed as a rationale for the selectivity obtained. The issue of the possible role played by the inductive effect of the oxygen substituent has not been addressed.

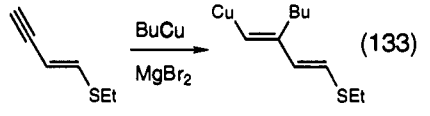
H. Organocopper Additions

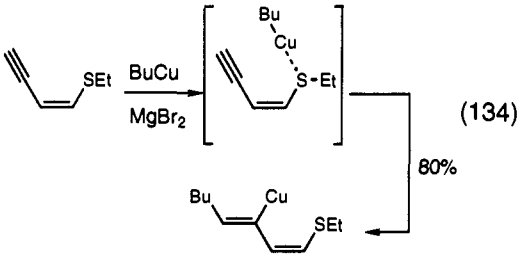
Internal delivery of the organometallic reagent is the suggested explanation for the anomalous regioselectivities observed in the addition of butyl copper to certain functionalized alkynes.[333] Whereas simple terminal acetylenes afford the 1,1-disubstituted olefin with high selectivity, homopropargylic amines and sulfides produce substantial quantities of the regioisomer (eq 132).



with X = NEt_2 n=2 No Regioselection
with X = SEt n=2 No Regioselection
with X = SEt n=3 Regioselection 20:1

Reaction of a bishomopropargylic sulfide furnishes the product of "normal" addition, consistent with the postulate that the diminished regioselectivity in the homoallylic cases is attributable to intramolecular delivery. The transformations of trans and cis enynes (eqs 133 and 134) provide additional support for this hypothesis. Thus, the trans isomer undergoes addition with the "normal" sense of regioselectivity, whereas the cis isomer affords the product of a directed reaction. A sulfide–organocopper complex is proposed to be an intermediate in the latter case.



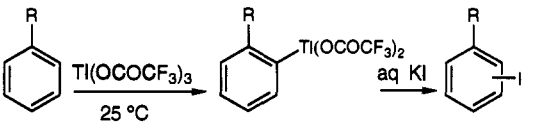


IX. Other Directed Reactions

A. Thallium Addition Reactions

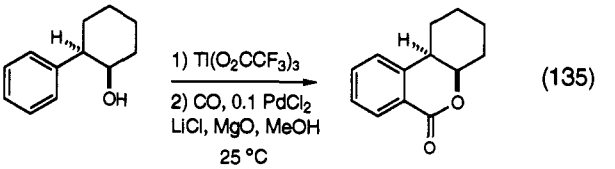
Table 53 provides evidence that electrophilic aromatic substitution reactions with thallium reagents are subject to heteroatom delivery.[334] Whereas propylbenzene preferentially affords the product of para addition (entry 1), arenes bearing oxygen-containing substituents can provide the ortho isomer predominantly (entries 2–9). When the reaction is performed under conditions leading to thermodynamic control of product distribution (for example, at elevated temperature), meta substitution is the main pathway. The following generalizations hold for arenes which bear acids, esters, alcohols, and ethers: (1) An oxygen bound to a carbon either α or β to the ring can deliver thallium to the ortho position (entries 2–9), but this ability is diminished beyond the β-position (entry 3). (2) Delivery of thallium is sensitive to steric effects (entries 3 and 4).

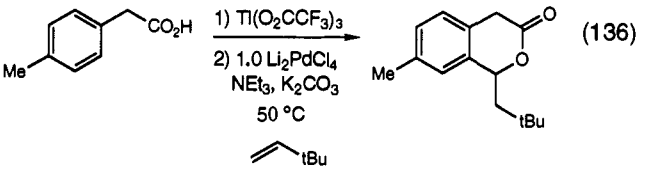
Table 53. Oxygen-Directed Thalium Addition Reactions



Entry	R	*ortho*	*meta*	*para*
1	$CH_2CH_2CH_3$	3	6	91
2	CO_2H	95	5	0
3	CH_2CO_2H	92	3	5
4	$CHMeCO_2H$	65	11	24
5	CO_2Me	95	5	0
6	CH_2CO_2Me	92	3	5
7	CH_2OH	>99	--	--
8	CH_2CH_2OH	83	6	11
9	CH_2OMe	>99	--	--

Palladium-mediated carbonylation or olefination of the arylthallium intermediate can provide a variety of aromatic compounds.[335] Equations 135 and 136 provide two examples.

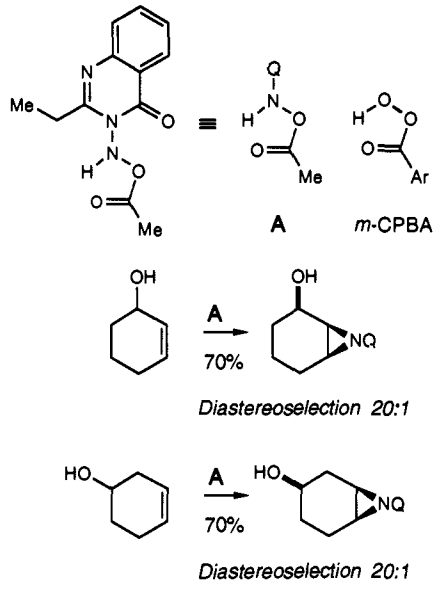




B. Aziridinations

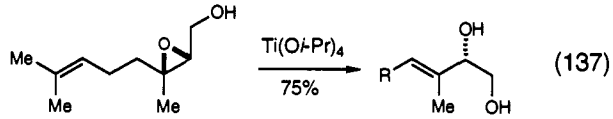
There are several reports on the hydroxyl-directed aziridination by 3-(acetoxyamino)-2-ethylquinazolone (A, Scheme 50; compare A and *m*-CPBA).[336] Treatment of 2-cyclohexen-1-ol with this reagent furnishes the syn isomer with high stereoselectivity. Under identical conditions, the derived acetate and methyl ether undergo aziridination more slowly and provide only the anti compound. The corresponding homoallylic alcohol undergoes reaction with high levels of stereocontrol as well; the derived homoallylic acetate provides a nearly equal mixture of the possible diastereomers. Reaction of geraniol occurs preferentially at the double bond proximal to the hydroxyl group (11:1), whereas that of geranyl chloride proceeds predominantly at the site distal from the heteroatom (6:1). Thus, A appears to be subject to stronger directivity effects than is *m*-CPBA, which affords 9:1 (syn:anti) face selectivity with 2-cyclohexen-1-ol and 1:2 site selectivity (preference for alkene α to alcohol) with geraniol. Since it seems reasonable that the transition structures for aziridination and epoxidation are similar (see section III), we may postulate that this difference arises from the greater basicity of the nitrogen in A vs the oxygen in *m*-CPBA.

