Stereochemical Control in Organic Synthesis Using Silicon-Containing Compounds

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Contents

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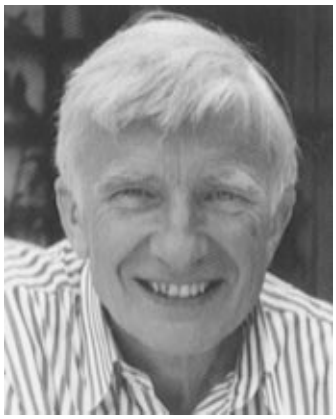


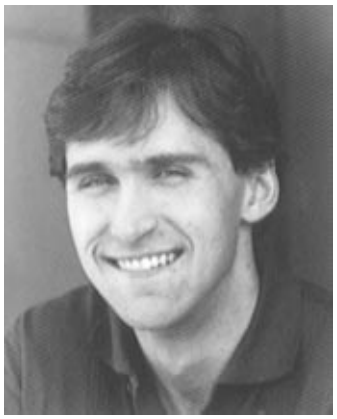
Ian Fleming was born in Staffordshire, England, in 1935. He studied at Pembroke College, Cambridge, where he obtained his B.A. in 1959 and his Ph.D. in 1962, the latter on the synthesis of acetylenic compounds and on the cyclobutane-forming reactions of enamines with electrophilic alkenes, supervised by Dr. John Harley-Mason. After a year as a Research Fellow at Pembroke College, he went to Harvard University in 1963 to work with Professor R. B. Woodward on the synthesis of vitamin B_{12}, where he was exposed for the first time to serious stereochemical problems. In the course of that work, he joined together two already resolved molecules, probably the first time that this had been done in an organic synthesis outside the areas of peptide and sugar chemistry. He then carried out a key reaction that established simultaneously both a C–C bond and two new stereogenic centers. He returned to Cambridge University in 1964, where he is currently a Reader in Organic Chemistry, a Fellow of Pembroke College, and a Fellow of the Royal Society. His research interests have spread widely over structural, mechanistic, and synthetic organic chemistry, but have most productively been associated with the development since 1972 of organosilicon chemistry as a tool in organic synthesis.

Asun Barbero was born in Burgos, Spain. She took a degree in chemistry in 1988 at the University of Valladolid, and her Ph.D. in 1992 at the same University under the supervision of Dr. F. J. Pulido, studying the stannylcupration of allenes and acetylenes. She then joined Dr. Fleming's group in Cambridge as a postdoctoral fellow, studying stereocontrol in nucleophilic attack on C=X systems in which the new stereogenic center has a 1,3-relationship to an existing stereogenic center. She is currently a postdoctoral research associate at the University of Valladolid.

I. Introduction

We review here the methods by which a silyl group, incorporated into an organic structure, has been used in organic synthesis to control stereochemistry, or has been an integral but peripheral part of a stereoselective reaction. A silyl group, typically trimethylsilyl, is a large electropositive substituent. As such it exerts a substantial effect in an organic structure, and quite frequently can be used to control the stereochemistry of the reactions taking place in its immediate neighborhood. However, the silyl group, although actually large, is also attached to the organic framework by a relatively long bond, and it does not always hinder reactions in its neighborhood as one might at first expect. In some cases, it is tempting to ascribe some of the effects to electronic factors, which often work in the same direction as the steric effects, but at the present stage of understanding, it is electronic factors that need to be demonstrated unambiguously, the steric effects being very evident in many cases. This of course is not so easy, and it is still a matter of debate whether the electronic component is of any importance in determining the stereochemistry of reactions taking place near or involving a silyl group. Whatever the cause, it is certainly becoming clear, as a result of much recent work, that the silyl group is a powerful force in controlling stereochemistry in organic synthesis. The silyl group has a striking advantage over many other possibilities for the role of a stereochemistry-determining group: the silicon−carbon bond is relatively robust toward many of the reagents used in organic synthesis, but, after the silyl group has exerted whatever influence it has, it can often be removed quite easily from the product, typically by protodesilylation or oxidation.

We have divided the review into 18 parts following this Introduction. Section II is about the control of double-bond geometry, where the silyl group is the electrofugal group in a β-elimination reaction. Section III is about the use of a silyl group, temporarily attached to the structure, to be a large group influencing stereochemistry without directly taking part in the reactions, and being replaced by a proton after it has done its job. Section IV is an introduction to



David Walter was born in Durham, England, in 1971, and studied at Churchill College, Cambridge, obtaining his B.A. in 1992. He is currently a graduate student in Dr. Fleming's group working on the chemistry of 1,1-disilylalkenes.

the use of a silyl group attached to carbon as a mask for a hydroxyl group into which it can be converted with retention of configuration, after it has been introduced with stereochemical control from elsewhere in the molecule. Sections V−XVII then review successively most of the functional groups carrying a silyl group, beginning with silicon attached to heteroatoms (sections V−VII), continuing with silicon attached to carbon (sections VIII−XVI), with an especially large section on allylsilanes, and ending with silicon hydrides (section XVII). These sections review the use of silicon-containing reagents in stereochemically controlled reactions, both those where the silyl group does not necessarily itself directly control the stereochemistry, and those where it is an integral part of the stereocontrol, as in the highly stereospecific S_E2' reactions of allylsilanes in section IX.F. Section XVIII describes how silicon can control stereochemistry by being part of a removable bridge bringing two molecules together and constraining the conformation of the transition structure. Finally, section XIX describes how a chiral silyl group, or a silyl group carrying chiral substituents on side chains not involved in the reaction, can be used to transfer chiral information to the organic framework.

In general, each of the sections VIII−XVI with silicon bonded to carbon begin with those cases where the silyl group is attached to the smaller reagent, which is generally the more simple stereochemically, and in which stereochemistry is principally determined by the substrate—usually an electrophile. In these reactions, the role of the silicon is mainly to increase the reactivity of the nucleophilic component and to be the electrofugal group, determining the position of a double bond. It is not always possible to identify its contribution to whatever stereochemical characteristics the reaction displays, since the alternative reaction without a silyl group is not always observable, but many silicon-containing reagents show selectivity different from their counterparts without the silyl group, even though the silyl group itself is not directly providing the stereochemical control. Given the very large number of reactions of silicon-containing nucleophiles such as silyl enol ethers, silyl azides, allylsilanes, ethynylsilanes, silyl nitriles, vinylsilanes, and silicon hydrides, in which there is stereochemical control largely from the substrate rather than the reagent, the sections dealing with all these reagents cannot reasonably be fully comprehensive. In these sections, we have tried only to illustrate enough examples to help everyone to appreciate the extraordinary range of reactions in which the presence of a silyl group exerts a profound influence.

We have tried to be comprehensive up to the end of 1995 but with a few references to papers published in 1996. We have also tried to be comprehensive in describing every *area* in which a silyl group has been used, either to control stereochemistry itself, or has been present as a necessary part of a structure involved in a stereoselective reaction. We have not described all the results in each paper that we cite, nor even every paper in a closely defined area, where we give references so that more examples can be found. By and large, we have chosen the best illustration of the main point in each paper, and where we have had to make choices, have used the example with the highest level of stereoselectivity, except that occasionally we have taken the best example giving a reasonably good yield. Thus we do not illustrate every *reaction* or *synthesis* having silicon involved in a stereochemically controlled event. The rather loose definition of our scope may well mean that papers that others might have included have been denied their place, to say nothing of the ones we have overlooked inadvertently.

One of us published a much smaller review on this subject in 1987,[1] since then the subject has expanded enormously. Aspects of stereocontrol in synthesis using silicon have been mentioned in a few other recent reviews: on selective reactions of allyl−metal compounds in general, but including allylsilanes,[2] on silicon tethered reactions,[3] on silylallyl anions,[4] on diastereoselective reactions of chiral allyl- and allenylsilanes,[5] and on the uses of silicon-containing compounds in the synthesis of natural products.[6]

We have used throughout the distinction between stereoselective and stereospecific first suggested by Zimmerman[7] and subsequently authoritatively championed by Eliel.[8] In any discussion of stereochemical events this usage is helpful and informative. We have also, somewhat reluctantly, adopted the term homochiral to mean chiral nonracemic, because it appears to be gaining in acceptability at a greater rate than other words or phrases for this important concept. We have not used the word chiral to mean chiral nonracemic, except occasionally in the shorthand use "chiral auxiliary", which in common usage is understood to mean a homochiral auxiliary. Although we have occasionally presented the degree of stereoselectivity in a reaction as a diastereomeric excess (de) or enantiomeric excess (ee), we have nearly always presented it as a ratio, using whole numbers normalized to add up to 100. Thus reports in the original of a ratio of stereoisomers of 25:1 or 100:1 are quoted here as 96:4 or 99:1. In reactions on carbonyl and related compounds having a neighboring stereogenic center, we have expressed the sense as Cram or anti-Cram, and have used Felkin or Felkin−Anh to refer only to the commonly accepted explanation.

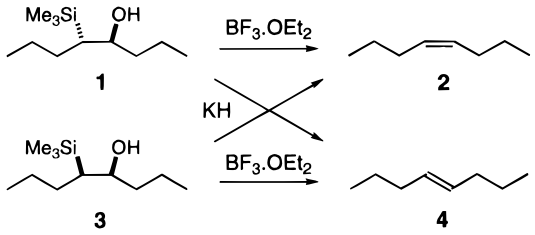
II. Control of Double-Bond Geometry

Silyl groups are frequently used in organic synthesis to control the position of a double bond,[9] and this use carries with it the possibility of controlling the double-bond geometry.

A. β-Elimination of β-Silyl Alcohols and Their Derivatives

Desilylative elimination is generally *anti*, with tetrahedral stereochemistry (**1** → **2** and **3** → **4**)[10,11] (Scheme 1).

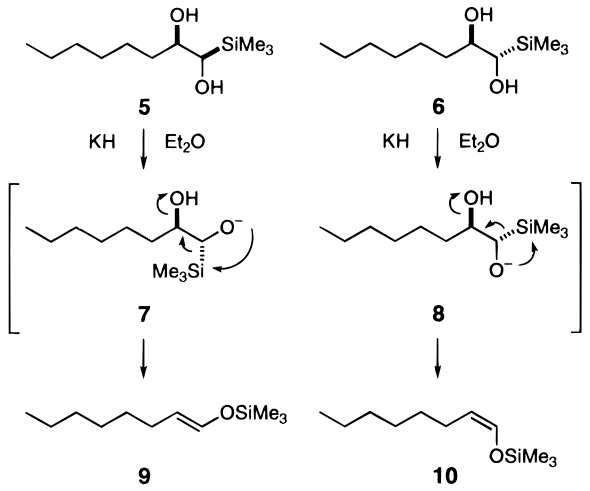
Scheme 1



The exception is the elimination of β-silyl alkoxides, often called Peterson elimination, which is *syn* (**1** → **4** and **3** → **2**). Both pathways are highly stereospecific; with diastereoisomerically pure starting materials, the alkenes are generally geometrically pure to better than >99:1. Peterson elimination is fast when the silyl group is on a carbon carrying an anion-stabilizing group, indicating that there is substantial breaking of the Si−C bond in the transition structure and the development of negative charge on the carbon atom. Elimination is also faster when the metal counterion is sodium or potassium, rather than, say, lithium or magnesium, and especially when it is well solvated.[12] The reaction is however sometimes diverted to give only the product of protodesilylation, without elimination, when the reaction is carried out using potassium *tert*-butoxide in DMSO,[13] which is further evidence of a substantially anionic transition structure or intermediate. The *syn* stereospecificity is occasionally eroded somewhat when the anion-stabilizing group is an ester and the *syn* stereospecific reaction would give a *cis* double bond.[14] Presumably an intermediate enolate is involved, which can lose its configurational identity by rotation before the elimination step.

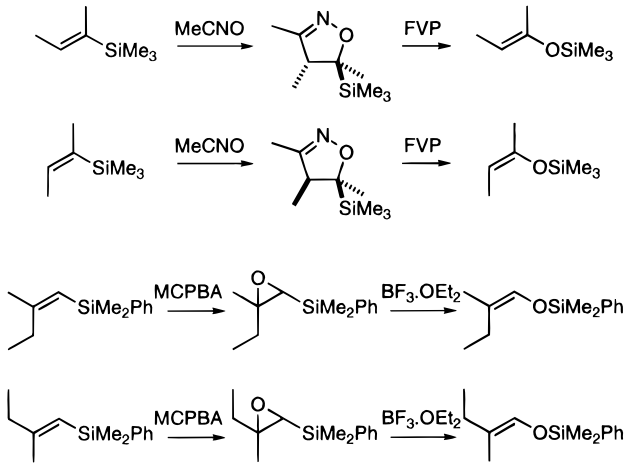
An exceptional situation arises when the β-silyl alcohol also has an α-hydroxyl group, as with the diastereoisomeric pair of diols **5** and **6**. Treating these diols with potassium hydride, followed by trimethylsilyl chloride, gave in each case largely the product of *anti* elimination, **9** (5:1) from **5** and **10** (2:1) from **6** (Scheme 2).[15] The mechanism appears to involve attack of the α-alkoxide ion on the silyl group, known as the Brook rearrangement, coupled with *anti* elimination of the β-hydroxide ion, summarized as **7** and **8**, respectively, instead of the usual attack of the β-alkoxide ion.

Scheme 2



A shift of the silyl group to an α-oxygen atom is also involved in some rearrangement reactions setting up silyl enol ethers stereospecifically with other substitution patterns (Scheme 3).[16] Although these

Scheme 3



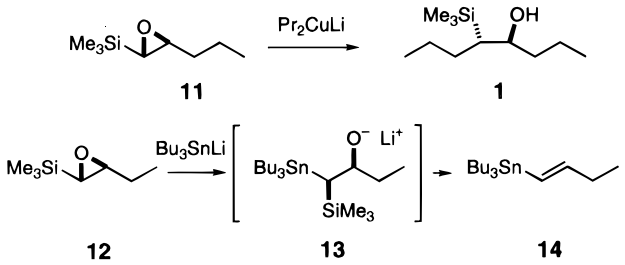
reactions are mechanistically related, they are not actually eliminations of β-silyl alcohols. There are also possibilities of elimination reactions with other nucleofugal groups than oxygen, but they are rare—an example can be found in the fragmentation reaction in Scheme 372.

For stereospecific eliminations like those in Scheme 1 to be useful, the synthesis of the β-silyl alcohols, or their derivatives, must also be stereocontrolled. Fortunately, there are many ways by which this can be achieved.

1. Carbon Nucleophiles and Epoxides

The starting materials in Scheme 1, for example, can be made by stereospecific alkylcuprate opening of vinylsilane epoxides, with the *trans* isomer **11**, for example, giving the alcohol **1** (Scheme 4).[11,17,18] The nucleophile selectively attacks at the carbon atom carrying the silyl group, and may be an aluminate in place of the cuprate.[19] If the nucleophile is a tin−lithium reagent, the product from the epoxide **12** is the *trans*-vinylstannane **14**, with the silyl group evidently removed in the intermediate **13** faster than a stannyl group (Scheme 4).[20] Other heteroatom

Scheme 4

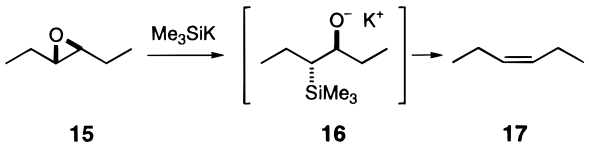


nucleophiles used in this way, include azide ion;[21] amines;[22] and bromide, acetate, methoxide, and acetamido ions.[23] On the other hand, opening of epoxysilanes under acidic conditions using hydrogen halides, leads to vinyl halides with inversion of configuration relative to that of the original vinylsilane (Scheme 36).[24]

2. Silyl Nucleophiles and Epoxides

Simple epoxides **15** can be opened by a silylpotassium reagent, and the intermediate **16** undergoes *syn* elimination *in situ* to give the alkene **17**, inverting overall the configuration of the double bond (Scheme 5).[25] The corresponding lithium reagent gives an intermediate that can be isolated, but the overall result is the same after base-induced elimination.[26]

Scheme 5

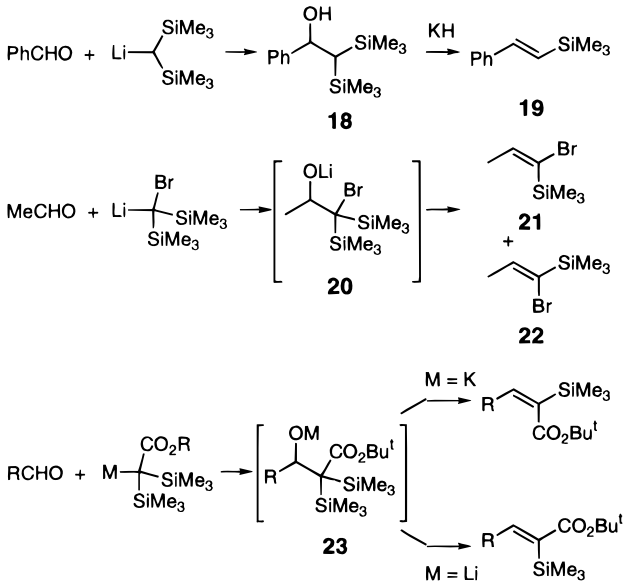


3. Carbon Nucleophiles Carrying an α-Silyl Group with Ketones or Aldehydes

This is the reaction known as Peterson olefination.[12] Organometallic carbon nucleophiles having an α-silyl group usually attack aldehydes with low stereoselectivity.[10,27] Thus α-silylbenzyllithium and benzaldehyde gave *trans*- and *cis*-stilbene in a ratio of about 60:40, with most of the obvious variables having only a small effect on this ratio.[28] Similarly, alkyl groups on both components typically lead to 50:50 mixtures of stereoisomers,[12] or at best to mild selectivity for the formation of the *E* isomer under the base-catalyzed conditions for the elimination step. The exception to this rule appears to be when the silyl group is hindered, when the selectivity in the first step favors the formation of the *Z* isomer in the second, a point that is discussed further in section XIII.B.[27]

Nevertheless, Peterson olefination shows some trends in stereoselectivity with two main classes of α-silylated nucleophile. The first is when the "anion" is stabilized, as it is to some extent by the presence of another metal group. Carbon nucleophiles carrying both an α-silyl group and another α-metal show high chemoselectivity for silyl removal over that of the other metal, and vinylboron,[29] vinylselenium,[30] vinyltin,[31] and vinyllead[32] compounds can be made this way, usually with fairly low levels of stereoselectivity in favor of the *Z* isomer. When the nucleophile has two α-silyl groups, creating an intermediate **18** with diastereotopic silyl groups, the one removed, normally, but not always, is that which leads to a *trans* double bond **19** (Scheme 6).[33,34] When there is

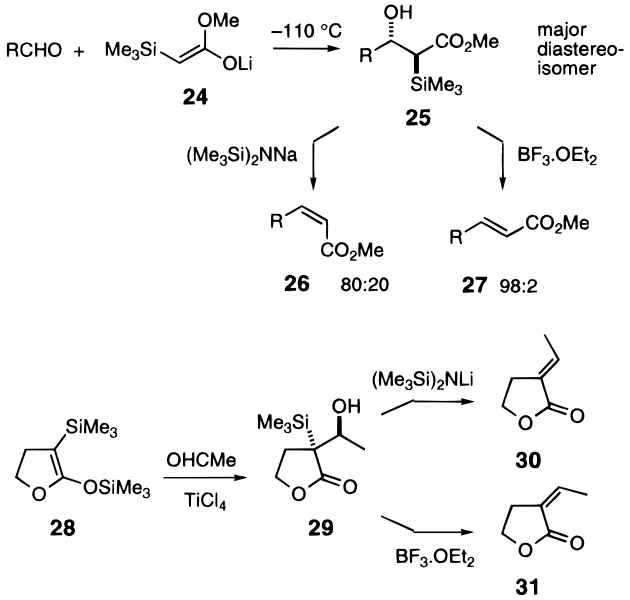
Scheme 6



another substituent, as with the bromide **20**, the elimination is not highly stereoselective, giving the (*E*)- and (*Z*)-vinylsilanes **21** and **22** in equal amounts.[35] However, in the intermediate **23**, the choice of metal counterion allows the stereochemistry to be controlled.[36]

With much better anion-stabilizing substituents, unsubstituted α-silyl enolates **24** are often, but not always,[37] selective in giving the *anti* isomer **25**, and hence the *cis* double bond **26** by Peterson reaction or the *trans* isomer **27** with acid.[38,39] When the enolate carries another substituent as well as the silyl group, selectivity in the overall reaction is still in favor of the (*Z*)-alkene, typically to the extent of about 75:25.[40] The lactone silyl enol ether **28**, however, gives the isomer **29**, and hence the (*E*)-alkene **30** in Peterson elimination and the *Z* isomer **31** with acid (Scheme 7).[41]

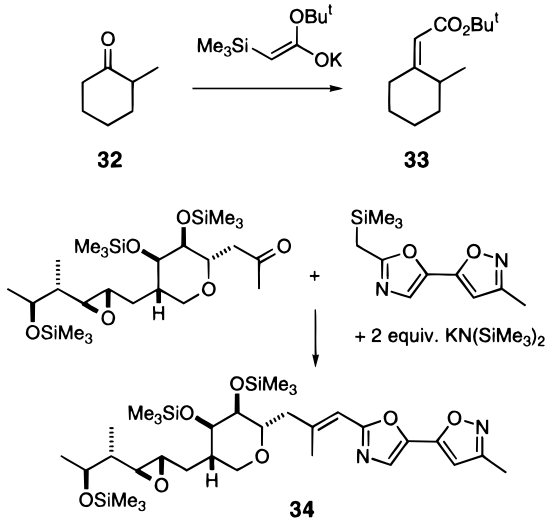
Scheme 7



The stereoselectivity with unsubstituted α-silyl enolates carries over to ketones **32**, when the major

product (89:11) is again the thermodynamically less favorable alkene **33**.[42] The stereoselectivity in this type of reaction can be controlled to a large extent by choice of base and silyl group,[43] as in a synthesis of the tris-silyl ether of the antibiotic BRL 49467 **34** (Scheme 8).[44] The *E*:*Z* selectivity in this reaction was

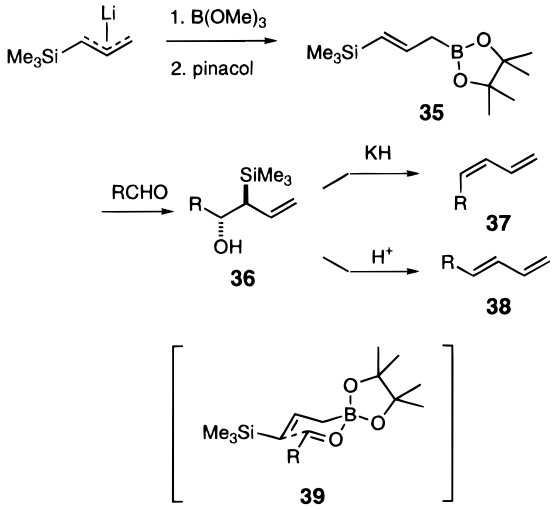
Scheme 8



13:1, but it could be changed to 1:7 by using butyllithium as the base, and having a *tert*-butyldimethylsilyl group in place of the trimethylsilyl group.

The second class of silylated nucleophile, this time regularly giving high selectivity, is found with 3-silylallyl metal compounds. Thus the allylboron oxide **35** in its reaction with aldehydes gave the *anti* β-silyl alcohol **36** and subsequently either the (*Z*)-**37** or (*E*)-**38** diene (Scheme 9).[45] Metals used in the allyl metal

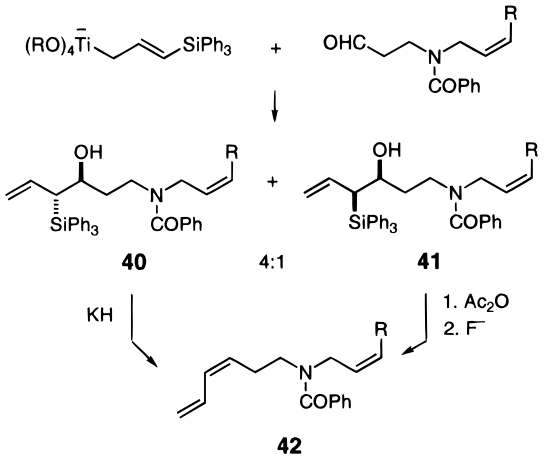
Scheme 9



component include lithium,[46] boron,[45,47] magnesium,[46] titanium,[48−50] and chromium.[51] The selectivity for the formation of the *anti* β-silyl alcohol in most of these reactions follows from the chairlike transition structure **39**, with the metal chelating both components of the reaction. A propargyl- (or allenyl-) lithium[52] or titanium[53] reagent with an α-silyl group likewise leads to a *Z*-enyne, but the lithium reagent can give the *E*-enyne if the reaction is carried out in HMPA.

It is therefore a simple matter to make alkenes, dienes, and enynes of either geometry. Alternatively, if the intermediate β-silyl alcohol is not formed with high stereoselectivity, it is possible to separate the diastereoisomers, and treat each with a different reagent. Thus *syn* Peterson elimination with the *anti* isomer **40**, and *anti* stereospecific elimination with the *syn* isomer **41** converges on the (*Z*)-alkene **42** (Scheme 10).[49] If the product is sensitive to acid, the

Scheme 10

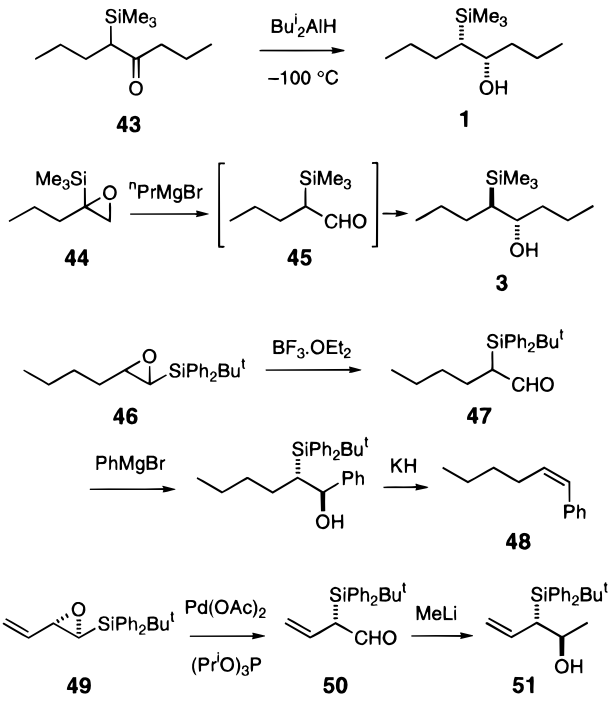


alternative method for achieving a stereospecifically *anti* elimination,[54] as used in this example, is to make the acetate of the intermediate β-silyl alcohol, and induce elimination with fluoride ion.[49] The *anti* stereospecificity, however, is lost when the silyl group is benzylic.[54] Except for this limitation, the possibility of separating the diastereoisomers of a β-silyl alcohol intermediate, and treating each differently, is available for convergent synthesis of a single alkene, whenever the intermediate can be isolated. It has not often been used.

