

Allylic 1,3-Strain as a Controlling Factor in Stereoselective Transformations

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1. Introduction

Stereoselective synthesis concerns the creation of new stereogenic centers (throughout this review the designation "stereocenter" will be used) by transformation of a prochiral group into a chiral one.¹ This can be achieved by (a) the use of a chiral reagent (reagent control of stereoselectivity)² or (b) as a consequence of asymmetric induction by stereocenters already present in the substrate (substrate control of diastereoselectivity). This latter approach (b) is the traditional one, which can be traced back through decades of diastereoselective syntheses to Emil Fischer's classical conversion of arabinose into glucose and mannose.³ The master of this approach, R. B. Woodward, demonstrated in many outstanding syntheses how one ster-



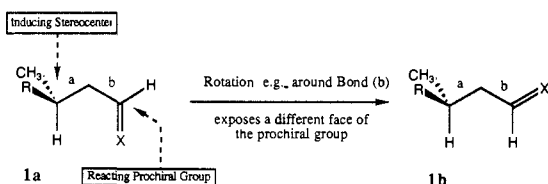
Prof. Reinhard W. Hoffmann was born in 1933 in Würzburg. He studied chemistry at the Universität Bonn from 1951 to 1958 and received his Dr. rer. nat. with a thesis under the direction of Prof. B. Helferich, a former student of Emil Fischer. Prof. Hoffmann spent 2 years as a postdoctoral fellow at The Pennsylvania State University with Prof. G. W. Brindley in the Department of Ceramic Technology followed by another postdoctoral year with Prof. G. Wittig at the Universität Heidelberg working in benzyne chemistry. Subsequent independent studies on heterolytic fragmentation of azo compounds led to the habilitation in 1964. In 1967 Prof. Hoffmann moved as a dozent to the Technische Hochschule Darmstadt and in 1970 to his present position as Professor of Organic Chemistry at the Philipps-Universität Marburg. Over the years Prof. Hoffmann held visiting professorships at the Universität Bern, University of Wisconsin, Madison, and the University of California, Berkeley. His research interests developed from nucleophilic carbenes and electron-rich olefins to the investigation of stereoselective transformations.

eo-center may be used to control the selective formation of another one, which in turn controls the generation of a third stereocenter, and so on. The synthesis of vitamin B₁₂⁴ serves as an example which involved the generation of many stereocenters which are embedded in cyclic carbon skeletons. Thus, by the work of a generation of chemists, a treasury has been filled with the knowledge on how to control the formation of stereocenters on cyclic substrates, particularly on six-membered rings. This was rendered comparatively easy due to the conformational rigidity of those substrates. Hence, when chemists began to tackle the syntheses of open-chain structures which contain many stereocenters, such as erythronolide, the early synthetic approaches⁵ utilized cyclic six-membered intermediates to guarantee high levels of stereocontrol. Eventually, however, methods for direct stereocontrol in reactions at acyclic systems had to be developed, and this has been the central issue of the past decade's developments of new stereoselective reactions.

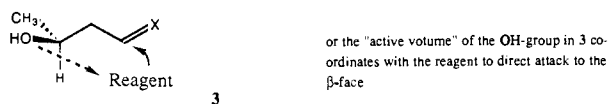
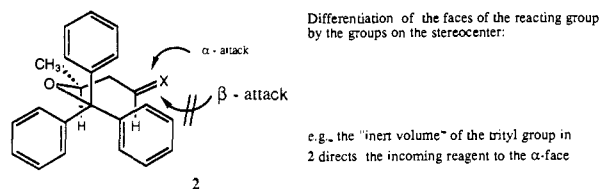
Consider substrate control of diastereoselectivity, i.e., cases in which the reacting prochiral group and the inducing stereocenter are part of the same molecule.

The two entities may be separated by one or at most two bonds, equivalent to 1,2- or 1,3-asymmetric induction, respectively. For efficient asymmetric induction in open-chain situations two conditions have to be met: First, the number of energetically favorable conformations of the bonds connecting the reacting prochiral group and the inducing stereocenter has to be restricted such that preferably only one conformation is available in the transition state of the stereogenic reaction. Second, this conformation should be such that the different substituents on the controlling stereocenter differentiate the diastereotopic faces of the reacting prochiral group. This differentiation can be twofold in nature: Either a large group at the controlling stereocenter shields the approach to one side of the reacting prochiral group (Winterfeldt⁶ designated the properties of such groups at the controlling stereocenter as that of an "inert volume") or one group at the controlling stereocenter coordinates with the incoming reagent and directs its mode of attack to this particular face of the reacting prochiral group (Winterfeldt designated the properties of such groups at the controlling stereocenter as that of an "active volume").

The primary aim, therefore, is to control the conformation around the bonds between the inducing stereocenter and the reacting prochiral group $C=X$, e.g., around bonds a and b in 1, because rotation around those bonds would expose different faces of the reacting prochiral group (cf. 1a and 1b) to a reagent.

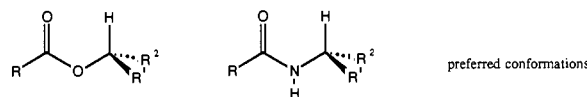


Assuming conformation 1b to be the preferred one, stereoselectivity depends on the differentiation of the faces of the reacting center by the groups at the controlling stereocenter, e.g., by the inert volume of a trityl group, as in 2, directing an incoming reagent to the α -face, or by the active volume of an OH group, as in 3, coordinating with the reagent to induce attack on the β -face.



The properties of various groups to act either by steric shielding or by coordinating to a reagent have been known for a long time from stereoselective reactions on cyclic substrates. Therefore the challenge in acyclic stereocontrol concerns the recognition of the principles which allow for conformational restriction around intervening bonds between the controlling

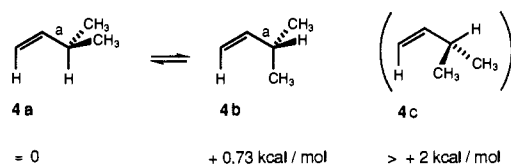
stereocenter and the reacting prochiral group. Consequently, information on the height of rotational barriers around various functional groups and the relative energy of the favored conformers⁷ take on added significance for synthetic organic chemistry. It therefore is no wonder that the well-known conformational preferences attributed to amide and ester functionalities were the basis for early attempts to design reactions which occur with asymmetric induction.



Another bond type with marked conformational preferences is the vinylic bond of highly substituted allyl systems, e.g., bond a in 7. This was recognized by F. Johnson 20 years ago, when he proposed⁸ the concept of allylic 1,3-strain. This principle has proved to be one of the most powerful tools in achieving conformational organization in acyclic systems and has aided chemists in achieving high levels of asymmetric induction in a predictable manner.

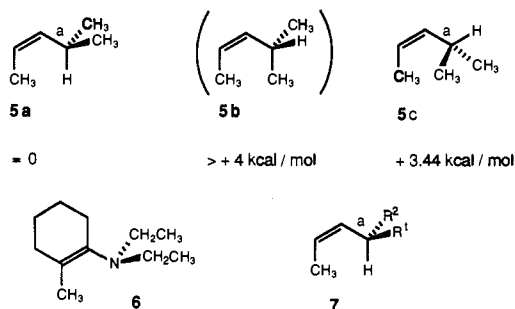
2. The Concept of Allylic 1,3-Strain

Consider rotation around bond a of the 3,3-disubstituted allylic system 4. Ab initio calculations (MP2-6-31G*//3-21G) for 3-methyl-1-butene (4) by Houk⁹ show that the minima in conformational energy are given by 4a and 4b with one substituent in the allylic position eclipsing the double bond. Conformation 4c does not represent an energy minimum and lies at least 2 kcal/mol above 4a in energy. This situation is similar to that calculated for 1-butene.¹⁰



The calculations on 4 show that conformation 4b is populated to a considerable extent in the ground state, thus presumably as well in the transition state of addition reactions at the double bond. This has consequences for systems with a stereocenter in the allylic position, because facial selectivity of attack of the double bond would not be expected to be directly related to differences in the active and inert volumes of the allylic substituents. Hence, in the absence of stereoelectronic effects, the level of asymmetric induction is often unpredictable and frequently low.

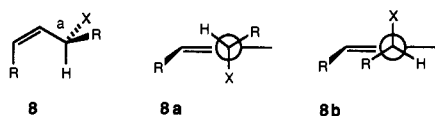
A quite different situation is found when there is a substituent on the double bond Z to the allylic center; cf. 5. In this case, the conformational equilibrium strongly favors 5a, because conformation 5b is destabilized substantially by allylic 1,3-strain to the point that 5b now represents an energy maximum determining the rotational barrier.¹¹ Conformation 5c, although being an energy minimum, lies 3.4 kcal/mol above 5a and can therefore be neglected when considering the conformer equilibrium.



Experimental data on the energy difference between **5a** and **5b** were obtained for the structurally related enamine **6**, the ground-state conformation of which is that shown. The height of the rotational barrier around the vinylic C–N bond has been determined to be 8.1 kcal/mol.¹²

Thus, for an allylic system **5** having a *Z* substituent at the double bond, conformation **5a** is strongly favored, since in this conformation allylic 1,3-strain is avoided. If the allylic center is a stereocenter (cf. **7**), the groups R^1 and R^2 are disposed in such positions that the differences in active or inert volume of the groups R^1 and R^2 may optimally induce facial selectivity for reactions which occur at the double bond.

We should, however, not entertain the notion that a molecule **5** is frozen in conformation **5a**. Changes in the dihedral angle around bond *a* in **5** of $\pm 30^\circ$ are possible at < 1 kcal/mol cost. This becomes important in those reactions at the double bond which proceed under stereoelectronic control from a substituent at the allylic center, e.g., **X** in **8**. This concerns the direction of electrophilic attack according to the principles delineated by Houk¹³ or the direction of nucleophilic attack according to the principles of Felkin and Anh.^{14,15} In order to interact with the HOMO or LUMO of the double bond in **8** the σ -bond to the substituent **X** has to be parallel to the π -orbital of the double bond (e.g., **8a** or **8b**). Fortunately there is enough leeway for partial rotation around bond *a* in **8** to reach conformation **8a** in response to stereoelectronic demands of reactions at the double bond. However, the other



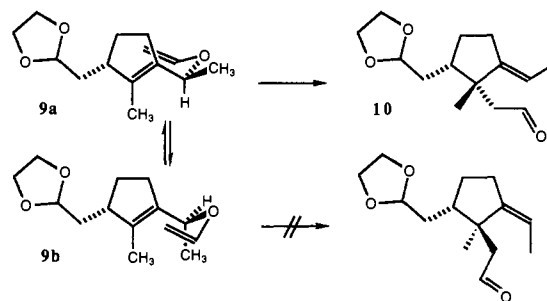
conformation **8b**, in which the C–X bond is likely parallel to the orbitals, is now of > 2 kcal/mol higher energy than **8a** due to developing allylic 1,3-strain. The difference in population of the conformers **8a** and **8b** is a significant factor affecting the level of asymmetric induction on reactions at the double bond of **8**. As a consequence, asymmetric induction in reactions at the double bond of **8** should be higher than on reactions of similar substrates lacking the substituent in the *Z* position of the double bond.

In summary: For reactions at the double bond of compounds such as **7**, one needs principally to consider the conformation shown, as well as related ones differing in the dihedral angle around bond *a* of ca. $\pm 30^\circ$. Provided that the groups R^1 and R^2 differentiate the two faces of the double bond, high levels of 1,2- or 1,3-asymmetric induction can be expected. In the past

20 years this situation has been utilized many times intentionally (cf. the seminal contributions of Kishi^{16–18} and Evans^{19,20}) as well as unintentionally to achieve high levels of asymmetric induction. The purpose of this review is to show that the principle of allylic 1,3-strain is of broad scope in asymmetric synthesis. The explanations given here for the reported stereoselectivities are those of the present author. These explanations may concur with or differ from those given in the original articles. Throughout this review diastereoselectivities are given in % ds.¹

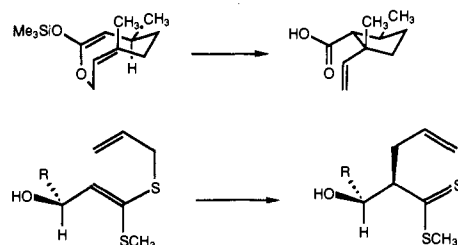
3. Control of Stereoselectivity in Pericyclic Reactions

3,3-Sigmatropic reactions in general occur with a high level of 1,3-transfer of chirality.²² However, there is sometimes need for an additional element of stereocontrol. For example, in the rearrangement of **9** the product **10** was desired,²³ the formation of which required an approach of the vinyl ether group at the sterically more hindered α -side.



This seemingly difficult task has actually been accomplished, since the conformer **9b** leading to bond formation at the β -side is severely destabilized by allylic 1,3-strain.