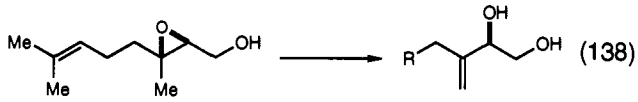
Scheme 50

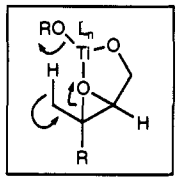


C. Cleavage of Epoxides

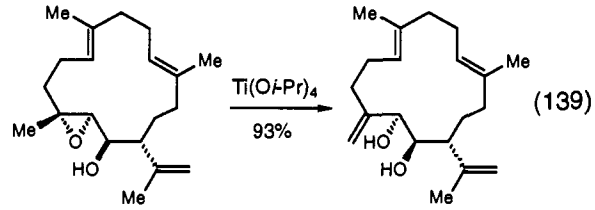
As exemplified in eqs 137 and 138, stoichiometric quantities of $Ti(O\textit{i}\text{-}Pr)_4$ mediate the regioselective opening of epoxy alcohols to allylic alcohols at 25 °C.[337] It is noteworthy that the reaction of 2,3-epoxynerol provides only the *trans*-olefin stereochemistry and that deprotonation occurs exclusively at the position cis to the hydroxymethyl group. The methyl ether of 2,3-epoxygeraniol is stable to the reaction conditions. On the basis of these observations, a transition structure involving a syn elimination within an epoxy alcohol–titanium alkoxide complex has been proposed.



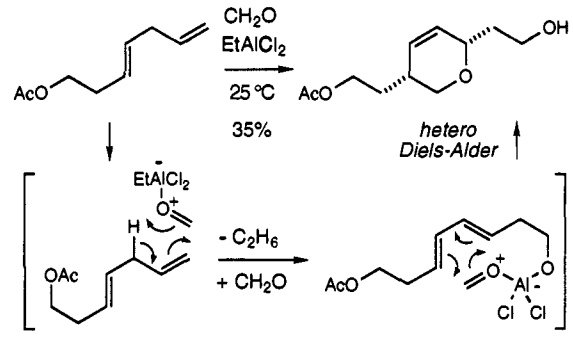




This directed epoxide cleavage reaction has found application in total synthesis.[338] For example, as shown in eq 139, in the course of studies directed toward the synthesis of (±)-asperdiol, exclusive formation of the depicted macrocyclic allylic alcohol was observed; interestingly, the compound epimeric at the hydroxyl-bearing carbon is converted into a complex mixture of



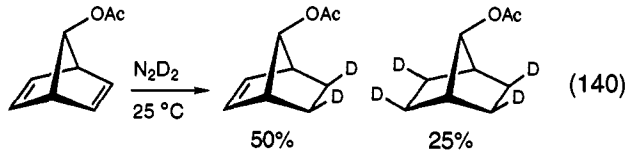
Scheme 51

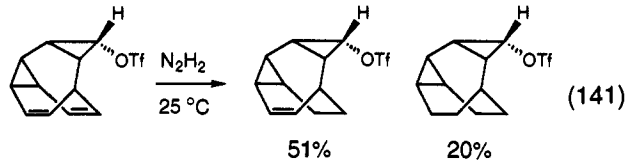


products under the same conditions. On the basis of ^1H NMR and X-ray crystallographic analyses, it was suggested that the latter substrate has no low-energy conformation with a geometry appropriate for elimination.

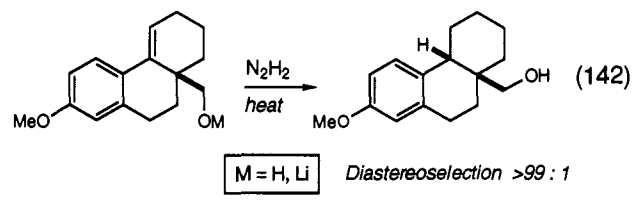
D. Diimide Reductions

Diimide reduction of 7-acetoxynorbornadiene preferentially affords the syn reduction product (eq 140), a result consistent with delivery by the ester.[339] The corresponding alcohol and *tert*-butyl ether react in a similar fashion. Other reports support the feasibility of oxygen delivery of diimide; the regioselective reduction of the depicted bullvalene derivative in eq 141 serves as an example.[340]





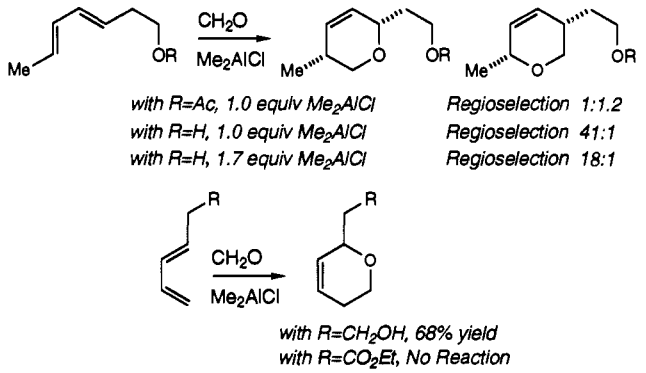
In the phenanthrene-derived system shown in eq 142, either the alcohol or the lithium alkoxide, but not the sodium or the potassium salt, is capable of directing reduction by diimide.[341] The nature of the interaction between oxygen and diimide that leads to delivery remains to be clarified.



E. Electrocyclic Reactions

The regioselectivity observed in several electrocyclic reactions has been attributed to delivery of the reagent by a substrate functional group. In the course of a formal total synthesis of pseudomonoic acids A and C, the directed hetero-Diels–Alder reaction illustrated in Scheme 51 was realized.[342] The first step of the sequence is a Lewis acid-catalyzed ene reaction, the product of which is an aluminum alkoxide complex. Evolution of ethane, coordination of formaldehyde, and cyclization

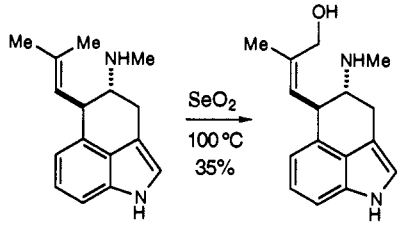
Scheme 52



then afford the desired trans-1,4-disubstituted pyran with high regioselectivity (16:1).