4. Hydride and Carbon Nucleophiles with α-Silyl Ketones or Aldehydes

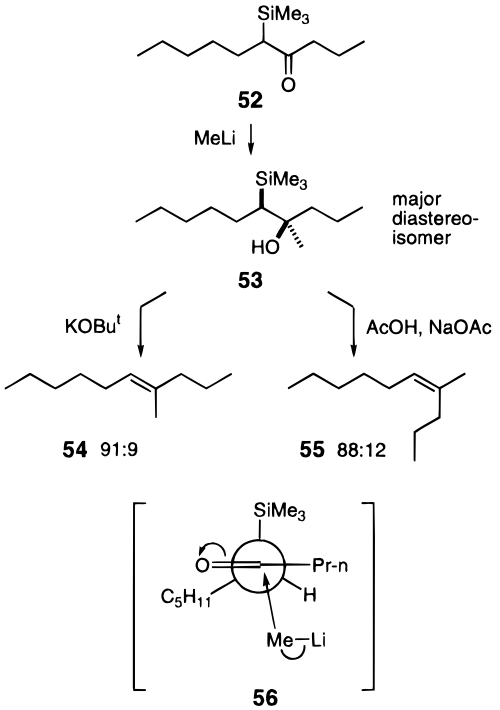
The alcohol **1** in Scheme 1 can also be made selectively by DIBAL reduction of the α-silyl ketone **43**,[10] and the diastereoisomeric alcohol **3** can similarly be made by reaction of the propyl Grignard reagent on 2-(trimethylsilyl)pentanal (**45**), with both reactions controlled by Cram's rule if the silyl group is taken to be the large substituent.[55] The α-silyl aldehyde **45** in this case was prepared *in situ* from the corresponding epoxide **44**, with the rearrangement **44** → **45** being catalyzed by the Grignard reagent or by magnesium bromide. α-Silyl aldehydes are usually rather unstable to loss of the silyl group, making them awkward starting materials, but they can be prepared from terminal silyl epoxides by treatment with Lewis acids, silica gel,[56] or Pd(0),[57] and isolated easily when the silyl group is hindered. Thus the aldehyde **47** is produced from the α-silyl epoxide **46**, and then used in a Peterson elimination to give the *cis*-alkene **48** (Scheme 11).[58] If the α-silyl epoxide is made enantiomerically enriched, as it can be by rearrangement of the epoxide **49**, the α-silyl aldehyde **50** derived from it can be isolated enantiomerically enriched to the same degree, and attack by methyllithium gives the homochiral alcohol **51** (Scheme 11).[59] Nucleophilic attack by silyl enol ethers on α-silyl aldehydes also follows Cram's rule in the same sense as for organometallic carbon nucleophiles.[60]

Scheme 11



The silyl group of the α-silyl ketone **52** also controls the diastereoselectivity of nucleophilic attack by a carbon nucleophile, as in the reaction **52** → **53**, which similarly follows Cram's rule. Base- and acid-catalyzed reactions now provide stereospecific routes to the trisubstituted alkenes **54** and **55** (Scheme 12).[27,61]

Scheme 12

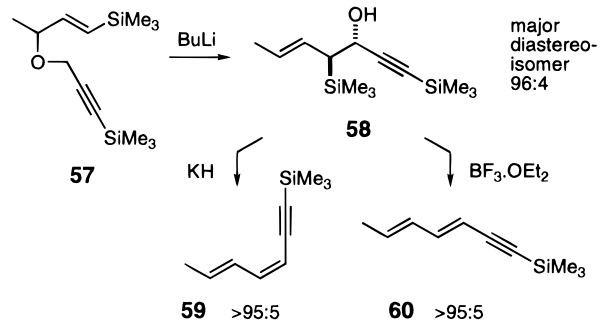


The Felkin–Anh picture **56** accounts for the direction of nucleophilic attack in the formation of the alcohol **53**. The relative importance of steric and electronic factors is a cause for speculation, but it is noteworthy that this picture places the electropositive element *anti* to the incoming nucleophile, whereas the usual idea, introduced by Anh, places the electronegative group in this position. It is not obvious which model is best, but Cieplak's theory argues that an electropositive substituent in this arrangement lowers the energy of the transition state even for nucleophilic attack.[62]

5. Sigmatropic Rearrangements

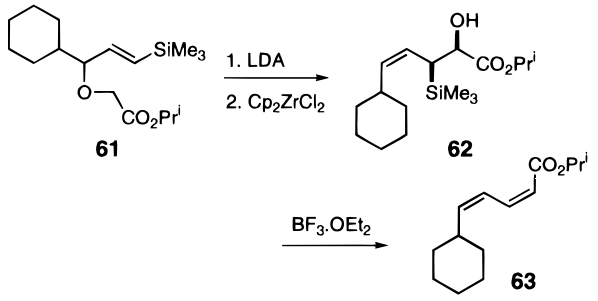
[2,3]-Wittig rearrangement of the allylic ether **57** gives the *anti*-*β*-silyl alcohol **58** with a *trans* double bond, and hence the *trans*,*cis*- and *trans*,*trans*-dienynes **59** and **60** (Scheme 13). A similar sequence was used to make the terminal trienes sarohornene B and C.[63]

Scheme 13



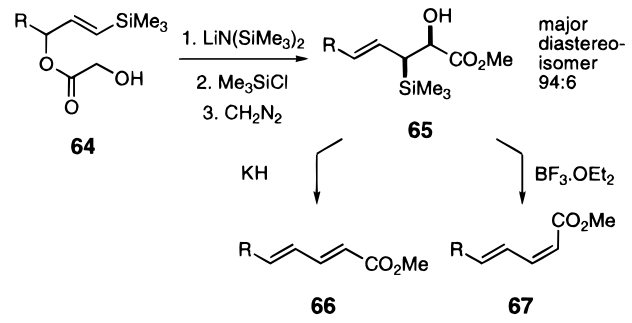
However, a similar zirconium enolate, derived from the ester **61**, selectively gives the *syn* arrangement **62** with a *cis* double bond, providing access to the *cis*,*cis*-diene **63** (Scheme 14).[64]

Scheme 14



[3,3]-Ireland–Claisen rearrangement of the allylic ester **64** also gives a *syn* isomer **65**, but this time with the *trans* double bond, and hence the *trans*,*trans*-**66** and *trans*,*cis*-**67** dienes, in the usual way (Scheme 15).[65]

Scheme 15

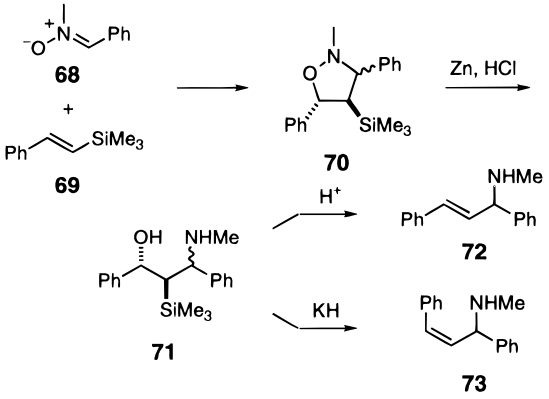


6. Nitrone Cycloaddition to a Vinylsilane

[1,3]-Dipolar cycloaddition of the nitrone **68** to the *trans*-vinylsilane **69** takes place suprafacially, and

reduction of the adduct **70** gives the *anti*-β-silyl alcohol **71**. Acid or base give the *trans*-**72** or *cis*-**73** allylamine (Scheme 16).[66] A similar cycloaddition, but using an allylsilane, and giving a β-silyl alcohol is illustrated in Scheme 48, and another, giving a homoallylamine, in Scheme 212.

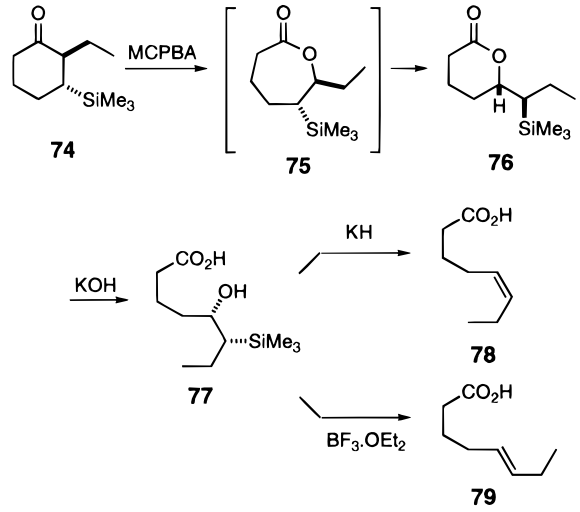
Scheme 16



7. Baeyer–Villiger Reaction of β-Silyl Ketones

The presence of a silyl group at the β-position of a ketone **74** controls the regiochemistry, other things being equal, of a Baeyer−Villiger reaction, making the lactone **75** cleanly the first formed product when there is both a β-silyl group and an α-alkyl group. However, the reaction does not stop here, but rearrangement takes place, to a greater or lesser extent, with inversion of configuration at both centers giving the lactone **76** (Scheme 17). Opening this lactone gives the corresponding hydroxy acid **77**, and elimination from this intermediate gives either the *cis*-alkene **78** or the *trans*-alkene **79**, which were used in syntheses of the *exo*- and *endo*-brevicomins, respectively.[67]

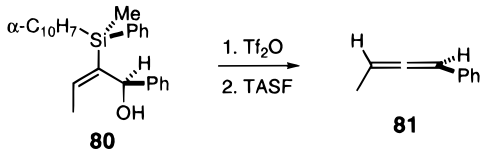
Scheme 17



8. Resolution

In a rather special case, the diastereoisomer **80**, enantiomerically pure at both stereogenic centers, was prepared by separating it from its diastereoisomer epimeric at the carbinol carbon. Stereospecific *anti* elimination then gave the enantiomerically pure allene **81** (Scheme 18).[68]

Scheme 18



9. Epoxidation Opening, Dihydroxylation, and Hydroxylation of Allyl- and Vinylsilanes

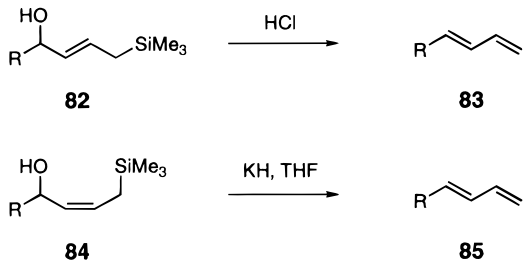
These pathways are discussed in section IX.D and elsewhere. Epoxidation and opening appears in Schemes 52, 224, 228, 236, 258−262, and 268. Osmium tetraoxide reacts cleanly with allyl- and vinylsilanes to give diols in which one of the hydroxyl groups is β to the silicon as in Schemes 50, 51, 226, 230, 264, 265, 268, and 269. The Sharpless asymmetric version is also available for absolute stereocontrol.[69] Hydroboration−oxidation of allylsilanes usually leads to γ-silyl alcohols (section IX.F.3.H), and with vinylsilanes to α-silyl alcohols, but if the substitution pattern is right it can lead to β-silyl alcohols, as in the example in Scheme 55.

The silylsilylation of an allylic alcohol is a complementary procedure discussed in section XVIII.A.3.

B. The Vinylogous Version

The vinylogous reaction is known both in acid-catalyzed **82** → **83**[70] and base-catalyzed **84** → **85** versions,[71] with the latter taking place only when the intervening double bond is *cis*. With terminal dienes, both reactions are stereoselective for the formation largely of the *trans* double bond (Scheme 19).

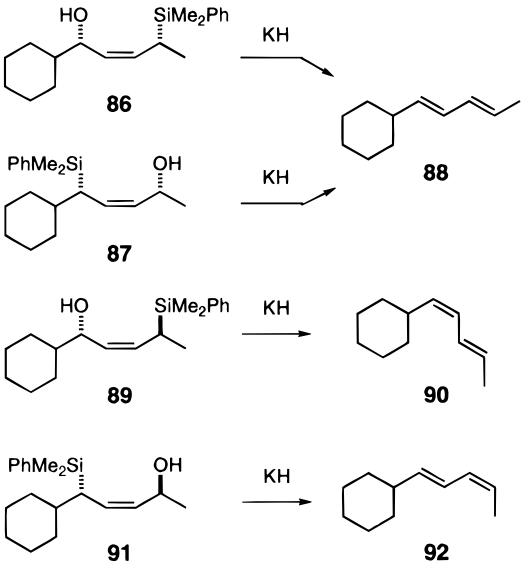
Scheme 19



With internal systems, where both the silyl and the hydroxyl group are on stereogenic centers, the acid-catalyzed reaction, and the fluoride promoted elimination of an acetate, are somewhat, but not usefully stereoselective, generally giving mixtures of stereoisomers.[72] The base-catalyzed reaction, the vinylogous Peterson elimination, which is only possible when the intervening double bond is *cis*, is stereospecifically *syn*, with one pair of diastereoisomers **86** and **87** giving the *trans*,*trans*-diene **88** and the other pair **89** and **91** giving different *cis*,*trans*-dienes **90** and **92**,

with high selectivity for forming the *cis* double-bond adjacent to the carbon atom that originally carried the hydroxyl group, whether that is at the more **89** or the less **91** hindered end (Scheme 20).[73]

Scheme 20

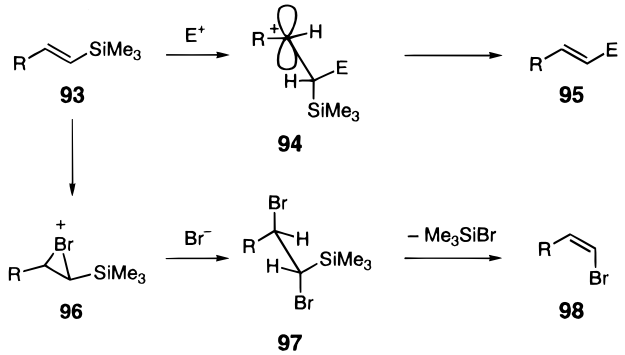


It is quite likely that all the acid-catalyzed eliminations in sections A and B above take place by way of β-silyl carbocations, since even primary β-silylalkyl halides show some of the features of an S_N1 pathway in their solvolysis.[74] If this is so, the well-known hyperconjugative stabilization of the β-silyl cation[75] evidently restricts rotation about the C−C bond well enough for it to maintain its configuration until a nucleophile takes the silyl group off.

C. The Electrophilic Substitution of Vinylsilanes[76]

The same restriction of rotation explains why most vinylsilanes react with electrophiles with retention of configuration **93** → **95**. Attack from above, and rotation about the C−C bond by the shortest path that brings the silyl group into position to stabilize the cation, leads to the cation **94**. The cation largely retains its configuration until the silyl group is removed in the second step **94** → **95** (Scheme 21). The

Scheme 21

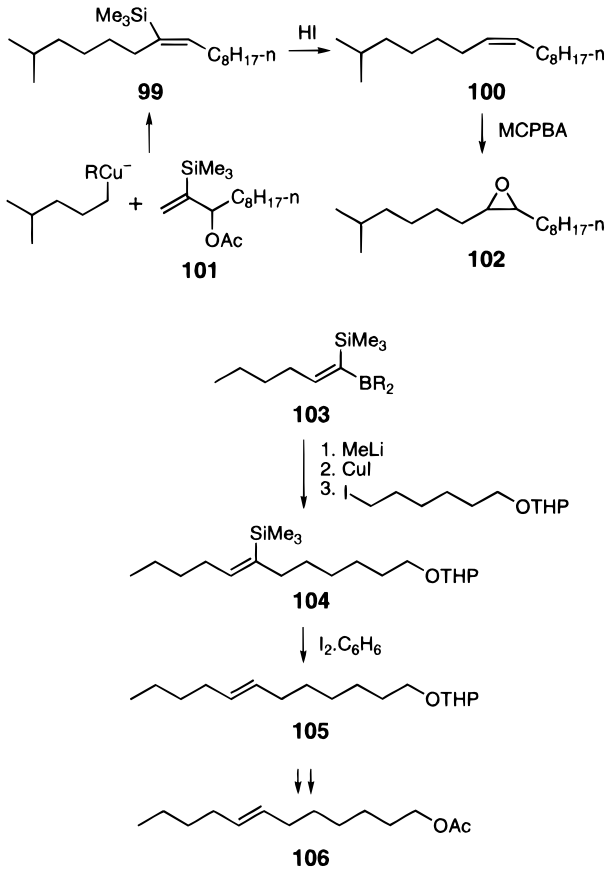


major exception to this pattern is chloro- and bromodesilylation, which usually give inversion of configuration,[77,78] because the intermediate halonium ion **96** opens stereospecifically *anti* to give a dihalide **97**, and elimination **97** → **98** is then stereospecifically *anti* in the usual way[79] (Scheme 21). In either case, the control of double-bond geometry is usually very good, and it has frequently been used in synthesis.

1. Protodesilylation

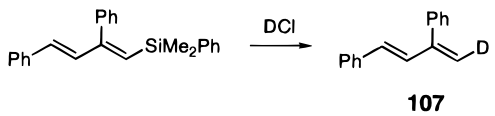
The protodesilylations **99** → **100** and **104** → **105** were used in the syntheses of disparlure (**102**),[80] and the pheromone **106** of the false codling moth (Scheme 22).[81]

Scheme 22



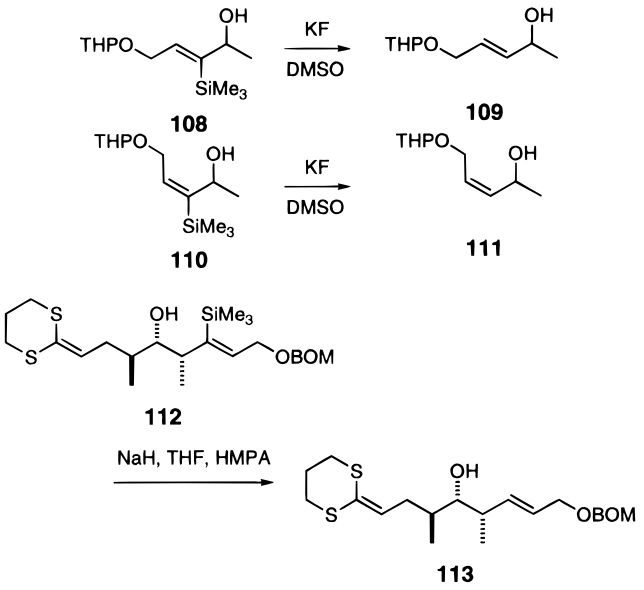
The stereospecificity is maintained even with highly stabilized cations as intermediates, as in the preparation of the deuterated butadiene **107**, used in a mechanistic study of the Diels−Alder reaction (Scheme 23).[82]

Scheme 23



Protodesilylation using base usually requires either anion-stabilizing groups or an allylic or homoallylic hydroxyl group to make the reaction intramolecular. The reaction is nevertheless still stereospecific **108** → **109**, **110** → **111**, and **112** → **113** with retention of configuration (Scheme 24).[83,84] One report of nonstereospecific protodesilylation with base was explained by an addition−elimination mechanism, since

Scheme 24

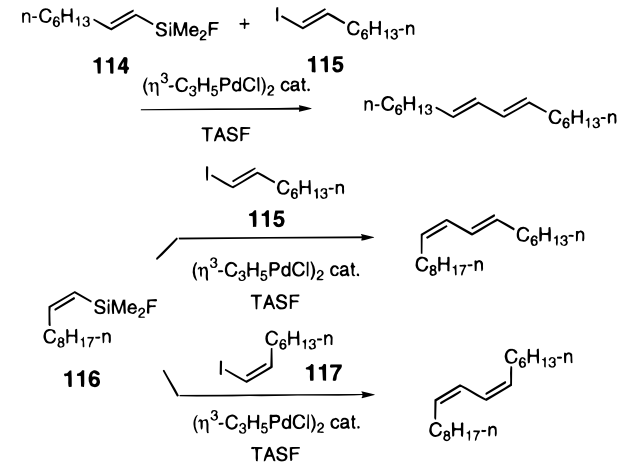


the vinylsilane in question was a 2,4-dienone with the silyl group on C-4.[85]

2. Reaction with Carbon Electrophiles

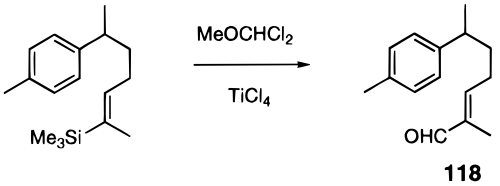
Vinylsilanes, especially if the silyl group carries one or more halogen atoms, typically fluorine, undergo palladium(0)-catalyzed coupling reactions with vinyl and aryl halides, with retention of configuration in the vinylsilanes **114** and **116** and in the vinyl halides **115** and **117** (Scheme 25).[86]

Scheme 25



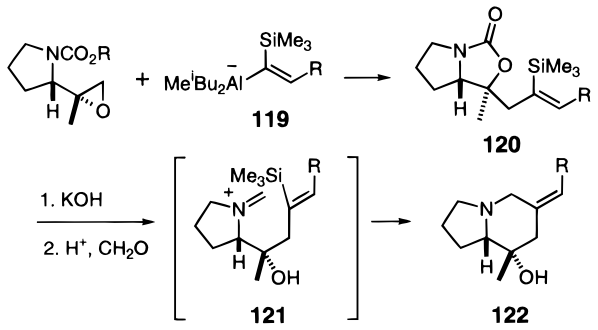
Otherwise, stereocontrolled reactions of vinylsilanes with carbon electrophiles have mostly been used in synthesis in intramolecular versions, although a few intermolecular reactions have been carried out and are known to take place with retention of configuration,[87,88] as in the synthesis of nuciferal **118** (Scheme 26).[89]

Scheme 26



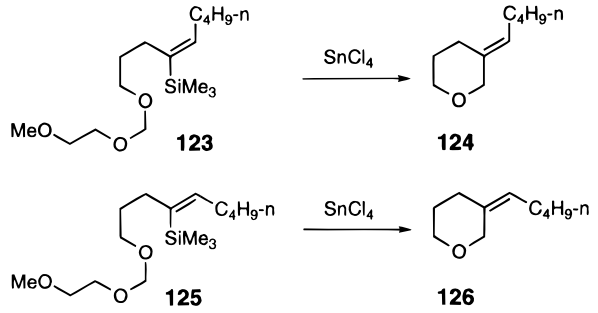
Intramolecular attack of a vinylsilane on an iminium ion **121** was used to control the geometry of the exocyclic double bond in syntheses of several pumiliotoxins **122** (Scheme 27)[90] and of geizzoschizine.[91]

Scheme 27



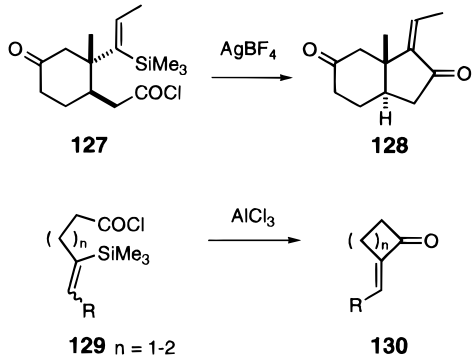
The corresponding reactions of the vinylsilanes **123** and **125** with oxygen in place of nitrogen are also stereospecific giving the exocyclic double bonds in the tetrahydropyrans **124** and **126** (Scheme 28).[92]

Scheme 28



The vinylsilane **127** reacted cleanly with the internal acid chloride group to give a cyclic ketone **128** with complete retention of configuration in the formation of the exocyclic double bond. The product could be equilibrated deliberately to its *E* isomer.[93] However, in another example, the acid chlorides **129** reacted only stereoselectively, with mixtures of stereoisomers **129** giving only the (*E*)-enones **130** (Scheme 29).[94]

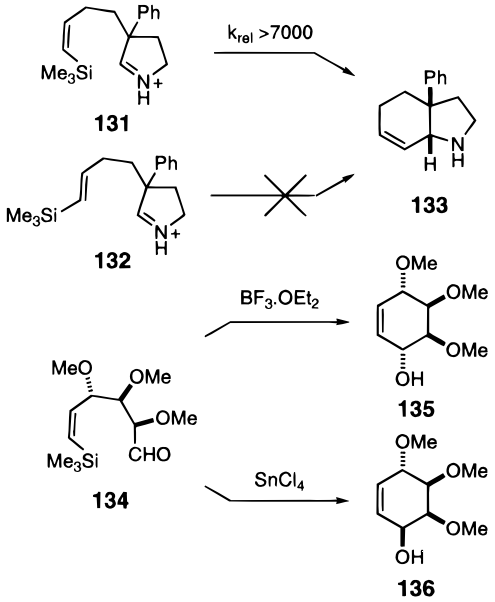
Scheme 29



When the double bond of the vinylsilane unit is endocyclic to the ring being formed, retention of

configuration is only possible with normal ring sizes when the vinylsilane is *cis*, as in the vinylsilanes **131** and **134** (Scheme 30).[95] The stereochemistry is not,

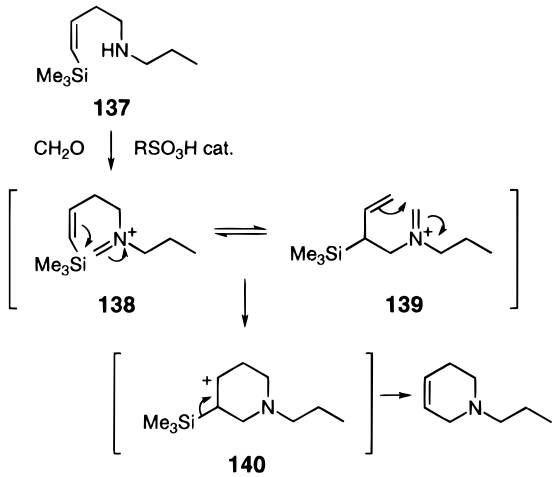
Scheme 30



therefore, necessarily determined by the double-bond geometry, but it affects it. The usual observation, whenever both stereoisomers have been tried,[95−97] is that the *cis*-vinylsilanes **131** react faster and more cleanly than the *trans*-**132**, but cyclization, with the inevitable inversion of configuration, has been seen many times with *trans*-vinylsilanes.[93,98] Sometimes, however, the *trans*-vinylsilane gives an anomalous product while the *cis* isomer is normal,[99] and the wrong geometry in the double bond, even when it is exocyclic, can lead to other anomalies.[100]

In the reactions in Scheme 30, the iminium ion and the carbonyl group are exocyclic to the ring being formed. When both the vinylsilane double bond and the iminium or oxenium ion are endocyclic, the reaction takes place by a different path, and the cyclization of the vinylsilane **137** by way of the intermediate **138** may well actually be the cyclization of an allylsilane **139**, with the allylsilane created by a fast aza-Cope rearrangement **138** → **139** (Scheme 31).[101,102] Whether it is a vinylsilane reacting or the

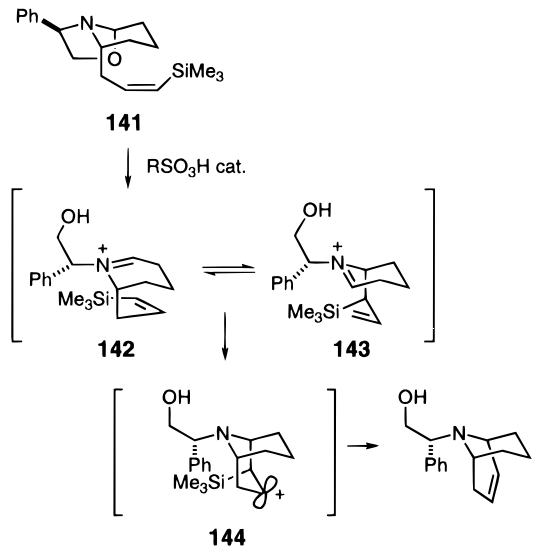
Scheme 31



allylsilane, they both give the same cation **140**. The fast aza-Cope rearrangement removes the distinction between the *cis*- and *trans*-vinylsilanes, because they equilibrate faster than cyclization. In consequence, they both participate equally easily in this reaction, and, as usual, increase the rate of reaction over that seen when there is no silyl group.[101,103] An acyliminium ion has been used similarly in a synthesis of (+)-strepazolin.[104]

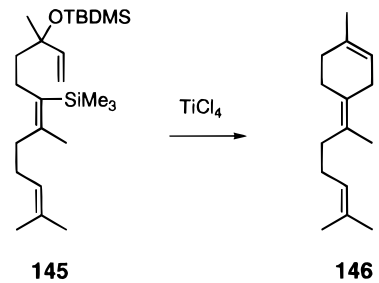
In a more constrained and rigid system derived from the vinylsilane **141**, the aza-Cope rearrangement **142** → **143** does not equilibrate the *cis*- and *trans*-vinylsilanes, because the stereochemical information is preserved in the allylsilane structure. Although the intermediate **142** derived from the *cis*-vinylsilane, and its allylsilane counterpart **143**, both give the same β-silyl cation **144**, and both have the silyl group oriented to stabilize the developing cation, the corresponding species derived from the *trans* vinylsilane would not, because the silyl group would have an equatorial orientation, nearly orthogonal to the empty p orbital of the cation. In consequence, the *cis*-vinylsilane **141** cleanly underwent cyclization, and the *trans* isomer did not (Scheme 32).[105]

Scheme 32



In one example, a tetrasubstituted double bond has been set up exocyclic to a six-membered ring in the synthesis of (*E*)-γ-bisabolene **146** from the *E* vinylsilane **145** (Scheme 33). The stereoisomer, (*Z*)-γ-bisabolene, had to be made by a different route, because the corresponding (*Z*)-vinylsilanes were not available.[106]

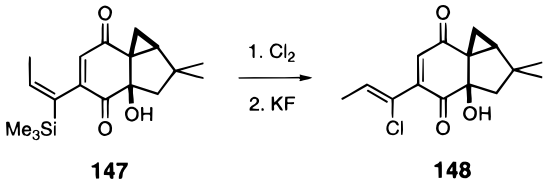
Scheme 33



3. Halodesilylation

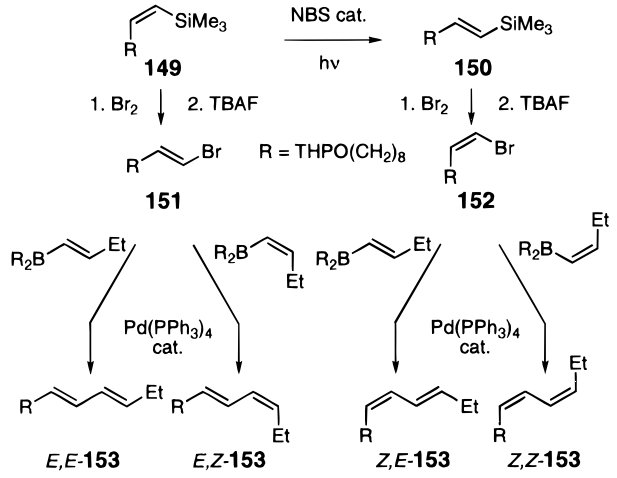
Chlorodesilylation takes place usually with inversion of configuration, and the second step normally needs to be encouraged by adding fluoride ion to the addition product.[107] It has been used as the final step in a synthesis of mycorrhizin A (**148**) from the vinylsilane **147** (Scheme 34)[108] and some related natural products.[85,109]

Scheme 34



Bromodesilylation has been used several times in synthesis,[78,110,111] especially as a prelude to transition metal-catalyzed coupling. Thus the *cis*-vinylsilane **149** gave the *trans*-vinyl bromide **151**. The same vinylsilane was equilibrated using NBS and light[112] to the *trans*-vinylsilane **150**, which similarly gave the *cis*-vinyl bromide **152**. The two bromides were then used in the synthesis of all four possible pheromone dienes **153** using Suzuki coupling (Scheme 35).[113]

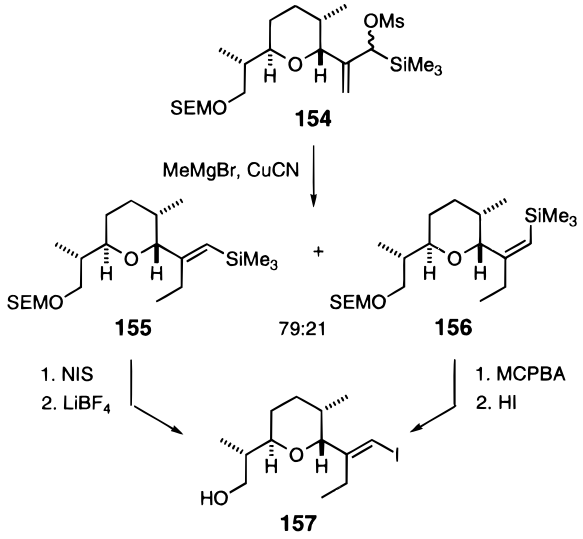
Scheme 35



In some cases, bromodesilylation takes place with retention of configuration, either because the intermediate cation is so well stabilized that *syn* addition of bromine takes place, as with styrenes[114] and *β*,*β*-disubstituted vinylsilanes[24] or because of *syn* elimination of the silyl bromide.[107,115]

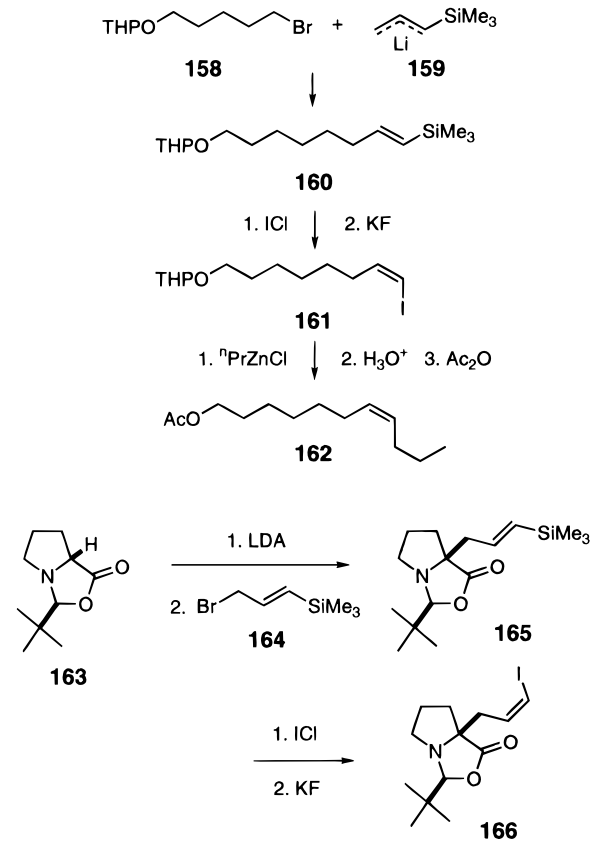
The stereochemistry of iododesilylation is dependent upon the iodinating agent and on the substitution pattern. Retention is normal when the vinylsilane is *β*,*β*-disubstituted,[24] where it has been used in syntheses both of rapamycin[116] and of indanomycin (Scheme 36),[117] the latter of which is notable for allowing convergence on the (*E*)-iodide **157** achieved by iododesilylation of the major (*E*)-vinylsilane **155** with retention of configuration, and by hydrogen iodide-opening of the corresponding epoxide of the minor (*Z*)-vinylsilane **156** with inversion of configuration, as discussed in section II.A.1.