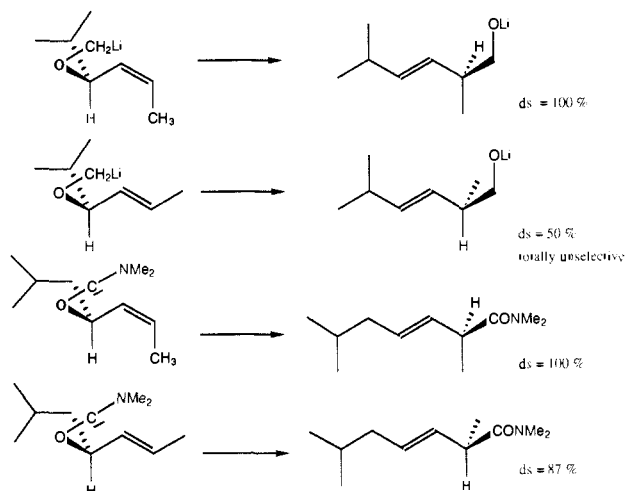
The following cases of stereoselectivity in Claisen rearrangements are clearly the consequence of conformational control in the transition states due to allylic 1,3-strain.²⁴



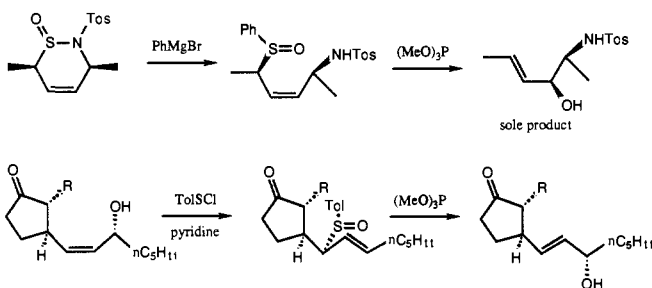
R = Ph	ds = 85 %
Me	90 %
Et	91 %
iPr	96 %
tBu	>96 %

2,3-Sigmatropic rearrangements proceed through conformationally flexible five-membered cyclic transition states. Hence, stereocontrol is much more difficult to attain.²⁵ In certain cases²⁶ use of allylic 1,3-strain may be the only reliable way to achieve high levels of chirality transfer. Accordingly, the extent of chirality

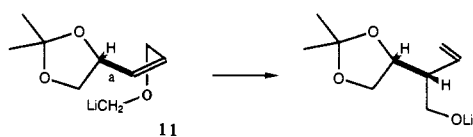
transfer increases on going from an (*E*)-allylic to an (*Z*)-allylic system.²⁵



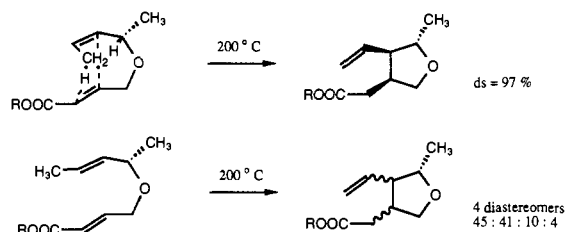
The allyl sulfoxide/allyl sulfenate rearrangement proceeds already in the absence of allylic 1,3-strain with good 1,3-transfer of chirality.²⁷ Nevertheless, if the starting allyl sulfoxide²⁸ or allyl sulfenate²⁹ contains a group in the *Z* position on the γ -carbon of the allyl system, control by allylic 1,3-strain as an additional factor renders the chirality transfer complete. In these examples the controlling stereocenter is "sacrificed"; in other words, it turns into a prochiral unit.



Asymmetric induction on the course of 2,3-sigmatropic rearrangements is also possible by a stereocenter next to the migration terminus. This has been demonstrated in the Wittig allyl ether rearrangement. For instance, the rearrangement of the *Z* isomer 11 proceeded with high levels of diastereoselectivity,³⁰ whereas, not unexpectedly, that of the corresponding *E* isomer occurred in a stereorandom fashion. Clearly, if the substrate has a *Z*-substituted double bond (cf. 11), consideration of allylic 1,3-strain makes it obvious that the molecule adopts the conformation shown with respect to bond a. The stereoelectronic effects described by Felkin and Anh¹⁴ then determine which diastereotopic side of the prochiral double bond is attacked in the Wittig rearrangement.³⁰



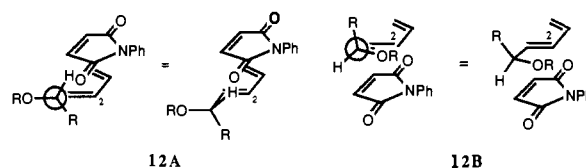
The ENE reaction is also classified as a pericyclic reaction. A particularly striking example of the stereoselectivity influenced by allylic 1,3-strain is given below.³¹



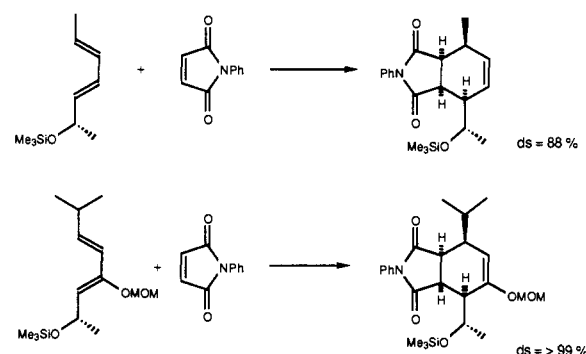
4. Stereoselective Cyclization Reactions Controlled by Allylic 1,3-Strain

4.1. Intermolecular Cycloadditions

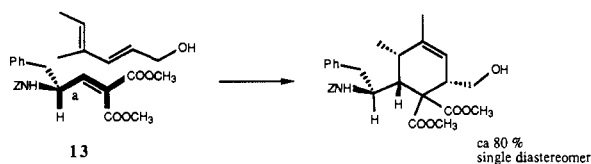
The facial selectivity of Diels–Alder reactions of dienes with a stereocenter bearing an electronegative group at one allylic position has been investigated by various research groups.^{32,33} The level of asymmetric induction is low in many cases and the direction of the facial selectivity depends on the nature of the dienophile. Among the various transition-state conformations discussed, both 12A and 12B would facilitate an electrophilic attack by the dienophile according to the concept put forth by Houk,¹³ because the electronegative OR group is placed in the plane of the diene moiety. Since in 12A and 12B opposite faces of the diene are shielded, the overall diastereoselection is understandably variable.



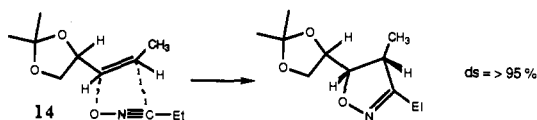
When there is an additional substituent on carbon 2, transition state 12B would be destabilized by allylic 1,3-strain. The attendant increase in asymmetric induction caused by allylic 1,3-strain is exemplified in the following cases.³³



Asymmetric induction can also be attained from a stereocenter next to the dienophile double bond.³⁴ In the case of 13, the conformation around bond a is controlled by allylic 1,3-strain. The direction of attack by the diene is then determined by the stereoelectronic factors discussed by Felkin and Anh.^{14,15}

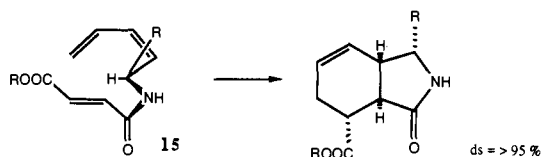


In nitrile oxide cycloadditions asymmetric induction by a stereocenter next to the dipolarophilic double bond has been investigated.³⁵ Excellent asymmetric induction was reported for the reaction of **14** in which allylic 1,3-strain allowed for only one conformation. In contrast, with the *E* isomer corresponding to **14** nitrile oxide cycloaddition resulted in low regio- and stereoselectivity.

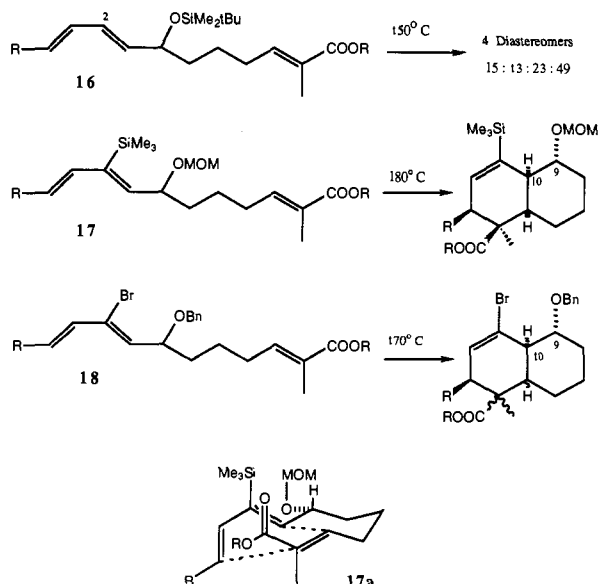


4.2. Intramolecular Cycloadditions

Cycloadditions such as the intramolecular Diels-Alder reaction allow the rapid assembly of bicyclic structures with the generation of up to four new stereocenters in a single transformation.³⁶ Asymmetric induction from a stereocenter in the chain linking the diene to the dienophile would hence be highly advantageous. However, the extent of stereocontrol ordinarily attained is variable.³⁶ In these situations utilization of overriding conformational control due to allylic 1,3-strain has been very fruitful. For instance, when the inducing stereocenter is next to a (*Z*)-diene unit as in **15**, the conformation of the transition state is fixed by allylic strain such that the formation of only one cyclization product is possible.³⁷

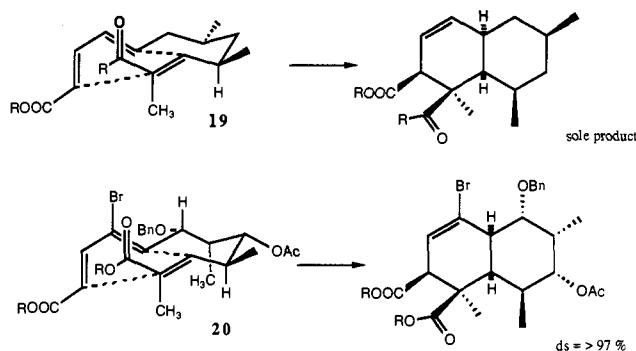


Even when starting with an (*E*)-diene, enhanced levels of asymmetric induction are possible if the substrate carries a substituent in the *Z* position relative to the allylic center at the diene unit. Although the cyclization of **16** occurred stereorandomly,³⁸ placement of a bulky dummy substituent in position 2 (cf. dienes **17** and **18**) cause the cyclization to proceed with high asymmetric induction, because allylic 1,3-strain restricts the conformations available in the transition state.³⁹

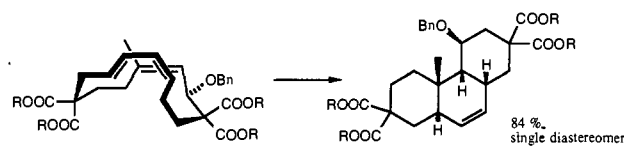


In both examples⁴⁰ the asymmetric induction in the generation of the new stereocenters at C-9 and C-10 is quantitative, while *exo/endo* selection in the cyclization (equivalent to the formation of *cis*- or *trans*-octalines) depends on other factors. The dummy substituent, Br or Me₃Si, which allowed for control of diastereoselectivity (cf. **17a**) was easily removed during subsequent transformations.

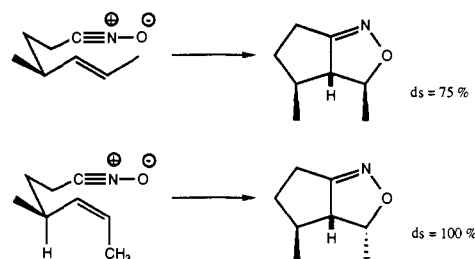
The inducing stereocenter may also be allylic to the dienophile part of the substrate. For example, in **19**⁴¹ the methyl group in the *Z* position of the dienophile is the source of conformational control by allylic 1,3-strain. This led to the formation of only one product,^{41,42} generating four new stereocenters in a single transformation. Likewise, in the case of **20**,⁴³ with conformational control by twofold allylic 1,3-strain, diastereoselection was essentially quantitative.