As illustrated in Scheme 52 subsequent study has provided support for the proposed intramolecular nature of the hetero-Diels–Alder reaction.[343] Cyclization of the diene acetate proceeds with poor regioselectivity, whereas the free alcohol undergoes a highly selective reaction. The decreased regioselectivity obtained in the presence of excess (1.7 equiv) Lewis acid is consistent with competitive intermolecular ring formation. The relative reactivities of the diene alcohol and ester shown below indicate that a substantial rate enhancement is associated with internal delivery of the dienophile.[344]

During the course of a synthesis of an ergot alkaloid, a selective oxidation by SeO_2 of the *cis*-methyl group of a trisubstituted olefin was observed (eq 143).[345] Since selenium dioxide generally displays a marked preference for oxidation of the *trans*-methyl substituent with this family of alkenes, coordination of the amino group to selenium has been invoked to explain the anomalous regioselectivity. Reaction of the derived tertiary amine might furnish insight into the nature of this interaction (for example, hydrogen-bond donation to the oxygen of SeO_2 vs nitrogen complexation to selenium).



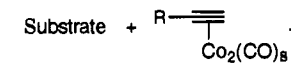
(143)

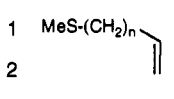
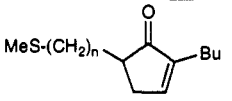
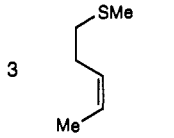
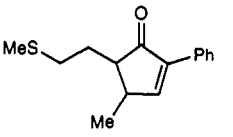
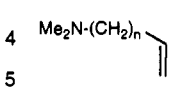
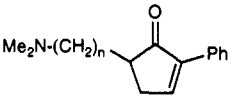
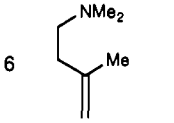
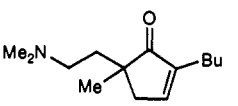
F. Cycloadditions

The intermolecular Pauson–Khand reaction of simple olefins typically provides cyclopentenones in low yield and with poor regioselectivity.[346] Incorporation of a Lewis basic sulfur or nitrogen ligand within the alkene results in moderate to high regioselectivity (Table 54) and improved yields (~65%).[347] The diminution in selectivity that occurs upon homologation is consistent with the directivity postulate (entries 1 vs 2 and 4 vs 5). Oxygen substituents such as alcohols and ethers afford equal mixtures of regioisomers.[348]

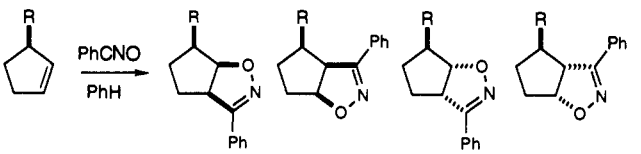
Olefin–nitrile oxide cycloaddition reactions have been reported to be subject to heteroatom delivery. Whereas reaction of the methylcyclopentene shown in Scheme 53 affords predominantly the cycloaddition product anti to the allylic substituent with poor regioselectivity, with the carbamate functionality at the allylic site, both high

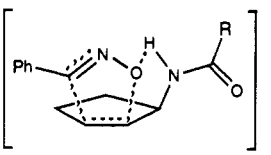
Table 54. Directed Pauson–Khand Cyclization



Entry	Substrate	Product	Selectivity
1			n = 2 8:1
2			3 3:1
3			40:1
		anti : *syn* = 19 : 1	
4			n = 2 5:1
5			3 3:1
6			18:1

Scheme 53





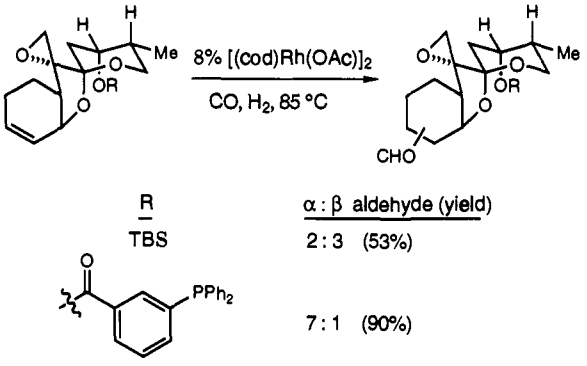
levels of stereo- and regiocontrol are attained. As the data below indicate, the hydroxyl group appears to be a weaker directing functionality. Solvent effects (e.g., CH_2Cl_2 vs DME) and alteration of the Lewis basicity of the allylic substituent [e.g., (*p*-OMe)C_6H_4NH vs (*p*-CF_3)C_6H_4NH] further support the contention that these transformations are directed by a bridging hydrogen atom (between the nitrile oxide and the directing group, as shown in Scheme 53).[349]

G. Hydrocarbonylations

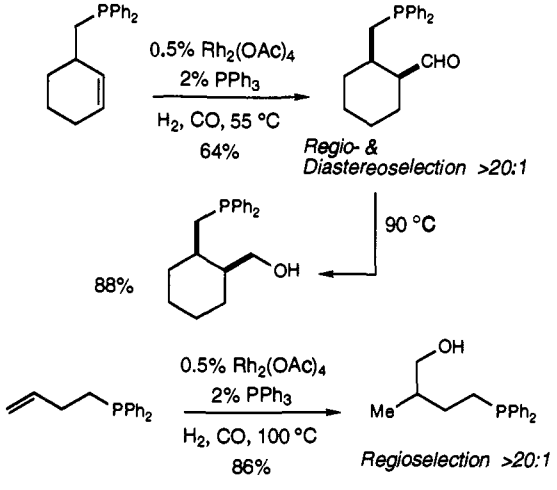
Several recent reports have established the feasibility of directing transition metal-catalyzed alkene hydrocarbonylation reactions. During the course of studies directed toward the synthesis of phyllanthocin, it was established that replacement of a silyl group with a *m*-(diphenylphosphino)benzoate reverses the face selectivity of a hydroformylation reaction (Scheme 54).[350] The observation that the para isomer reacts much more slowly than does the meta compound is consistent with the postulate that the role of the phosphine is to effect intramolecular delivery.

Recent reports indicate that phosphine delivery in the hydroformylation of cyclic and acyclic olefins is feasible (Scheme 55).[351] Reaction of 4-(diphenylphosphino)-1-butene affords the product derived from carbonylation of the internal position, whereas hydro-