Scheme 36



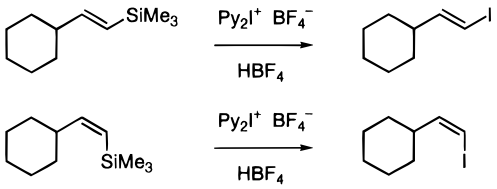
On the other hand, terminal vinylsilanes give mainly inversion of configuration, especially when iodine chloride is used to encourage the addition−elimination pathway, as in the synthesis of the pheromone of the oriental fruit moth **162** by way of the iododesilylation **160** → **161**,[118] and in the synthesis of cephalotaxine by way of the iododesilylation **165** → **166** (Scheme 37).[119]

Scheme 37



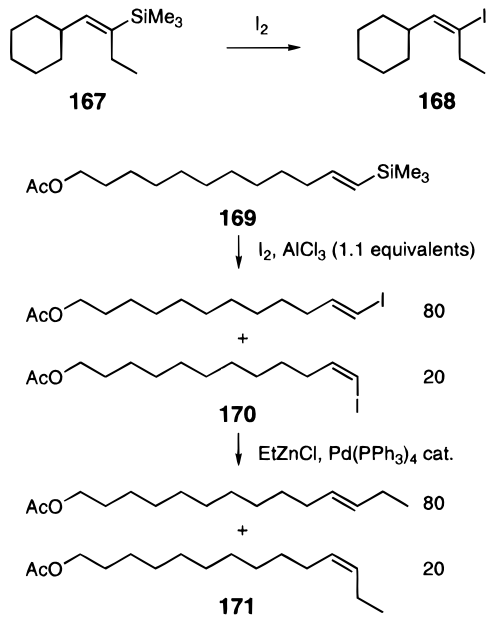
In contrast, retention of configuration can be made cleanly the major outcome with terminal vinylsilanes by using *N*,*N*-dipyridyliodonium tetrafluoroborate as the iodinating agent (Scheme 38).[120]

Scheme 38



Iododesilylation with iodine itself, however, is not as stereochemically reliable as with the other reagents, nor is it as reliable as bromodesilylation with bromine. Retention of configuration is quite common, especially with internal vinylsilanes **167** → **168** (Scheme 39), but inversion is the major

Scheme 39



pathway with terminal vinylsilanes.[87,121] By including Lewis acids in the mixture, retention of configuration can be made more favorable for terminal vinylsilanes. The apparently unpromising formation of mixtures of stereoisomers has been turned to advantage: by adjusting the amount of Lewis acid, it is possible to tailor the proportions of stereoisomers to match the natural proportion found with some pheromones. The natural 80:20 mixture of the pheromone **171** of the oak leaf roller moth was prepared in this way from the 80:20 mixture of iodides **170** produced by iodination of the *trans*-vinylsilane **169** using just the right amount of aluminum chloride (Scheme 39).[122]

4. Stereoselective Synthesis of Vinylsilanes

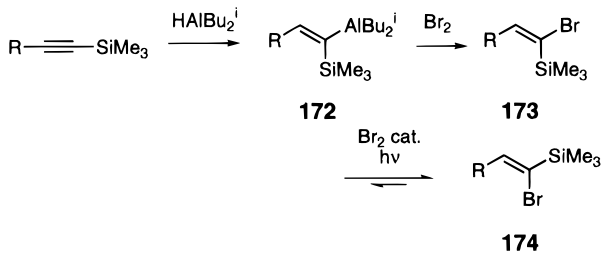
All these reactions require that the vinylsilane geometry be controlled in the first place;[123] fortunately this proves to be readily achieved by a variety of methods, many of which are illustrated in the schemes above.

Thus the addition of organometallic carbon nucleophiles to silylated allylic alcohol derivatives usually gives the (*E*)-vinylsilane as the major product, as in the conversion of the allylic acetate **101** into the vinylsilane **99** (Scheme 22), and of the allylic mesylate **154** into the mixture of vinylsilanes **155** and **156** (Scheme 36). Attaching an unsaturated three-carbon unit carrying a terminal silyl group to an organic residue is a good route to terminal vinylsilanes, as in the alkylation of the silylated allyl anion **159** by an alkyl halide to give the (*E*)-vinylsilane **160** (Scheme 37) (and the vinylsilane **169** was made similarly), and, in an umpolung version, the alkylation of the enolate of the ester **163** by the silylated (*E*)-allyl bromide **164** (Scheme 37).

Hydrogenation of an ethynylsilane, or alternatively hydroalumination−protodealumination, or hydroboration−protodeboronation, give terminal (*Z*)-vinylsilanes. This method was used in the synthesis of the vinylsilanes **131**, **134** (Scheme 30), and **149** (Scheme 35). Equilibration can then be used to make the corresponding (*E*)-vinylsilanes, as in the synthesis of the vinylsilane **150** (Scheme 35). Hydroboration or hydroalumination of ethynylsilanes can be used to prepare internal vinylsilanes. Thus hydroboration to make the vinylborane **103**, followed by metallation to give the boronate, and copper-catalyzed coupling, was used in the synthesis of the vinylsilane **104** (Scheme 22). Similarly, but more popular, hydroalumination and metalation gave the vinylaluminate **119**, which was used directly as a carbon nucleophile in the synthesis of the vinylsilanes **120** (Scheme 26).

Hydroalumination can be controlled to be *syn* or *anti* stereospecific by the inclusion of Lewis bases or not.[124] The intermediate vinylaluminum reagents **172** can be used to prepare the corresponding (*E*)-vinyl bromides **173** by stereospecific bromodealumination.[77,125] (*E*)-Vinyl bromides can be equilibrated to give largely (*Z*)-vinyl bromides **174** using bromine and light (Scheme 40). The bromine in either the (*Z*)-

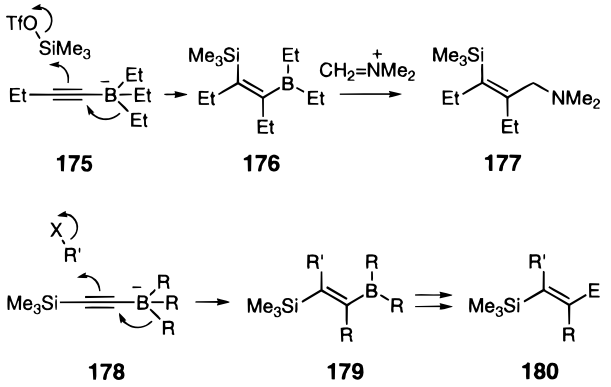
Scheme 40



or the (*E*)-vinyl bromide can then be used as a source of vinyllithium reagents for coupling to carbon electrophiles, as in the synthesis of the vinylsilanes **123** and **127**, respectively, and of the vinylsilanes in Scheme 24. There is some risk of loss of stereochemistry in this step unless appropriate care is taken.[125]

Acetylenes can be used in a different way, starting with ethynylboronates. Trimethylsilyl triflate attacking at the β-position sets off a rearrangement **175** of one of the boronate substituents to the α-carbon atom.[126] The vinylborane **176** can then be used to introduce another carbon substituent **177** (Scheme 41). This route was used in the synthesis of the trisubstituted vinylsilane **145** (Scheme 33). A variant on this theme uses a carbon electrophile, R′X, to set off the rearrangement **178**, and this can be followed either by protodeboronation of the borane

Scheme 41



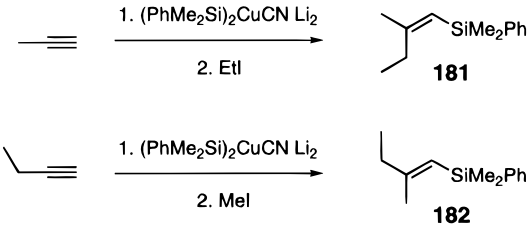
175 **176** **177**

178 **179** **180**

179 to give a disubstituted vinylsilane **180** (E = H), or by a further rearrangement, set off by treatment with iodine, to give a trisubstituted vinylsilane **180** (E = R).[127]

Other stereoselective methods of making vinylsilanes not illustrated in the sequences above include the stereospecifically *syn*-silylcupration of acetylenes, which can be followed by protonation of the vinylcuprate intermediate or by its reactions with carbon electrophiles,[128] which was used in the synthesis of two of the vinylsilanes **181** and **182** used in Scheme 3 (Scheme 42).

Scheme 42

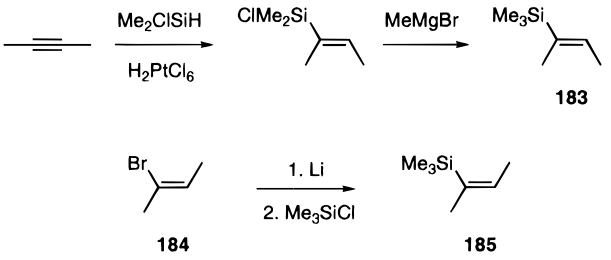


181

182

Hydrosilylation[129] of acetylenes is usually *syn* stereospecific, and, like silylcupration and protonation, provides easy access to *trans* terminal vinylsilanes like that used in Scheme 25, and to (*E*)-2-butenylsilanes **183**. The corresponding (*Z*)-vinylsilane **185** is available by silylation of the (*Z*)-vinyl lithium reagent derived from the vinyl bromide **184** (Scheme 43).[130]

Scheme 43



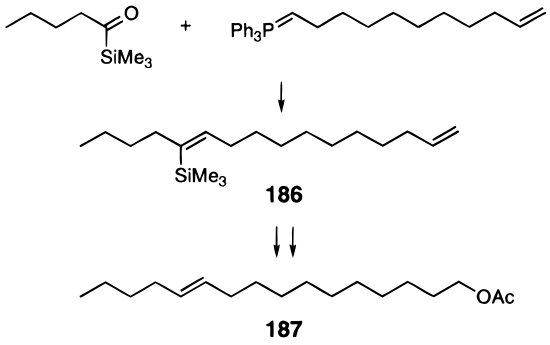
183

184 **185**

Terminal vinylsilanes are also available by changing the catalyst for hydrosilylation to one that is *anti* selective.[131]

Wittig reaction between a salt free ylide and an acylsilane is highly selective for the formation of the (*Z*)-vinylsilane **186** and was used in a synthesis of the pheromone **187** using protodesilylation (Scheme 44).[132]

Scheme 44



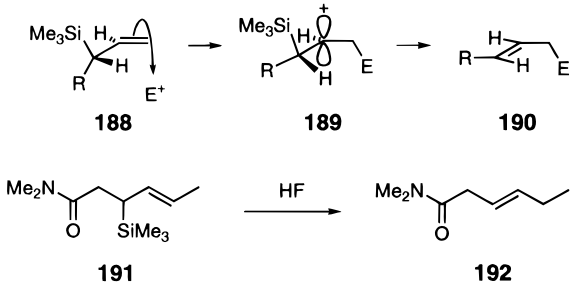
186

187

D. Electrophilic Attack on Allylsilanes

In the reactions of electrophiles with allylsilanes, some of which are known to take place by way of cationic intermediates,[133] the double bond produced, when it is 1,2-disubstituted, is usually *trans*. Other things being equal, the electrophile attacks the allylsilane in a conformation close to its most stable conformation, approximated by the structure **188**, which is described as having the hydrogen atom on the stereogenic center "inside", in other words eclipsing or partly eclipsing the double bond. The diastereoselectivity of this attack is covered in section VI.E, but for now the important point is that the intermediate cation **189** retains its configuration because of the hyperconjugative overlap of the Si−C bond with the empty p orbital, and the double bond produced by loss of the silyl group **190** is therefore largely *trans*, as in the protodesilylation of the allylsilane **191**, which gives the alkene **192** with a *trans*,*cis* ratio of 94:6 (Scheme 45).[134]

Scheme 45

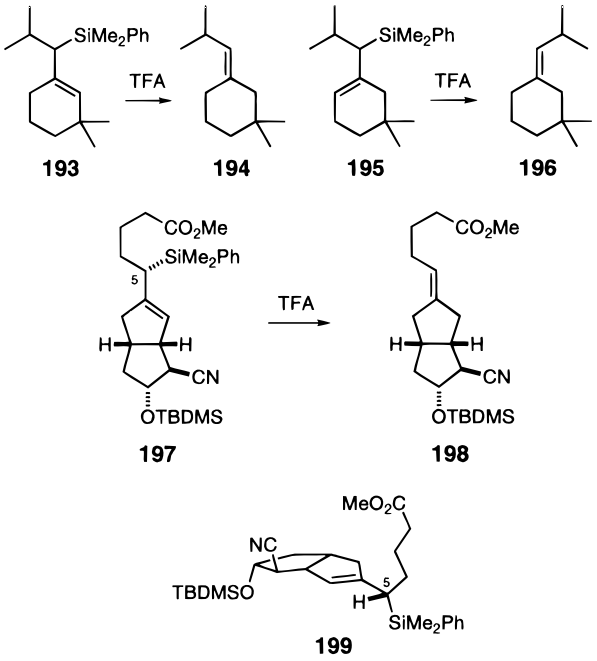


188 **189** **190**

191 **192**

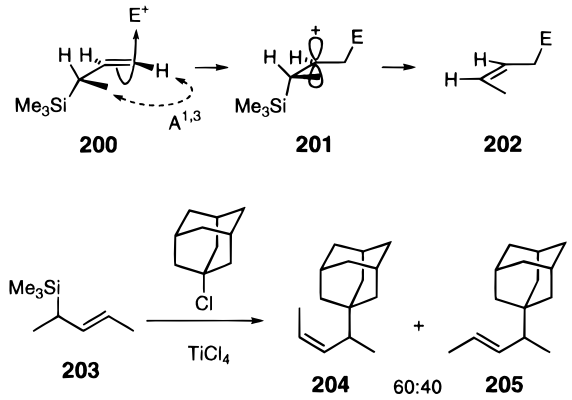
Protodesilylation of allylsilanes has been used to control exocyclic double-bond geometry. The allylsilane **193** gave largely (91:9) the (*E*)-alkene **194**, and its regioisomer **195** gave largely (92:8) the (*Z*)-alkene **196** (Scheme 46).[135] This device was used to control the exocyclic double-bond geometry to better than 96:4 in a synthesis of a carbacyclin **198** by protodesilylation of the allylsilane **197** (Scheme 46). The relative configuration at C-5 in the allylsilane **197** was important, because the conformation **199** matched the preference for *exo* attack on the bicyclic system with attack *anti* to the silyl group in the conformation with the hydrogen atom on the inside. The diastereoisomer at C-5, where the two stereochemical constraints are in opposition, still gave more of the exocyclic double-bond geometry of the carbacyclin **198**, but less selectively (67:33).[136]

Scheme 46



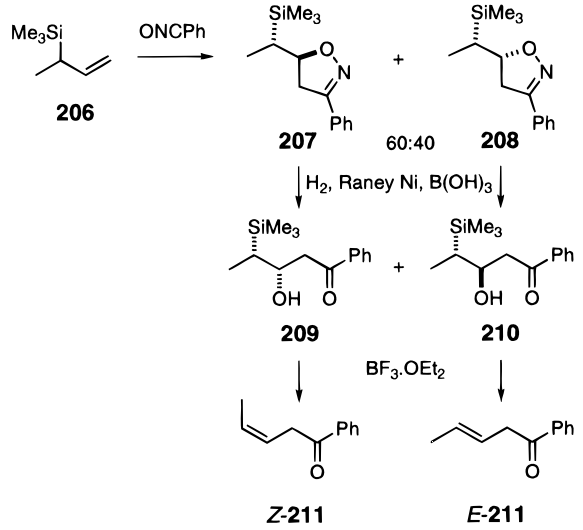
The exception to the pattern of reaction in a conformation close to **188** is when the carbon substituent on the stereogenic center is a small group like methyl and when the allylsilane has, at the same time, only a hydrogen atom *cis* to the stereogenic center. In this situation, the alternative conformation **200** with the methyl group "inside", is populated, because the $A^{1,3}$ interaction[137] between the methyl group and the vinyl hydrogen is not particularly severe. The intermediate cation **201** again retains its configuration (but see below), and the product **202** with a *cis* double bond can be formed to a substantial, but rather unpredictable, extent. In the S_E2' reaction **203** → **204** + **205**, the *cis* isomer **204** is actually the major product (Scheme 47), although it is not entirely clear why the conformation **200** should be more reactive than the conformation **188**.[138]

Scheme 47



This feature also explains the poor stereoselectivity in the nitrile oxide dipolar cycloaddition in Scheme 48, where the major product **207** corresponds to attack on the upper surface of the conformation **200**, and the minor product **208** corresponds to attack on the lower surface of the conformation **188**. Thus the stereochemistry of the double bonds in the alkenes **211** can only be controlled if the adducts **207** and **208**, or their reduction products **209** and **210**, can be

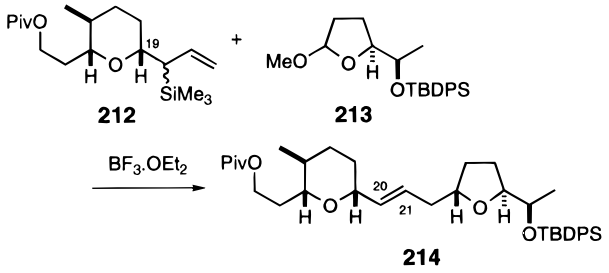
Scheme 48



separated.[139] The stereoselectivity is improved to 88:12 when a (*tert*-butyldimethylsilyl)oxy group is present on the stereogenic center in place of the methyl group, presumably because the electronegative oxygen adopts the inside position making the alkene more reactive than when the C−O bond is conjugated to the double bond.[140]

In contrast, the allylsilane **212**, with a much larger group than methyl on the stereogenic center, reacts with the acetal **213** to give only the product **214** with a *trans* double bond between C-20 and C-21, implying that it reacted largely in the conformation **188** (Scheme 49).[141]

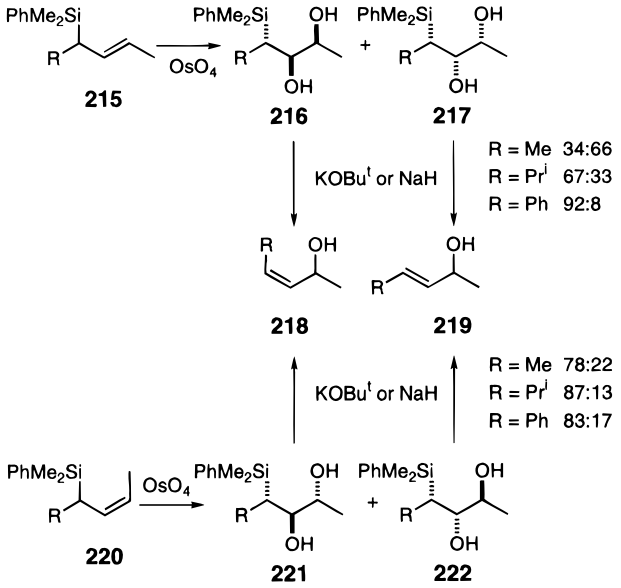
Scheme 49



The same problem arises with osmium tetraoxide reactions on allylsilanes having a methyl group on the stereogenic center, where the major adduct **217** (R = Me) with osmium tetraoxide corresponds to attack in the sense **200** and the minor **216** (R = Me) in the sense **188**. This stereochemistry is revealed by the *syn* stereospecific Peterson elimination giving the *trans*-alkene **219** from the major product and the *cis* **218** from the minor (Scheme 50).[142] However, when the substituent R on the stereogenic center is larger than methyl, the major adduct is **216** and the alkene derived from it **218** is *cis*.[143] Presumably, the $A^{1,3}$ interaction is now worse than it was with just a methyl group, and attack takes place in the conformation and sense **188**. Similarly, the protodesilylations of the allylsilanes **193** and **195** in Scheme 46 are stereoselective in the control of the double-bond geometry only when the substituent on the stereogenic center is a large group like isopropyl. When the substituent is only a methyl group the selectivity for the exocyclic double-bond geometry is much

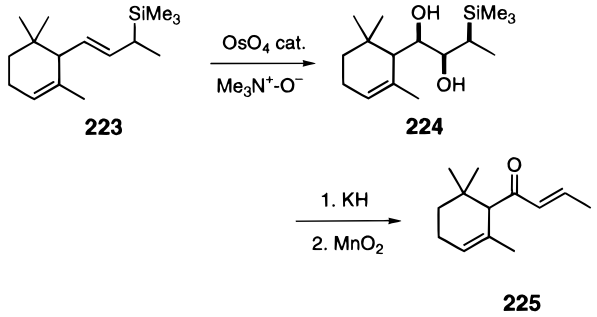
less.[135] Changing the double bond in the starting material from *trans* to *cis* has the same effect, and for the same reason (Scheme 50).[116,142,143] The diol **221** is the major product from the *cis*-allylsilane **220**, and hence the *cis*-alkene **218** is the major alkene derived from it, even when R is a methyl group. Although only the Peterson elimination is illustrated, any of the intermediate β-silyl alcohols **216**, **217**, **221**, or **222** could be converted in the usual way into either alkene **218** or **219**, as discussed in section II.A.

Scheme 50



The selectivity for attack in what is usually the less favorable sense was used to set up the *trans* double bond in a synthesis of α-damascone. The *trans*-allylsilane **223**, which has only a methyl group on the stereogenic center, apparently gave a single diol **224** and hence the *trans*-alkene **225** (Scheme 51).[144]

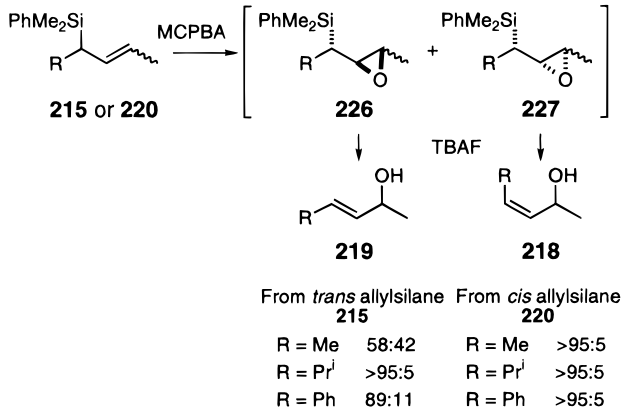
Scheme 51



Epoxidation is somewhat more selective in the general sense **188** than dihydroxylation with osmium tetraoxide. With epoxides there is no option of using the Peterson elimination, because allylsilane epoxides like **226** and **227** are usually unstable to isolation or manipulation, undergoing *anti* stereospecific desilylative elimination directly to the (*E*)- and (*Z*)-alkenes **219** and **218**, respectively. The former can now be prepared with high overall stereoselectivity, especially when the group R is large and/or the double bond in the starting material is *cis* (Scheme 52).[116,142,143]

However, intramolecular delivery of the epoxidising reagent from a hydroxyl group, as with the alcohols **228** and **232**, gave epoxides **230** and **234** with

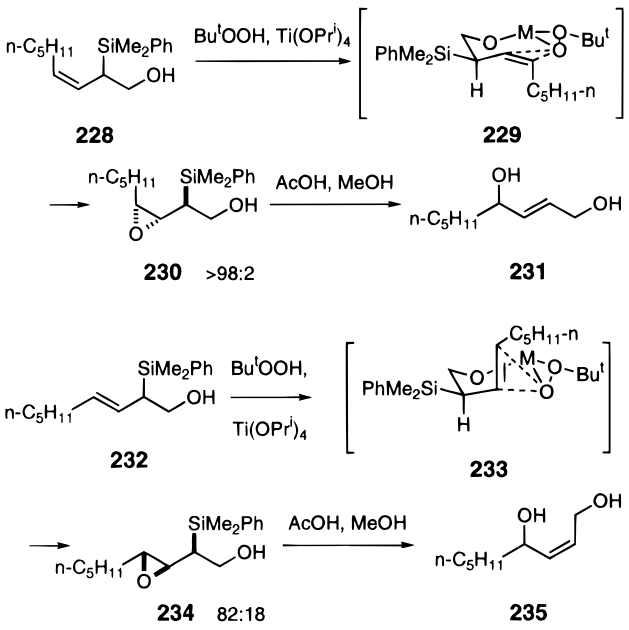
Scheme 52



From *trans* allylsilane **215**		From *cis* allylsilane **220**	
R = Me	58:42	R = Me	>95:5
R = Pri	>95:5	R = Pri	>95:5
R = Ph	89:11	R = Ph	>95:5

opposite selectivity, the former in a cyclic version **229** of conformation **188**, as usual with allylsilanes having a *cis* double bond, and the latter in a cyclic version **233** of conformation **200**, but with unusually high selectivity in this sense. Both epoxides **230** and **234** undergo elimination stereospecifically *anti*, the former to give the *trans* alkene **231** and the latter to give the *cis*-alkene **235** (Scheme 53).[145]

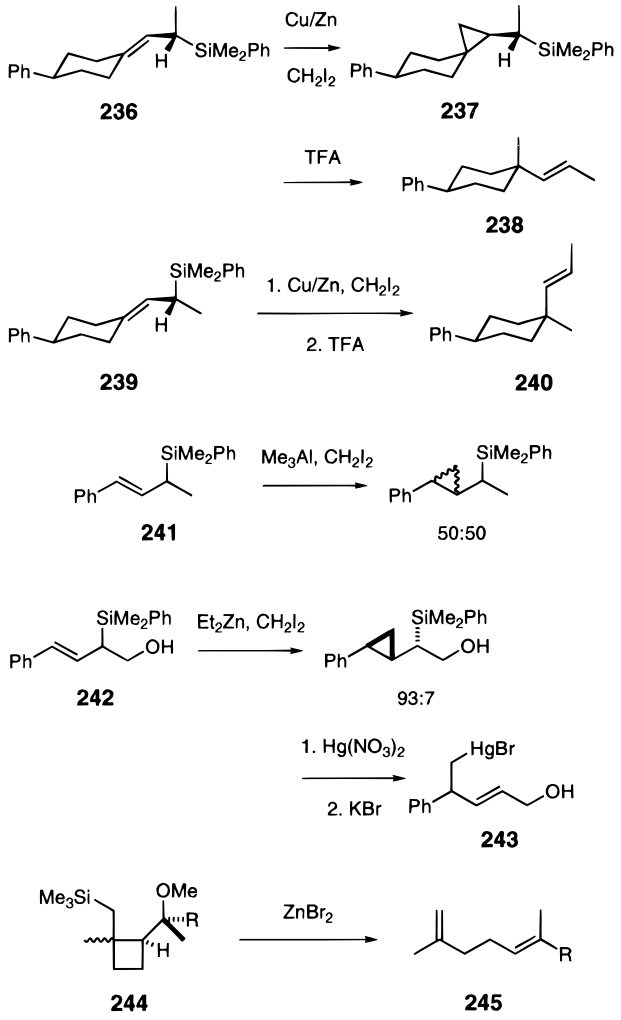
Scheme 53



Simmons−Smith and other methylenation reactions show very similar stereoselectivity to epoxidation, as in the reaction with the allylsilanes **236** and **239**, but the electrophile-induced opening of the cyclopropylmethylsilanes, to give the *trans*-alkene products overall of methylation **238** and **240**, is not always as straightforward as it is with protons (Scheme 54).[143,146] This example works well because the ring residue is *cis* to the stereogenic center more or less fixing the conformation in the sense **188**. Other reactions of this type work with allylsilanes having *cis* double bonds for the same reason, but allylsilanes with a *trans* double bond, like **241**, are not well controlled in Simmons−Smith reactions.[143] However, internal delivery of the reagent in a homoallylic alcohol can give high stereoselectivity in favor of the *anti* product, not only when the double bond is *cis*, as usual, but also with a *trans* double bond, as in the allylsilane **242**. A further advance is

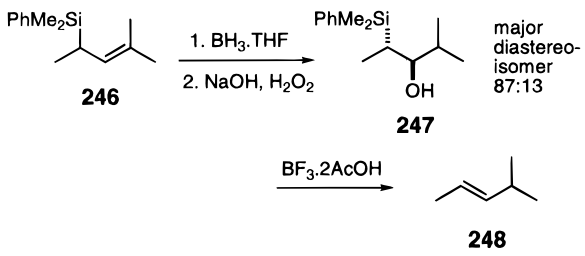
the discovery that mercuration is a clean method for selectively opening the cyclopropane ring toward the less-substituted carbon creating a functionalized methyl group **243** and a *trans* double bond (Scheme 54).[147] The opening of a cyclobutane **244** gave selectively a *trans* double bond **245** as a result of an *anti* fragmentation,[148] whereas the corresponding fragmentation opening a cyclopropane was not stereospecific.[149]

Scheme 54



Hydroboration of allylsilanes usually leads to the boron attaching itself to C-3, and hence, after oxidation to the formation of γ-silyl alcohols (see section IX.F.3.H, Scheme 274). If the substitution pattern is appropriate, however, as with the β,β-disubstituted allylsilane **246**, the major product after oxidation of the borane is the β-silyl alcohol **247**, as a result of attack by the hydroborating agent in the stereochemical sense **188**. Under acidic conditions, this alcohol specifically gives the *trans*-alkene **248** (Scheme 55).[150]

Scheme 55



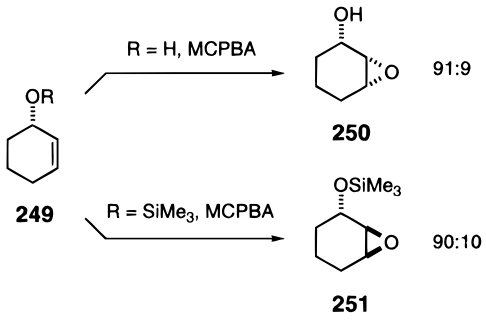
III. A Silyl Group as a Bulky but Removable Group

A silyl group can be used to control two- and three-dimensional stereochemistry, without directly taking part in the chemistry, when it either bulks up part of a molecule during the stereochemistry-determining step or imparts a stereochemistry that would not exist without it. In this application, one of its major virtues is the ease with which it can be replaced by a proton after it has done its job.