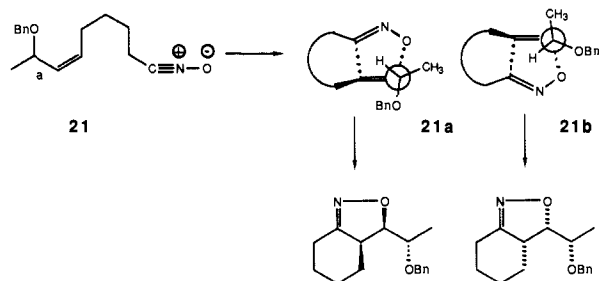
Moreover, in a transannular tricyclization reaction asymmetric induction was complete as a consequence of local conformer control due to allylic 1,3-strain.⁴⁴



Similar effects of control by allyl 1,3-strain have been noted in stereoselective intramolecular nitrile oxide cyclizations.⁴⁵



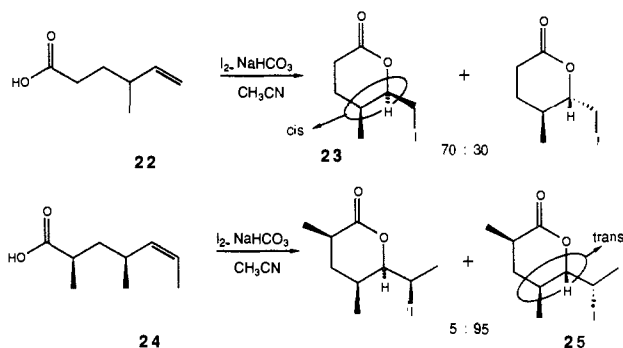
Asymmetric induction in intramolecular cycloadditions can also be effected by stereocenters which are not part of the linking carbon chain: An example is given by **21**,⁴⁶ in which due to allylic 1,3-strain only those conformations of bond a are populated which have the smallest substituent (H) on the allylic center in the "inside" position. The preference of transition state **21A**, attack anti to the benzyloxy group, over **21B** is then dictated by the Felkin-Anh principle.¹⁴



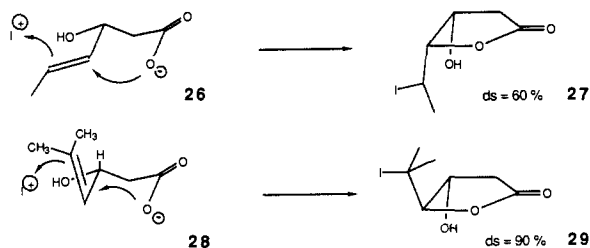
When the *E* isomer of **21** was subjected to similar cyclization conditions, the asymmetric induction was lower, likely due to the absence of allylic strain control.

4.3. Iodolactonization Reactions and Related Processes

Iodolactonization is one of the traditional ways to functionalize a double bond with the generation of new stereocenters. For instance, kinetically controlled iodolactonization of **22** resulted in preferential formation of the *cis* product **23**. The corresponding substrate **24**, however, having a *Z* substituent on the double bond, was cyclized in turn preferentially to the *trans* product **25**.⁴⁷

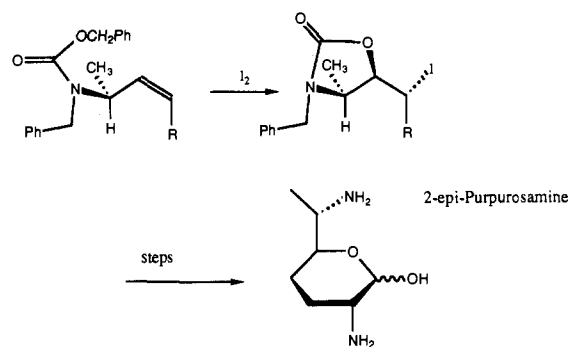


Mercurilactonization or selenolactonization of **24** similarly led with >95% diastereoselectivity to the stereoisomer corresponding to **25**. Likewise, the iodolactonization of **26** produced besides δ -lactones only the *cis* γ -lactone **27**.⁴⁸ Apparently, the electrophilic attack on the double bond proceeds in such a manner that the "inside" position for the hydroxy group is preferred on stereoelectronic grounds.¹³ This type of asymmetric induction can be reversed if a substituent in the *Z* position of the double bond (cf. **28**) destabilizes the O-inside transition state due to allylic 1,3-strain. The inducing stereocenter and the reacting double bond are now held in a conformation which allows cyclization only to the *trans* γ -lactone **29** besides the formation of δ -lactones.

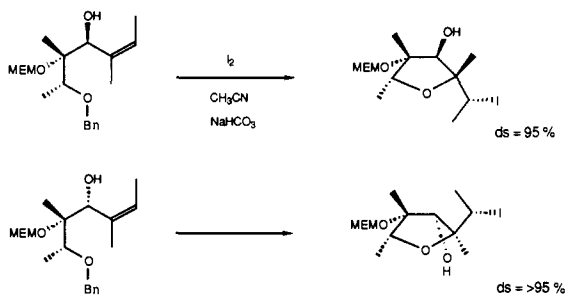


In general, higher stereoselectivity is attained in the kinetically controlled iodolactonization of (*Z*)-olefins

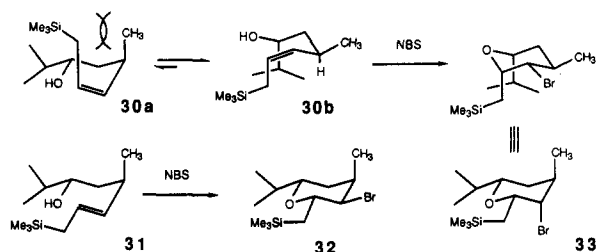
compared to that of (*E*)-olefins; cf. the recent synthesis of 6-epipupurosamine.⁴⁹



Several other examples are recorded for haloetherification, selenoetherification, and mercurioetherification wherein the stereoelectronically favored formation of a *cis* product (cf. **26** \rightarrow **27**) can be suppressed by allylic 1,3-strain to give the *trans* product, provided the reacting double bond carries a substituent in the *Z* position relative to the inducing stereocenter.^{21,50} A particularly impressive case⁵¹ of stereocontrol due to allylic 1,3-strain is given below. On the basis of the phenomenon of allylic 1,3-strain "the reasons for this complete reversal of stereoselectivity" become clear.

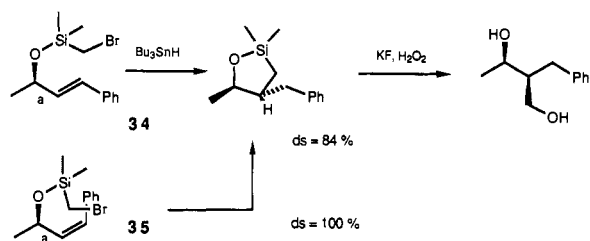


Likewise, the seemingly unexpected transformation of **30** by bromoetherification into **33**,⁵² in which the bromine atom occupies an axial position, can be ascribed to the transition-state conformation **30b** as a consequence of allylic 1,3-strain. The isomeric substrate **31** cyclized normally to a product **32** with an equatorial bromine atom. In the latter case the conformation of the transition state is controlled by the greater preference of an isopropyl group versus a methyl group for the equatorial position.

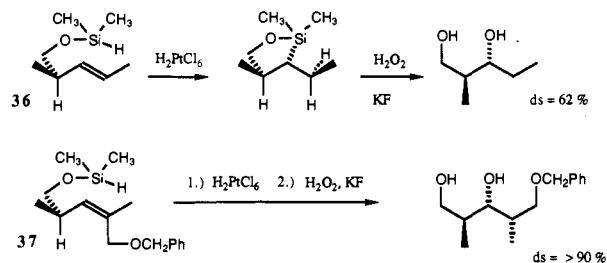


4.4. Other Intramolecular Cyclization Reactions

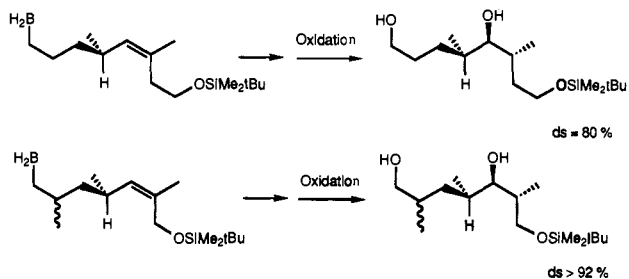
Nishiyama recently investigated the free radical cyclization of the two stereoisomeric substrates **34** and **35**.⁵³ The diastereoselectivity is higher in the case of the *Z*-substituted styrene, in which only one conformation of bond a is populated as a consequence of allylic 1,3-strain.⁵⁴



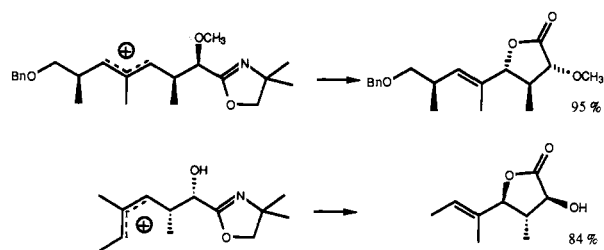
Similarly, on intramolecular hydroboration of the homoallyl alcohol derivatives **36** and **37**⁵⁵ much higher stereoselectivity was noted on reaction of **37**, which has a *Z* substituent on the double bond.



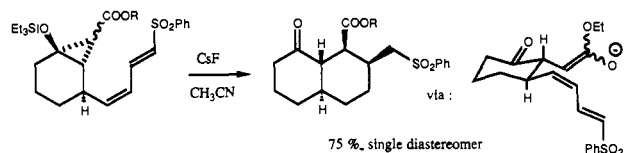
Cases with high stereoselectivity were reported for related intramolecular hydroboration reactions.⁵⁶



The stereospecificity of the following cationic cyclizations can be ascribed to conformational control due to allylic 1,3-strain.⁵⁷



Finally, the high stereoselectivity of the following intramolecular enolate/vinyl sulfone addition⁵⁸ is in accord with a conformation of the reacting enolate which is controlled by allylic 1,3-strain.

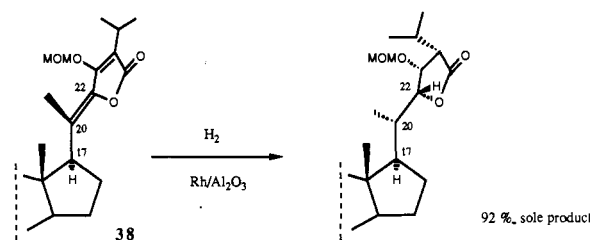


5. Stereoselective Intermolecular Addition Reactions to Double Bonds Controlled by Allylic 1,3-Strain

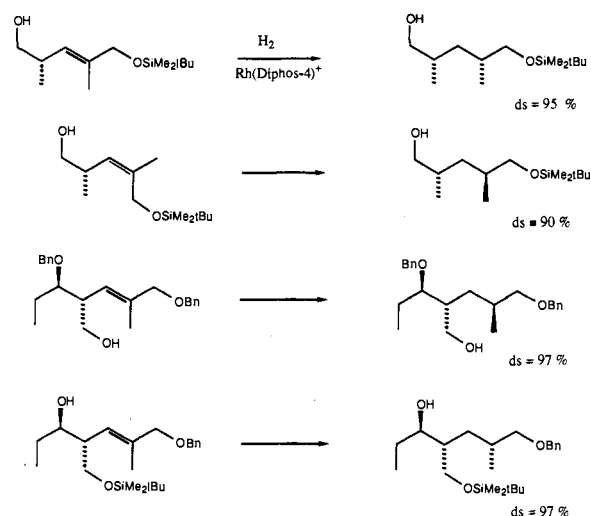
5.1. Hydrogenation

Catalytic hydrogenation of a double bond usually occurs predominantly from the less hindered face. For example, in the steroid derivative **38**⁵⁹ the conformation

of the C-17/C-20 bond appears to be fixed by allylic 1,3-strain arising from the lactone oxygen on C-22. As a consequence, hydrogenation occurred exclusively from the more accessible face.

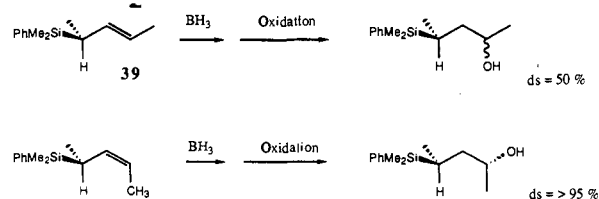


The Rh⁺-catalyzed hydrogenation of allylic alcohols in turn proceeds through a preequilibrium coordination of the hydroxy group to the rhodium catalyst.⁶⁰ This has been exploited for stereoselection in the hydrogenation of noncyclic olefins in which the steric disposition of a hydroxymethyl group at the inducing stereocenter is fixed relative to the prochiral double bond due to allylic 1,3-strain. The following examples²⁰ demonstrate the synthetic flexibility available by permutation of either the substituents on the prochiral double bond or the roles of protected and nonprotected hydroxymethyl groups as inert and active volumes.^{20,61}



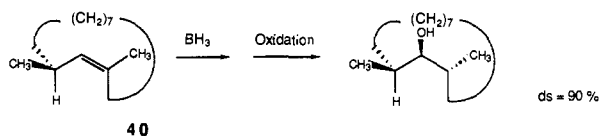
5.2. Hydroboration

The stereoselectivity and regioselectivity of the hydroboration reaction are sensitive to steric effects. Hydroboration of a double bond next to a stereocenter should result in high diastereoselectivity if one of the groups at this stereocenter shields one side of the double bond effectively. For this purpose the conformation around the bond between the controlling stereocenter and the double bond has to be fixed. The efficiency of achieving this by allylic 1,3-strain is shown in the following examples.^{62,63} There both the bulk of the phenyldimethylsilyl group and its stereoelectronic effect cooperate to result in selective attack at one face of the double bond.