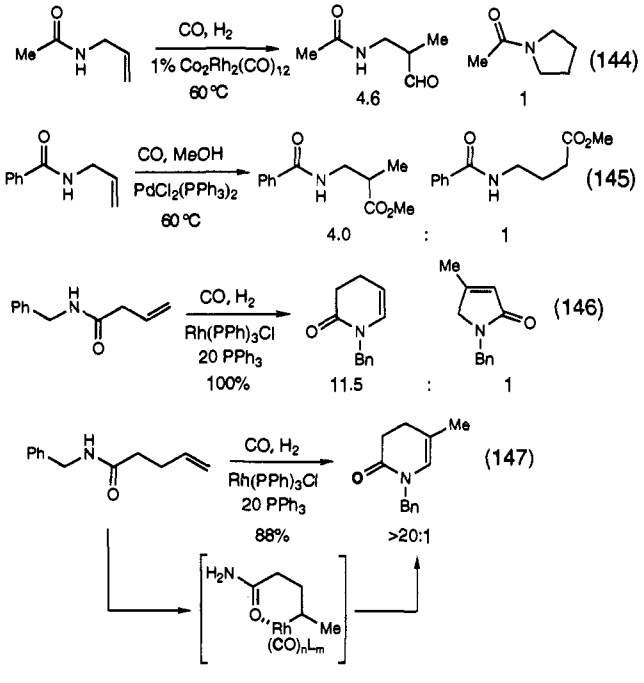
Scheme 54



Scheme 55

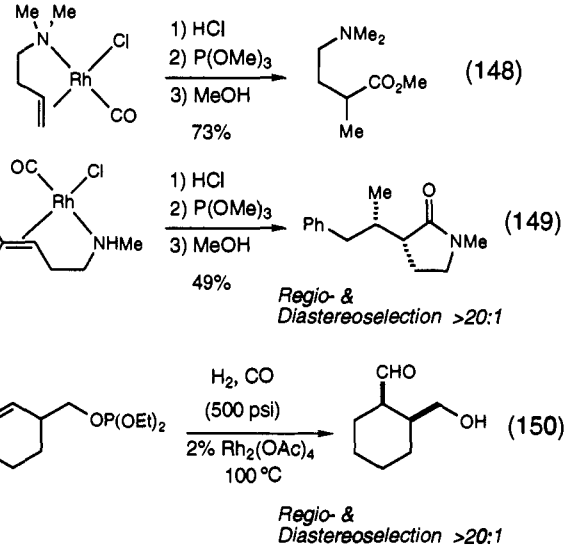


formylation of the corresponding phopshine oxide or of 1-hexene furnishes the unbranched aldehyde preferentially. Lower regioselectivity is observed in the reaction of the homoallylic phosphine in the presence of 50 equiv of PPh_3, as well as with the homologous olefinic phosphines. These data are consistent with the proposal that these transformations are directed by the Lewis basic phosphine group.



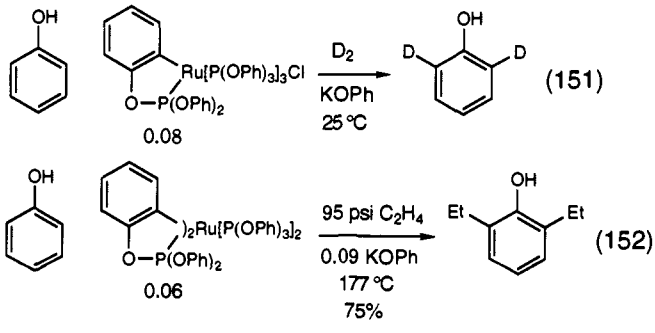
Amides can direct the hydrocarbonylation of alkenes.[352] *N*-Allylamides undergo hydroformylation with a modest preference for formation of the branched aldehyde (eqs 144 and 145),[353] in contrast to unfunctionalized alkenes, which yield the linear aldehyde preferentially. Reactions of unsautrated benzylamides result in high levels of regiocontrol (eqs 146 and 147). These reactions are thought to proceed through chelated transition structures, as illustrated in eq 147.[354]

As illustrated in eqs 148–150, amines[355] and phosphites[356] are suitable directing functionalities for the carbonylation reaction. Reactions with amines are preformed with stoichiometric amounts of Rh complexes, whereas those of phosphites are catalytic. Treatment of a homoallylic amine with $[(CO)_2RhCl]_2$ provides a chelated substrate–metal complex. Addition of HCl furnishes a Rh(III) hydride intermediate, which then undergoes sequential insertions to form an alkyl and then an acyl–rhodium complex. Cyclic and acyclicsubstrates can be employed, and high levels of regio- and diastereoselection are achieved.



H. Orthometalations

Equations 151 and 152 depict regiospecific ruthenium-catalyzed ortho deuteration[357] and ortho ethylation[358] of phenol. Both reactions appear to involve transesterification and orthometalation of the triphenylphosphite.

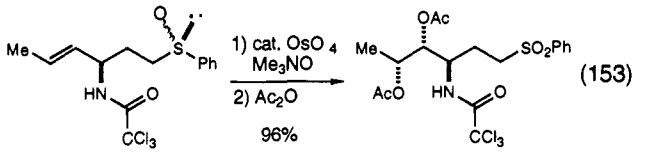


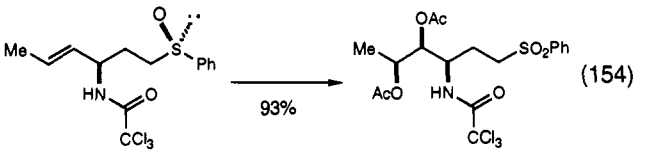
I. Oxidations

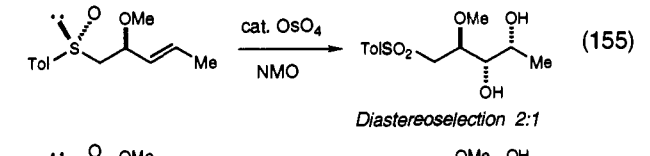
1. Osmium-Mediated Oxidations

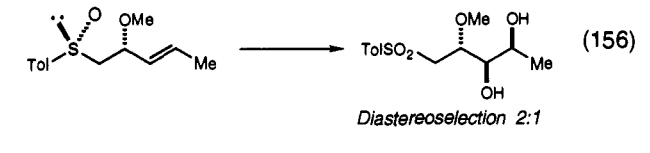
There are no general methods available for effecting a delivered osmylation, but several groups have made

important findings, albeit limited in scope.[359] Several reports indicate that osmylation reactions can be directed by sulfoxides[360] and sulfoximines.[361] Osmylation of either of the two bishomoallylic sulfoxides shown below (eqs 153–154) is highly stereoselective; product stereochemistry is dictated by the sulfur center. Reactions of the corresponding olefinic sulfide and sulfone proceed with low stereoselection (2;1). The relative rate of osmylation of these olefins is reported to be sulfone > sulfoxide ≫ sulfide.[362] In the presence of excess alkene, only the diol sulfone and the starting material are recovered, indicating that once complexation to osmium occurs, complete conversion to products follows. On the basis of a hard–soft acid–base argument, it has been suggested that binding takes place through the sulfoxide oxygen. It is worthy of note that this type of process may not be performed stereoselectivity with all homoallylic sulfoxides (eqs 155 and 156).[363]









Sulfoximines can direct bis-hydroxylation in cyclic systems, thereby providing a route to enantiomerically pure dihydroxycycloalkanones.[362] As shown in Scheme 56, after introduction of the chiral auxiliary to an olefinic ketone, osmylation of either of the resulting diastereomers affords a single triol product. Since reaction of the corresponding sulfone proceeds with poor stereoselection (2:1), it was concluded that the high level of facial selectivity may be ascribed to the presence of the methylimino group.[364] The resulting diol can be desulfurized with Raney nickel or thermolyzed, producing enantiomerically pure triols or diols, respectively. Two additional examples involving cyclic substrates are shown in Scheme 56; extension of this strategy to acyclic systems has been unsuccessful.