A. A Silyl Group on Oxygen or Nitrogen

A silyl group can be used to protect an alcohol group and thus prevent it from hydrogen bonding. This can have stereochemical consequences, as in the epoxidation of allylic alcohols. Thus the free alcohol **249** (R = H) directs the peracid to the *syn* face of the double bond to give largely the epoxide **250**, whereas the silyl group in the silyl ether **249** (R = $SiMe_3$) shields the *syn* face and epoxidation takes place *anti* to give largely the epoxide **251** (Scheme 56).[151]

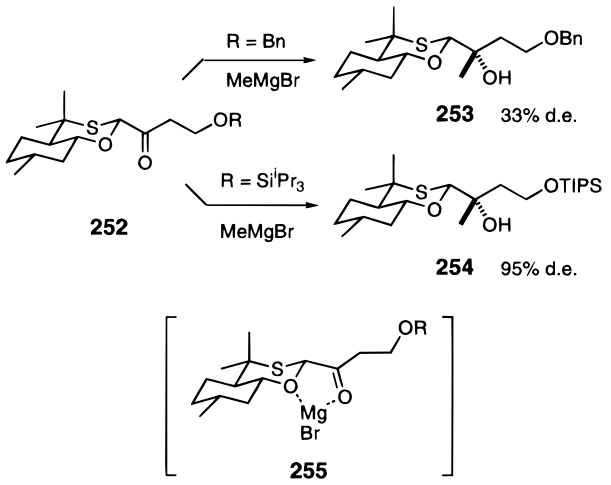
Scheme 56



If the silyl group in a silyl ether is large enough, it can also reduce the capacity of the oxygen atom as a Lewis base. Thus the ketone group in the benzyl ether **252** (R = Bn) is attacked by nucleophiles to give a mixture of diastereoisomeric alcohols only moderately rich in the isomer **253**, because the side chain oxygen function competes with the acetal group for the Lewis acid. Even a trityl group is unable to suppress Lewis salt formation completely. However, with the triisopropylsilyl ether **252** (R = $SiPr^i_3$), the silyl group electronically and sterically protects the side chain oxygen from coordination, and the major product **254** is formed in high diastereoisomeric excess in a reaction controlled by chelation by the magnesium ion between the ketone group and the acetal group **255** (Scheme 57). The product **254** was used in a synthesis of (*S*)-(+)-mevalonolactone.[152]

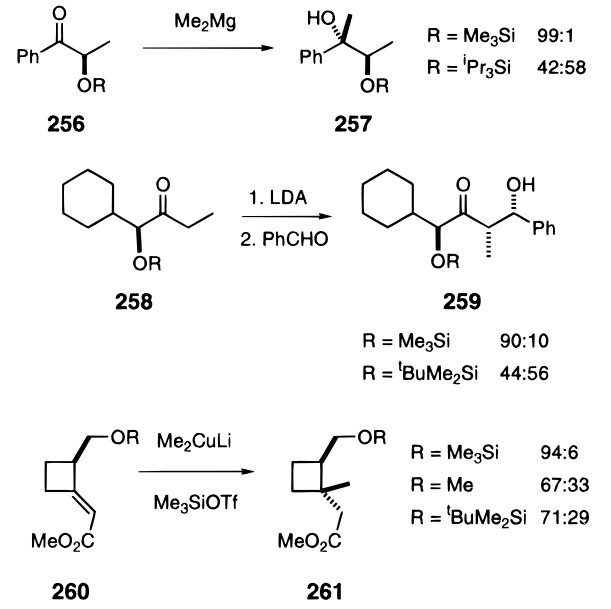
Similarly, the α-silyloxy ketone **256** reacted with dimethylmagnesium with high stereoselectivity in favor of the chelation-controlled adduct **257** when the silyl group was trimethylsilyl, but with little diastereoselectivity when the silyl group was triisopropylsilyl, which limits chelation (Scheme 58).[153] Likewise, the lithium enolate of the α-silyloxy ketone **258** undergoes aldol condensation with benzaldehyde with high selectivity in favor of one diastereoisomer **259** when the silyl group is trimethylsilyl, indicating good chelation control, but with poor selectivity with the bulkier *tert*-butyldimethylsilyl group (Scheme

Scheme 57



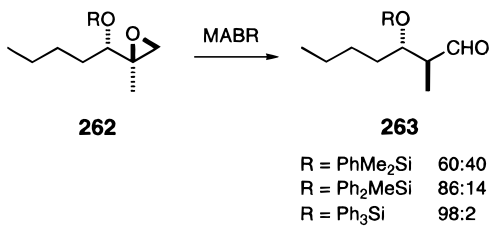
58).[154] A trimethylsilyloxy group influences a conjugate addition reaction by the dimethylcuprate reagent, where the unsaturated ester **260** with a trimethylsilyloxy group delivers the nucleophile *syn* to give the ester **261**, but neither a methoxy nor a larger silyloxy group is as effective (Scheme 58).[155]

Scheme 58



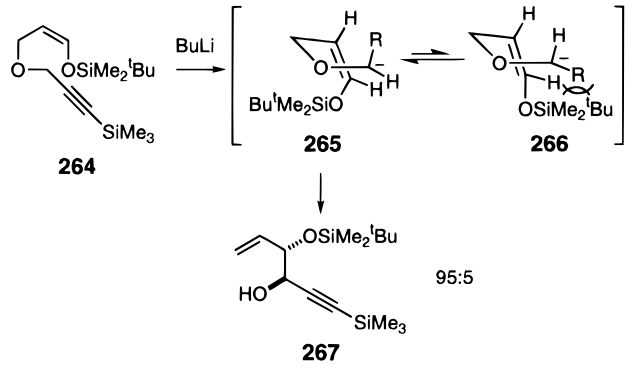
There also appears to be an electronic effect of silyl substituents. Thus in the Lewis acid-catalyzed rearrangement of the *erythro* epoxy ether **262** giving the *β*-silyloxy aldehyde **263**, the stereoselectivity in favor of the *anti* isomer increases with the electronegativity of the silyl substituents (Scheme 59).[156] There is another example of a silyl group on oxygen preventing it from chelating to a Lewis acid in Scheme 399. On the other hand, even the hindered (*tert*-butyldimethylsilyl)oxy group does not lose its capacity to coordinate to Lewis acids, and such coordination is critically important in controlling the stereochemistry of some intramolecular carbenoid insertions into a double bond.[157]

Scheme 59



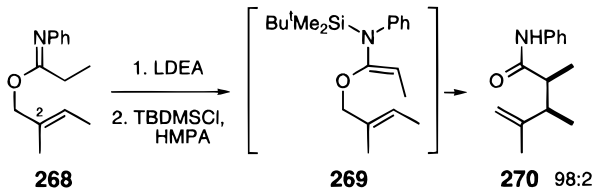
In a [2,3]-Wittig rearrangement the presence of the silyloxy group on the double bond of the ether **264** leads to the formation of the *anti* diastereoisomer **267** with high selectivity. The bulk of the silyloxy group makes a transition structure close to the conformation **265** lower in energy because it avoids the steric constraint in the alternative conformation **266**. In the absence of the silyloxy group the major product is *syn* (Scheme 60).[158]

Scheme 60



The Claisen rearrangement of the *N*-silyl enamine **269** proves to be diastereoselective leading to the *anti* *γ*,*δ*-unsaturated amide **270**. The diastereoselectivity is higher and opposite in sense to the corresponding rearrangement of the non-silylated enamine. These results are compatible with a predominant *Z* configuration in the *N*-silyl enamine **269**, presumably made more favorable by the presence of a large substituent on nitrogen, undergoing rearrangement in a chair conformation (Scheme 61).[159]

Scheme 61



Silylated homochiral amines give better stereoselectivity in conjugate addition reactions of their anions to α,*β*-unsaturated esters than the corresponding anions without the silyl group.[160]

B. A Silyl Group on Carbon

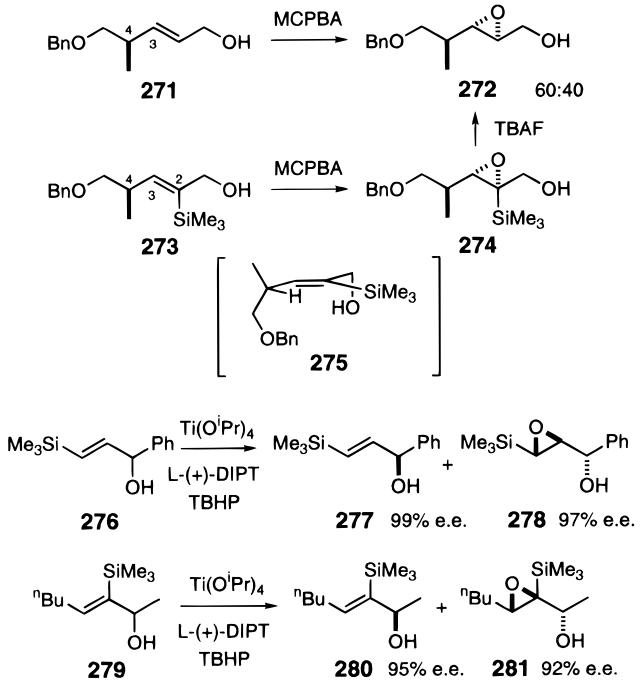
Silyl groups have been attached to the 3 and 3′ positions in chiral auxiliaries and catalysts of the binaphthyl type to provide space-filling bulk and to buttress the active coordinating functions at the 2 and 2′ positions. Such catalysts have been used in Wittig rearrangements,[161] hetero-Diels−Alder reactions,[162] and Claisen rearrangements.[163] In these reactions the silyl group is on the catalyst, and it is not important to be able to remove it or use it in any other way.

In stoichiometric reactions, however, the silyl group is in the product and its further chemistry does

matter. When it is attached to oxygen or nitrogen, it can, of course, be removed easily, but removal of a silyl group from a carbon framework is less easy. It is however not too difficult using such reactions as acid-catalyzed protodesilylation of vinylsilanes, or nucleophile-catalyzed protodesilylation, with alkoxide or fluoride, when the carbanion produced is relatively well stabilized, as with vinylsilanes and epoxysilanes, or by Brook rearrangements. Such reactions are also stereospecific, with the anionic intermediate, whatever its nature, retaining its configuration at carbon and leading to retention of configuration in protodesilylation. The major limitation is that protons are often the only reliable electrophiles. However, this type of reaction is a powerful device in synthesis, because one can build a silyl group into a structure, allow it, by virtue of its size, to modify the stereochemistry of reactions in its vicinity, and then remove it at the end of the sequence of reactions.

Thus, in the absence of a silyl group, the epoxidation of the allylic alcohol **271** gave the diastereoisomer **272** with little selectivity (60:40) in its favor, because the conformation about the bond between C-3 and C-4 is not well controlled. In contrast, a trimethylsilyl group on C-2 in the allylic alcohol **273** fixes the conformation about this bond as **275**, in which the hydrogen atom on the stereogenic center is inside, and both the hydroxy and the benzyloxy groups help to deliver the reagent to the lower surface. As a result, epoxidation gives only the epoxide **274**, and the silyl group could then be removed with retention of configuration to give the desired epoxide **272** (Scheme 62).[164] The presence of

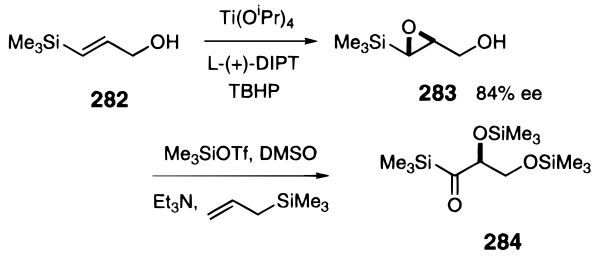
Scheme 62



a silyl group in the vinylic position of the allylic alcohol **276** makes it an exceptionally good substrate for kinetic resolution using Sharpless asymmetric epoxidation. The reaction occurs with high selectivity leading to the allylic alcohol **277** and the epoxide **278** of its enantiomer with a high enantiomeric excess for each (Scheme 62). The selectivity is just as high with alkyl groups in place of the phenyl, but in the absence of the silyl group, the corresponding allylic alcohols are poor substrates for kinetic resolution. Having a silyl group on C-2, as in the alcohol **279**, also improves the level of kinetic resolution in the formation of the allylic alcohol **280** and the epoxide **281**, although not quite to the same extraordinarily high level (Scheme 62).[165]

Sharpless epoxidation of β- or γ-silylated allylic alcohols has been used many times in synthesis.[166] Thus, as just one example, the epoxide **283** derived from the achiral alcohol **282**, was oxidized to give the homochiral acylsilane **284**, which is an acylsilane equivalent of glyceraldehyde (Scheme 63).[167]

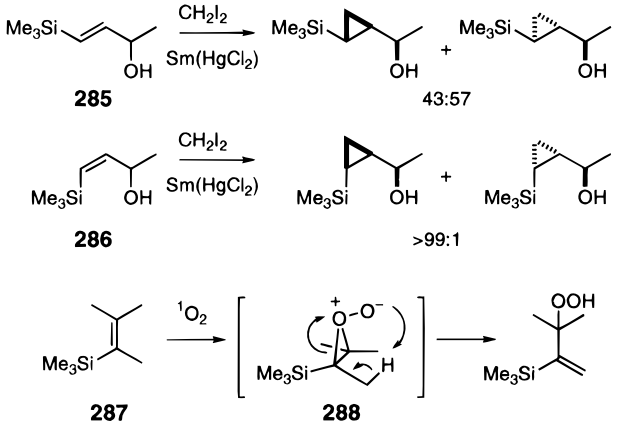
Scheme 63



Enzymatic resolution is another way in which γ-silylated allylic alcohols can be prepared enantiomerically enriched.[168] The epoxidation of the α-silylated silyl enol ether **1025** in Scheme 263 provides another example of a *C*-silyl group controlling the stereochemistry and being removable.

In addition to epoxidation, Simmons−Smith and similar reactions can give stereocontrol stemming from the presence of the silyl group. Cyclopropanation of the γ-silylated allylic alcohols **285** and **286** gave cyclopropylmethanols, but with high diastereocontrol only when the silyl group was *cis* on the double bond, ensuring that the conformation had the hydrogen inside (Scheme 64).[169] A silyl group can

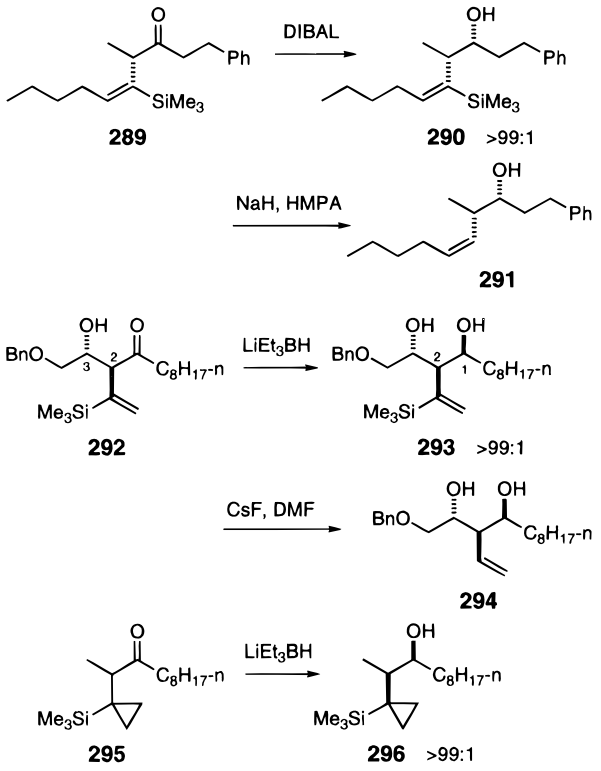
Scheme 64



similarly help in gaining high enantiomeric excess when a homochiral catalyst is present.[170] Silyl groups on a double bond also markedly affect the stereoselectivity of singlet oxygen reactions. The σ-donor capacity of the Si−C bond in the vinylsilane **287** repels the distal oxygen, making it selectively *anti* to the silyl group in the intermediate **288**, and also highly selective for the removal of the hydrogen closer to the carbon atom carrying the silyl group (Scheme 64).[171]

A silyl group affects Cram selectivity when it is attached to one of the substituents on the stereogenic center in an α-substituted ketone. The reduction of the β,γ-unsaturated ketone **289** took place in the usual Cram sense with the silylated vinyl group as the large group. In the absence of the silyl group, the *anti*:*syn* ratio was only 60:40, but with the silyl group bulking up the vinyl group, the selectivity was better than 99:1, and the *anti* alcohol **290** could be desilylated, with retention of configuration (Scheme 65).[172] This level of control was unaffected by a

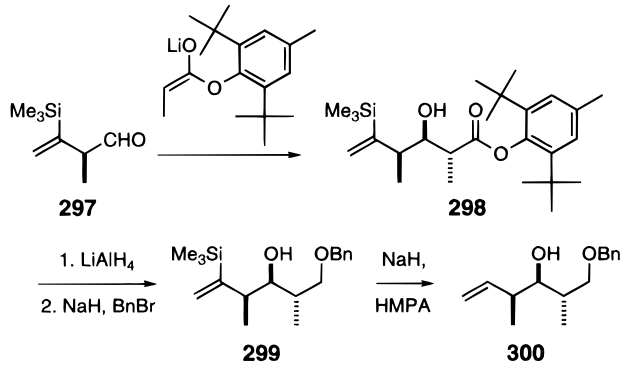
Scheme 65



second stereocenter at C-3, with the β-hydroxy ketone **292** giving the diol **293** with the same very high level of control. In this series, the ketone analogous to **292**, but without the silyl group, gave the opposite relationship between C-1 and C-2. The diastereoisomer of the ketone **292**, epimeric at C-3, gave the same relationship between C-1 and C-2. The silyl group could easily be removed from the vinyl groups, giving the homoallylic diols **291** and **294**. The latter was used in a synthesis of isoavenaciolide.[173] A similar improvement in selectivity took place in nucleophilic attack by allyltrimethylsilane on the aldehyde corresponding to the ketone **292**, with higher chelation control, in favor of the diastereoisomer at C-1, when the vinyl group had the silyl group attached to it.[174] The same pattern was found with a cyclopropane in place of the double bond, as in the reduction of the ketone **295** to the alcohol **296**, with high selectivity (>99:1) (Scheme 65). The corresponding compound without the silyl group was significantly less selective (78:22), and again the silyl group could be removed with cesium fluoride.[175]

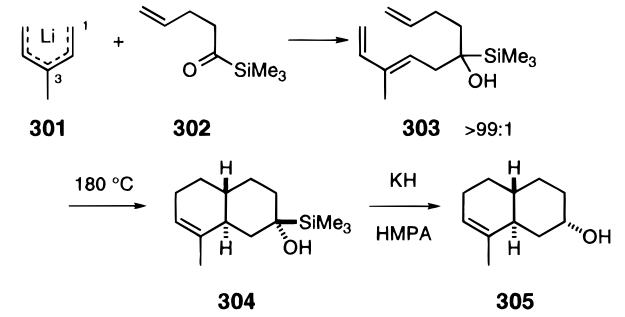
Similarly in the aldol reaction **297** → **298**, two new centers are set up with better Cram control than without the silyl group on the double bond. The silyl group can easily be removed later **299** → **300** (Scheme 66).[176]

Scheme 66



Pentadienyllithiums show a different regiochemistry in their attack on acylsilanes from that of their attack on the corresponding aldehydes. 3-Methylpentadienyllithium (**301**) attacked 4-pentenoyltrimethylsilane (**302**) with high selectivity for attack at the terminus C-1, where the nucleophile is less hindered, to give the α-silyl alcohol **303**, whereas the corresponding aldehyde suffered largely (78:22) attack from C-3. The bulk of the silyl group was used a second time, this time to control stereochemistry in work directed at the synthesis of eudesmane sesquiterpenes. An intramolecular Diels−Alder reaction gave very largely the octalin **304**, as a result of cyclization taking place with the silyl group in an equatorial position. Again, the silyl group could be removed in a Brook rearrangement with retention of configuration to give the axial alcohol **305** (Scheme 67).[177] The corresponding secondary alcohol without the silyl group gave a mixture in the Diels−Alder reaction (42:58) in favor of the equatorial alcohol.[178] Some other reactions of acylsilanes are discussed in section VI.L.

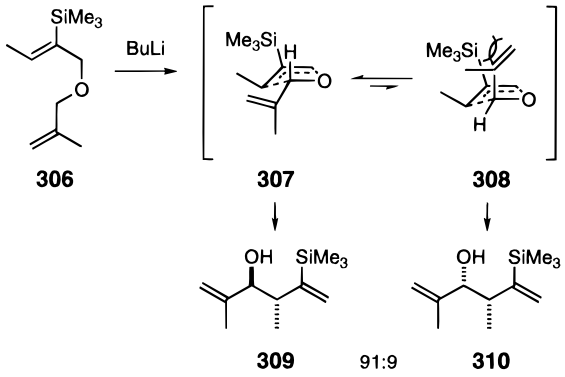
Scheme 67



The silyl group on the double bond in the [2,3]-Wittig rearrangement of the ether **306** increases the stereoselectivity in favor of the *anti* alcohol **309** to 91:9 by way of the envelope transition structure **307**. Presumably the silyl group raises the energy of the alternative transition structure **308**, which leads to the *syn* isomer **310**, for in the absence of the silyl group, the selectivity was only 72:28 (Scheme 68).[179] This selectivity for the *anti* isomer can be combined with a moderate level of control of double-bond geometry when there is a substituent at the double-bond terminus.[180]

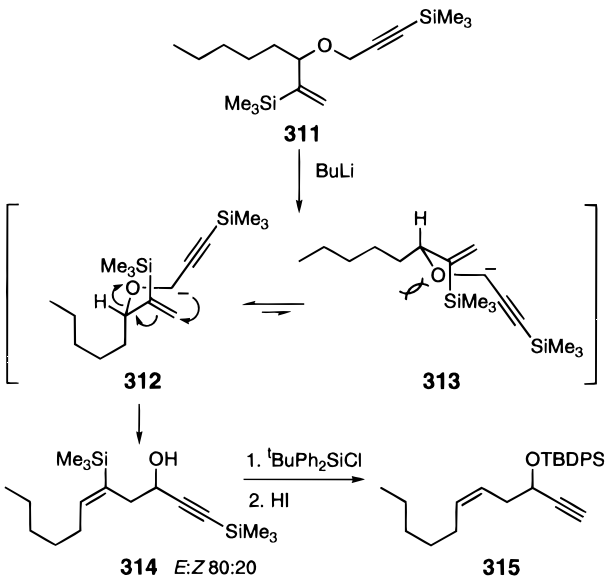
In another Wittig rearrangement, the silyl group on the double bond of the ether **311** ensures the

Scheme 68



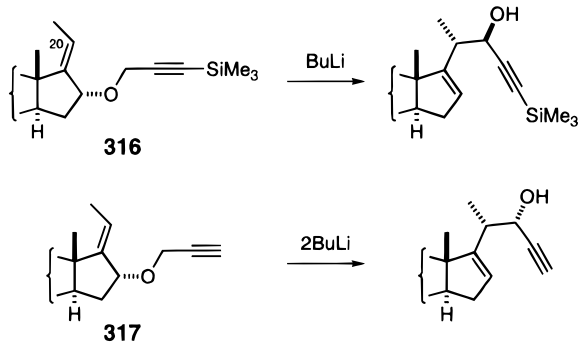
formation of the (*E*)-vinylsilane **314**, which gave the desired *cis*-alkene **315** after stereospecific protodesilylation. Evidently, the silyl group forces the pentyl side chain into a pseudoaxial conformation in the envelope transition structure **312**, avoiding the steric compression in the alternative conformation **313**. The *trans*-alkene is the major product in the absence of the silyl group (Scheme 69).[84]

Scheme 69



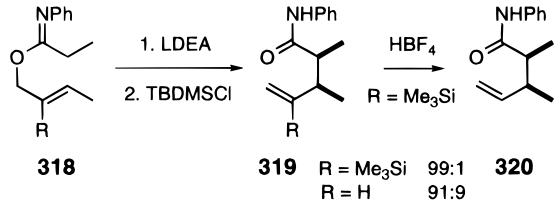
Somewhat more surprisingly, the silyl group on the triple bond in the steroidal side chain of the propargyl ether **316** changed the stereoselectivity completely from that in the dianion of the propargyl ether **317**, possibly because of an increase in the steric repulsion with the C-20 methyl group (Scheme 70).[181]

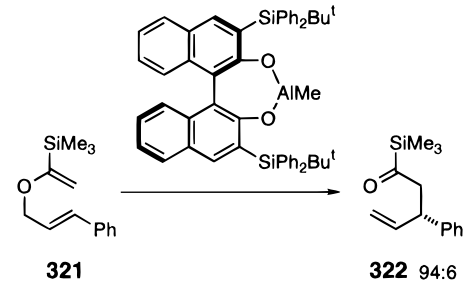
Scheme 70



In the Claisen rearrangement discussed in Scheme 61, the high selectivity for the *anti* arrangement was better when the group on C-2 of the allyl system in the imidate **268**, was not hydrogen, probably because a larger group in that position decreased the proportion of reaction taking place with a boat transition structure. So to synthesize the amide **320** it is better to use the allyl imidate **318** (R = $SiMe_3$), and then to remove the silyl group by protodesilylation of the *anti* rearrangement product **319** (Scheme 71).[159] The

Scheme 71

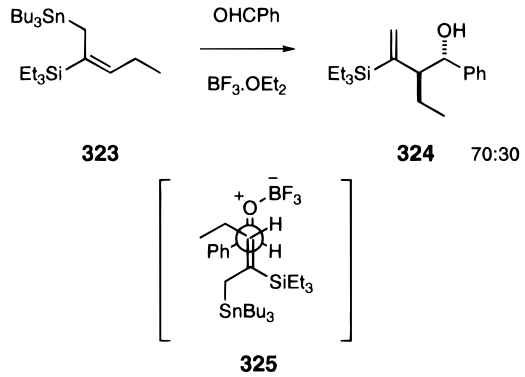




presence of the silyl group in the Claisen rearrangement of the enol ether **321** made the reaction possible—without it, only C–O bond cleavage took place—but the silyl group can also be expected to favor the chair transition structure. Its presence therefore allowed the rearrangement to be carried out in the presence of a homochiral Lewis acid to give an enantiomerically enriched acylsilane **322**, from which the silyl group could easily be removed or used in further construction (Scheme 71).[163]

A silyl group, or a *tert*-butyl group, on the double bond of the allylstannane **323** increased substantially the selectivity in favor of the unusual *anti* relationship along the carbon chain in the formation of the product **324**, presumably by increasing the proportion of reaction taking place by way of the antiperiplanar transition structure **325** (Scheme 72).[182]

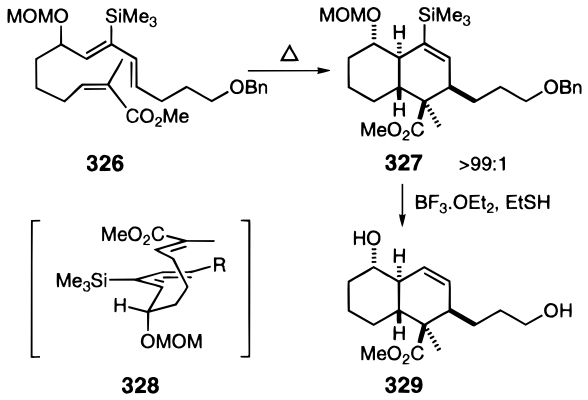
Scheme 72



In an intramolecular Diels–Alder reaction, the presence of the silyl group on the double bond of the diene **326** increases the stereoselectivity in the

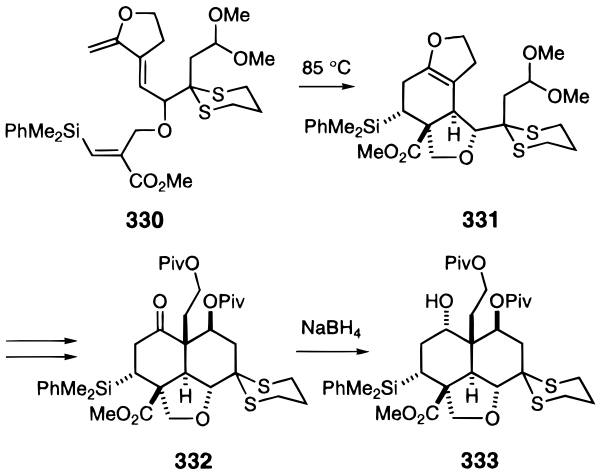
formation of the adduct **327**, because the silyl group makes the conformation **328** more reliably that with the hydrogen inside. In the absence of the silyl group, all four diastereoisomers were formed, with the adduct corresponding to **327** only 15% of the mixture. Removal of the silyl group, along with the protecting groups, gave the *trans*-fused octalin **329** suitable for a synthesis of chlorothricolide (Scheme 73).[183]

Scheme 73



The presence of a silyl group on the double bond of the dienophile component of the intramolecular Diels−Alder reaction **330** reversed the *exo* selectivity (89:11) of the corresponding compound without the silyl group, and made the *endo* adduct **331** the major product (70:30). Presumably the silyl group avoided the *endo* orientation and forced the methoxycarbonyl group to be *endo*. In this example, designed for a synthesis of azadirachtin, the silyl group was not discarded after it had done its job. It was used for a second time to control stereochemistry by increasing the stereoselectivity of the reduction **332** → **333**, in which the hydride had been delivered equatorially, *anti* to the silyl group (Scheme 74). Finally the silyl group was converted (section V) into a hydroxyl, which was needed in the final structure.[184]

Scheme 74

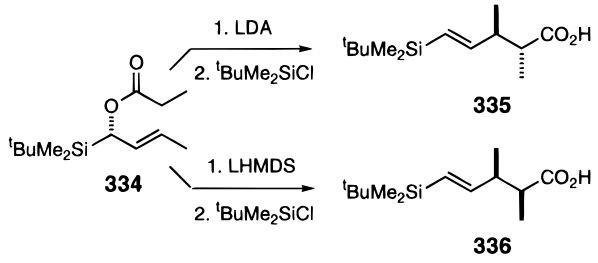


C. A Silyl Group To Create Chirality

A 2-trimethylsilyl group in a boracyclopentane has been used as a chiral auxiliary in allylborane chemistry and is an example of a silyl group being present to create chirality in a reagent simply by occupying space.[185] The surprising result in this case was that one silyl group made the allylborane more enantioselective than two. In this work, the chiral auxiliary containing the silicon was not part of the structure being synthesized.