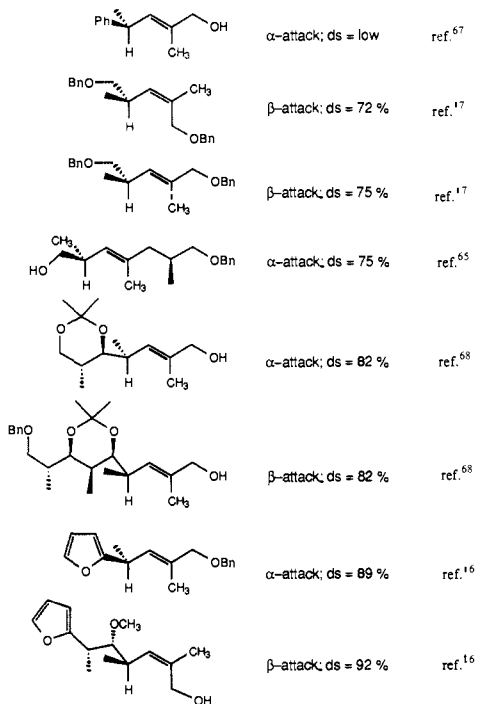
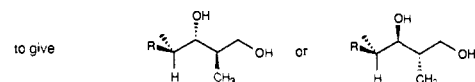
With 9-BBN as hydroborating agent, high asymmetric induction can be attained even with *E* isomers such as **39**.⁶³

A very efficient shielding of one side of a double bond holds for medium-ring cyclic olefins. Allylic 1,3-strain can be used to restrict the number of local conformations available to the allylic system as shown for **40**. As a consequence, hydroboration occurred with good selectivity from the more accessible face of the double bond.⁶⁴



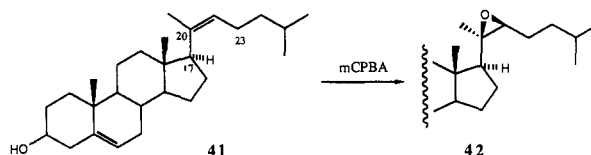
Of course, if the residues at the inducing stereocenter of an allylic system differ less in steric bulk, asymmetric induction in the hydroboration reaction will be less marked, as the following examples indicate.^{16,17,65} In some of these cases stereodifferentiation may be aided by stereoelectronic effects.⁶⁶

Diastereoface Selectivity on Hydroboration of Prochiral Olefins with BH_3

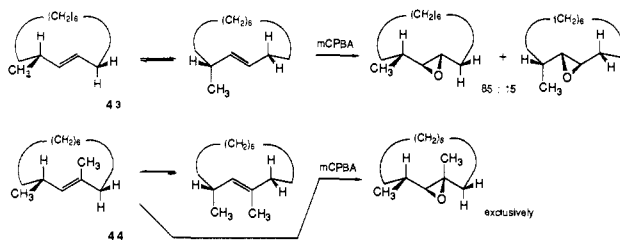


5.3. Epoxidation and Cyclopropanation

The stereochemical outcome of epoxidation of a double bond by *m*-chloroperbenzoic acid is often influenced by steric factors. When the double bond is adjacent to a stereocenter, the conformation of the bond between the stereocenter and the prochiral double bond will play a major role in the differentiation of the two faces of the double bond. In the steroid derivative **41** allylic 1,3-strain involving C-23 determines the predominant conformation of the allylic unit. Consequently, the peracid approaches the double bond from the less hindered side to give solely the product **42**.⁶⁹

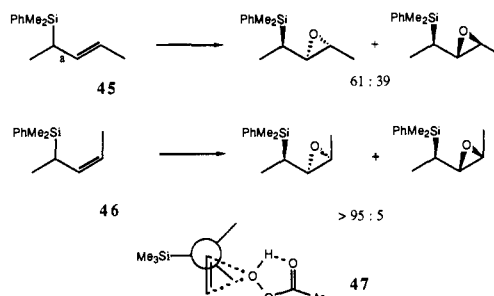


In medium-ring cyclic olefins one face of the double bond is always shielded by the rest of the ring. Reactions at the double bond occur at the accessible face only. Stereoselectivity is then determined by the nature of the local conformations available by rotation around the vinylic bonds. This is apparent from the epoxidation of **43**, which occurred with modest stereoselectivity. A *Z* substituent at the double bond shifts the equilibrium of local conformers to one side as a consequence of allylic 1,3-strain. Hence, epoxidation of **44** proceeded to give a single epoxide.⁶⁴



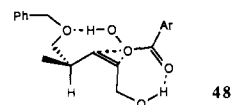
Stereoselectivity in the epoxidation of several medium-ring olefins has been attained⁷⁰ by favoring a particular local conformer due to allylic 1,3-strain.

Epoxidation of allylsilanes proceeds preferentially via a transition state **47**, in which the carbon-silicon bond is antiperiplanar to the forming carbon-oxygen bonds for both steric and stereoelectronic reasons. Hence, the conformation around bond **a** in **45** determines which face of the double bond is epoxidized preferentially. The selectivity of epoxidation of the (*E*)-allylsilane **45** was found to be low.^{71,72}

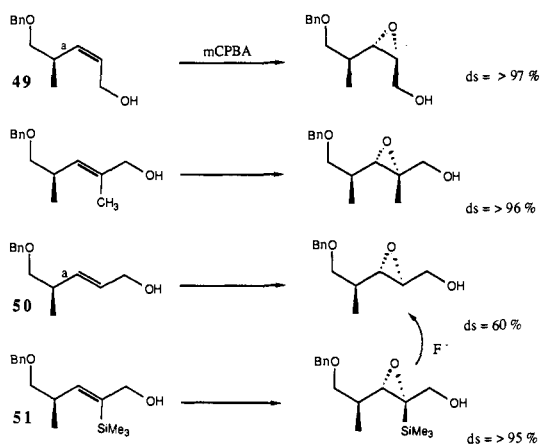


Allylic 1,3-strain, once again, is the underlying principle which dictates the more accessible face of the alkene in the (*Z*)-allylsilane **46**; asymmetric induction in epoxidation or osmylation of this substrate was excellent.^{71,72}

The direction of epoxidation of double bonds by *m*-chloroperbenzoic acid can also be controlled through additional coordination of the peracid to a nearby ether group; cf. **48**. Hence, if the stereocenter next to the double bond carries an alkoxyalkyl group, as in **49** or **50**, the direction of the epoxidation is being controlled by this group.

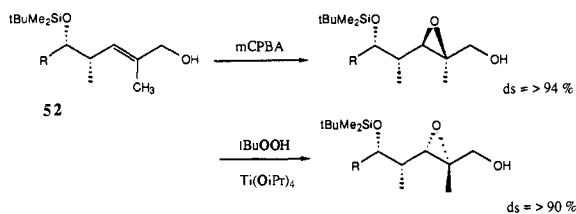


With an (*E*)-alkene, as in **50**, several conformations around bond *a* are energetically equally favorable and, consequently, the level of diastereoselectivity on epoxidation is low.

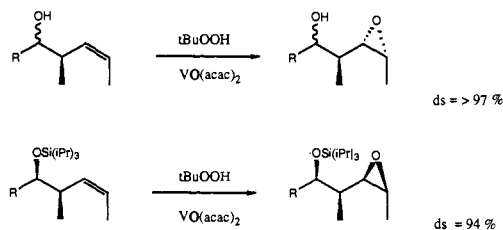


With the (*Z*)-alkene **49** only one conformation around bond *a* is favored, such that epoxidation proceeded with high asymmetric induction.¹⁸ Of course, if the synthetic objective does not require the presence of a substituent in the *Z* position, the temporary introduction of a dummy substituent, as in **51**, will result in equally high levels of asymmetric induction.^{18,73}

Similarly, **52**⁷⁴ exists in a preferred conformation around bond *a* due to allylic 1,3-strain. As discussed above, epoxidation with *m*-chloroperbenzoic acid is directed by the silyloxy group as an active volume. In contrast, the titanium- or vanadyl-catalyzed epoxidation with *tert*-butyl hydroperoxide is not activated by an alkoxy or a silyloxy group. Such a constituent therefore becomes an inert volume in these types of epoxidation reactions.

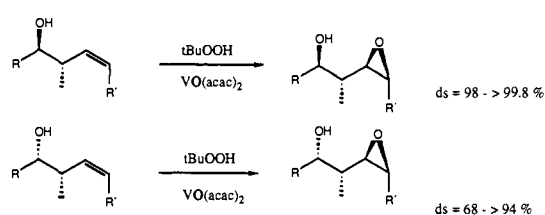


In epoxidation of alkenes with hydroperoxides, however, a hydroxyalkyl group coordinates with the reagent and acts as an active volume. This becomes clear on comparing the sense of asymmetric induction in the two cases⁷⁵ shown below, where the high diastereoselectivity is the result of the conformational organization by allylic 1,3-strain.

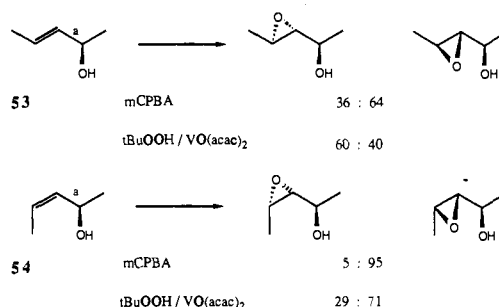


The change from the shielding silyloxy group to the directing hydroxy (or acetal) group allows for high flexibility in synthesis design. Accordingly, the combination of a hydroxyalkyl group as the substituent on an allylic stereocenter with a *Z*-substituted double bond has frequently been used to achieve high asymmetric

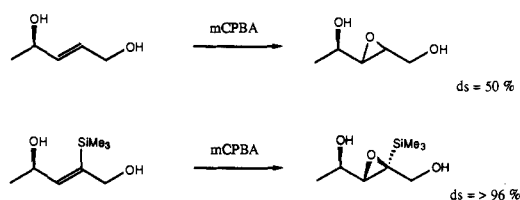
induction in epoxidation reactions.⁷⁶ The following examples⁷⁷ illustrate cases where asymmetric induction is clearly induced by the stereocenter α to the double bond.



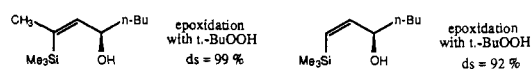
So far, we have considered cases in which the directing hydroxyl group is separated from the prochiral double bond by two single bonds (homoallyl alcohols). In the case of chiral allylic alcohols, epoxidation of a conformationally flexible system such as **53**, either with peracids or with hydroperoxides, led to low asymmetric induction.⁷⁸



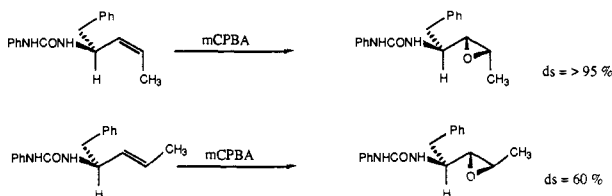
However, if only one conformation around bond *a* is accessible due to allylic 1,3-strain, as in **54**, peracid epoxidation gives high asymmetric induction. Obviously, the insufficient asymmetric induction on epoxidation of **53** with an *E* double bond can be boosted to high values by temporary incorporation of a dummy substituent ensuring conformational control by allylic 1,3-strain.^{18,79}



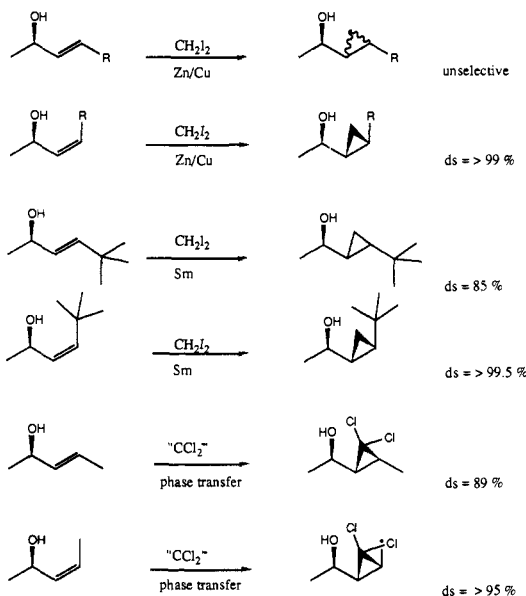
Nevertheless, vanadyl-catalyzed epoxidation of allylic alcohols gave low diastereoselectivity even with *Z*-substituted allylic alcohols such as **54**. Apparently, the transition-state conformations as well as steric and stereoelectronic requirements are different in epoxidation by *m*-chloroperbenzoic acid on the one hand and by hydroperoxides on the other hand.^{79,80} However, if the substituent in the *Z* position of the allylic alcohol is bulky enough, such as a trimethylsilyl group, even the vanadyl-catalyzed epoxidation by hydroperoxides gave high levels of asymmetric induction as a consequence of allylic 1,3-strain.⁸¹



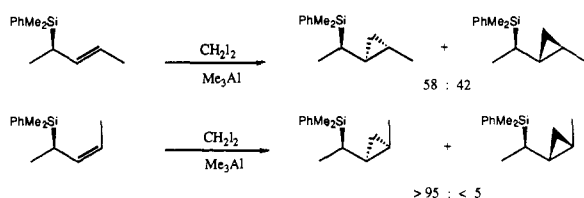
Good levels of 1,2-induction in the epoxidation of chiral allylureas⁸² have been reported when conformational control due to allylic 1,3-strain is operating. The urea function serves as an active volume.