A number of reports indicate that nitro groups can direct dihydroxylation processes.[365] Osmylation of the substrate shown in entry 1 of Table 55 furnishes the product arising from reaction on the more hindered olefin face, whereas oxidation with $KMnO_4$ produces the corresponding diastereomer. Control experiments implicate the nitrosulfonylmethane substituent as the directing group (entries 2 and 3). On the basis of

Scheme 56

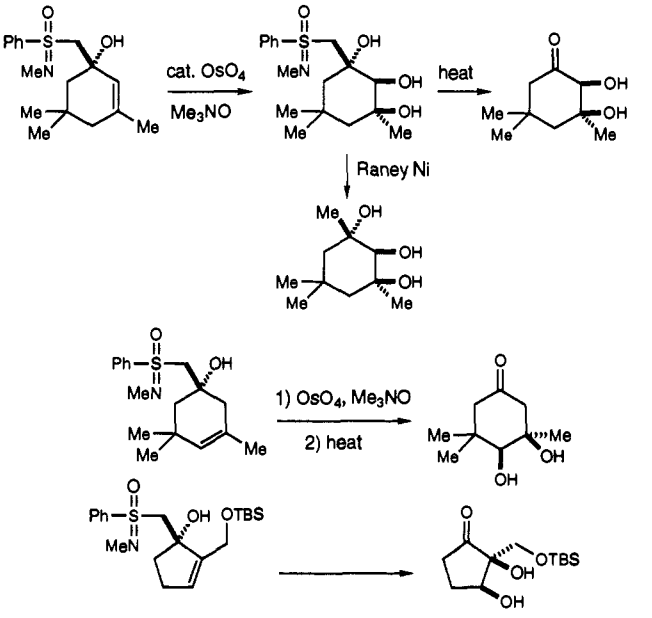
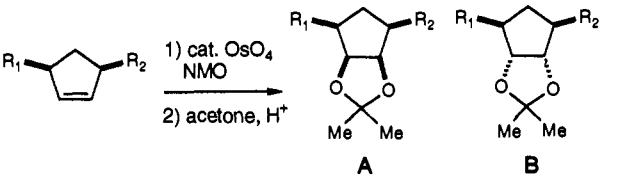
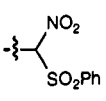
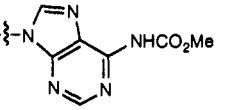
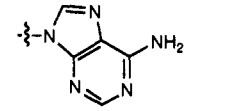
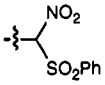
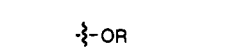


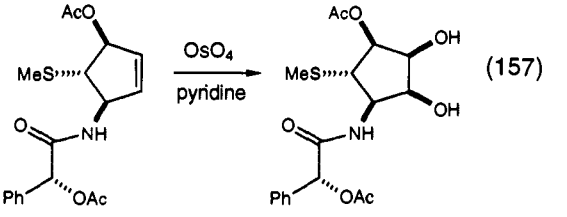
Table 55. Nitro-Directed Dihydroxylation Reactions



Entry	R_1	R_2	Product
1			A
2			B
3			A

previous reports,[361,362] which provide no evidence for sulfone direction, it is postulated that stereocontrol in this reaction arises from interaction of the nitro group with osmium.

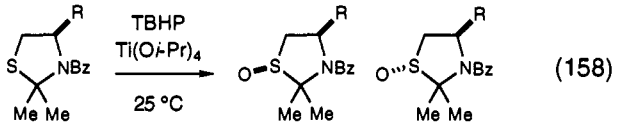
The highly stereoselective osmylation shown in eq 157 is presumably a directed process, as the dihydroxylation occurs at the more hindered diastereotopic face of the alkene.[366] Whether the carbamate or the acetate



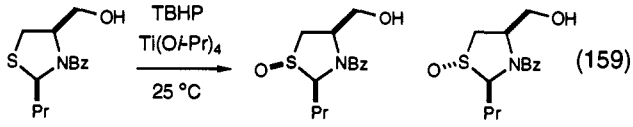
groups (or both, cooperatively) serve to deliver the oxidant is not clear and has not been addressed.

2. Titanium-Mediated Oxidations

Several examples of directed oxidation have been described.[367] There are a number of examples of hydroxyl-delivered oxidation of sulfides to sulfoxides by *tert*-butyl hydroperoxide/Ti(O*i*-Pr)$_4$.[368,369] Whereas reaction of the ester-substituted thiazolidine affords a roughly equal mixture of sulfoxide diastereomers, oxidation of the corresponding hydroxymethyl compound results in highly selective oxo transfer to the face syn to the hydroxyl group (eqs 158 and 159). A mechanism involving complexation of the substrate to titanium, followed by oxidation of the sulfide, has been proposed.



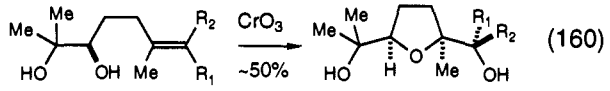
with R=CO$_2$Me *No Diastereoselection*
with R=CH$_2$OH *Diastereoselection >20:1*



Diastereoselection 3:1

3. Chromium-Mediated Oxidations

Upon treatment with Collins reagent or pyridinium chlorochromate, 5,6-dihydroxyalkenes undergo oxidative cyclization to provide syn 2,5-disubstituted tetrahydrofurans with > 99% selectivity (eq 160).[370] The addition to the alkene proceeds in a cis fashion stereospecifically. If the hydroxyl remote from the olefin is protected, the γ–δ enone is formed in high yield, indicating a role for this OH group in facilitating the cyclization reaction.