Because of the several ways of removing a silyl group after it has been used to control stereochemistry, it has been a useful group to impart chirality into a structure that would otherwise be achiral. Thus, in the first application of this idea, the enantiomerically enriched allylic alcohol **334** undergoes the Ireland−Claisen rearrangement to give either the acid **335** or the acid **336**, depending upon the geometry of the enolate used. The silyl group, being large, guarantees the formation of a *trans* double bond, and hence efficient transfer of chiral information from the single stereogenic center of the starting material to the two new centers. This device can only work when a substituent is present on the only tetrahedral carbon atom in the cyclic transition structure, since chirality is dependent upon the existence of such a substituent. Having served its turn, the silyl group can be removed in the usual way by protodesilylation, so that its net effect is to impart a temporary chirality to the starting material (Scheme 75).[186]

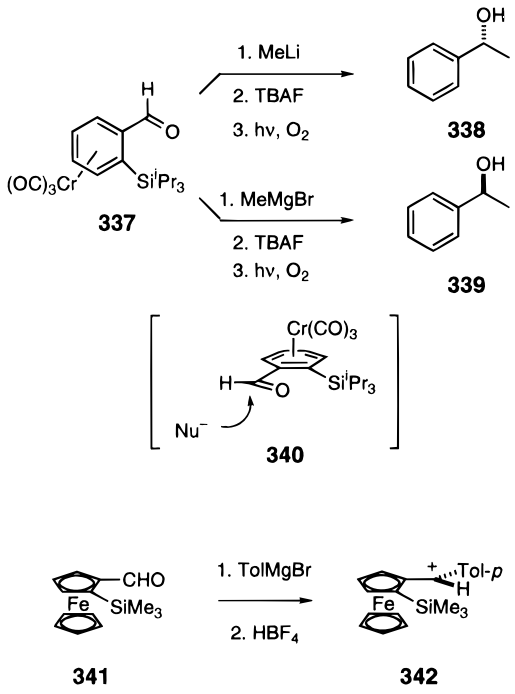
Scheme 75



In the chromium tricarbonyl-complexed aromatic ring **337**, the presence of a silyl group renders the molecule chiral, and it could be resolved by derivatization of the aldehyde group. Either the (*R*)-**338** or the (*S*)-1-phenylethanol **339** could be obtained with complete stereocontrol, the one from the reaction of methyllithium on its own, and the other from the methyl Grignard reagent in the presence of magnesium bromide. This extraordinary result is explained if both reagents attacked from the surface away from the chromium ligand, and selectivity was controlled by the orientation of the carbonyl group with respect to the silyl group. The methyllithium attacked the carbonyl group when it was oriented in the conformation **340**, in order that the incoming nucleophile could avoid the silyl group. Complexation of magnesium bromide to the carbonyl oxygen did not leave enough space between the oxygen and the silicon for this conformation to be populated, the carbonyl group rotated to point in the other direction, exposing the opposite face to the Grignard reagent (Scheme 76).[187] A similar example of a silyl group making a complexed benzaldehyde chiral can be found in Scheme 138, where the aldehyde is attacked by a silyl enol ether. A ferrocene is another complexed aromatic ring with the same opportunity to use an *ortho*

substituent to render it chiral. Thus the aldehyde **341** has been prepared in homochiral form[188] and used to make a homochiral carbocation **342** (Scheme 76).[189]

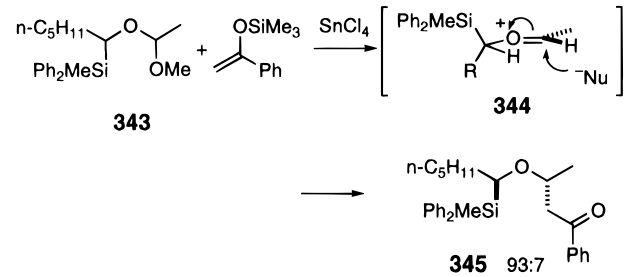
Scheme 76



Aromatic rings with other substituents than aldehydes have also been made homochiral. Thus a homochiral base can deprotonate selectively *ortho* to a suitable substituent such as methoxy, and the lithium derivative silylated directly making a homochiral chromium-complexed aromatic ring.[190]

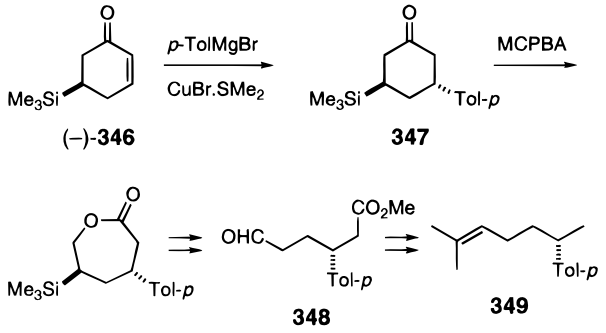
In the Mukaiyama aldol reaction of the acetal **343** with the silyl enol ether of acetophenone, the presence of the silyl group makes the intermediate **344** chiral, and also gives substantial selectivity in favor of the formation of the diastereoisomer **345**, suggesting that this might be a useful chiral auxiliary in the homochiral series (Scheme 77).[191]

Scheme 77



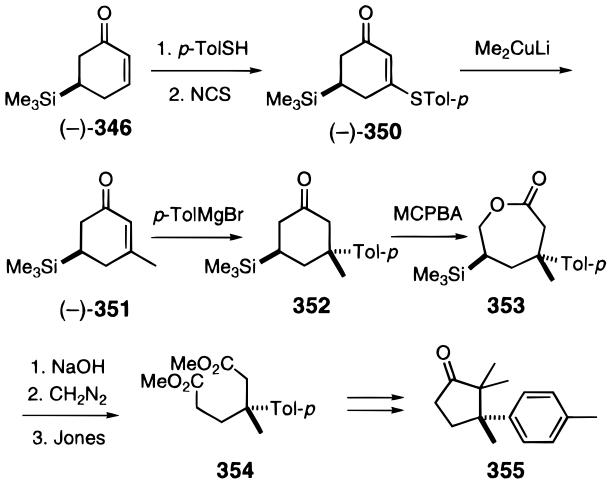
The presence of a substituent at C-5 in a cyclohexenone has long been known to make nucleophilic attack selective for attack on the opposite side of the ring from the substituent, because axial attack on a chair conformation with the substituent equatorial leads to the chair enolate.[192] The silyl group is no exception, and this has proved to be a fruitful device in several total syntheses using 5-(trimethylsilyl)-2-cyclohexenone (**346**). The presence of the silyl group makes the cyclohexenone **346** chiral, and it can be prepared enantiomerically pure in either sense equally easily by kinetic resolution[193] or by stereoselective synthesis.[194] The (−) enantiomer gives the conjugate addition product **347** with high selectivity, the *cis* isomer being undetectable in the ^{13}C NMR spectrum.[195] The silyl group β to the ketone in **347** was removed by silicon-directed Baeyer−Villiger reaction[67] followed by ring opening and oxidation to give the C-6 aldehyde **348**, from which the silyl group had been lost by enolization. The aldehyde was then used to synthesize (+)-cucurmene (**349**, Scheme 78).[195]

Scheme 78



The conjugate addition also works for setting up a quaternary center, as in the synthesis of (+)-α-cuparenone (**355**), which relies upon the ease with which the β-substituted enone **351** can be prepared from the β-thio enone **350** by conjugate addition of the methyl cuprate reagent. The silyl group was removed again by silicon-directed Baeyer−Villiger reaction and oxidation to the ester level **354** rather than the aldehyde (Scheme 79).[196] The enantiomer of (−)-**351** can also be made from the enone (−)-**346** by adding methyllithium instead of the methyl cuprate, and oxidizing the tertiary allylic alcohol. This route was used in a synthesis of (−)-axisonitrile.[197]

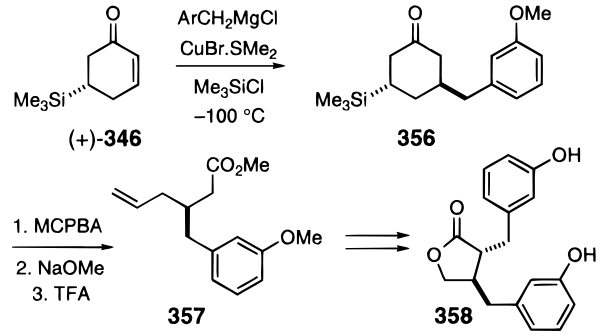
Scheme 79



In a similar sequence starting from the enantiomer (+)-**346** leading to a synthesis of (−)-enterolactone **358**, the conjugate addition only worked with reasonably high selectivity (83:17) in favor of the ketone **356** in the presence of trimethylsilyl chloride at very low

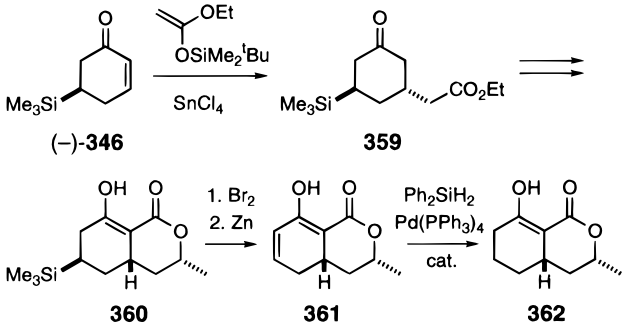
temperature. The silyl group was removed this time by opening the lactone followed by acid-catalyzed elimination giving the terminal alkene **357** for further manipulation (Scheme 80).[198]

Scheme 80



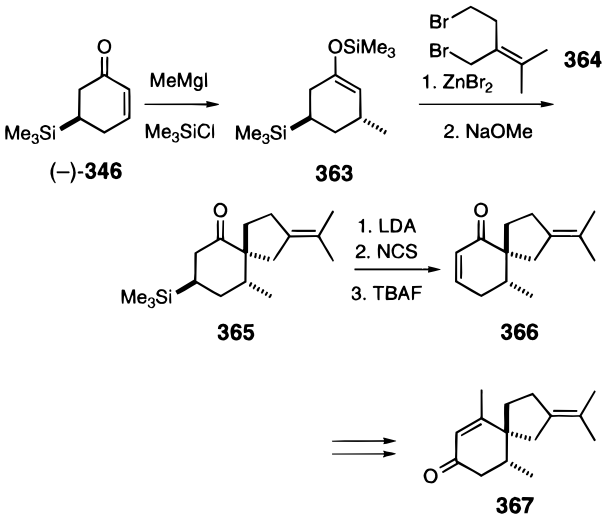
Michael additions of stabilized enolates are not always as stereochemically well controlled with these ketones, although malonate itself is effective (91:9), but Mukaiyama−Michael and Sakurai reactions of silyl enol ethers and allylsilanes, respectively, are reliably more selective, and so are additions of alkyl radicals. Thus the reaction of the silyl enol ether derived from ethyl acetate and the ketone (−)-**346** gave the ester **359**, which was converted in several steps, culminating in an intramolecular Claisen condensation, into the β-keto lactone **360**. The silyl group had been left untouched up to this point, but bromination of β-silyl ketones was known to set up a β-elimination with loss of the silyl group, and hence the formation of α,β-unsaturated ketones with the double bond placed specifically between the ketone group and the site of the original silyl group.[199] In the series in Scheme 81, it results in a cyclohexene **361** with the double bond on the other side of the ring from its original position in the starting material **346**. Some over-bromination was corrected by reduction with zinc, and hydrogenation removed the double bond to give (+)-ramulosin (**362**, Scheme 81).[200]

Scheme 81



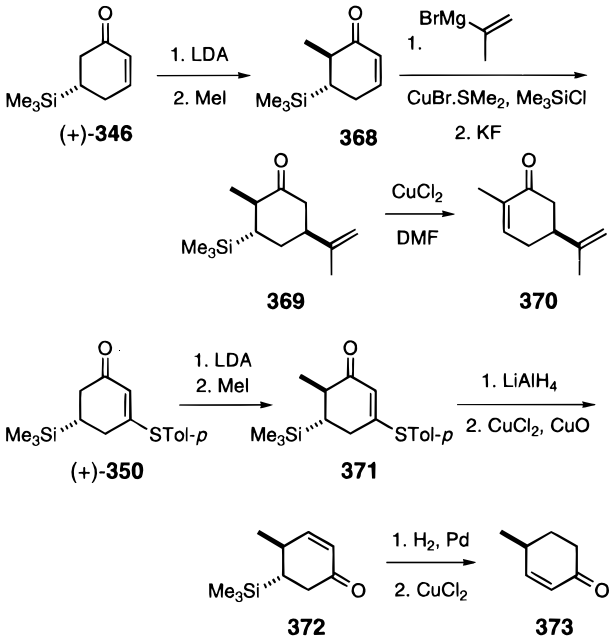
The intermediate enol derivative from the conjugate addition step can be alkylated. Thus the silyl enol ether **363** reacted with the allylic bromide **364** with the stereochemistry-determining step being the second alkylation, which is selectively *anti* to the methyl group, to give the ketone **365**. The silyl group was removed by enolate chlorination, since there was no regiochemistry of the halogenation to control, and the silyl group removed to give the enone **366** in a synthesis of β-vetivone (**367**, Scheme 82).[201]

Scheme 82



In a synthesis of (−)-carvone (**370**), the first step **346** → **368** was to introduce a methyl group α to the silyl group, with temporary stereocontrol in the normal sense for the alkylation of an enolate with a β-silyl group (section V.A), followed by the conjugate addition **368** → **369** setting up the stereogenic center.[202] The desilylation was carried out using copper(II) chloride, which had been found[203] superior to the bromination−desilylbromination procedure with many of these silylated cyclohexanones. Alternatively, the stereochemistry of the alkylation step can be preserved, as in the reaction making the methyl ketone **371**, and used to set up the homochiral 4-substituted cyclohexenones **372** and **373** (Scheme 83).[202]

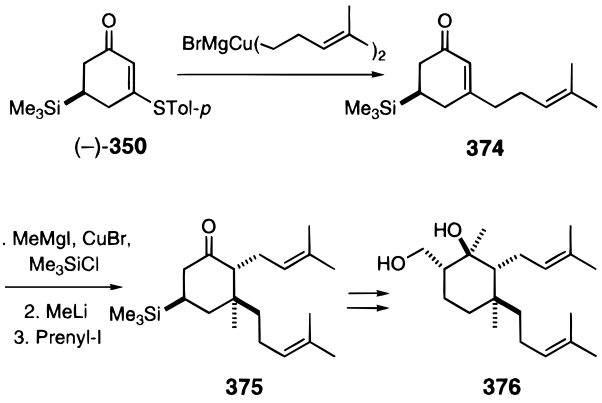
Scheme 83



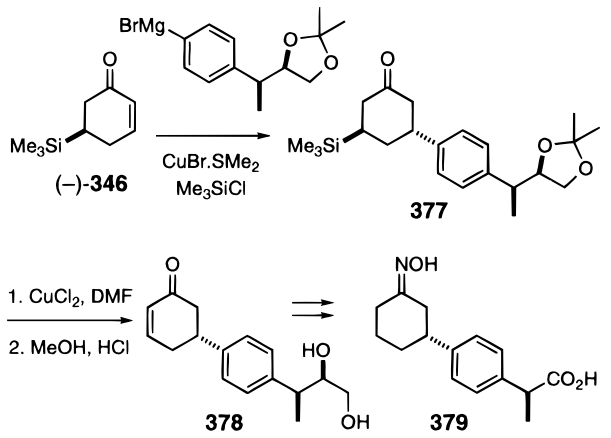
Other syntheses that have used 5-silylcyclohexenone to set up six-membered rings, with absolute

stereocontrol, and with some of the intermediate diastereocontrol stemming from the presence of the silyl group, include those of (+)-magydardiendiol (**376**, Scheme 84),[204] all four stereoisomers of ximoprofen (**379**), with only one illustrated (Scheme 85),[205] and (+)-ptilocaulin (**382**, Scheme 86).[206]

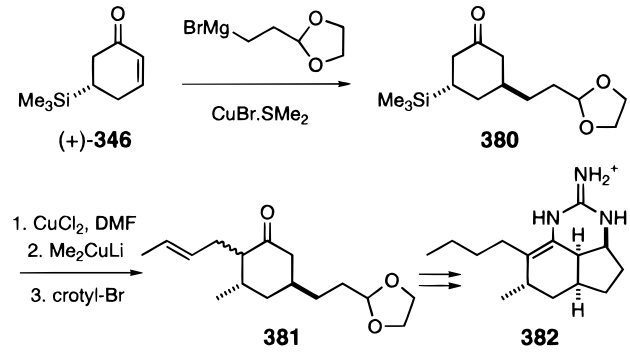
Scheme 84



Scheme 85

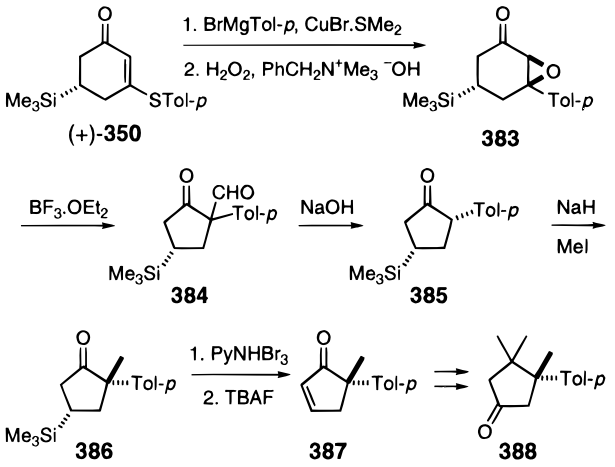


Scheme 86



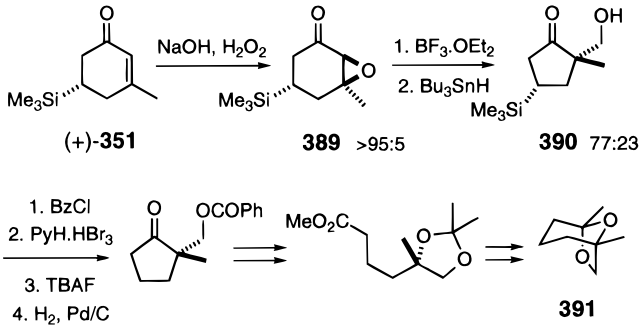
Ring contractions in this series to make cyclopentanone systems have been achieved in two ways. Boron trifluoride-catalyzed rearrangement of the epoxide **383**, itself prepared stereoselectively from the enone **350**, gave a mixture of the 2-formylcyclopentanones **384**, from which the formyl group could be removed by a retro-Claisen reaction to give the cyclopentanone **385**. Regioselective methylation gave the cyclopentanone **386**, with high selectivity (>91:9) for attack *anti* to the silyl group across the five-membered ring. Bromination and desilylbromination gave the cyclopentenone **387**, which was used in a synthesis of (+)-*β*-cuparenone (**388**, Scheme 87).[207]

Scheme 87



This method of ring contraction does actually show some stereoselectivity in the formation of the intermediate aldehyde. Thus the epoxide **389** gave a mixture (77:23) of the corresponding aldehydes, which could be reduced selectively at the aldehyde group to give the alcohol **390** with fair overall stereoselectivity. This alcohol was used in a synthesis of (−)-frontalin (**391**, Scheme 88) and a similar alcohol, with a long chain alkyl group in place of the methyl group, was used in a synthesis of (−)-malyngolide.[208]

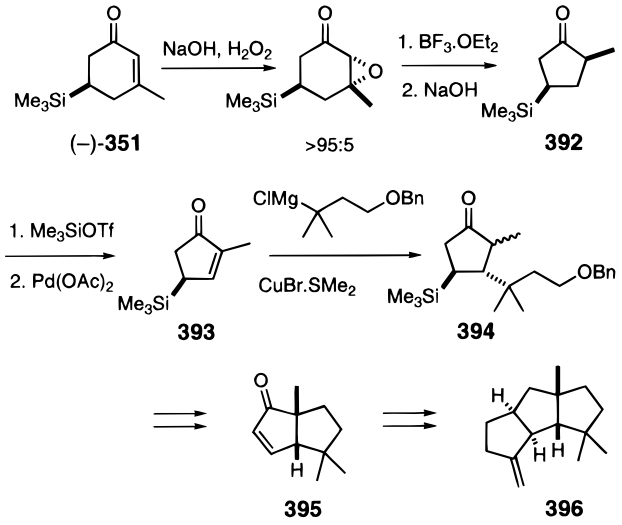
Scheme 88



A similar epoxidation rearrangement, with a retro-Claisen deformylation instead of reduction, was used to prepare the ketone **392** and hence the unsaturated ketone **393**. In the stereochemistry-determining step, conjugate addition took place selectively *anti* to the neighboring silyl group to give the ketone **394**, which was used in a synthesis of the ketone **395**,[209] a precursor for the synthesis of (−)-capnellene (**396**, Scheme 89).[210]

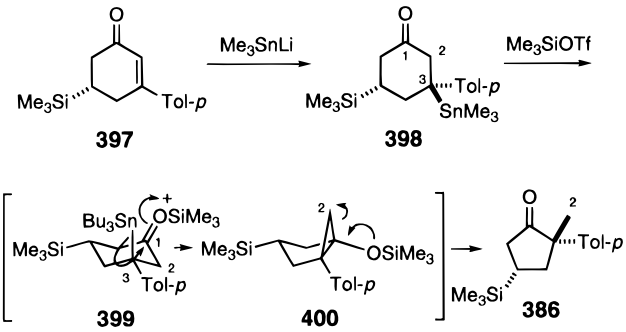
The alternative method for ring contraction uses a *β*-stannyl ketone. The enone **397** stereoselectively gave the *β*-stannyl ketone **398**, which reacted with trimethylsilyl triflate to give ring contraction **398** → **399** → **400** → **386**, in which the ring methylene group C-2 is extruded as the methyl group, and with

Scheme 89



stereochemistry that stems from stereospecific inversion of configuration at C-3 in the formation of the bond between C-3 and C-1 (Scheme 90).[211] The

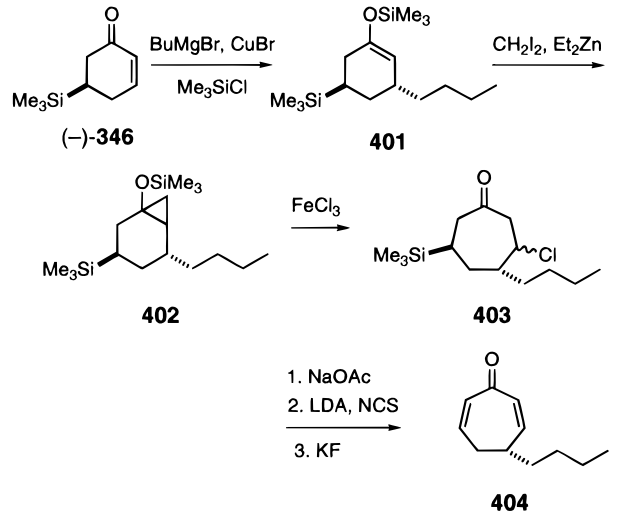
Scheme 90



cyclopentanone **386** had already been converted into (+)-*β*-cuparenone (**388**, Scheme 87).

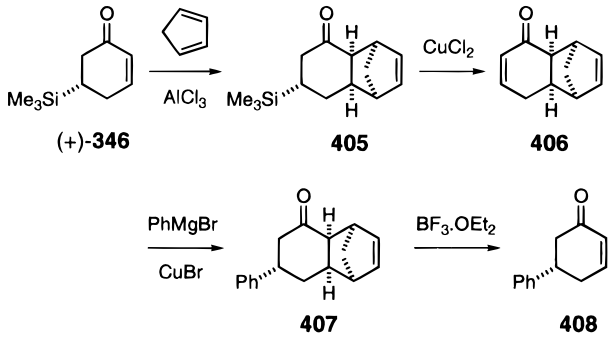
Ring expansion **401** → **402** → **403** has also been used in a synthesis of (+)-4-butylcyclohepta-2,6-dienone (**404**) found in marine algae (Scheme 91).[212] A similar ring expansion was used in syntheses of neoambrosin, parthenin, and dihydroisoparthenin.[213]

Scheme 91



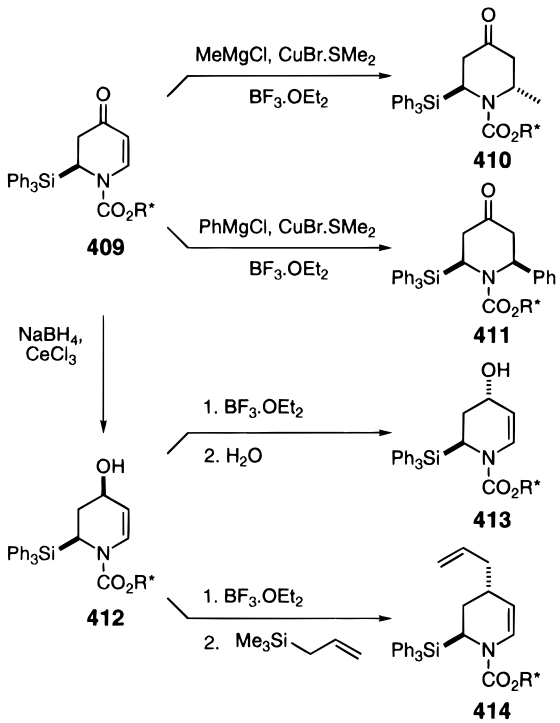
In addition to the conjugate addition reactions above, Diels–Alder reactions are also stereoselective, with cyclopentadiene giving the adduct **405** with high selectivity (93:7), although it is not clear in this case whether the minor product is the *exo* adduct with respect to the Diels–Alder reaction or the *endo* adduct *syn* to the silyl group. The adduct **405** can be used to prepare the cyclohexenone **406** that is formally an adduct of the cyclohexadienone tautomer of phenol. This adduct can be used to reinstate a 5-substituted cyclohexenone **408**, but with a different group in place of the original silyl group, by taking advantage of the reversibility **407** → **408** of the Diels–Alder reaction (Scheme 92).[214]

Scheme 92



In heterocyclic system **409**, conjugate addition is not quite so regular, with the reagent making a surprising and unexplained difference to the sense of the stereoselectivity. The copper-catalyzed methyl Grignard reagent gave the expected product **410**, with the incoming group *anti* to the silyl group, but the phenyl Grignard gave the unexpected diastereoisomer **411**. On the other hand, direct nucleophilic attack at the carbonyl group **409** → **412**, and at the acyliminium cation derived from it **412** → **413** and **412** → **414**, were all reliably *anti* to the silyl group, leaving the phenyl Grignard reaction as the only anomaly (Scheme 93).[215]

Scheme 93



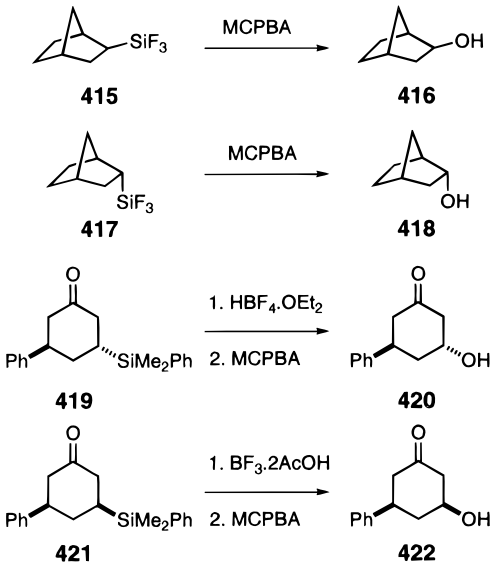
Other examples of silyl groups being present to impart chirality are illustrated in Schemes 251 and 256, which fit naturally into a different category.

IV. A Silyl Group as a Masked Hydroxyl Group[216]

In almost all of the reactions described above, the silyl group, having done its job, is either lost as the electrofugal group or is replaced by a proton. With the invention of a reaction in which a silyl group can be replaced by a hydroxyl group, a whole new area of organic chemistry has been opened up, in which the silyl group is carried into a reaction, marking a site in the molecule for a future hydroxyl group, without having the hydroxyl group there with all its attendant chemistry.

In order to achieve this transformation, the silyl group must be oxidized, typically using peroxides or peracid, and it must carry a nucleofugal group, like a halogen, an alkoxy or amino group, or even just a hydrogen atom, that can be displaced by the peroxide. Such substrates can be oxidized directly using hydrogen peroxide and a base and/or fluoride ion.[217] On the other hand, if the silane carries four carbon groups, one of them must first be removed, and replaced by a nucleofugal group. This can be done by protodesilylation, bromodesilylation, or mercuridesilylation of the benzene ring in a phenylsilane, and the latter pair can be combined with peracetic acid to allow a phenyldimethylsilyl group to be converted into a hydroxyl in one pot.[218] Other removable groups include, among others, allyl, furyl, silyl, and aminomethyl. Whatever the situation, the overall conversion of a silyl into a hydroxyl takes place stereospecifically with retention of configuration with both pairs of diastereoisomers **415** and **417**[219] and **419** and **421**,[218] giving the appropriate pairs of alcohols **416** and **418** and **420** and **422** (Scheme 94).

Scheme 94

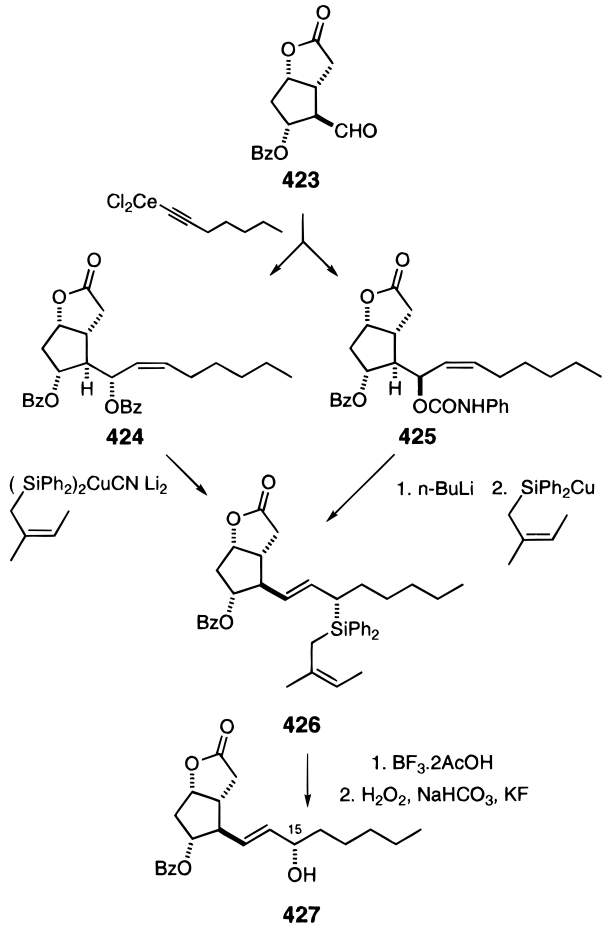


Many examples of this type of reaction will be found later in this review under the appropriate headings. This section establishes the idea and then deals only with those areas not easily fitting into the later sections.