Stereoselectivity in hydroxyl-directed *cyclopropanations* is related to that in hydroxyl-directed epoxidations. Thus the asymmetric induction in cyclopropanation of chiral (*E*)-allylic alcohols was found to be variable. In cyclopropanation of chiral (*Z*)-allylic alcohols, however, a single stereoisomer was obtained in all cases examined.⁸³

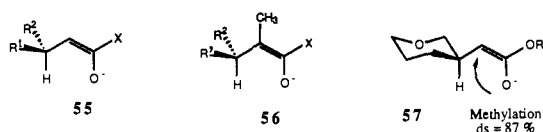


The stereoselectivity in cyclopropanation of allylic silanes increases markedly when changing from an (*E*)- to a (*Z*)-allylsilane:⁷²



6. Diastereoselective Enolate Alkylations Controlled by Allylic 1,3-Strain

Ester and amide enolates with a disubstituted β -carbon should exist predominantly in conformation **55** due to allylic 1,3-strain. Hence, the approach of electrophiles to either side of the enolate should depend on the difference in active or inert volume of R^1 and R^2 . This holds irrespective of the enolate geometry being *E* or *Z*, as can be seen when X and O^- in **55** are interchanged.

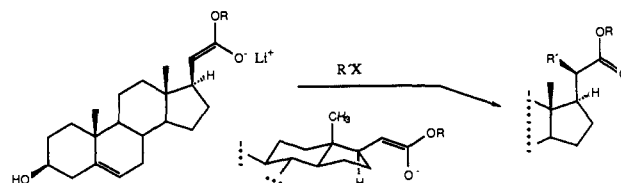


A classical example of such a differentiation involves the steroid skeleton and results in stereoselective alkylation.⁸⁴ Likewise highly diastereoselective alkyla-

TABLE I. Diastereoselectivity in the Methylation of the Enolates **55 and on Protonation of the Enolates **56****⁸⁶

entry	R^1	R^2	% ds	
			55	56
1	CH ₃	Ph	55	79
2	CH ₃	<i>n</i> -Bu	65	70
3	CH ₃	CH ₂ OSiR ₃	89	
4	CH ₃	SiPhMe ₂	91–99	
5	CH ₃	SnMe ₃	97	91
6	CH ₃	SnBu ₃	98	
7	CH ₃	(SCH ₃) ₂ CPh	99	96
8	CH ₃	(SCH ₃) ₂ CSiMe ₃	99	99
9	CH=CHCH ₃	SiMe ₃	95	

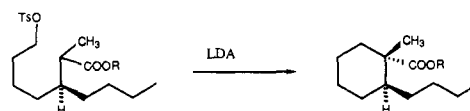
tions of ester enolates on a furanose skeleton have been reported.⁸⁵



The data in Table I show that on methylation of the enolates **55** high diastereoselectivity has been realized only if the difference in the size of the groups R^1 and R^2 is marked. Perhaps, this is due to an early transition state in alkylation reactions.

The increase in diastereoselectivities in going from entry 2 to entry 3 of Table I may be due to stereoelectronic enhancement of the attack of the electrophile anti to the alkoxymethyl group; cf. the illuminating experiment by McGarvey⁸⁷ on **57**. This demonstrates that delocalization of the lone pair on oxygen makes an alkoxyalkyl group a stronger σ -donor than an alkyl group.

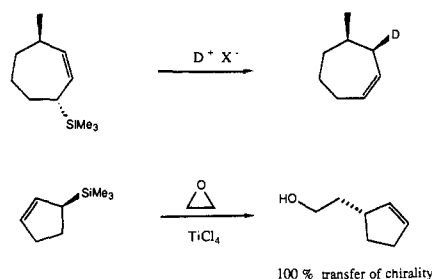
Asymmetric inductions of similar magnitude have been recorded for the protonation of the related enolates **56**; cf. Table I. Moreover, on the basis of the preferred conformation of **56**, the stereochemical outcome of the following cyclization⁸⁸ is easily rationalized.



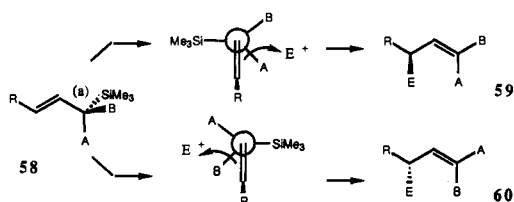
Related effects of allylic 1,3-strain control are of course also noted on alkylation and protonation, respectively, of ketone enolates related to **55** and **56**.⁸⁹

7. Chirality Transfer in Reactions of Allylsilanes and Allylboronates

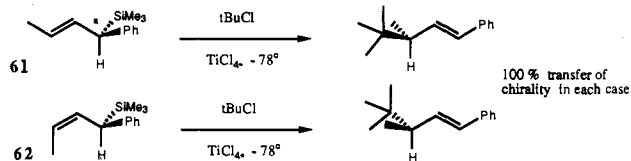
Generally, electrophiles attack allylic silanes anti to the silyl group as can be seen from the following reactions⁹⁰ of cyclic substrates.



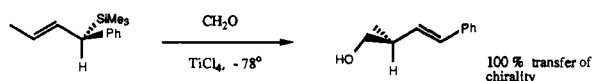
Assuming that this transition-state geometry holds for the reactions of open-chain allylsilanes **58** as well, two reaction paths have to be considered that lead to the two stereoisomeric products **59** and **60** which differ at the configuration of the newly formed stereocenter. The difference of the competing transition states lies in the conformation around bond a.



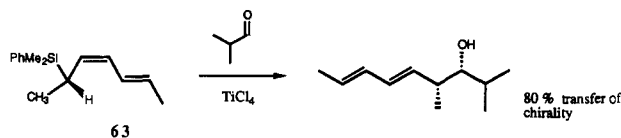
One transition state is favored in the reaction of the chiral allylsilanes **61** and **62** with *tert*-butyl chloride. Reaction of both the *E* and the *Z* isomers resulted in quantitative chirality transfer.⁹¹



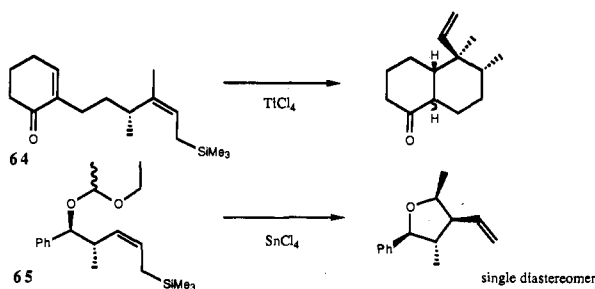
Likewise, the reactions of chiral allylsilanes with aldehydes proceeded with high levels of chirality transfer, even with allylsilanes having an *E* double bond.⁹¹



The fact that not only (*Z*)- but also (*E*)-allylsilanes react with high levels of chirality transfer shows that the additional stereocontrol provided by allylic 1,3-strain in the *Z* isomer is not needed in such cases. However, to achieve the more difficult 1,5-transfer of chirality on a dienyl silane, Fleming⁹² used (*Z,E*)-dienyl silane **63**; an acylation reaction of a corresponding (*E,E*)-dienyl silane is proceeded with only 65% chirality transfer.⁹³

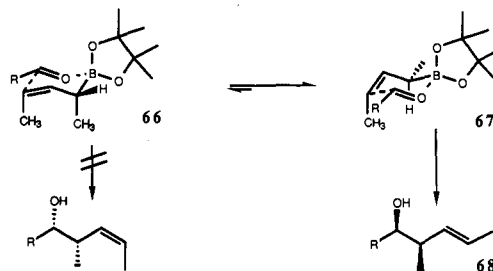


Conformational control due to allylic strain may be of importance for asymmetric induction in the following intramolecular cyclization reactions^{94,95} of the allylsilanes **64** and **65**.

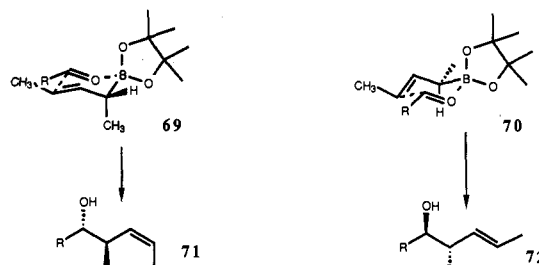


Allylic 1,3-strain is the primary reason for the high levels of chirality transfer found in reactions of (*Z*)-

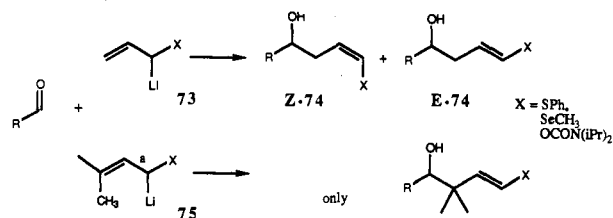
pentenylboronates with aldehydes. Of the two conceivable transition states for the reaction, **66** and **67**, the former is destabilized by allylic 1,3-strain, so that the reaction proceeded with high selectivity through transition state **67**⁹⁶ to give solely the homoallyl alcohol **68**.



In contrast, the addition of the isomeric (*E*)-pentenylboronates to aldehydes⁹⁷ proceeded via both transition states **69** and **70** to give a mixture of stereoisomeric products **71** and **72**. For related observations in the addition of crotyl siliconates to aldehydes, see ref 98.



Not only the configuration of the newly formed stereocenters in **71** and **72** but also that of the newly formed double bond, *E* or *Z*, are determined by the nature of the transition state **69** or **70** of the reaction. Thus, when the reaction proceeds through only one transition state due to allylic 1,3-strain, e.g., via **67**, the newly formed double bond in **68** has uniform *E* geometry. Likewise on addition of α -substituted allyllithium compounds **73** to aldehydes, the products **74** are mixtures of *E* and *Z* isomers.

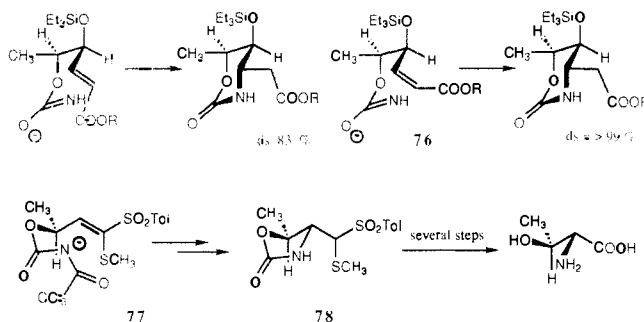


On reaction of the corresponding prenyllithium derivatives **75**, however, allylic 1,3-strain restricts the conformations with respect to bond a. Consequently, the addition products obtained have an *E* double bond.⁹⁹

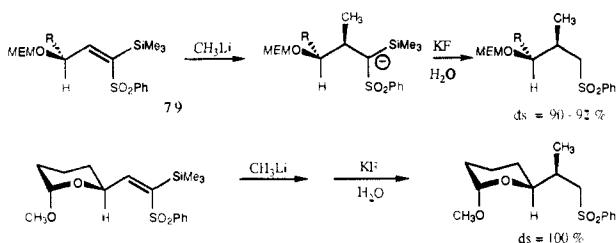
8. Nucleophilic Addition to Double Bonds Controlled by Allylic 1,3-Strain

Nucleophilic addition to double bonds having electronegative substituents on the allylic center proceeds under stereoelectronic control of the type described by Felkin and Anh.^{14,15} Accordingly, in the following examples,¹⁰⁰ the addition of a nucleophilic nitrogen group to an α,β -unsaturated ester prefers an approach anti to a C-O bond on the neighboring carbon.