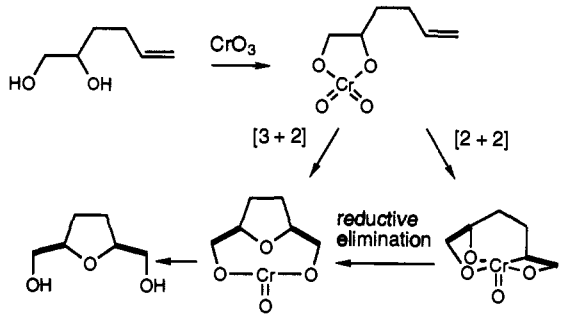


R_1 = CH_2OAc, R_2 = H
R_1 = H, R_2 = CH_2OAc

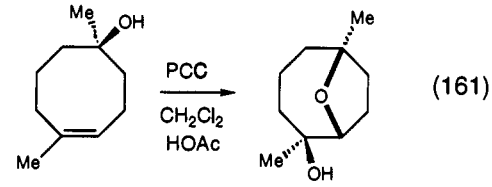
Diastereoselection >25:1

The two mechanisms proposed for this oxidative cyclization are shown in Scheme 57. Rapid formation of the chromium(VI) diester is followed by a concerted [3 + 2] cycloaddition, or by a sequence involving [2 + 2] cycloaddition–reductive elimination, to furnish the complexed product, the tetrahydrofuran diol. Molecular models indicate that syn ring stereochemistry should be preferred with either mechanism.

Scheme 57



Addition of high-valent oxonium reagents to alkenes is also subject to heteroatom delivery. Treatment of the unsaturated alcohol shown in eq 161 with pyridinium chlorochromate (PCC) affords the bicyclic alcohol with high regio- and stereoselectivity. Coordination of the hydroxyl group with the chromium oxidant has been proposed to account for the selective outcome of this class of oxidative ring-forming reactions.[371]

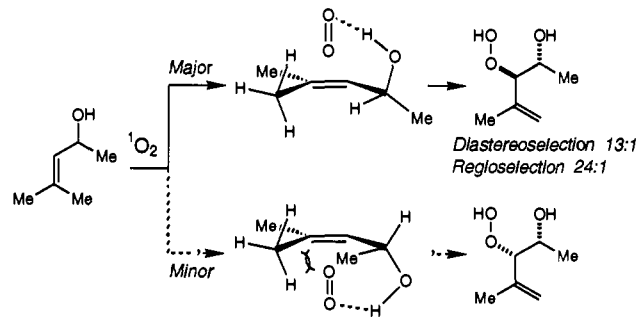


Regio- & Diastereoselection >20:1

4. Oxidations with Singlet Oxygen

Recently, it has been demonstrated that the directing ability of a hydroxyl functional group may be extended to the singlet oxygen-mediated oxidations of some allylic alcohols; formation of the C–O bond, as is shown in Scheme 58, occurs with excellent levels of regio- and diastereocontrol.[372] Arguments based on hydrogen bonding of oxygen molecule with the hydroxyl group though the lowest energy transition structure (minimization of unfavorable allylic interactions) readily accounts for the observed trends and levels of stereochemical control.

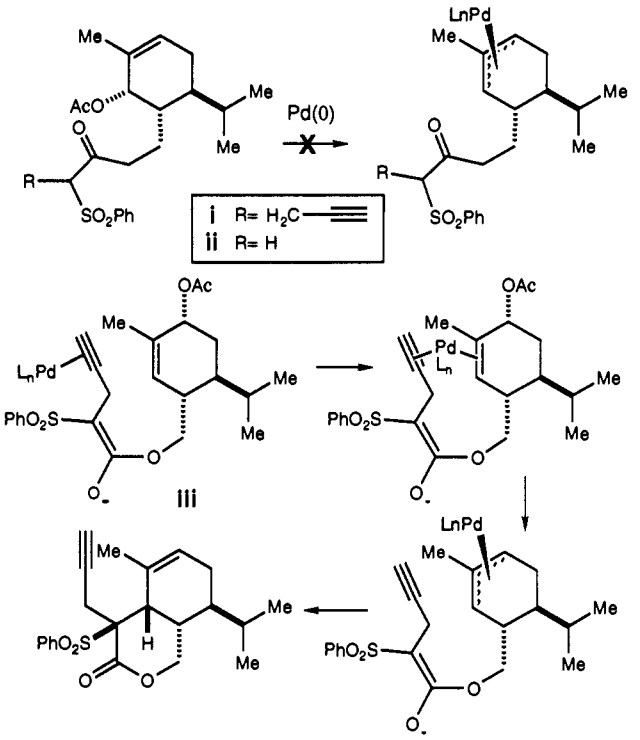
Scheme 58



J. Metal–Olefin Complexation

When allylic acetate i (Scheme 59) is treated with Pd(0) catalysts, no π-allyl complex formation occurs; starting material is recovered unreacted. In contrast, the isomeric acetate iii affords the π-complex, leading to the cyclization product in 65% yield and > 20:1 diastereocontrol.[373] Since ii did not show any reaction as well, it was suggested that the difference in reactivity between i and iii may be due to the initial association of the transition metal with the alkyne group. The metal complex would thus be delivered to the allylic acetate site. In i, the acetylene group cannot deliver the transition metal to the alkene because of geometric constraints.

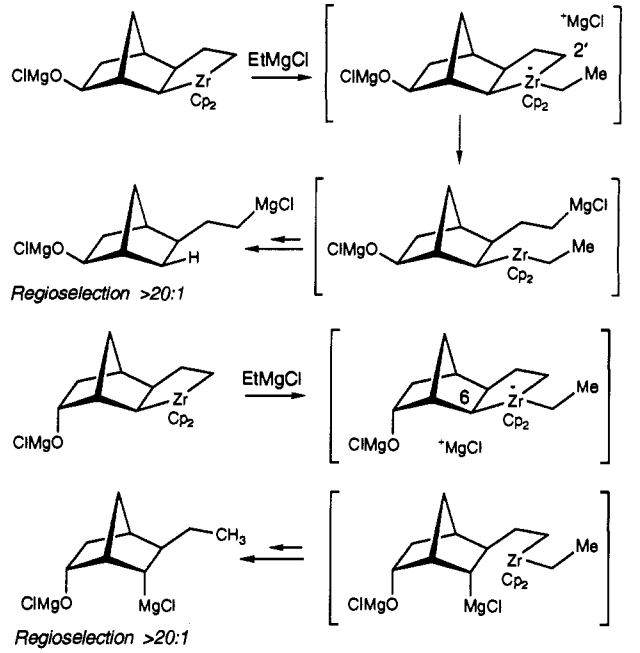
Scheme 59



K. Cleavage of Metallacycles

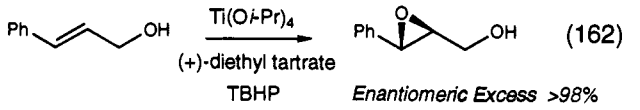
Cleavage of zirconacyclopentanes, formed by the regioselective addition of a zirconacyclopropane to an alkene, is effected by alkylmagnesium chlorides and can be directed by a neighboring heteroatom functionality.[374] Whereas the bicyclic system with the exo oxygen substituent (Scheme 60) affords cleavage at the sterically less hindered C2′–Zr bond, with the endo derivative, exclusive rupture at the C6–Zr bond is observed. Association of the magnesium metal with the endo heteroatom accounts for this complete reversal of regioselectivity.