A. Silyl Nucleophiles as Masked Hydroxide Anions

The [2-methylbut-2-enyl(diphenyl)silyl]cuprate reagent[220] reacted stereospecifically *anti* with the allyl benzoate **424**, derived from the aldehyde **423**, to give the allylsilane **426**. The diastereoisomeric allyl carbamate **425**, also derived from the aldehyde **423**, gave the same allylsilane **426** by a *syn* stereospecific route, in a complementary procedure to be discussed in connection with Scheme 282. Silyl-to-hydroxy conversion[218] then gave the corresponding alcohol **427** with the prostaglandin stereochemistry at C-15 (Scheme 95).[221] The 2-methylbut-2-enyl group had been deliberately incorporated into the silyl-cuprate reagent to be a group exceptionally easily removed from silicon by protodesilylation. This was necessary in order to prevent the protodesilylation step that functionalizes the silicon taking place by attack on the less-substituted allylsilane double bond, as it would have if the silyl group had been the more usual phenyldimethylsilyl group.

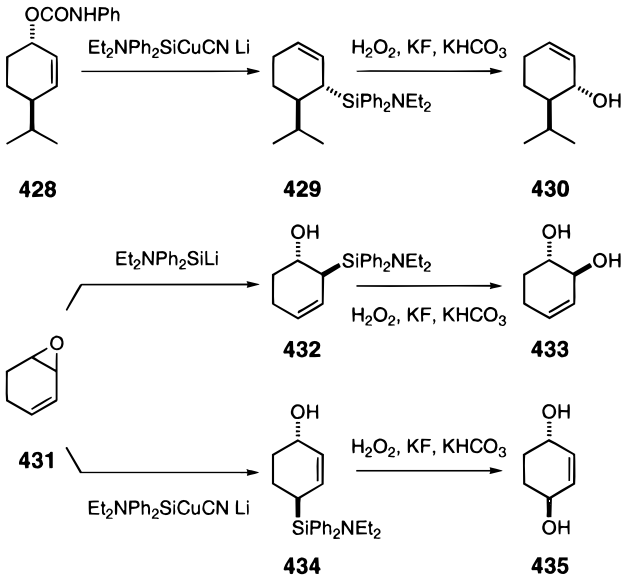
Scheme 95



The allylic alcohol **428** was similarly converted regiospecifically into the allylsilane **429**, which, because it was already a functionalized silyl group, could be converted immediately into a hydroxyl **430**, achieving overall suprafacial allylic inversion (Scheme

96). Similarly, the epoxide **431** could be opened with the silyllithium or the silylcuprate reagent with complementary regioselectivity, giving the 1,2-diol **433** or the 1,4-diol **435** after silyl-to-hydroxy conversion[217] (Scheme 96).[222]

Scheme 96

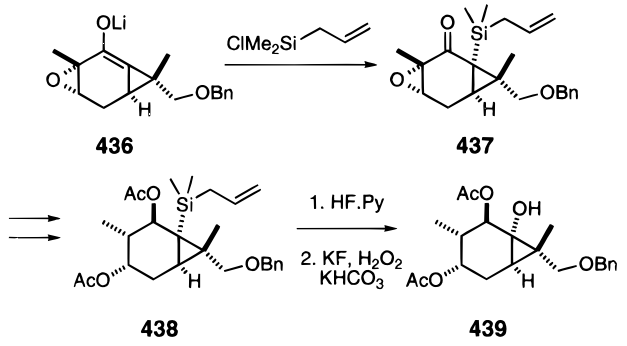


The sequences in Schemes 365, 366, 373, and 374 are also examples of a silyl nucleophile acting as the equivalent of a hydroxide ion.

B. Silyl Electrophiles as Masked Hydroxonium Cations

Direct silylation of a carbanion introduces a silyl group, which, if it is suitably functionalized, can later be converted into a hydroxy group. This has been used in synthesis with stereochemical consequences, in the *C*-silylation of the strained enolate **436** to give the α-allyldimethylsilyl ketone **437**. A few steps later in the synthesis, the allylsilane **438** was converted with retention of configuration into the corresponding alcohol **439** for a synthesis of phorbol analogs (Scheme 97).[223]

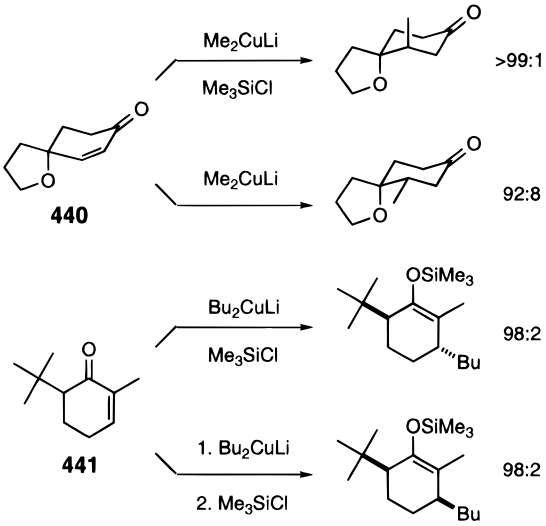
Scheme 97



V. Silicon-Based Lewis Acids

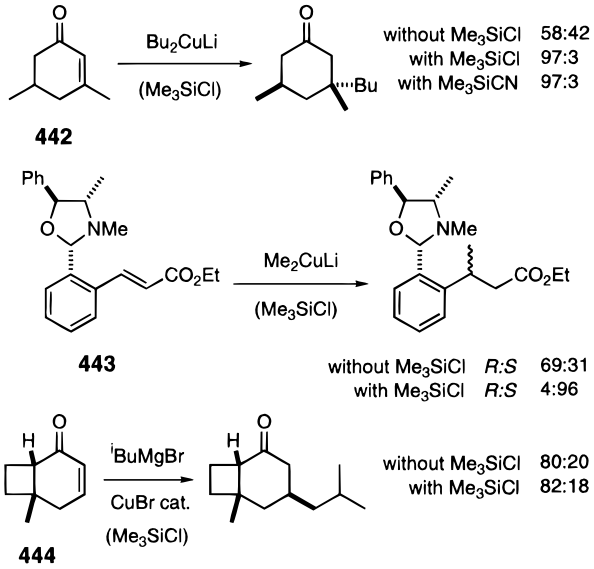
The presence of a silyl halide accelerates 1,4-additions of alkylcuprates[224] and copper-catalyzed Grignard reagents[225] to α,β-unsaturated carbonyl compounds. Sometimes the stereochemistry is also affected by having the silyl halide present. Thus the electronically biased, but only marginally sterically biased system **440** gives strikingly different stereochemistry in the presence and absence of the silyl chloride (Scheme 98).[226] Similarly the cyclohexenone **441** also gives opposite selectivity with and without the trimethylsilyl chloride (Scheme 98).[227]

Scheme 98



More usually, there is a smaller effect,[228] as in the improvements in selectivity seen in the reactions, in descending order of effectiveness, of the enones **442**,[229] **443**,[230] and **444**[231] (Scheme 99).

Scheme 99

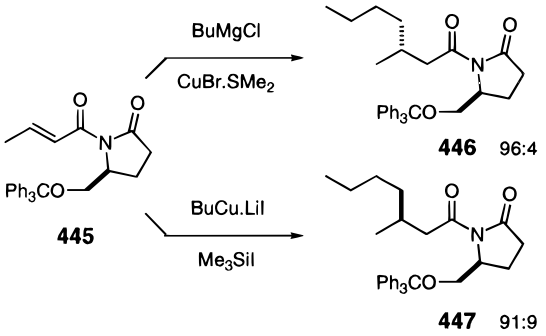


These reactions are discussed here under the heading Lewis acids, but there is evidence that the silyl halide is not simply acting as a Lewis acid by coordinating to the starting enone. It appears rather to influence which facial diastereoisomer, produced by coordination of the cuprate to the enone, decomposes more rapidly.[232,233] Lewis acidity alone is certainly not the only effect, since trimethylsilyl cyanide is comparable to trimethylsilyl chloride in enhancing the stereoselectivity of the reaction of the ketone **442**.

Silyl halide- or triflate-assisted cuprate reactions have been used several times in stereocontrolled syntheses,[234] including those of olivin,[235] cortisone,[236] grandisol,[155] and secokainic acid,[237] in most of which the presence of the silyl halide or triflate was necessary for reaction to take place, but in some it also manifestly cleaned up the stereochemistry of attack relative to resident stereogenic centers. Silyl halides can also affect the degree of enantioselectivity of attack on prochiral enones by cuprates coordinated to chiral auxiliaries.[238]

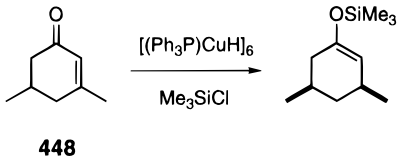
Trimethylsilyl iodide induces the opposite sense of diastereoselectivity in conjugate addition to imides **445** incorporating Koga's chiral auxiliary. Whereas magnesium halides coordinate to both oxygens, leading the cuprate to attack from the side opposite to the (trityloxy)methyl group to give the adduct **446**, trimethylsilyl iodide is exceptional, and for whatever reason leads to attack on the other surface to give the adduct **447**, presumably in the alternative conformation with the carbonyl groups opposed (Scheme 100).[239]

Scheme 100



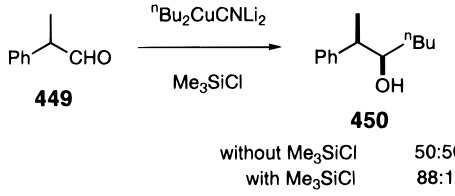
Conjugate addition of hydride also takes place faster in the presence of trimethylsilyl chloride with hydride approach from the less-hindered surface of stereodefined cyclohexenones **448** (Scheme 101).[240]

Scheme 101



Silyl halides also accelerate the 1,2-additions of alkylcuprates to aldehydes and at the same time enhance the Cram selectivity. Thus 2-phenylpropanal (**449**) reacted with dibutylcuprate in the presence of trimethylsilyl chloride to give significantly more of the *syn* (Cram) alcohol **450** than it did in the absence of the silyl halide (Scheme 102).[241]

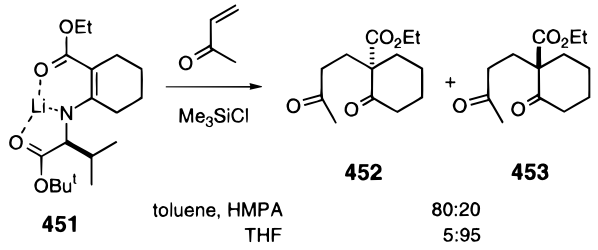
Scheme 102



Silyl halides and triflates are unmistakably acting as Lewis acids in catalyzing a wide range of reactions,[242] typically those of allylsilanes and silyl enol ethers with acetals, many of which are illustrated in section VI. They are usually much like other Lewis acids in their effect on stereochemistry, but in a few cases they have been found to be unusually effective. The following three examples illustrate this possibility.

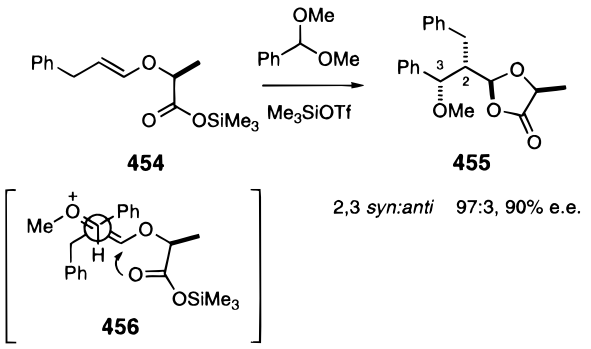
The Michael reaction **451** → **452** + **453** gave the highest transfer of chirality in either sense with trimethylsilyl chloride as the Lewis acid catalyst, with a solvent effect caused by coordination of HMPA to the lithium cation. Trimethylsilyl chloride evidently has just the right balance of Lewis acidity to catalyze the reaction but not coordinate to the HMPA. Other Lewis acids like trimethylsilyl triflate or boron trifluoride were not as effective (Scheme 103).[243]

Scheme 103



Relaying the chiral information efficiently from the silyl ester **454** to the aldol-like product **455** was made possible by silyl group transfer to and from the trimethylsilyl triflate catalyst. The stereochemistry observed indicates an antiperiplanar transition structure **456** with *syn* addition of the electrophile and the carboxylate oxygen (Scheme 104).[244]

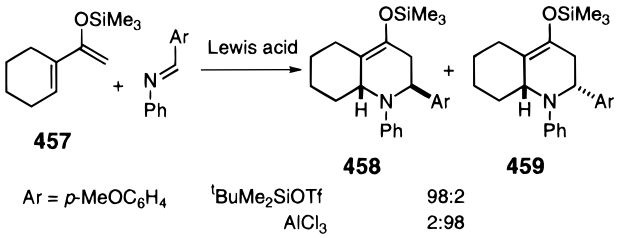
Scheme 104



The hetero-Diels−Alder reaction **457** → **458** + **459** was most stereoselective in the kinetic, *exo* sense with *tert*-butyldimethylsilyl triflate as the Lewis acid, with the optimized procedure using catalytic amounts for the minimum time. More powerful Lewis acids caused more or less equilibration to the *endo* isomer **459**, with the optimized procedure using molar amounts (Scheme 105).[245]

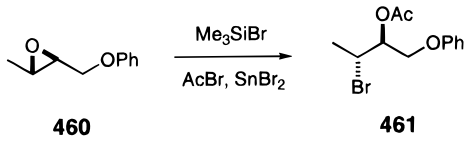
Trimethylsilyl chloride has also found use in enantiocontrol in the deprotonation of symmetrical ketones with homochiral bases, where the selectivity was notably better in the presence of the silyl chloride than in its absence.[246] A similar effect was found with *ortho* deprotonation of chromium-complexed anisole.[190] The effect however is not attributable to the silyl group, but to the presence of chloride ion, since lithium chloride has a similar effect.[246,247]

Scheme 105



Silyl halides are a good source of halide ion for stereospecific and often regioselective opening of epoxides forming halohydrins, as in the reaction **460** → **461** (Scheme 106).[248]

Scheme 106



VI. Silyl Enol Ethers

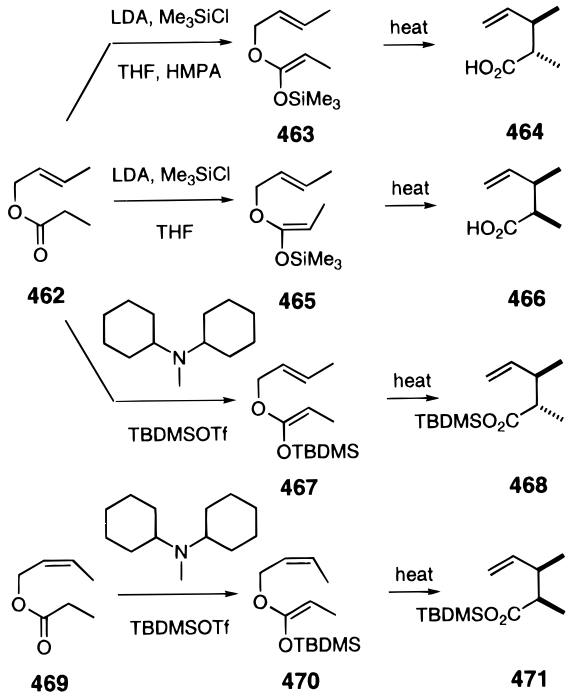
The order of the discussion in this large section is first (section A) with the idea of silyl enol ethers being used in pericyclic reactions, notably Ireland−Claisen rearrangements. Silyl enol ethers, however, are most often used as d^2 carbon nucleophiles. Intermolecular reactions in this sense are covered first, in the order for the electrophiles: carbonyl groups (section B), iminium ions (section C), enones (section D), and then a few other electrophiles (section E). In each section, stereocontrol from the electrophilic component is dealt with before stereocontrol from features within the silyl enol ethers. Intramolecular reactions are covered in section F, except for those in which the components are linked through the silyl group, which are covered later in section XVIII. A few stereoselective reactions of silyl enol ethers, where a chiral substituent is attached to the silicon, are discussed in section XIX.

The levels and even the sense of the stereocontrol in all these reactions are sometimes affected by whether the silyl enol ether is derived from a ketone, an ester (when it is often, but not always helpfully, called a silyl ketene acetal), a thioester, or an amide, so it should not be assumed that anything illustrated here for one of these types of silyl enol ether can safely be carried over to any of the others.

A. Silyl Enol Ethers in the Ireland–Claisen Rearrangement

Silyl enol ethers are, of course, intermediates in the much used Ireland version[249] of the Claisen rearrangement, and are integral to the stereocontrol of that powerful reaction by virtue of allowing the separate preparation of each of the geometrically isomeric silyl enol ethers **463** and **465** that then follow a chairlike transition structure leading, after hydrolysis, to the diastereoisomeric carboxylic acids **464** and **466** (Scheme 107).[250] Frequently a hindered silyl group is used to make the intermediate silyl enol ethers easier to handle. Using a hindered amine and a hindered silyl group in the formation of the silyl enol ether, (*Z*)-silyl enol ethers **467** and **470** can be set up without recourse to the usual recipe involving HMPA (Scheme 107).[251]

Scheme 107



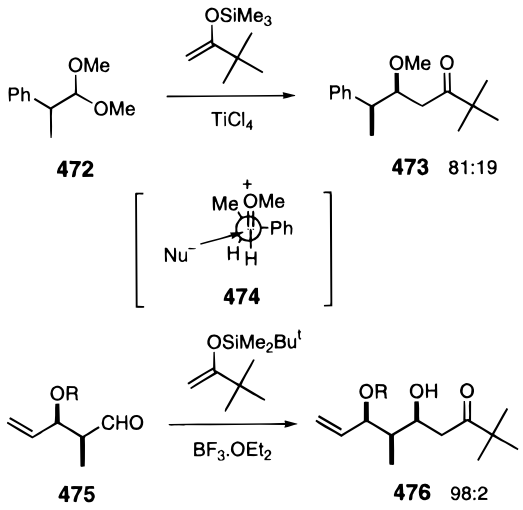
B. Intermolecular Attack on Carbonyl Groups and Acetals[252]

The reaction of silyl enol ethers with aldehydes, ketones, and their acetals is known as the Mukaiyama aldol reaction.[253] The first section below covers stereochemical control at the electrophilic center from silyl enol ethers having two identical substituents on the nucleophilic carbon. The second section deals with simple diastereoselection in reactions in which adjacent stereocenters are set up, one from the nucleophilic and the other from the electrophilic carbon. The third section then covers those reactions combining both features and other more complicated events.

1. Stereocontrol Only from the Electrophile

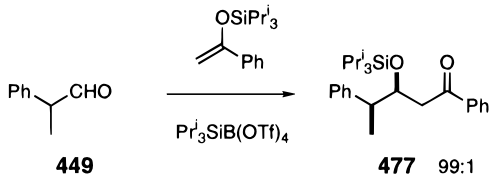
Aldehydes and their acetals with stereogenic centers adjacent to the electrophilic carbon show Cram or chelation control, depending upon the conditions and structure of the aldehyde, with higher than usual Cram control illustrated by the acetal **472**[254] giving, in the usual Felkin−Anh picture **474**, largely the ether **473**, and the aldehyde **475** giving largely the alcohol **476** (Scheme 108).[255] With boron trifluoride as the Lewis acid there is no chelation within the aldehyde **475**, and silyl enol ethers therefore react with simple Cram control. In contrast, lithium enolates react with the corresponding aldehydes in the opposite stereochemical sense by way of the Zimmerman−Traxler-chelated transition structure. The reaction with an acetal cannot of course be carried out using a lithium enolate.

Scheme 108



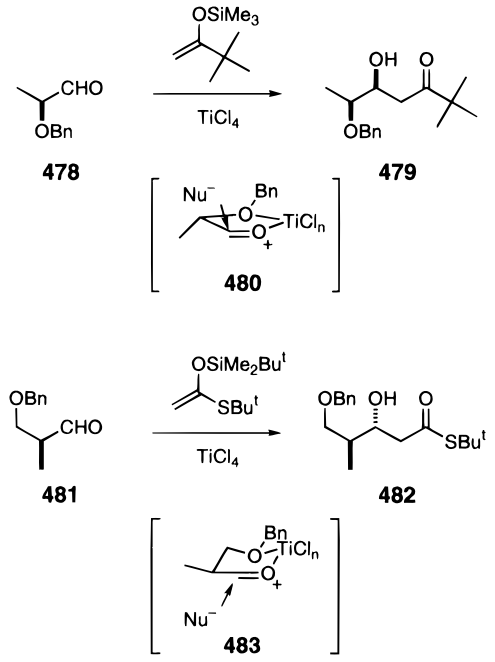
Exceptionally high levels of Cram control can be achieved using the "supersilylating" agents with silyl enol ethers having large silyl groups. The degree of selectivity, typified by the reaction of the aldehyde **449** with the triisopropylsilyl enol ether of acetophenone giving the *syn* silyl ether **477**, is correlated with the steric bulk of the silyl group (Scheme 109).[256] Dithioacetals also show high Cram selectivity, interestingly affected by the size of the arylthio groups.[257,258]

Scheme 109



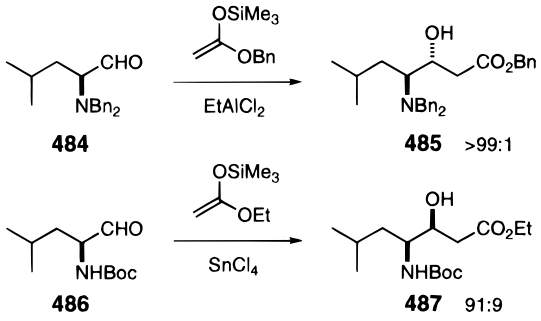
Chelation control is illustrated by the aldehydes **478**[259] and **481**[260] giving the alcohols **479** and **482** in the presence of chelating Lewis acids by way of transition structures **480** and **483** (Scheme 110). Similar reactions take place with silyl dienol ethers.[261]

Scheme 110



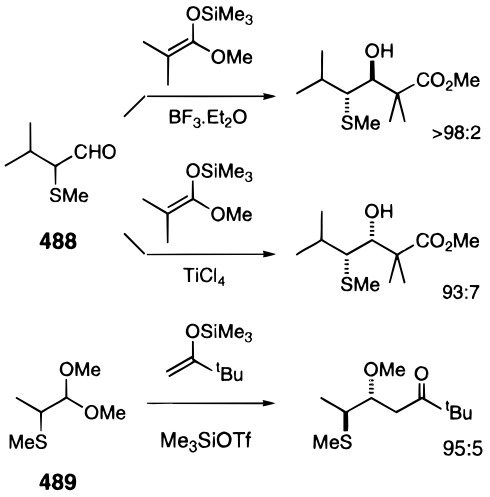
α-Amino aldehydes **484** and **486** also show Cram and chelation control, the former with the nonchelating Lewis acid giving Cram control in favor of the *anti* arrangement **485**, and the latter, with a chelating Lewis acid, giving chelation control in favor of the *syn* arrangement **487** (Scheme 111).[262]

Scheme 111



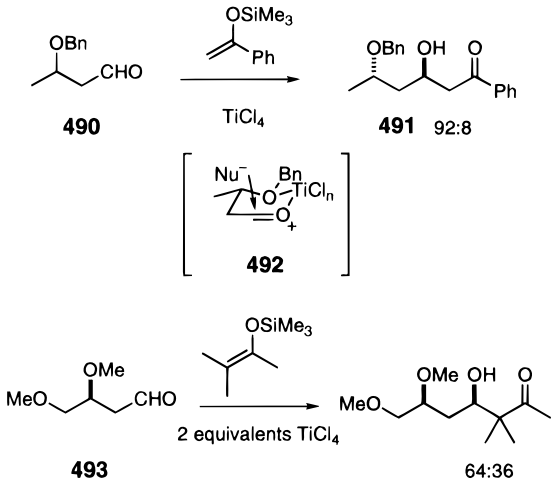
Similar control by choice of Lewis acid can be used with an α-thio aldehyde **488**,[263] and Cram control following the Felkin−Anh rule for the corresponding acetal **489** (Scheme 112).[264]

Scheme 112



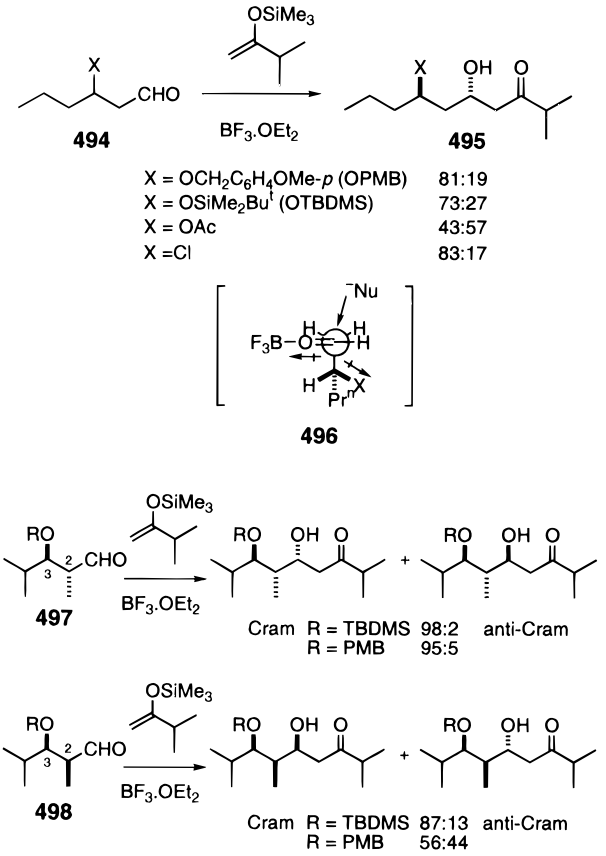
More distant stereogenic centers in the electrophile can control stereochemistry, as in the ether **490**, which reacts with chelation control similar to that shown by the *β*-benzyloxy aldehyde **481**, but now with attack from above **492** leading to a chair conformation and hence the 1,3-*anti* relationship **491** (Scheme 113).[265] The aldehyde **490**, however, can be made to give a different result if 2 equiv of the Lewis acid are added to the aldehyde, coordinating both oxygens and preventing chelation. Stereocontrol is then based on a stereogenic center in an open chain with a 1,3-relationship to the aldehyde carbon, and is correspondingly less. This idea was suggested as a method to overcome a problem (Scheme 179) in the synthesis of pederin, where the aldehyde **493** was induced to give moderate selectivity in favor of the required 1,3-*syn* product (Scheme 113).[266]

Scheme 113



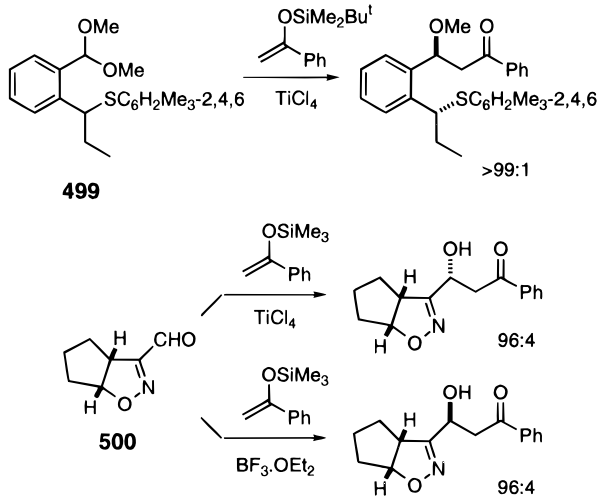
In a more thorough search for 1,3-control in the Mukaiyama aldol reaction, the aldehydes **494** were found to give surprisingly good 1,3 control in favor of the *anti* isomer **495**, even without chelation, when the group X provided a helpful dipolar contribution to the proposed transition structure **496** (Scheme 114). This open-chain 1,3-control can then be combined with Cram control, with C-2 and C-3 matched in the aldehyde **497** and mismatched in the aldehyde **498**. The former gave a high level of stereoselectivity and the latter only a low level (Scheme 114).[267]

Scheme 114



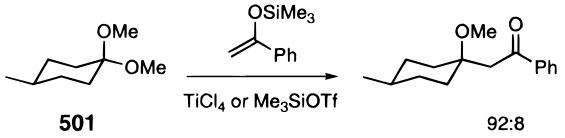
An α-arylthiopropyl group *ortho* to an acetal group, as in the acetal **499**, although nominally 1,4-related, brings the resident stereogenic center closer to the electrophilic atom, making the large size of the aryl group an important contributor to stereocontrol (Scheme 115). The same arylthio group only works moderately well in a conformationally free open-chain system.[268] A wide range of oxazoline aldehydes **500** can be made to give good levels of stereocontrol in either sense, by using chelating or nonchelating Lewis acids to control the orientation of the formyl group (Scheme 115).[269]

Scheme 115



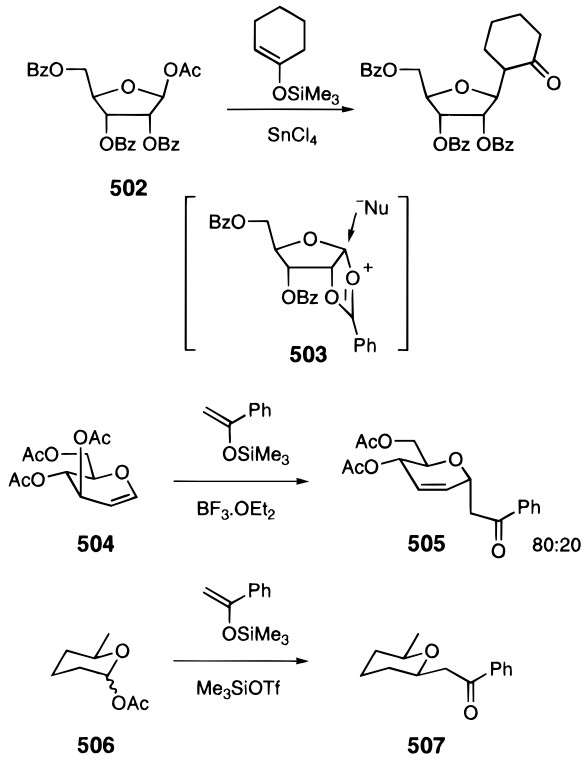
Towards cyclic systems, silyl enol ethers attack cyclohexanone acetals **501** from the equatorial direction with higher selectivity than that shown toward the corresponding ketone (Scheme 116).[270]