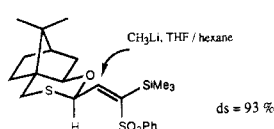
The diastereoselectivity of this process has been substantially increased (to >99:1) by using the substrate **76** with a *Z* double bond.



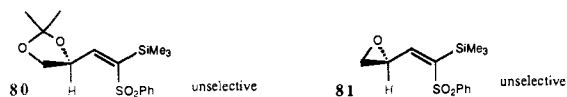
When an α -(methylthio)vinyl sulfone is used as an acceptor such as in **77**, the double bond carries a substituent in the *Z* position, securing conformational control by allylic 1,3-strain. Hence, cyclization to the oxazolidinone **78** occurred with complete asymmetric induction.¹⁰¹ Many examples of high asymmetric induction in the nucleophilic addition to silylated vinyl sulfones can be found in the work of Isobe.¹⁰² Here, allylic 1,3-strain restricts the conformation of the starting material to that shown in **79**. In the reaction of **79** with methyllithium the acetal oxygens serve as a directing group.



On the basis of these findings Isobe developed a highly efficient method for asymmetric carbon-carbon bond formation¹⁰² using the chiral auxiliary developed by Eliel.

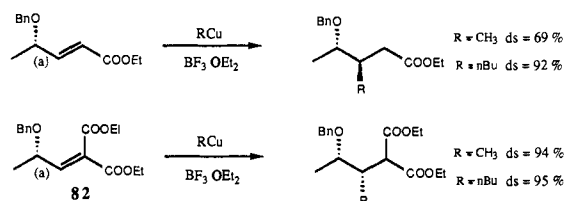


Many more examples of related 1,2-asymmetric inductions are given in Isobe's work. Surprisingly, the addition of methyllithium to the α,β -unsaturated sulfones **80** and **81** proceeded indiscriminately on both diastereotopic faces of the double bond,¹⁰³ no explanation was offered for this observation.

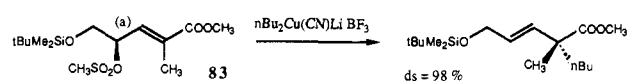


The addition of organocuprates to enones and ene esters is an important method for the formation of carbon-carbon bonds. This reaction is subject to 1,2-asymmetric induction when there is a stereocenter in the allylic position. The factors which control both the sense and the extent of asymmetric induction (stereoelectronic effects or kinetic vs thermodynamic control)¹⁰⁴ are not yet fully understood. Nevertheless, control of the conformation around bond *a* of the starting materials such as **82** by allylic 1,3-strain as a

consequence of a second *Z*-positioned ester group should be possible; cf. the X-ray structures of related *E* and *Z* ene esters.¹⁰⁵ This could be the reason for the increased levels of asymmetric inductions¹⁰⁶ in the reactions of **82**.

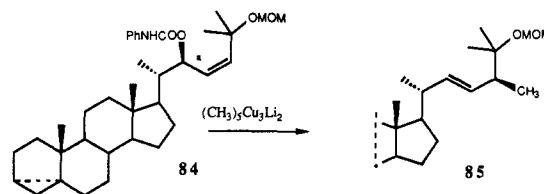


S_N2' -Allylic substitution reactions by organocuprates proceed with clean anti stereochemistry. Hence, in reaction of open-chain substrates the extent of asymmetric induction depends on the conformation around bond *a* of the substrate, e.g., of **83**. The high stereoselectivity in the following transformation¹⁰⁷ has been ascribed to the control of the transition-state conformation by allylic 1,3-strain.

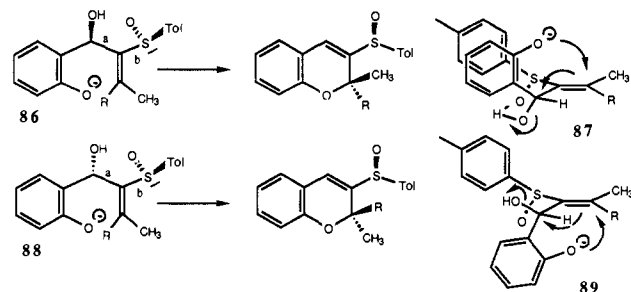


However, similar substitutions on substrates lacking the *Z*-positioned CH_3 group on the double bond also proceeded with high levels of chirality transfer.¹⁰⁸ Apparently, the additional stereocontrol provided by allylic 1,3-strain is not needed in this type of reaction.

Among the cuprate substitution reactions, those of carbamates are special, since the cuprate coordinates first to the carbamate so that the net result is a syn 1,3-allylic substitution of an alkyl group for the carbamate. If the allylic carbamate is part of an acyclic structure, the conformation around the vinylic bond can be manipulated by having a substituent in the *Z* position of the double bond. In this way the stereochemical course of the substitution is fully determined as shown in the case of **84**, which led solely to product **85**.¹⁰⁹



A particularly interesting case of a stereoselective intramolecular allylic substitution under control of allylic 1,3-strain was reported by Solladié:¹¹⁰

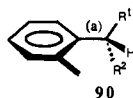


The stereochemistry of this cyclization depended only on the configuration at the benzylic carbon bearing the hydroxyl group. Since the alkene is tetrasubstituted the preferred conformation around bond *a* is determined by allylic 1,3-strain: Thus diastereomer **86** reacts

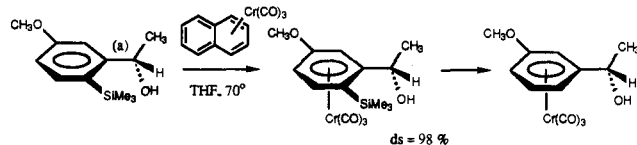
through transition state **87**, whereas diastereomer **88** reacts through the transition state **89**. A preferred conformation around bond **b** may also be defined by allylic 1,3-strain (cf. section 10.5), but this has no effect on the stereochemistry of this cyclization reaction, as the configuration of the new stereocenter appears not to depend on the chirality at sulfur.

9. Reactions of Benzylic Systems Controlled by Allylic 1,3-Strain

Allylic 1,3-strain may also dictate the preferred, lower energy, conformation of ortho-substituted aromatic systems such as **90**.¹¹¹

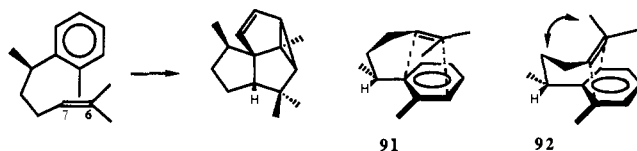


A difference in R^1 and R^2 may then be used to direct reagents to either of the diastereotopic faces of the aromatic system. The stereoselective formation of a chromium tricarbonyl complex,¹¹² which is assisted by a hydroxyl group at the benzylic stereocenter, serves as an example.



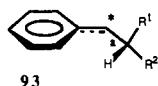
In this case the preferred conformation around bond **a** is induced by the trimethylsilyl group temporarily introduced for this purpose into the ortho position.

For the same reason, the following intramolecular photocycloaddition proceeded with complete asymmetric induction.¹¹¹

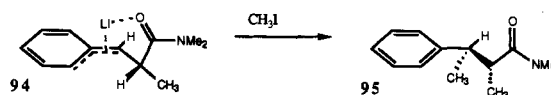


In this photocycloaddition even the mode selectivity (cf. **91** vs **92**) may be controlled by allylic 1,3-strain, which this time involves the C-6/C-7 double bond influencing the folding of the unsaturated chain.

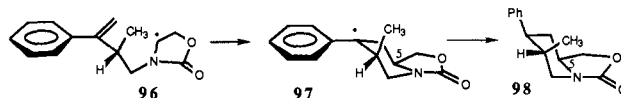
Conformational control around bond **a** due to allylic strain should also be possible in benzylic anions, radicals, and cations such as **93**, since stabilization of those intermediates by benzylic delocalization results in coplanarity of all the atoms in **93** except R^1 and R^2 . This could possibly lead to high 1,2-asymmetric inductions in the reactions of such intermediates.



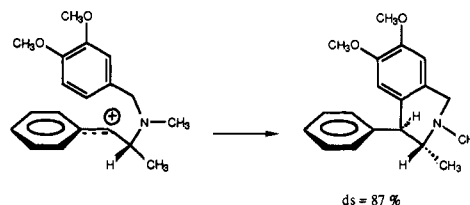
Two examples illustrate the above postulate. In the benzyllithium species **94** the amide group at the stereocenter coordinates to the lithium cation. Alkylation of the organolithium compound by methyl iodide occurs under inversion at the lithium-bearing carbon. In line with this rule alkylation of **94** proceeded to give **95** with high diastereoselectivity.¹¹³



Another case involves a benzylic radical adjacent to a stereocenter. Cyclization of the radical **96** to **97** occurs only if the phenyl group can stabilize the incipient radical by delocalization, i.e., if the phenyl group is coplanar with the double bond. As a consequence, the methyl group occupies an axial position in the transition state and ultimately in the intermediate **97** in order to avoid allylic 1,3-strain. This determines the relative configuration of the newly formed stereocenter at C-5. Thus, eventually the product **98** was obtained as a single diastereomer.¹¹⁴



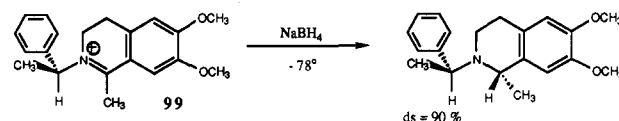
A case in which a benzylic cation cyclized stereoselectively under the control of allylic 1,3-strain has been reported as well.¹¹⁵



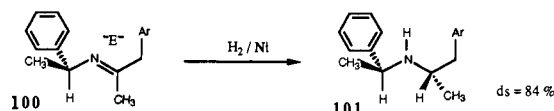
10. Allylic 1,3-Strain Control of Diastereoselective Reactions Involving Heteroallyl Systems

10.1. 2-Azaallyl Systems

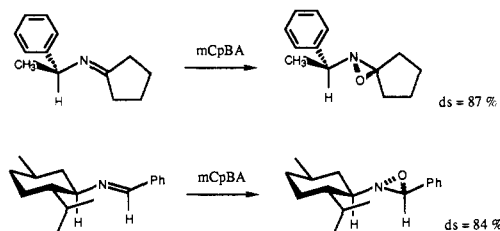
A clear-cut case of a 2-azaallyl system in which one conformation is preferred due to allylic 1,3-strain is shown in **99**. The phenyl and the methyl groups at the stereocenter differentiate the approach to the prochiral immonium group so that NaBH_4 reduction resulted in good diastereoselectivity.¹¹⁶



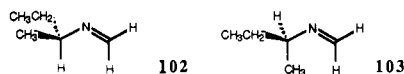
In related Schiff bases such as **100**, conformational control by allylic 1,3-strain differentiates the diastereotopic faces of the imine function. This should lead to high asymmetric induction in addition reactions at the imine group, provided the geometry of the Schiff base is stereohomogeneous (*E* or *Z*). The Schiff base **100** probably exists as the *E* isomer, as hydrogenation occurred with good diastereoselectivity¹¹⁷ to create the new stereocenter in **101** with *S* configuration.



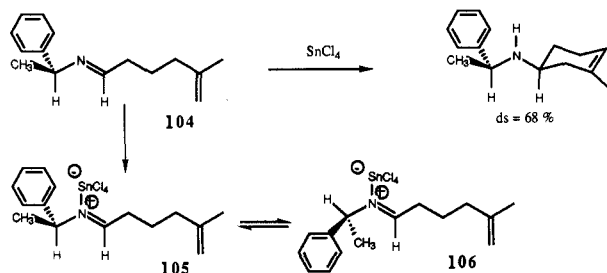
Asymmetric induction has also been recorded for the epoxidation of Schiff bases derived from chiral amines.¹¹⁸



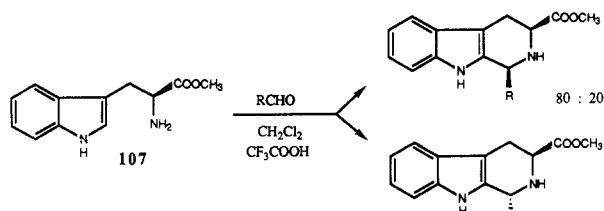
These data suggest that aldimines should also have a notable preference for the conformation in which the two hydrogen atoms eclipse each other. This is borne out by MMP2 calculations which show a 2 kcal/mol preference for **102** over **103**.¹¹⁹



Indeed, **102** was shown by NMR spectroscopy to exist mainly in the conformation depicted.¹²⁰ Consequently, reactions at the C=N group of such aldimines, e.g., the SnCl₄-catalyzed cyclization of **104**, resulted in modest 1,3-asymmetric induction.