Scheme 60



X. Summary of Advances in Asymmetric Directed Reactions

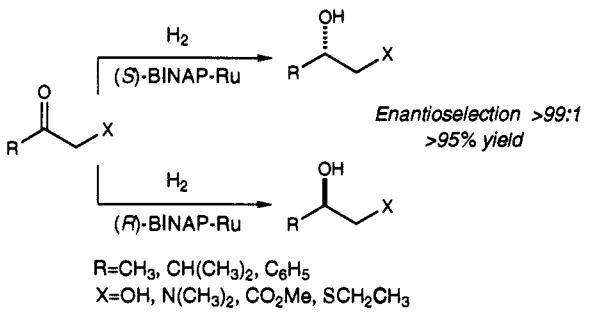
The discussions that were presented above clearly illustrate that directed transformations are of wide ranging utility in organic chemistry. Reduced degrees of freedom resulting from association of a heteroatom with the reagent renders these reactions excellent candidates for affording systems that are stereoselective in both the relative and the absolute sense. As has been demonstrated in the metal-catalyzed epoxidation reaction, introduction of asymmetry into the transition-metal catalyst by a C_2-symmetric chiral ligand (tartrate-based) results in high levels of enantiotopic face selectivity in reactions of achiral alkenes; an example of this widely used process is illustrated in eq 162.[375]



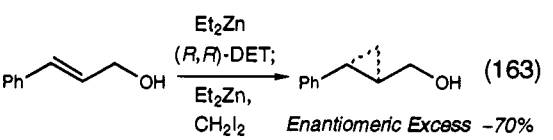
(162)

A transition metal-catalyzed reaction that is effectively influenced by an internal heteroatom can be developed to reach regio- and stereoselectivity levels often attained with natural enzymes, but with the added bonus that the man-made catalyst enjoys much wider substrate compatibility. The metal-catalyzed epoxidation reaction (section IV) is not an exception and the underlying principles that have emerged from the study of this process can be employed for the development of other transformations. Progress in the area of asymmetric hydrogenation (see section V), as represented in Scheme 61, bears testimony to this claim.[376]

Scheme 61



A recent report indicates that asymmetric versions of the directed cyclopropanation reaction (section II) may be forthcoming. As is shown in eq 163, treatment of an allylic alcohol with Et_2Zn and (*R*,*R*)-diethyl tartrate, followed by a sequential addition of Et_2Zn and CH_2I_2 leads to the formation of the cyclopropylcarbinol with ~70% enantiomeric excess.[377]



(163)

XI. Acknowledgments

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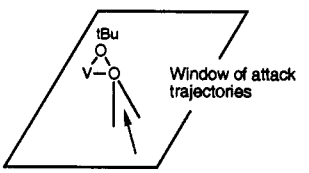
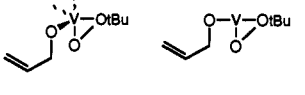
(114) Transition-state models proposed herein incorporate the following constraints. (*1*) *Trajectory of attack on the hydroperoxide O–O bond by the alkene.* Attack by the nucleophile on the electrophile should occur preferentially in the plane defined by the metal and the two oxygen atoms of the alkyl peroxide ligand. Within this plane, there could be some latitude with respect to the favored trajectory. Although backside attack along the O–O axis may be preferred for *m*-CPBA epoxidations (see section II.3), the directed metal-catalyzed epoxidation may well favor a somewhat different geometry since the bond undergoing cleavage forms part of a three-membered ring. By analogy with cyclopropane, ethylene oxide, and diazirine, there may be distortion of the bonding electrons away from the internuclear axis; one would expect the orientation of the O–O antibonding orbital to be altered accordingly (Jorgensen, W. L.; Salem, L. *The Organic Chemist's Book of Orbitals*; Academic: New York, 1973; see refs d and e below). This relaxation of the preference for strict backside attack during epoxidation is of greatest consequence for allylic alcohols, wherein the shortness of the tether between the ligating hydroxyl and the nucleophilic alkene makes achieving this trajectory particularly difficult.



(*2*) *Geometry at the metal.* The trigonal bipyramid and the square pyramid, with the oxo ligand occupying an apical position (Gourdon, A.; Jeannin, Y. *Acta Crystallogr., Sect. B* **1980**, *36*, 304–309), are probably energy minima for the postulated five-coordinate intermediate (Figure 6, ii). The bidentate alkyl peroxide should prefer to occupy idealized coordination sites which require the oxygens to span as small an angle as possible, i.e., 90°. To simplify the analysis, we have assumed that for the square pyramid geometry, the vanadium lies nearly in the basal plane. We therefore consider two geometries for the three participating oxygen ligands:

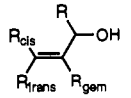


(*3*) *Conformation of the carbon backbone.* This is only relevant for homoallylic and bishomoallylic alcohols. We assume that a staggered conformation is preferred. (*4*) *Other aspects of the transition state model.* Spiro geometry. Bond distances (see: ref 78b): V—O (covalent) = 1.9 Å; V—O (dative) = 1.95 Å; V=O = 1.6 Å; C—O (epoxide) = 2.0 Å; O—O = 2.2 Å. (A similar analysis

of molybdenum-catalyzed epoxidation was inconclusive.) The structure of the active catalyst is less well understood than in the case of vanadium. For leading references on epoxidation transition states, see: (a) ref 78a. (b) Jorgensen, K. A.; Wheeler, R. A.; Hoffmann, R. *J. Am. Chem. Soc.* **1987**, *109*, 3240–3246. (c) Jorgensen, K. A.; Hoffmann, R. *Acta Chem. Scand., Ser. A* **1986**, *40*, 411–419. (d) Bach, R. D.; Wolber, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1410–1415. (e) Bach, R. D.; Wolber, G. J.; Coddens, B. A. *J. Am. Chem. Soc.* **1984**, *106*, 6098–6099. (f) Plesnicar, B.; Tasevski, M.; Azman, A. *J. Am. Chem. Soc.* **1978**, *100*, 743–746.

(115) There is a modest degree of flexibility in this angle (±10°). Sharpless has estimated a dihedral angle of 50° (ref 57).

(116) In the following discussion, the substituents of the allylic alcohol by the indicated labels are referred to as follows:



(117) Table 22 references: (a) Entries 1–5, ref 113b. (b) Reference 113c. (c) Narula, A. S. *Tetrahedron Lett.* **1982**, *23*, 5579–5582.

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(119) For an earlier application of this strategy to *m*-CPBA epoxidation, see: Hasan, I.; Kishi, Y. *Tetrahedron Lett.* **1980**, *21*, 4229–4232.

(120) Protiodesilylation at an epoxide carbon proceeds with retention of configuration: Chan, T. H.; Lau, P. W. K.; Li, M. P. *Tetrahedron Lett.* **1976**, 2667–2670.