Scheme 116



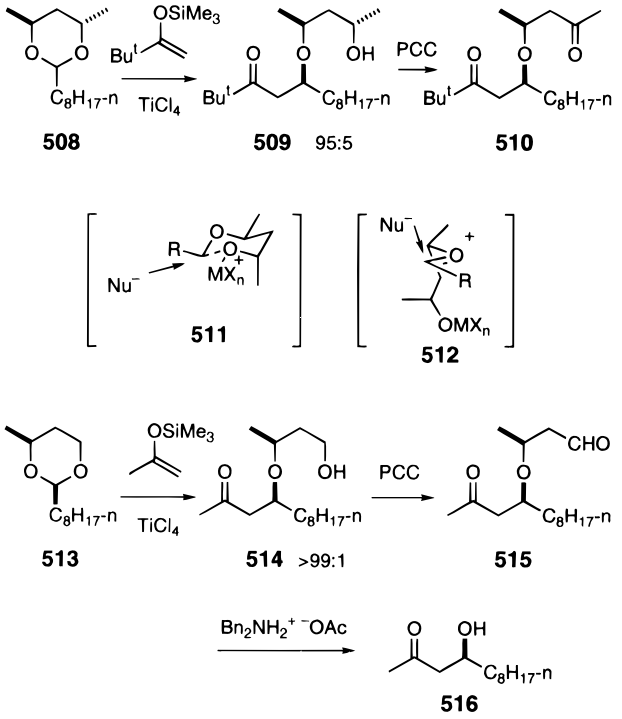
More often of importance in cyclic systems are the reactions with sugar-derived acetals, but allylsilanes are usually used rather than silyl enol ethers with these substrates. When the same substrate has been treated with both silyl enol ethers and allylsilanes, the results are closely similar. The pentose tribenzoate **502** gives the product of β-attack with silyl enol ethers, presumably because the 2-benzoyloxy substituent bridges the lower surface **503** (Scheme 117).[271] The corresponding tribenzyl ether gives the product of α-attack.[272] Glycosidic acetals like the glycal **504** show kinetic selectivity toward silyl enol ethers attacking from the axial direction, *anti* in the anomeric sense to the oxygen lone pair, to give the ketone **505** (Scheme 117).[273,274] The inherent possibility that products like **505** might epimerize, by β-elimination of the glycosidic oxygen and readdition, appears not to be a problem, and a similar reaction has been used in a synthesis of swinholide.[275] Some indication that equilibration might sometimes be a problem comes from the observation that the simple acetal **506** gives only the diequatorial anomer **507** (Scheme 117),[276] but this result and others like it have been explained by ion pairing, in which the oxacarbenium ion holds the triflate ion on the anomerically stabilized face, with the nucleophile attacking from the opposite face.[277]

Scheme 117



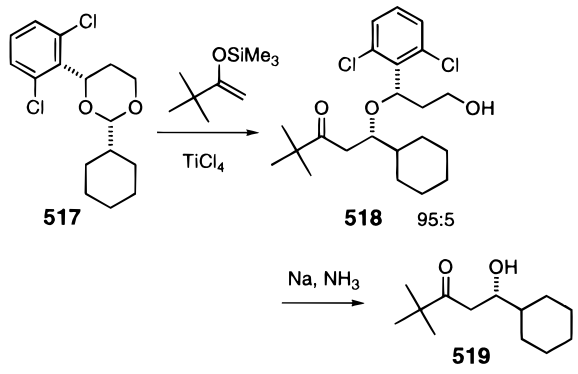
Cyclic and acyclic acetals carrying stereogenic centers in the alcohol portion of the acetal react well, and with high levels of stereocontrol, with a variety of carbon nucleophiles including silyl enol ethers in the presence of Lewis acids, with the acetal **508** giving largely the aldol-like product **509**.[254] The early explanation for the stereoselectivity was that the Lewis acid coordinates more easily to the acetal oxygen adjacent to the axial methyl group, and that C−C bond formation is essentially an S_N2-like reaction **511**, with inversion of configuration at the acetal carbon. There is however, growing evidence, that this is not the whole story, and that the selectivity may be explained by an S_N1 type of reaction with an open-chain transition structure **512**.[254,278] With this particular acetal, there is a problem in the removal of the chiral auxiliary, which does not arise when other silicon-containing nucleophiles like allylsilanes are used. Oxidation to the diketone **510** sets up two β-alkoxycarbonyl arrangements and hence two possible β-eliminations. One solution to this problem was to dispense with one of the methyl groups—in neither explanation **511** nor **512** is the axial methyl group playing any part. The homochiral cyclic acetal **513** gives, therefore, the aldol-like product **514**, in general with even better stereoselectivity than when there are two methyl groups in the auxiliary. The removal of the chiral auxiliary by oxidation to the aldehydo ketone **515** still sets up two β-alkoxycarbonyl arrangements, and hence two possible β-eliminations, but this time it is possible, by a careful choice of base, to induce the β-alkoxy aldehyde **515** to undergo elimination to give the aldol product **516** faster than the elimination within the β-alkoxy ketone part of the structure (Scheme 118).[279,280] A similar reaction using a silyl dienol ether was used in the synthesis of a mevinolin analog.[281] Silyl enol ethers of esters also work, and present no problem in carrying out the selective removal of the chiral auxiliary, as shown by a synthesis of lipoic acid.[282]

Scheme 118



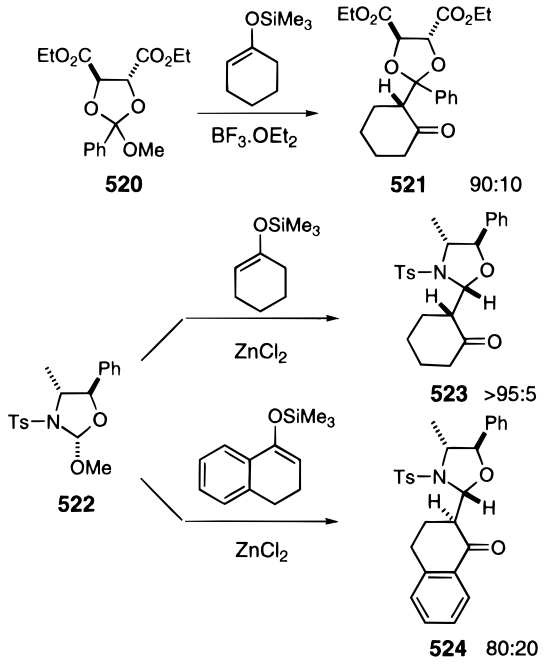
The removal problem has also been solved by having a 2,6-dichlorophenyl group in place of the methyl group, as in the reaction of the silyl enol ether derived from pinacolone with the acetal **517**, giving the aldol-like product **518**. The ether group can be removed by reduction with sodium in ammonia to give the β-hydroxy ketone itself **519** (Scheme 119).[283]

Scheme 119



Other chiral acetals that have been used include, among others,[284] the ortho esters **520**[285] and **522**,[286] which effectively give products **521**, **523**, and **524** of acylation, with the latter giving the opposite stereochemistry when the silyl enol ether has an aromatic ring next to it (Scheme 120). The reaction in Scheme 77 is another example of stereocontrol from a chiral acetal.

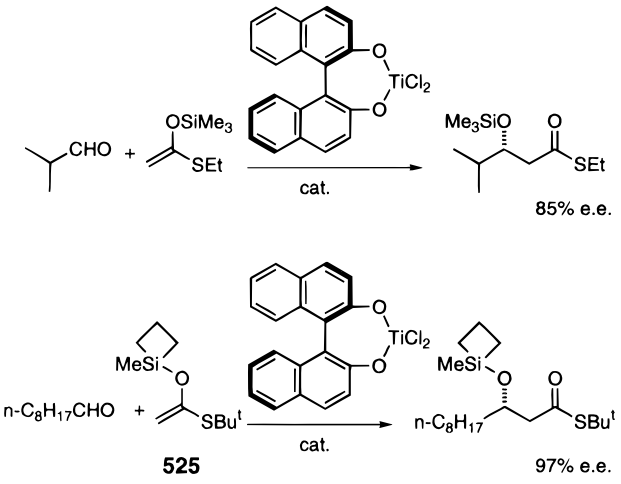
Scheme 120



Menthyl pyruvate induces moderate diastereoselectivity in reactions with silyl enol ethers.[287]

A wide variety of homochiral Lewis acid catalysts have been found to give high levels of enantiocontrol. Among those showing substantial enantiocontrol, in the absence of simple diastereocontrol, are catalysts based on various derivatives of proline,[288,289] other α-amino acids,[290] tartaric acid,[291] menthone,[292] camphor,[293] diphenylethylenediamine,[294] and BINAP (Scheme 121).[295,296] Silyl enol ethers **525** with a

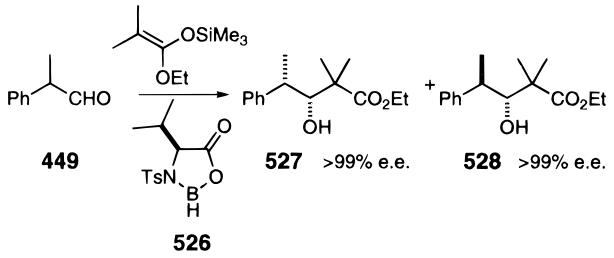
Scheme 121



silacyclobutane ring show enhanced sensitivity to the use of the last of these homochiral catalysts (Scheme 121).[297] The successful reactions are characterized by the absence of water and any other pathway in the catalytic cycle that generates trimethylsilyl triflate or perchlorate, either of which catalyzes the aldol reaction with no enantiocontrol.[298] Chiral tetralkylammonium fluorides have also shown moderate enantiomeric excesses in catalyzing simple aldol reactions.[299]

Powerful enantiocontrol from one of these catalysts **526** completely overcame Cram selectivity, with each enantiomer of the racemic aldehyde **449**, giving different diastereoisomers **527** and **528** (Scheme 122).[300]

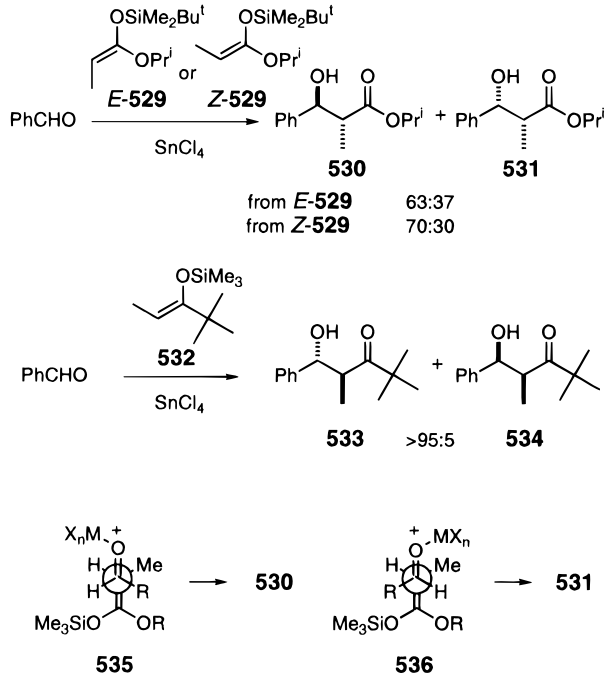
Scheme 122



2. Simple Diastereoselection

Silyl enol ethers carrying a substituent at the nucleophilic carbon can react with aldehydes or their acetals with simple diastereoselectivity, but these reactions are not as well controlled stereochemically, or as predictable, as the corresponding reactions of lithium or boron enolates, which have cyclic transition structures. The stereochemistry of the silyl enol ethers of esters can easily be controlled,[250,251,301] but in a simple system with benzaldehyde, the (*E*)- and (*Z*)-silyl enol ethers (*E*)-**529** and (*Z*)-**529** give the *anti* and *syn* aldols **530** and **531** in comparable amounts, usually in favor of the former,[302] although there is a report of high selectivity with somewhat similar substrates.[303] Most Lewis acids, whether chelating or not, seem to make little difference to the ratio. Many ketone-derived silyl enol ethers are similar to the ester-derived silyl enol ethers, with occasional exceptions such as **532**, which gives high diastereoselectivity in favor of the *anti* aldol **533** (Scheme 123).

Scheme 123

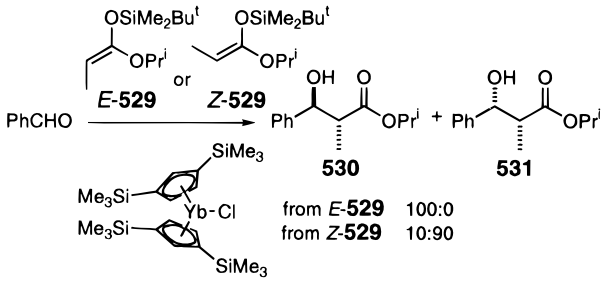


Even a small change in the structure of an exceptional case like this can change the selectivity significantly: replacing the methyl group in the silyl enol ether **532** by a fluorine atom reduces the selectivity in favor of the *anti* isomer to 60:40.[304] For

ketone-derived silyl enol ethers, there is a trend for those reactions catalyzed by boron trifluoride to favor the *syn* arrangement, and for those reactions catalyzed by titanium tetrachloride to favor the *anti* arrangement.

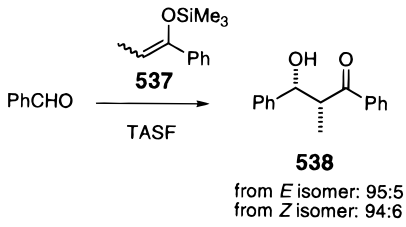
The stereoselectivity is believed to arise from simple nonbonded interactions, probably in antiperiplanar transition structures like **535** and **536**, and chelation to the silicon-bearing oxygen is only rarely suggested. The two transition structures are not obviously very different in energy, with a balance of interactions between the group R, the methyl group, and the Lewis acid coordinated to the oxygen atom. With such a delicate set of forces, it is perhaps not surprising that silyl enol ethers can be made to give high selectivity in one sense or another in specific cases, by suitable variation of the aldehyde or its acetal, the substituent at the nucleophilic carbon, the catalyst, and the type of carbonyl group from which the silyl enol ether is derived. Thus, a europium(III) catalyst reduces the diastereoselectivity in favor of the *anti* isomer in reactions with (*E*)-silyl enol ethers derived from esters,[305] but adding triphenylphosphine to a titanium tetrachloride-catalyzed reaction increases the *anti* selectivity.[306] Trityl perchlorate is apt to lead to rather better selectivity in favor of the *anti* isomer than other Lewis acids.[307] An ytterbium catalyst unusually shows selectivity related to the geometry of the silyl enol ether, with the (*E*)-silyl enol ether (*E*)-**529** giving the *anti* product **530**, and the corresponding (*Z*)-silyl enol ether (*Z*)-**529** giving the *syn* product **531** (Scheme 124),[308] indicative of a cyclic transition structure like that of Zimmerman and Traxler.

Scheme 124



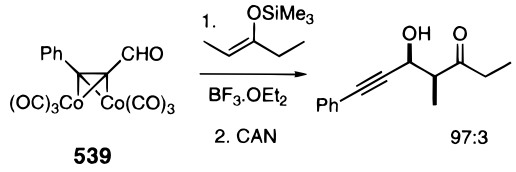
Fluoride ion catalysis is also diastereoselective in favor of the *syn* isomer **538**, regardless of the geometry of the ketone-based silyl enol ether **537**, suggesting an antiperiplanar transition structure (Scheme 125).[309]

Scheme 125



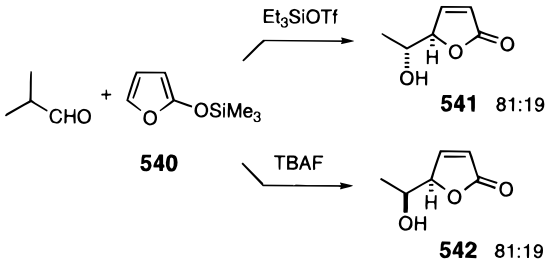
Silyl enol ethers derived from thioamides are also highly *syn* selective with fluoride ion catalysis but give mixtures, with the *anti* isomer predominating, as usual, with Lewis acid catalysis.[310] In contrast, Lewis acid-catalyzed reactions with alkynyl aldehydes **539** complexed to cobalthexacarbonyl are *syn* selective with most silyl enol ethers (Scheme 126).[311]

Scheme 126



The contrast between Lewis acids and fluoride ion also shows up with silyl dienol ether reactions, as with the silyloxyfuran **540**, Lewis acid giving the lactone **541** and fluoride ion its diastereoisomer **542** (Scheme 127).[312] A Lewis acid-catalyzed reaction

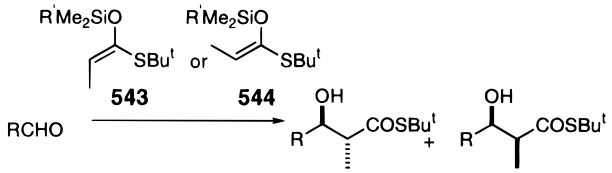
Scheme 127



giving the wrong diastereoisomer was used on a ketone, dihydroionone, in a synthesis of cavernosine, but the fluoride ion-catalyzed step did not work, and could be used only to equilibrate the diastereoisomeric products.[313]

Both stereoisomeric silyl enol ethers **543** and **544** derived from a thioester, in contrast to ester-derived silyl enol ethers, react with aldehydes in the presence of Lewis acids, with good selectivity in favor of the *anti* isomer.[314] However, adding stannic chloride to the silyl enol ether gives a *C*-stannyl intermediate, which reacts with the aldehyde to give largely the *syn* diastereoisomer. Fluoride ion catalysis is, as usual, also selective for the *syn* isomer (Scheme 128).[315]

Scheme 128

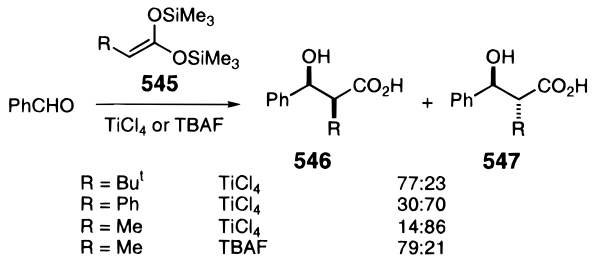


$BF_3.OEt_2$	R = Ph	95:5	from **543**	R' = Bu^t
$BF_3.OEt_2$	R = Ph	96:4	from **544**	R' = Bu^t
$SnCl_4$	R = Pr^i	1:99	from **543** or **544**	R' = Me
TBAF	R = Ph	5:95	from **543**	R' = Me
TBAF	R = Ph	43:57	from **544**	R' = Me

The silyl enol ether **545**, which has only one geometry, gives, with Lewis acid-catalyzed reactions, largely the *syn* isomer **546** when the substituent R is *tert*-butyl, but largely the *anti* isomer **547** when it

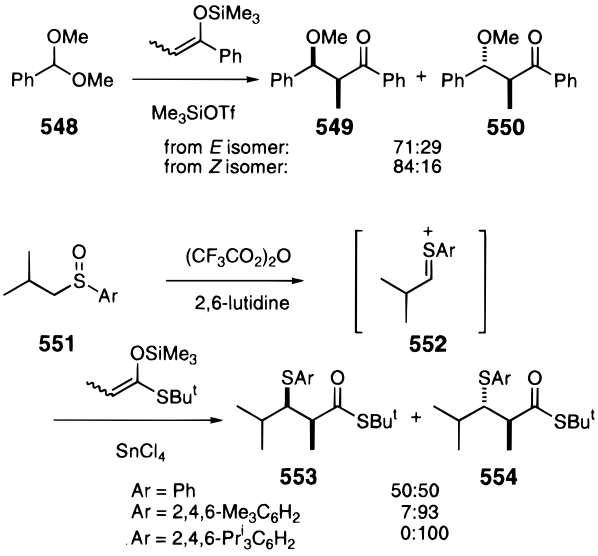
is phenyl or methyl. The corresponding fluoride-catalyzed reaction is, as usual, selective for the *syn* isomer (Scheme 129).[316]

Scheme 129



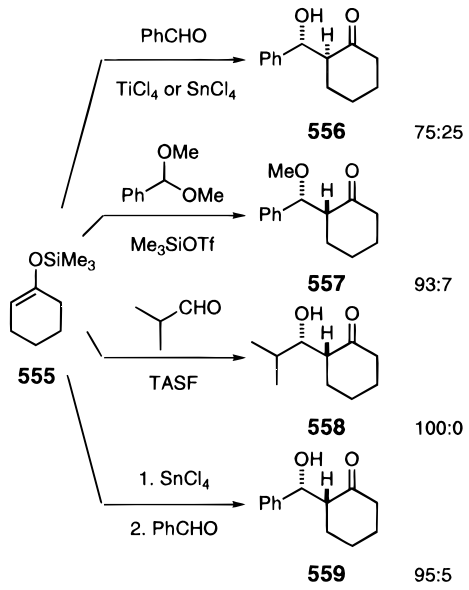
Reactions with acetals **548** are apt to be selective for the *syn* isomer **549** regardless of the geometry of the silyl enol ether,[277] but thioacetals, or better the thienium ion intermediate **552** derived from a Pummerer reaction on the sulfoxide **551**, can be made to be selective for the *anti* isomer **554** (Scheme 130).[257]

Scheme 130



The silyl enol ethers of cyclic ketones show simple diastereoselectivity similar to that of their open-chain analogs. Thus the Lewis acid-catalyzed reaction of the silyl enol ether **555** of cyclohexanone and benzaldehyde gives mainly the *anti* isomer **556**,[317] the reaction with acetals gives mainly the *syn* isomer **557**,[277,318] and the fluoride-catalyzed reaction with isobutyraldehyde also gives mainly the *syn* isomer **558** (Scheme 131). In the last reaction, TASF gives good stereocontrol, only with a nonaromatic aldehyde, and there is evidence of equilibration with both TBAF[319] and TASF.[309] If a silyl enol ether is first treated with stannic chloride, an α-trichlorostannyl ketone is produced, and this then reacts with aldehydes with a high level of stereoselectivity, by way of a cyclic transition structure, in favor of the *syn* isomer **559** (Scheme 131). The normal Mukaiyama aldol reaction, in which the Lewis acid is added to the aldehyde first or is added to the mixture of aldehyde and silyl enol ether, does not therefore take place by way of this kind of intermediate.[320] Other

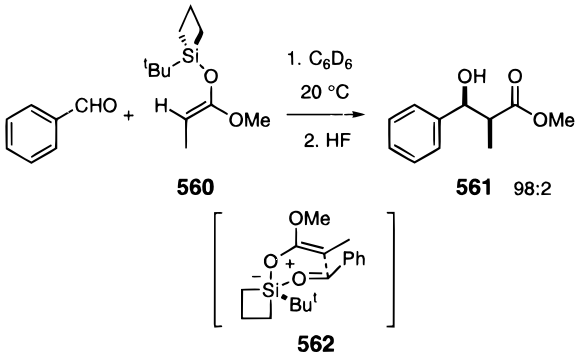
Scheme 131



Lewis acids favor the formation of the *syn* isomer,[321] as also does the use of high pressure[322] or water.[323] In the latter cases reaction takes place by way of a cyclic transition structure in which the silyl group itself acts as the Lewis acid.

Silyl enol ethers with a silacyclobutane ring and *E* geometry **560** give the *syn* alcohols **561**, with a high level of selectivity (Scheme 132). The silyl enol ethers

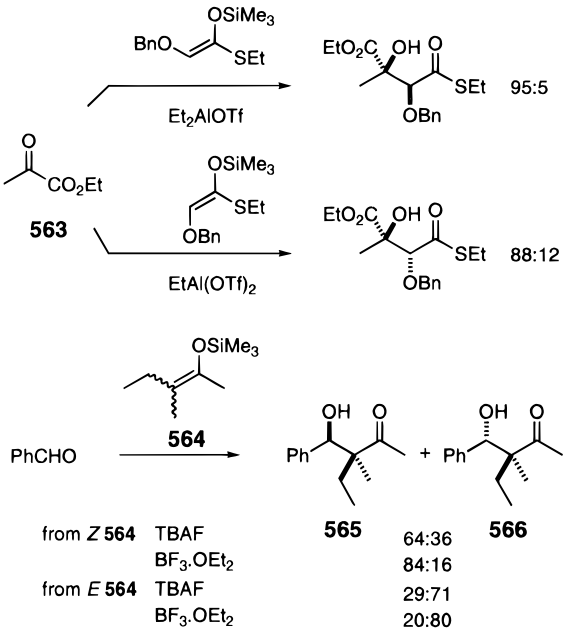
Scheme 132



may be derived from ketones, esters, thioesters, or amides. The reactions proceed at a temperature higher than the usual Mukaiyama aldol reactions, but without added catalyst, probably through a boatlike transition structure **562**, in which the silicon, acting as Lewis acid, coordinates to the aldehyde, and the *tert*-butyl group on the silicon is influential in balancing the nonbonded interactions that make the boat preferred over the more usual Zimmerman–Traxler-like chair. The electrophilicity of the silicon is a consequence of the release of strain in the four-membered ring that accompanies coordination by a Lewis base. Surprisingly, the corresponding *Z* isomers are not usefully stereoselective, but they are much less reactive, so that minor amounts of them in the starting silyl enol ethers do not interfere with obtaining a diastereomerically pure product.[324,325]

Simple diastereoselection has also been found, by careful choice of catalyst and other variables, for reactions with α-keto esters **563**,[326] and for the formation of quaternary centers **565** and **566** from the disubstituted silyl enol ether **564** (Scheme 133).[327]

Scheme 133

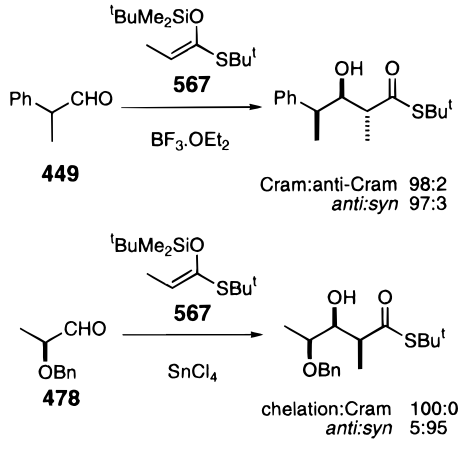


3. Simple Diastereoselection Combined with Stereoselectivity from the Electrophile

Simple diastereoselection can be combined with Cram or chelation control on α and *β*-chiral aldehydes, with many of the examples quoted in connection with allylsilanes in Schemes 108−113 having their counterparts with silyl enol ethers carrying a substituent on the nucleophilic carbon.

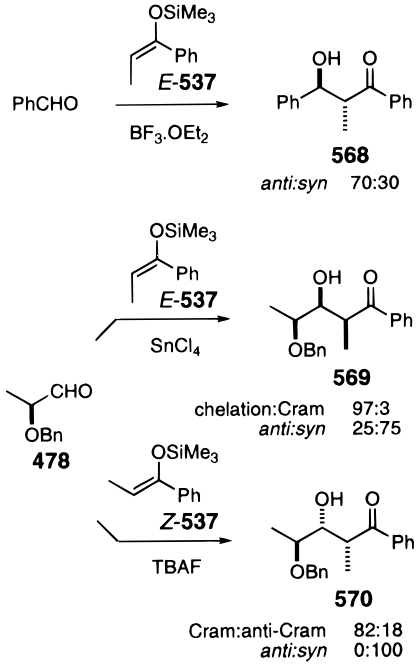
The well-behaved silyl enol ether **567** of a thioester reacted with 2-phenylpropionaldehyde (**449**) to give largely the product of Cram control with the *anti* arrangement between the two new stereogenic centers.[328] With a substrate **478** having an α-coordinating substituent, and using a chelating Lewis acid, the same silyl enol ether **567** gave only chelation control, but now largely *syn* with respect to the two new stereogenic centers (Scheme 134).[328]

Scheme 134



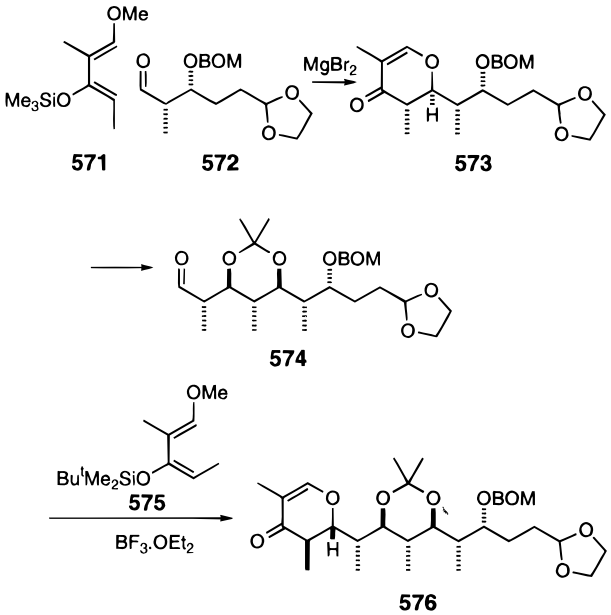
Simple ketone-derived silyl enol ethers are just as chelation selective, but are usually, although not always, depending upon their structure and geometry, less selective with respect to the new stereogenic centers than the thioester-derived silyl enol ethers. On the other hand, the simple diastereoselection is again reversed, and greatly improved, when it is combined with chelation control. Thus, whereas benzaldehyde reacts with the silyl enol ether (*E*)-**537** with moderate *anti* selectivity to give the aldol **568**, as usual, the chelated chiral aldehyde **478** reacts with it with high *syn* selectivity to give largely the all *syn* aldol **569** (Scheme 135).[302,329] The aldehydes **481**[328,329] and **490**[265] are similar. The usual selectivity for the *syn* aldol **570**, but combined with Cram control, is produced by catalysis with fluoride ion.[329]

Scheme 135



A special case is the reaction between one of Danishefsky's dienes **571** and the aldehyde **572** giving the product **573** of chelation control with respect to the aldehyde, and with a high level of simple diastereoselection, because it is a hetero-Diels−Alder reaction. Subsequently, in this synthesis of zincophorin, a later intermediate **574** was treated with another of Danishefsky's dienes **575**, giving the product **576** (Scheme 136).[330] This latter reaction is Cram selective on the aldehyde, since the

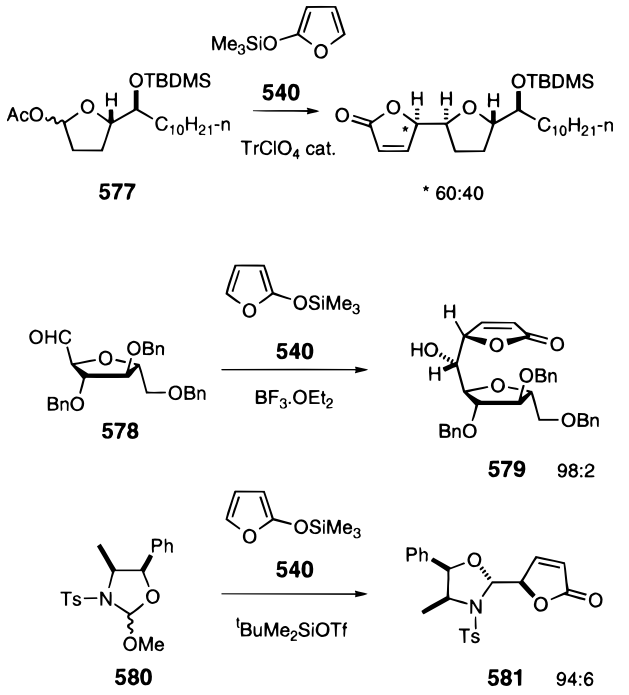
Scheme 136



Lewis acid is not able to chelate, but it does not appear to be a Diels−Alder reaction. Supported by evidence from several other examples,[331] it is probably a Mukaiyama aldol reaction giving simple diastereoselection in the *anti* sense, but somewhat unusually in this case dependent upon the geometry of the silyl enol ether, since the simple diastereoselection with the *Z* isomer of **575** took place in the *syn* sense. A silicon-containing nucleophile was used a third time for stereocontrol in this synthesis, when the glycal acetate derived by reduction of the dihydropyrone **576** was treated with (*Z*)-crotyltrimethylsilane, in a reaction similar to that in Scheme 204.