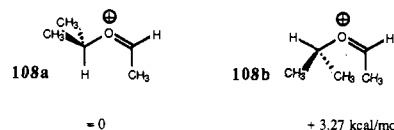


Actually the observed diastereoselectivity, albeit low, is a result of the conformational preference of the intermediate SnCl₄ adduct **105**. For this intermediate the alternate conformation **106** may be populated to a considerable extent as a consequence of allylic 1,2-strain⁸ between the bulky tin group and the substituents at the stereocenter. The use of a smaller Lewis acid, e.g., a proton, should therefore lead to higher asymmetric induction. A slightly better diastereoselectivity¹²¹ has indeed been reported for the proton-catalyzed cyclization of **107**.



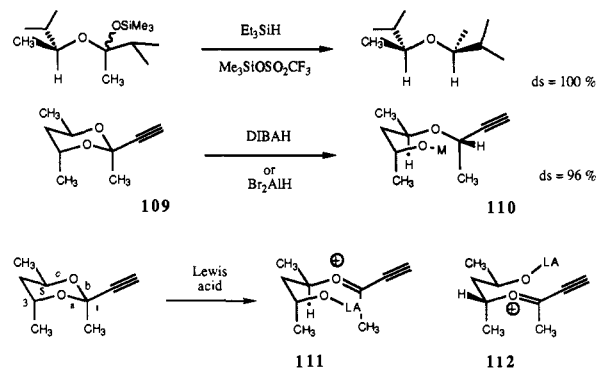
10.2. 2-Oxonlaallyl Systems

Since there is no principal differences between the 2-aza- and the 2-oxoniaallyl systems, asymmetric induction based on conformational control due to allylic 1,3-strain is to be expected for the latter system as well. Results from MP2/6-31G*//6-31G* ab initio calculations⁹ show that **108** has two conformational minima, **108a** and **108b**. The one, **108a**, in which the methyl group eclipses the hydrogen was calculated to be the more stable conformation.



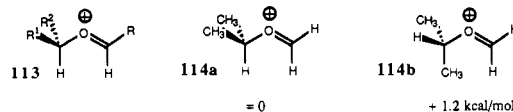
The higher conformational preference for **108a** compared to the carbon analogue **4a** is a consequence of the shorter C-O bond distances and the smaller C-O-C bond angle in **108**.

The conformational preference of such oxoniaallyl systems may be the reason for the high asymmetric induction observed in the reduction of the following ketals.¹²²

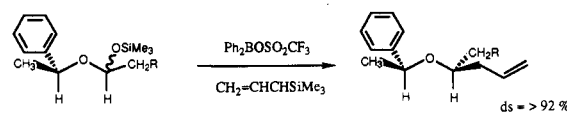


E.g., treatment of **109** with a Lewis acid resulted in preferential cleavage of bond a over bond b, because the former process relieves the steric interactions between the axial methyl groups on C-1 and C-3. Moreover, the oxonium ion **111** generated by rupture of bond a is produced in a conformation which has no allylic 1,3-strain, whereas opening of bond b would lead to an oxonium ion in the high-energy conformation **112** destabilized by allylic 1,3-strain. The diastereofacial preference of the subsequent chemical reactions at the prochiral center thus generated depends on the reaction system: If the Lewis acid simply serves as a steric shielding group, nucleophiles should attack **111** from the rear side. However, if the Lewis acid itself contains a nucleophilic group, such as found in reductions with DIBAL or Br₂AlH,¹²² the hydride is delivered from the front side to give **110** with high diastereoselectivity.

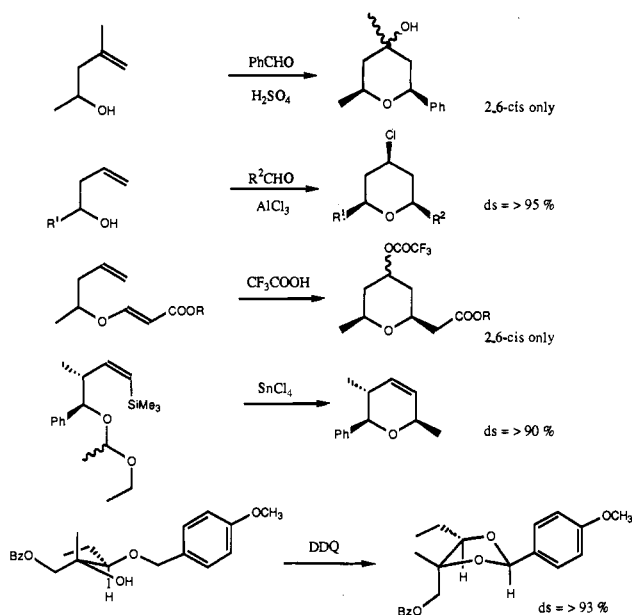
Even aldehyde-derived oxonium ions such as **113** apparently have a strong tendency to react through the conformation shown. This conformational preference has been pointed out by Overman,¹²³ and results from MP2/6-31G*//6-31G* ab initio calculations⁹ show that conformation **114a** is by 1.20 kcal/mol more stable than conformation **114b**.



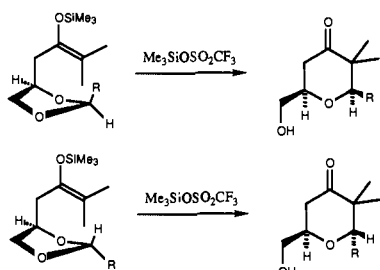
This may be a contributing factor for the high stereoselectivity of the following transformations.¹²⁴



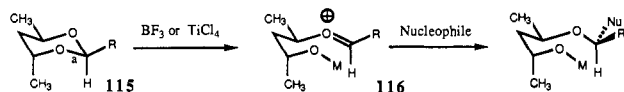
When one of the groups R¹ or R² in **113** carries a nucleophilic center, cyclization reactions with very high 1,3-asymmetric inductions have been realized^{95a,123,125} as shown by the following examples.



Oxonium ions of the type 113 are frequently generated from acetals. But not all reactions of acetals under Lewis acid catalysis proceed through oxonium ions. Depending on the Lewis acid applied and on the nature of the nucleophile, some of the reactions may proceed by a S_N2 -type process.¹²⁶ In such cases free oxonium ions are not generated as intermediates and therefore their conformational preferences cannot determine the stereochemical outcome of the reaction; cf. the following example:¹²⁷



Johnson¹²⁸ developed a highly useful asymmetric C-C bond-forming reaction using the chiral acetals 115.

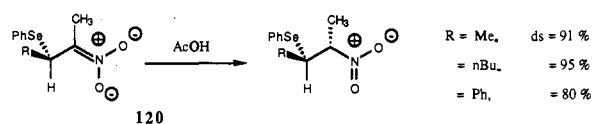
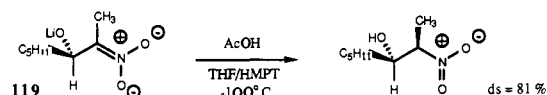
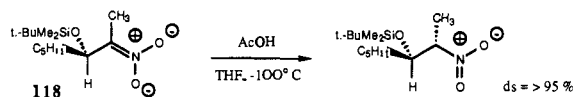
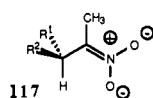


While it is not established which of these reactions proceed via a S_N2 -type reaction^{126,129} and which involve the oxonium ion 116 as an intermediate, the stereochemistry of the reactions proceeding through the ion 116 can easily be rationalized: First, the Lewis acid induces preferential cleavage of bond a to generate the oxonium ion 116 in its preferred conformation. Since the Lewis acid is coordinated to the former leaving group, it shields one side of the oxonium ion 116, and attack of various nucleophiles occurs then with $>90\%$ diastereoselectivity from the opposite face.

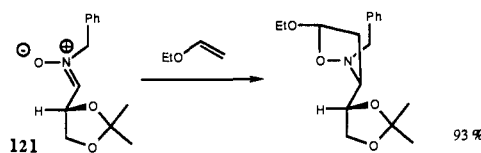
10.3. Nitrones

α -Disubstituted nitronates 117 should exist in the conformation shown, in order to avoid allylic 1,3-strain. Provided that R^1 and R^2 differ sufficiently in either active or inert volume, diastereoselective protonation of the nitronates is possible. Indeed, excellent diastereoselectivity was reported for the kinetically controlled protonation of 118,^{130,131} the silyloxy group serving as an inert volume. The opposite sense of asymmetric induction was noted on protonation of 119.¹³⁰ Apparently, the alkoxide function serves as an active volume. This explanation is deceptively simple and neglects all stereoelectronic effects. Other explanations, such as those given by Seebach,¹³⁰ are therefore by no means less likely. Nevertheless the notion of a preferred conformation 117 and differences in inert volume controlling the diastereoselectivity are similarly borne out in the protonation of 120,¹³² a case in which polar effects are less likely to interfere.

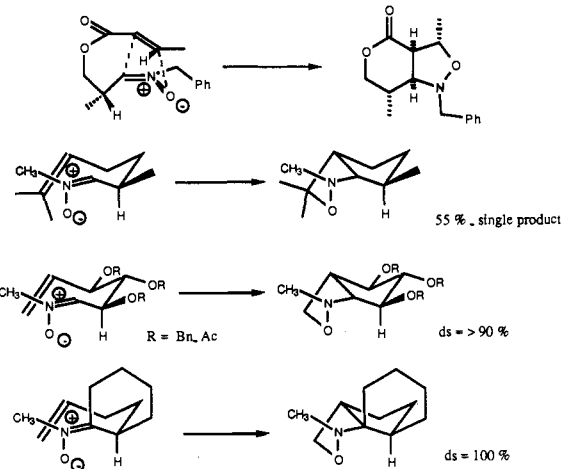
Asymmetric induction in intermolecular nitronate cycloadditions caused by an adjacent stereocenter has also been reported. In order to avoid allylic 1,3-strain nitronate 121 should exist predominantly in the conformation shown. The facial selectivity of the cycloaddition to ethoxyethene is then controlled by steric effects.¹³³



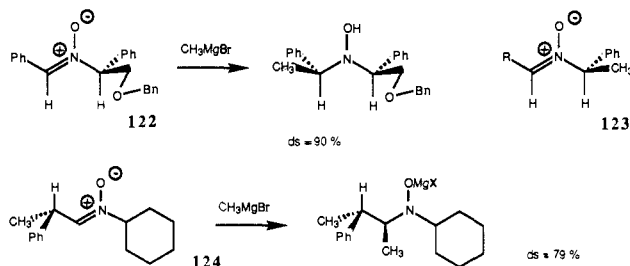
Similarly, in intramolecular nitronate cycloadditions high stereoselectivity has been realized which can be attributed to allylic 1,3-strain as a control element.¹³⁴



Similarly, in intramolecular nitronate cycloadditions high stereoselectivity has been realized which can be attributed to allylic 1,3-strain as a control element.¹³⁴



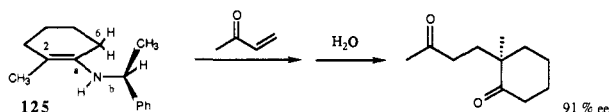
The stereochemistry of nucleophilic addition to nitrones, such as Grignard additions, can also be controlled by allylic 1,3-strain. Thus, on addition of methylmagnesium bromide to the nitron 122 the attendant diastereoselectivity can readily be accounted for by assuming 122 as the reactive conformation and the benzyloxy group serving as an active volume to coordinate the Grignard reagent.¹³⁵



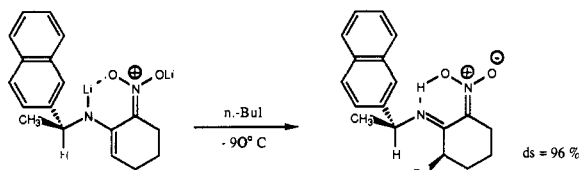
However, in the Grignard addition to the nitron 124, where a stereocenter is α to the sp^2 carbon, the stereochemical outcome did not correspond to what would be expected by consideration of allylic 1,3-strain.¹³⁶ In a cycloaddition of vinyl acetate to a related nitron 123, facial selectivity was only 70%.¹³⁷ For this type of reaction the difference in inert volumes of Ph and CH_3 may not be marked enough.

10.4. Other Azaallylic Systems

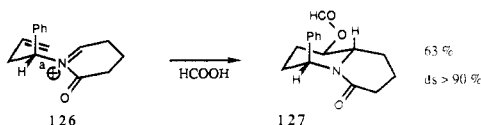
Finally, 1,4-asymmetric induction was realized in Michael additions of the enamine 125, in which the conformation around bond a is locked by (i) allylic 1,3-strain involving the vinylic methyl group and (ii) orbital overlap. Since bond a has partial double bond character, the conformation around bond b is also confined by allylic 1,3-strain involving the C-6 hydrogens.