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(124) For a threo-specific epoxidation of a 1,1-disubstituted allylic alcohol bearing a remote sulfonamide group, where nitrogen participation in the transition state is proposed to account for the turnover in stereochemistry, see: Morimoto, Y.; Oda, K.; Shirahama, H.; Matsumoto, T.; Omura, S. *Chem. Lett.* **1988**, 909–912.

(125) See also: Depezay, J.-C.; Dureault, A. *Tetrahedron Lett.* **1978**, 2869–2872.

(126) (a) Yasuda, A.; Tanaka, S.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1701–1704. (b) Reference 113a.

(127) Studies on the epoxidation of divinylcarbinol: Holland, D.; Stoddart, J. F. *Carbohydr. Res.* **1982**, *100*, 207–220.

(128) (a) Equation 32: Ohloff, G.; Giersch, W.; Schulte-Elte, K. H.; Enggist, P.; Demole, E. *Helv. Chim. Acta* **1980**, *63*, 1582–1588. See also: (b) Yoshii, E.; Takeuchi, Y.; Nomura, K.; Takeda, K.; Odake, S.; Sudani, M.; Mori, C. *Chem. Pharm. Bull.* **1984**, *32*, 4767–4778. (c) Sudani, M.; Takeuchi, Y.; Yoshii, E.; Kometani, T. *Tetrahedron Lett.* **1981**, *22*, 4253–4256. (d) Equation 33: Corey, E. J.; Dittami, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 256–257.

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(130) Table 24 references: (a) Entries 1 and 5, ref 113c (b) Entries 3 and 4, ref 117c.

(131) (a) Equation 34: Fung, S.; Siddall, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 6580–6581. (b) Equation 35: Lellouche, J. P.; Breton, P.; Beaucourt, J. P.; Toupet, L.; Gree, R. *Tetrahedron Lett.* **1988**, *29*, 2449–2452. (c) Equation 36: Boeckman, R. K., Jr.; Starrett, J. E., Jr.; Nickell, D. G.; Sum, P.-E. *J. Am. Chem. Soc.* **1986**, *108*, 5549–5559. See also: Takatsuto, S.; Yazawa, N.; Ishiguro, M.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Perkin Trans. 1* **1984**, 139–146. Ishiguro, M.; Takatsuto, S.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Chem. Commun.* **1980**, 962–964.

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(134) Partridge, J. J.; Toome, V.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1976**, *98*, 3739–3741.

(135) (a) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690–7692. See also: (b) Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 6191–6194. (c) Mohr, P.; Tamm, C. *Tetrahedron Lett.* **1987**, *28*, 391–394.

(136) Table 27 references: (a) Entry 1, Bartlett, P. A.; Jernstedt, K. K. *J. Am. Chem. Soc.* **1977**, *99*, 4829–4830. (b) Entries 2 and 3, ref 135a. (c) Entry 4, Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495–4499. (d) Entries 5, 7, and 8, Kobayashi, Y.; Uchiyama, H.; Kanbara, H.; Sato, F. *J. Am. Chem. Soc.* **1985**, *107*, 5541–5543. (e) Entry 6, Hull, C.; Mortlock, S. V.; Thomas, E. J. *Tetrahedron Lett.* **1987**, *28*, 5343–5346.

(137) A tetrahedral vanadate ester has been involked as a tenable intermediate, as it provides a better predictive model than does a trigonal bipyramidal metal. See ref 113b.

(138) For a related epoxidation, see: Katsuki, T.; Hanamoto, T.; Yamaguchi, M. *Chem. Lett.* **1989**, 117–118.

(139) (a) Equation 39: Hoppe, D.; Tarara, G.; Wilckens, M.; Jones, P. G.; Schmidt, D.; Stezowski, J. J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1034–1035. See also: Hoppe, D.; Lussmann, J.; Jones, P. G.; Schmidt, D.; Sheldrick, G. M. *Tetrahedron Lett.* **1986**, *27*, 3591–3594. Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932–948. (b) Equation 40: Roush, W. R.; Michaelides, M. R. *Tetrahedron Lett.* **1986**, *27*, 3353–3356. (c) Entry 41: Bruckner, R. *Tetrahedron Lett.* **1988**, *29*, 5747–5750. For other selected examples of diastereoselective epoxidation of homoallylic alcohols: (d) Mosset, P.; Yadagiri, P.; Lumin, S.; Capdevila, J.; Falck, J. R. *Tetrahedron Lett.* **1986**, *27*, 6035–6038. (e) Smith, A. B., III; Huryn, D. M. *J. Org. Chem.* **1985**, *50*, 1342–1344. (f) Wang, Z.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 31–34.

(140) See also: Friedrich, D.; Bohlmann, F. *Tetrahedron* **1988**, *44*, 1369–1392.

(141) This is perhaps the only example of site-specific directed epoxidation in a molecule that carries two homoallylic alcohol systems. For a site-selective epoxidation of a primary allylic alcohol in the presence of a tertiary, see: Chappuis, G.; Tamm, C. *Helv. Chim. Acta* **1982**, *65*, 521–537.

(142) Tsuzuki, K.; Nakajima, Y.; Watanabe, T.; Yanagiya, M.; Matsumoto, T. *Tetrahedron Lett.* **1978**, 989–992.

(143) Van Tamelen, E. E.; Leopold, E. J. *Tetrahedron Lett.* **1985**, *26*, 3303–3306.

(144) For a related example, see: Oikawa, Y.; Nishi, T.; Yonemitsu, O. *J. Chem. Soc., Perkin Trans. 1* **1985**, 7–17. Three possible competitive reactions may be considered: (1) delivery by the allylic alcohol; (2) delivery by the homoallylic alcohol; (3) delivery by the two hydroxyl groups acting in concert. (Note that the catalytically active vanadium complex (Figure 5) includes an exchangeable spectator alkoxide ligand.) In studies relevant to the plausibility of the third reaction pathway, Holland and Stoddart have reported problems epoxidizing $(VO(acac)_2$/TBHP) closely related triols and have ascribed their difficulties to tridentate binding, which blocks ligation of the hydroperoxide: Holland, D.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1553–1571. Paquette has observed a significant increase in the rate of epoxidation when one of the two hydroxyl groups of an olefinic diol is protected: Paquette, L. A.; Ross, R. G.; Springer, A. P. *J. Am. Chem. Soc.* **1988**, *110*, 6192–6204.

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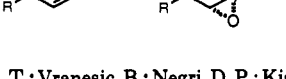

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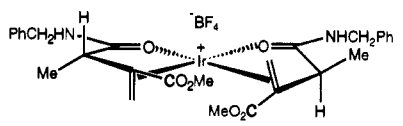

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