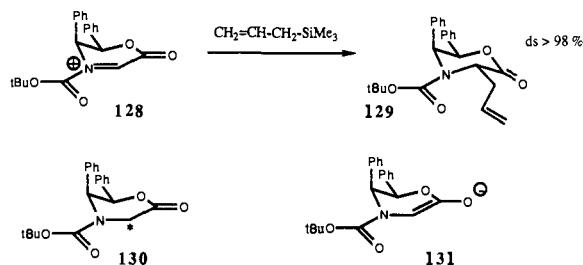
Since the conformations around the two single bonds a and b between the chiral center and the reacting prochiral carbon C-2 are thus fixed, Michael addition occurred specifically from the less hindered β -face.¹³⁸ Another case of high 1,4-asymmetric induction on reaction of a metalloenamine has been reported recently.¹³⁹



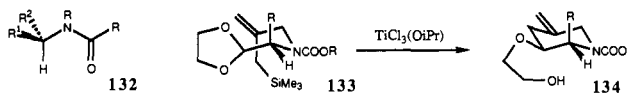
The effect of allylic 1,3-strain on *N*-acyliminium ion cyclizations has been investigated by Hart.¹⁴⁰ Allylic 1,3-strain affects the conformations around bond a in 126 such that the allyl group is held on the lower side of the molecule. Cyclization then proceeded to give the product 127 with high stereoselectivity.



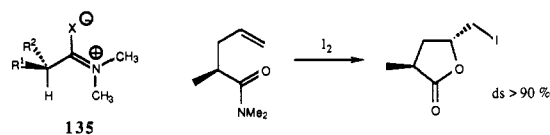
In the acyliminium ion 128 allylic 1,3-strain causes the phenyl groups to be in a pseudoaxial position. This group thus sterically shields the top side of the molecule. As a consequence, nucleophiles added with high stereoselectivity to the bottom side of the ion.¹⁴¹ If the shielding group was smaller (methyl instead of phenyl) cis-axial attack predominated on reaction of a related substrate.¹⁴² The same stereochemical argument holds for the stereoselective reactions of the radical 130¹⁴¹ and anion 131.¹⁴³



Due to the partial double bond character between the nitrogen and the carbonyl group in carboxamides, amides of α -branched amines should exist predominantly in conformation 132 to avoid allylic strain. While the consequence of this conformation for determining the secondary structures of proteins is well recognized, application of this phenomenon as a key element for asymmetric transformations is rare. One utilization is seen in the allylsilane cyclization reaction¹⁴⁴ of 133 giving solely the cis diastereomer of the product 134.



As a consequence of amide resonance, allylic 1,3-strain also affects certain conformations of α -branched *N,N*-disubstituted carboxamides and -thioamides 135. The strain-free conformation is shown.



Manifestation of this conformational preference has been found in iodolactonization and related cyclization reactions which proceeded with high asymmetric induction.¹⁴²

10.5. Vinyl Sulfoxides

6-31G*/3-21G ab initio calculations¹⁴⁵ on methyl vinyl sulfoxide show that vinyl sulfoxides have two conformations 136 and 137 which are energy minima, the one with the oxygen eclipsing the double bond, 137, being preferred by 1.6 kcal/mol. In each of these conformers a different face of the double bond is shielded by the alkyl or aryl residue on sulfur.

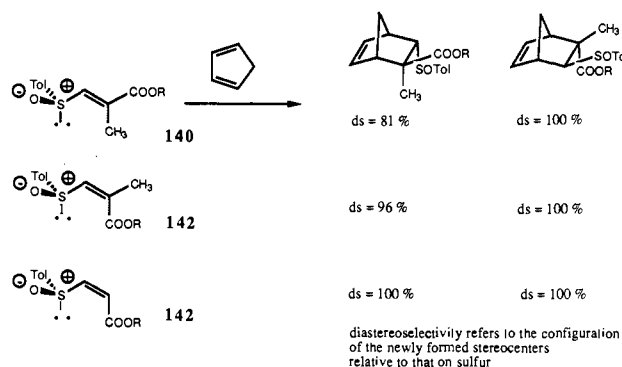


In view of the small energy difference between the ground-state conformers 136 and 137, which may not prejudice the energy difference between the transi-

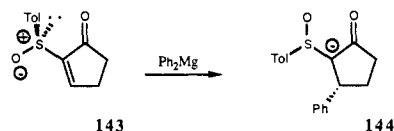
tion-state conformers, it is not surprising that addition reactions, such as Diels–Alder additions to simple vinyl sulfoxides, proceeded with low diastereoselectivities.¹⁴⁸



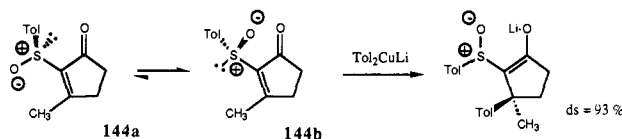
The situation is different when a *Z* substituent is introduced. Now allylic 1,3-strain destabilizes conformer 139 and shifts the conformer equilibrium heavily toward 138. Reactions now proceed mainly through conformer 138, and, as a consequence, higher diastereoselectivities have been attained. E.g., Diels–Alder additions on 140, 141, and 142 occurred with high selectivity from the β -face.¹⁴⁷



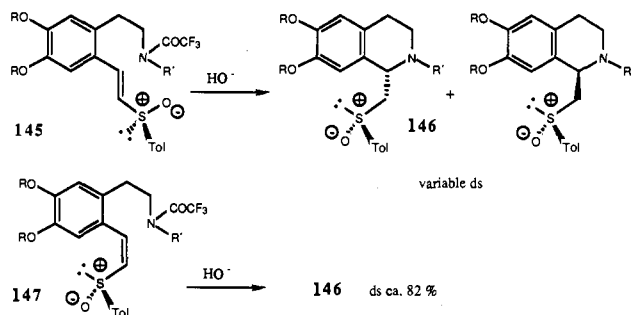
Posner has reported that diorganomagnesium reagents add to the keto vinyl sulfoxide 143 mainly from the α -face to give 144;¹⁴⁸ more Lewis acidic Grignard reagents add under chelation control to the β -face. It is assumed that 143 prefers in the ground and transition states the conformation shown in which the S–O and C–O dipoles result in the smallest net dipole. In this conformation the β -face of the vinyl group is shielded by the tolyl residue on the sulfur. This conformation is not a result of allylic 1,3-strain.



A similar reaction carried out on the keto vinyl sulfoxide 144 showed the opposite stereoselectivity.¹⁴⁸ While this may be due to a change in the reagent from a Grignard to a cuprate, it seems likely that the additional methyl group causes 1,3-allylic strain in conformation 144a, and, hence, the reactant conformation becomes 144b in which the α -face of the double bond is shielded by the tolyl group. It should be noted, however, that the addition of silylcuprates to both (*E*)- and (*Z*)-vinyl sulfoxides proceeded with similar diastereoselectivity (*ds* = ca. 80%),¹⁴⁹ i.e., the stereochemistry of this reaction did not respond to the conformational restraints imposed by allylic 1,3-strain.

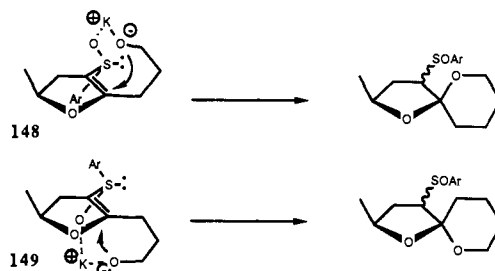


Pyne¹⁵⁰ studied the intramolecular Michael addition of an amine function to a vinyl sulfoxide in 145 and 147.



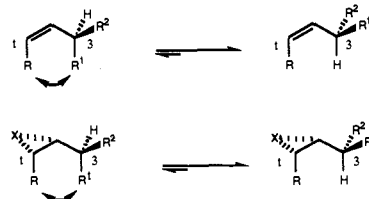
With the (*E*)-vinyl sulfoxide 145 both the sense and extent of asymmetric induction were variable. With the corresponding (*Z*)-sulfoxide 147, the sense of the asymmetric induction was uniform and the diastereoselectivity was higher than in the reaction of 145. The preferential formation of 146 from 147 can now be accounted for by assuming that the amine approaches the double bond from the side of the smaller and potentially hydrogen bond accepting sulfoxide oxygen. This direction of approach to vinyl sulfoxides by nucleophiles corresponds to the earlier findings of Sterling.^{151,152}

The stereoisomeric vinyl sulfoxides 148 and 149 both have a tetrasubstituted double bond. The conformation of the vinyl–sulfur bonds should be the ones that minimize allylic 1,3-strain. The intramolecular alkoxide addition to the vinyl sulfoxide proceeded stereospecifically.¹⁵³ The sense of the asymmetric induction is in line with the assumption that the alkoxide approaches the double bond from the side of the sulfoxide oxygen aided by chelation of the potassium counterion.



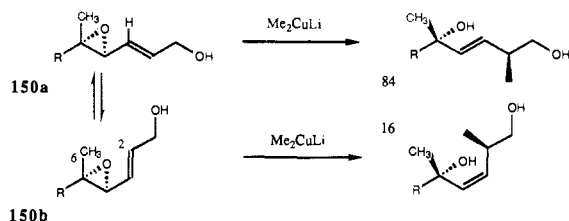
11. Conformational Control around Bonds to Three-Membered Rings Related to Allylic 1,3-Strain

Allylic 1,3-strain is one member of the group of phenomena of torsional strain. Allylic 1,3-strain arises when two substituents are being held in close proximity in a 1,3-distance on a rigid skeleton. The rigid structures so far considered have been of allylic or benzylic type.

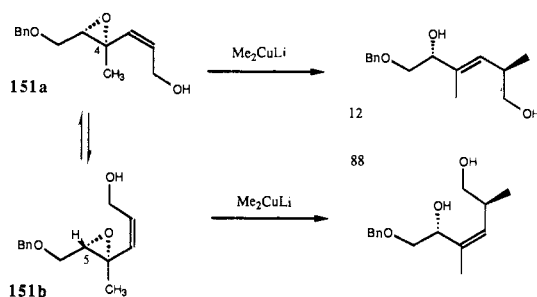


Related situations can occur with three-membered rings or bicyclic or polycyclic structures as backbones, on which side chains may be held in a distinct conformation to avoid torsional strain. Some transformations of vinyl epoxides may illustrate this point. The reaction of vinyl epoxides with cuprates proceeds through a

transition state in which the epoxide oxygen and the incoming cuprate must be antiperiplanar on stereoelectronic grounds. Thus, the substrate **150** might, in principle, react through either of the two conformers **150a** or **150b**. The allylic-type 1,3-strain interaction in **150b** between C-2 and C-6 causes the reaction to proceed predominantly via transition state **150a**.¹⁵⁴



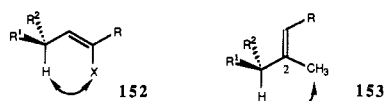
It is of additional interest to learn which allylic strain, that across a double bond or that across a three-membered ring, is more marked. Information on this point can be gained from the reaction of the substrate **151**, which involves the two conformers **151a** and **151b**.



The product ratio is now determined by a competition between the allylic strain in **151a** involving the C-4 methyl group and the steric interactions in **151b** involving the C-5 hydrogen. The product ratio obtained¹⁵⁴ reveals that the former interaction is more severe than the latter.

12. Epilogue

The concept of allylic strain was introduced by F. Johnson 20 years ago. It has been of consequence in many areas of organic chemistry, not the least in controlling asymmetric induction. For high 1,2- and 1,3-asymmetric induction in reactions at the diastereotopic faces of a double bond it is essential that the conformation around all single bonds between the chiral center and the prochiral reaction center is fixed as rigidly as possible. One of the most powerful ways to achieve this is to utilize the conformational restraints imposed by allylic 1,3-strain. This requires the presence of a substituent X on the double bond in a Z position relative to the chiral center; cf. **152**. If the synthetic objective does not require or tolerate such a substituent X, it is advisable, for the sake of high 1,2- or 1,3-asymmetric induction, to introduce such a substituent temporarily. A trimethylsilyl group has served admirably for this purpose.



Johnson also introduced⁸ the concept of allylic 1,2-strain concerning an allylic system such as **153** carrying a substituent at C-2. In order to avoid allylic 1,2-strain, conformation **153** will be favored in which the vinylic

methyl group and the α -hydrogen eclipse each other. Control of asymmetric induction by allylic 1,2-strain has also been observed on several occasions.^{55,60,155} This effect, while frequently smaller than that of allylic 1,3-strain, may merit a separate review.

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