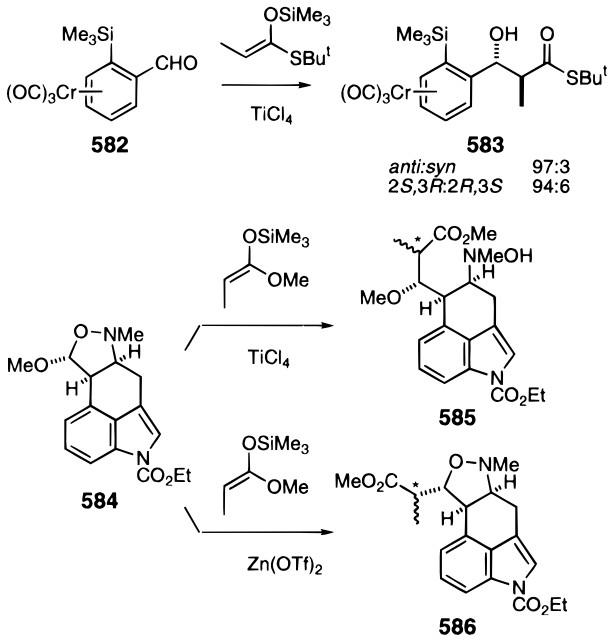
Simple diastereoselection can also be combined with anomeric attack on sugars, but this has been little studied with silyl enol ethers. The pentose tribenzoate **502** from Scheme 117 and the silyl enol ether of cyclohexanone are reported to give one diastereoisomer from β-attack, but the corresponding tribenzyl ether gives two products of α-attack, but with the ratio not reported.[272] A related reaction is the attack by 2-[(trimethylsilyl)oxy]furan (**540**) on the acetal **577**, which is selectively *anti* to the resident substituent, but shows little simple diastereoselection (Scheme 137).[332] On the other hand, simple diastereoselection with sugar aldehydes has been studied extensively using the same silyl dienol ether **540**,[333] extending the reaction illustrated in Scheme 127. For example, this silyl dienol ether reacted with the aldehyde **578** in the presence of boron trifluoride etherate to give the lactone **579** with complete Cram selectivity and the usual high simple diatereoselection (98:2) (Scheme 137).[334] The product **579**, with a double bond easily dihydroxylated, is easily converted into a sugar with four more hydroxylated carbon atoms than the starting material **578**. Sequences like this, and others based on it using silyloxythiophens and pyrroles, have been used several times for stereoselective chain extension of sugars,[335] and for the synthesis of highly functionalized thiosugars,[336] amino and aza sugars,[337] sugar lactams,[338] amino acids,[339] and alkaloids.[340] The same silyl dienol ether **540** can be combined with a homochiral formyl cation reagent **580**, as in the synthesis of the lactone **581** (Scheme 137).[341] Simple diastereoselection of this kind is also evident in the reaction of the related formyl cation equivalent **522** in Scheme 120.

Scheme 137



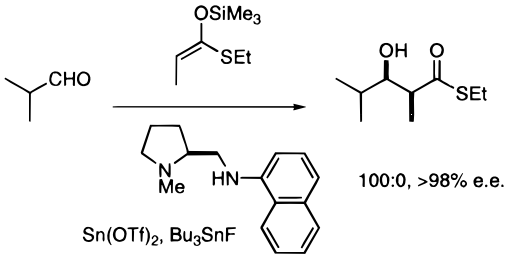
Other homochiral substrates adding absolute control to simple diastereoselection include the chromium complexed aldehyde **582**, which gave normal diastereocontrol in favor of the *anti* isomer **583**, and high enantiocontrol, and from which both the chromium and the silyl groups can be removed.[342] The more elaborate acetal **584**, gave good Cram selectivity with titanium tetrachloride and good *exo* attack on the bicyclic system with zinc triflate, but in neither case was there any simple diastereoselection at the stereogenic centers marked with an asterisk in the products **585** and **586** (Scheme 138).[343]

Scheme 138



Simple diastereoselection can be combined with the presence of a homochiral Lewis acid catalyst to give very largely single diastereoisomers in high enantiomeric excess. Most of the catalysts listed earlier as inducing high enantiomeric excesses can be combined with simple diastereoselection, including those based on proline (Scheme 139),[289,344] on tartaric acid,[291] on menthone,[292] on BINAP,[345] and on a 2,5-diphenylboracyclopentane.[346]

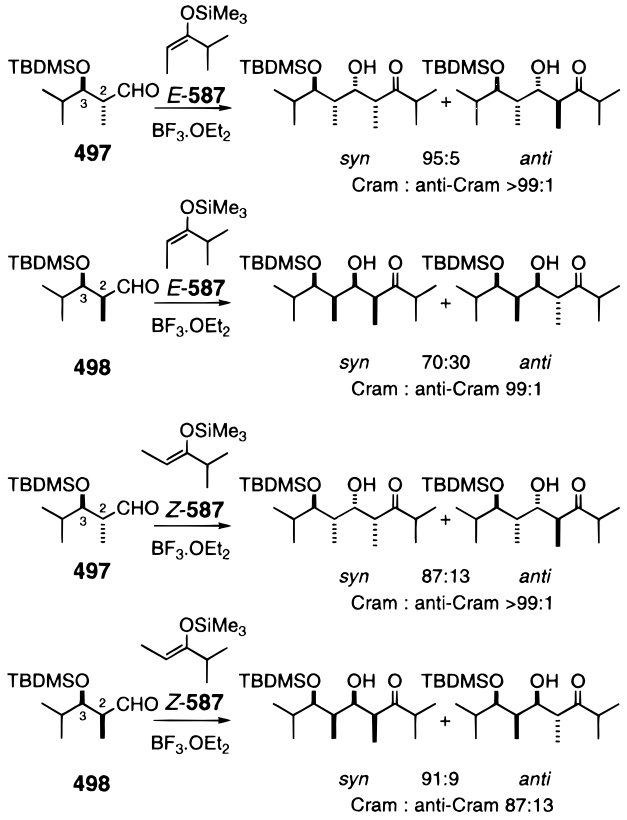
Scheme 139



The combined effects of Cram control and control from C-3 that were illustrated in Scheme 114 can be added to simple diastereoselection, with both the (*E*)-

and (*Z*)-silyl enol ethers **587** reacting with high selectivity in favor of the *syn* adducts, and with high levels of Cram control (Scheme 140).[347]

Scheme 140

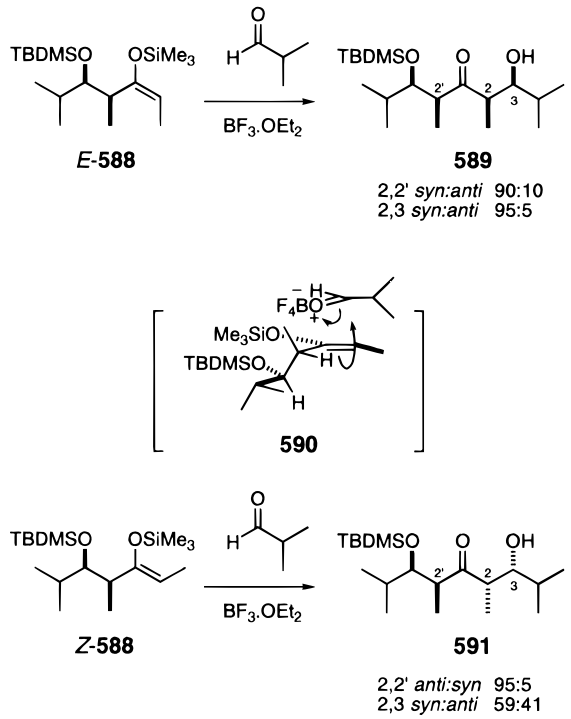


4. Diastereoselection Controlled Only by the Silyl Enol Ether

Silyl enol ethers offer much more scope than allylsilanes to have the stereocontrol elements built into the silyl enol ether structure. We shall review first those systems where the carbon framework is stereochemically biased, where there are many examples showing good stereoselectivity. Secondly we shall review those cases where the ester or amide group in the silyl enol ethers of esters or amides can carry a chiral auxiliary. Finally, we defer to section XVIII those reactions of silyl enol ethers where the silyl group itself is chiral or carries a chiral substituent.

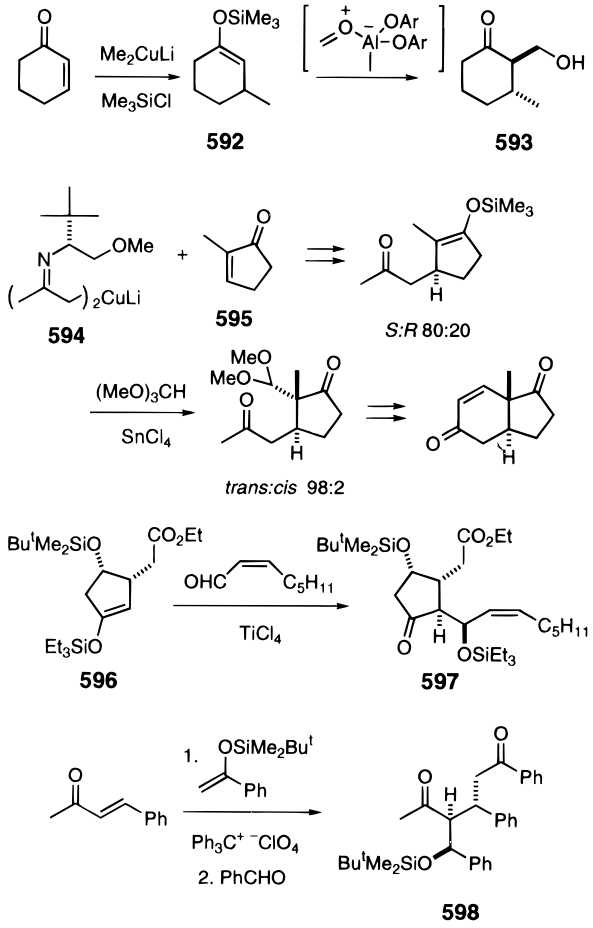
With silyl enol ethers having allylic stereogenic centers there is substantial open-chain control of the relative stereochemistry across the ketone group, with (*E*)- and (*Z*)-silyl enol ethers giving different products. Thus the (*E*)-silyl enol ether (*E*)-**588** gives largely the product **589** with the *syn* relationship between C-2 and C-2′ across the ketone group, and, as usual in this system, the *syn* relationship at the two new stereogenic centers C-2 and C-3. A plausible transition structure **590** is related to that for the allylsilane system **157** with the electrophile attacking *anti* to the large group. The corresponding (*Z*)-silyl enol ether (*Z*)-**588** gives highly selectively the *anti* relationship **591** between C-2 and C-2′, but only a moderate degree of selectivity in favor of the *syn* relationship between C-2 and C-3 (Scheme 141).

Scheme 141



In simple cyclic enones, conjugate addition and trapping with a silyl chloride sets up a biased silyl enol ether like **592** apt to be attacked *anti* to the recently introduced substituent to give alcohols like **593** (Scheme 142).[348] More elaborately, the addition of a homochiral equivalent of acetone, the hydrazone

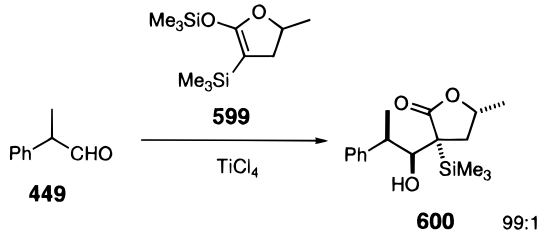
Scheme 142



cuprate **594**, to 2-methylcyclopentenone **595**, followed by reaction with methyl orthoformate was used in a synthesis of the *trans* steroidal CD ring system (Scheme 142).[349] The conjugate addition does not have to be by a cuprate: the Mukaiyama−Michael reaction can also be followed by a Mukaiyama aldol reaction giving the cyclopentanone **596** → **597**, in which the incoming group is *trans* to both resident side chains in a synthesis of prostaglandin $F_{2\alpha}$ (Scheme 142).[350] A silyl enol ether can also be used to set up the *trans*-disposed prostaglandin chains by a coupling reaction with a vinylborane.[351] In an open-chain system giving the diketone **598** three contiguous stereogenic centers are set up with a good level of stereoselectivity (Scheme 142).[352]

With more distant stereogenic centers on a ring, the sense of attack, *syn* or *anti* to the resident center, depends upon the relationship and the ring size. 1,3-Relationships are usually set up *trans*, both in five- and six-membered rings. The most dramatic example is between the racemic aldehyde **449** and the racemic silyl enol ether **599**, setting up a racemic lactone **600** with four stereogenic centers (Scheme 143). This reaction demonstrates how a high level

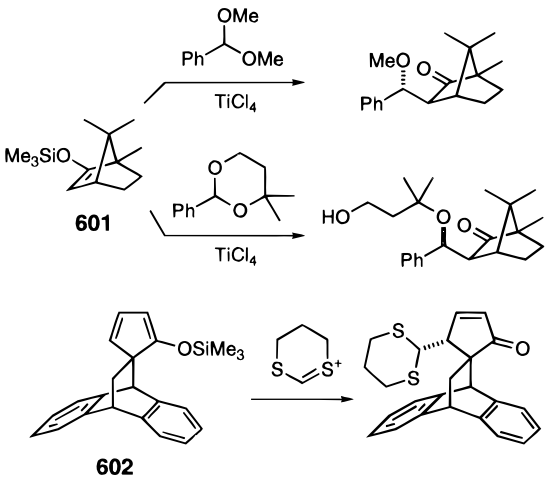
Scheme 143



of diastereocontrol, coupled with Cram control, and a high level of 1,3-attack *anti* to the resident substituent leads to a high level of chiral recognition between the two partners.[353] There are several more simple examples of 1,3-control in the *anti* sense,[354] and one example of 1,4-control in the *syn* sense.[309]

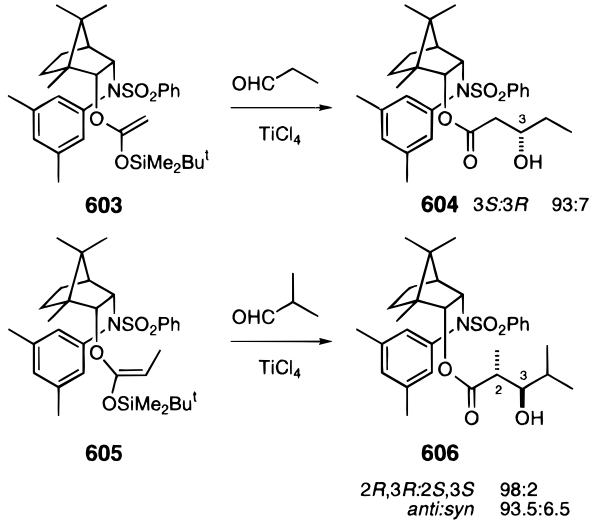
The rather less predictable bicyclic system of camphor (**601**)[355] and the tricyclic system **602** also give good control, with the latter used in a synthesis of sarkomycin, where the phenanthrene ring system protected the exocyclic double bond as well as providing stereocontrol (Scheme 144).[356]

Scheme 144



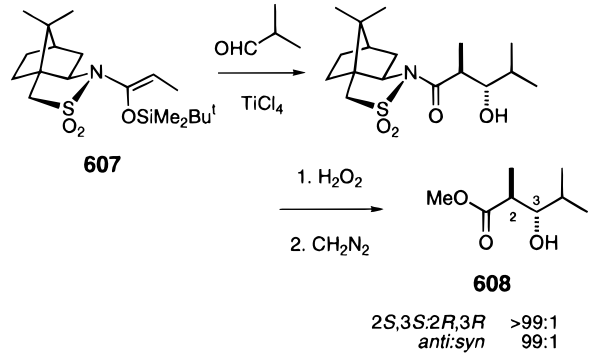
The ester or amide group in the silyl enol ethers of esters or amides can carry a chiral auxiliary, temporarily attached, and this has proved to be a fruitful way to introduce enantiomeric control into organic synthesis. Thus a camphor-derived chiral auxiliary has given a high level of control to the Mukaiyama aldol reaction of the silyl enol ether **603** with no substituents on the nucleophilic atom, and the level of control was better than that with the corresponding lithium enolate. The (*E*)-silyl enol ether **605**, where there is a substituent on the nucleophilic atom, similarly gave high control, but in the opposite sense, with a high level of simple diastereoselectivity in favor of the *anti* isomer combined with a high level of enantiocontrol to give largely one product **606** (Scheme 145).[357]

Scheme 145



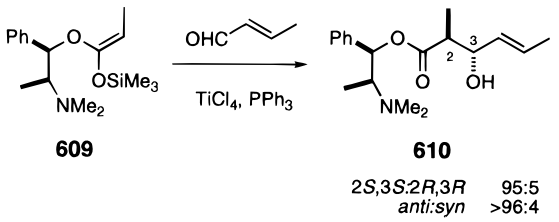
A different camphor-derived chiral auxiliary attached as an imide to the (*Z*)-silyl enol ether **607** has been used for aldol reactions (Scheme 146),[358] where the product **608** is easily removed from the auxiliary. A similar chiral auxiliary has been used for the synthesis of α-amino acids.[359]

Scheme 146



The most studied of chiral auxiliaries for use with silyl enol ethers are those based on ephedrine, which have been used with many electrophiles, including Mukaiyama aldol reactions such as **609** → **610**

Scheme 147

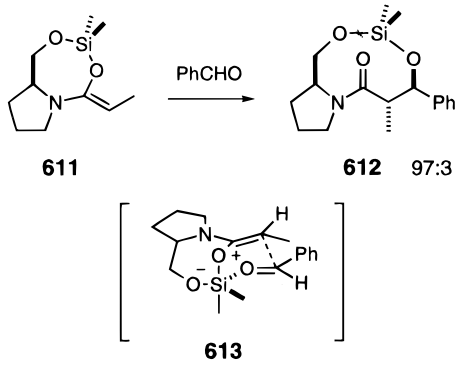


(Scheme 147),[306,360] and another used in a synthesis zincophorin.[361]

Variations in the ephedrine-derived chiral auxiliary have been studied in order to identify its key features: an aryl group proves to be essential.[362] Other chiral auxiliaries have been based on valine[363] and mandelic acid,[364] and used for alkylation and hydroxylation, respectively. It is of course essential in all of this work to control the geometry of the double bond of the silyl enol ether, and this has proved to be troublesome with esters of 8-phenylmenthol.[365]

A rather different chiral auxiliary has been tied not only to the nitrogen of the silyl enol ether **611** of an amide, but also to the silyl group. The higher Lewis acidity of the silicon atom, since it now has two electronegative groups attached to it, allows the aldehyde to coordinate to it and creates a highly ordered transition structure **613** with a boatlike conformation for attack on the double bond reminiscent of that seen in the transition structure **562**. The result is the clean formation of the *anti* product **612** (Scheme 148).[366] This example could as reasonably

Scheme 148

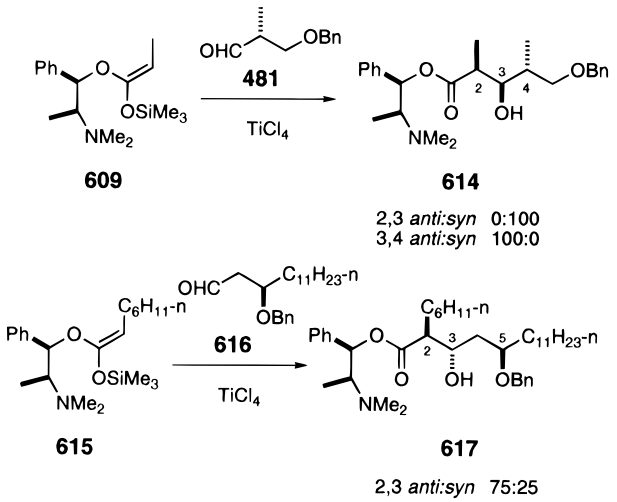


have belonged in sections VI.F, XVIII.B, or XIX.A, where there are other examples of silyl enol ethers showing stereochemical control stemming from bridging or from chirality attached to the silyl group.

5. Multiple Diastereoselection

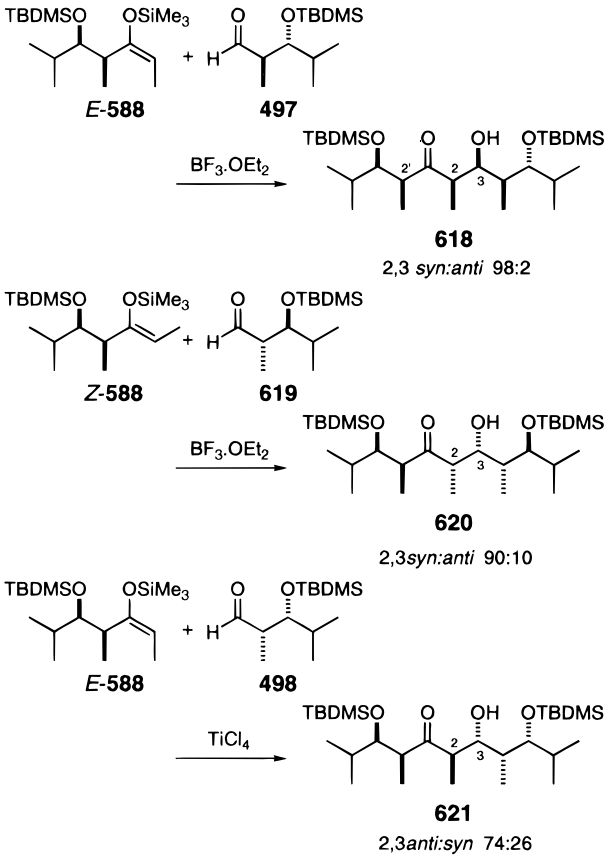
When both the silyl enol ether and the aldehyde have a preferred stereoselectivity, there is an even greater number of possible products, but matching the stereochemical preferences of the silyl enol ether and the aldehyde, can lead to clean reactions, even in the absence of a cyclic transition structure, provided, of course, that both components are homochiral. Thus the combination of the silyl enol ether **609** and the homochiral aldehyde **481** combine to create in the product **614** the same absolute stereochemistry at C-2 as in **610** and, because of chelation control in the electrophile, the *anti* relationship between C-3 and C-4. In consequence, a *syn* relationship is set up between C-2 and C-3 (Scheme 149).[360] In a synthesis of tetrahydrolipstatin, the silyl enol ether **615** gave the usual absolute stereocontrol at C-2, and chelation control from the aldehyde **616** at C-3, but this time setting up a 2,3-*anti* relationship **617** (Scheme 149).[367]

Scheme 149



Without the benefit of chelation, and continuing the open-chain story from Schemes 114 and 140, the (*E*)-silyl enol ether (*E*)-**588** and the aldehyde **497** were a fully matched pair. When combined, they gave the aldol product **618** with high diastereoselectivity in the creation of both new stereogenic centers in the Cram sense, with the usual preference for the *syn* aldol, and the preference for the *syn* relationship between C-2 and C-2′ across the ketone group. The corresponding (*Z*)-silyl enol ether (*Z*)-**588** was not intrinsically as diastereoselective, because the substituent on the double bond *cis* to the stereogenic center at C-2 is only hydrogen, nor is it as selective in favor of the *syn* product, but matching its diastereoface selectivity to that of the aldehyde **619**, which is the enantiomer of **497**, still created largely the *syn* product **620** (Scheme 150). The related *anti* aldols cannot be prepared as efficiently, because full matching is no longer possible, but titanium tetrachloride, which does show some preference for giving the *anti* aldols, can be used, and, in otherwise matched pairs, such as the combination of the silyl enol ether (*E*)-**588** with the aldehyde **498**, gives quite good control in favor of the aldol product **621** (Scheme 150). The combination of silyl enol ether and aldehyde is now becoming stereochemically more predictable—even the effect of the stereocenter β to the carbonyl group can be harnessed to give further levels of matching,[368] and a reaction similar to (*Z*)-**588** + **619** → **620**, but in an even more substantial pair of reagents, has been used in a synthesis of erythronolide.[347]

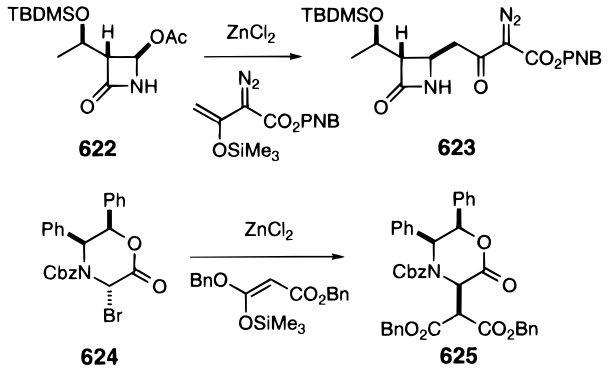
Scheme 150



C. Intermolecular Attack on Iminium Ions[369]

Cyclic iminium ions and acyliminium ions such as those derived from the β-lactam **622**[370] and the glycinate **624**[371] react with silyl enol ethers with control by the resident substituent(s) giving the incoming group *trans*-**623** or *cis*-**625** to the resident groups (Scheme 151).

Scheme 151

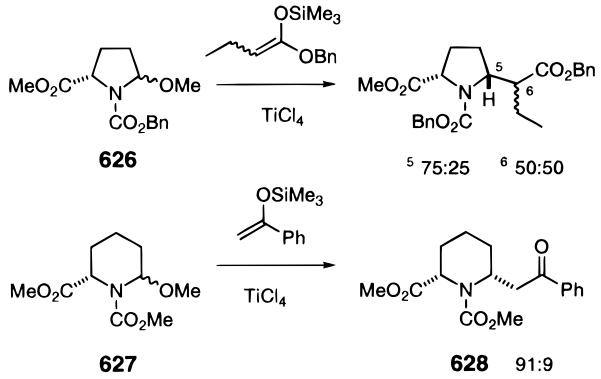


There are similar reactions with pyrrolidines **626**[372] and piperidines **627**, also quite frequently setting up a *syn* relationship across the ring, as in the piperidine **628**[373] (Scheme 152).

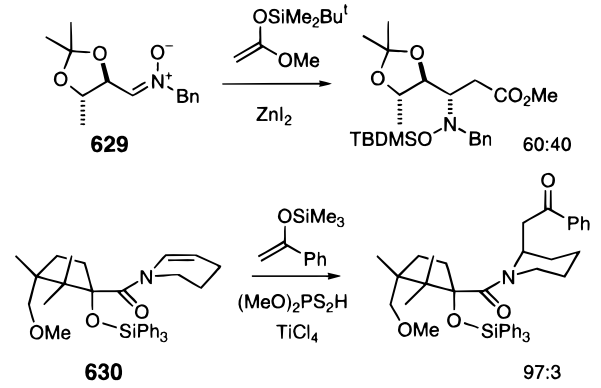
Neighboring and more distant stereogenic centers in open-chain imines can also influence the diastereoselectivity, as in the reactions of the nitrone **629**[374] and of the enamide **630**[375] (Scheme 153).

A stereogenic center adjacent to the nitrogen atom provides a chiral auxiliary that can be removed later,[376] and can be joined to an aldehyde *in situ* without having to isolate the imine.[377] Thus a phenylglycine-derived chiral auxiliary in the imine

Scheme 152

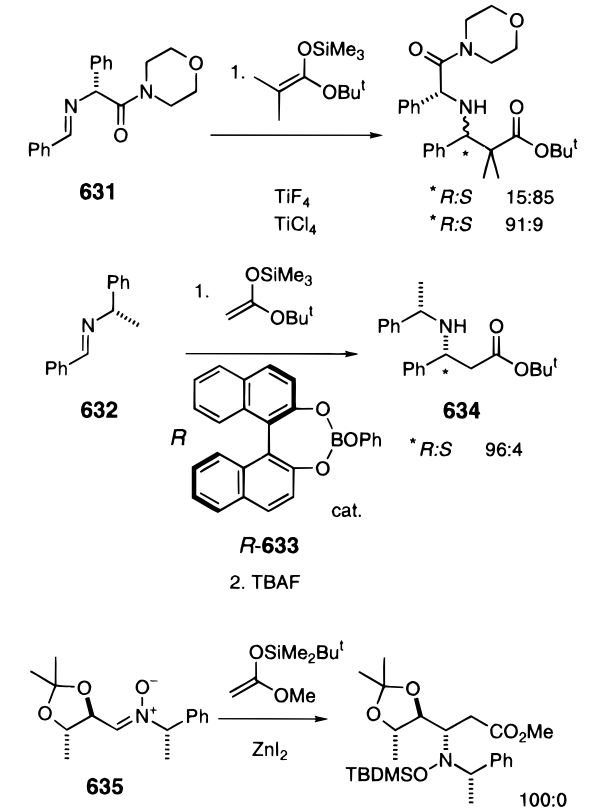


Scheme 153



631 gave opposite enantiomers with different Lewis acids (Scheme 154).[378] The stereocontrol from such

Scheme 154

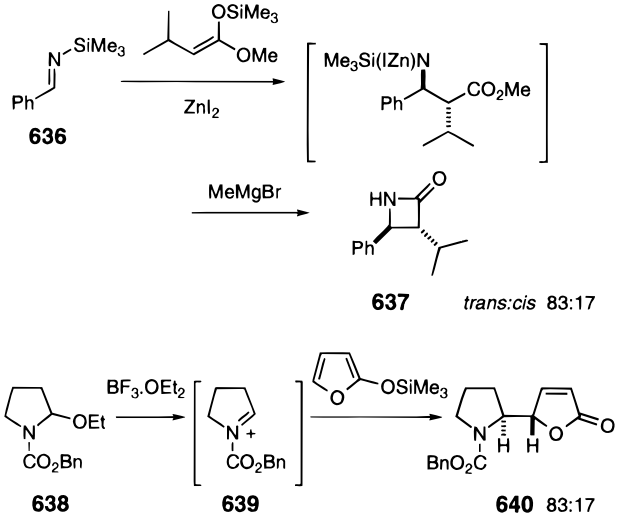


a chiral auxiliary can be augmented with other stereocontrol features. Thus, although moderately effective alone, the α-methylbenzylamine group attached to the nitrogen can be combined with a

homochiral catalyst, as in the reaction of the imine **632**, where the matched pair is the *S* amine and *R* catalyst **633** giving the (*R*)-β-amino ester **634** (Scheme 154).[379] Similarly, in the reaction of the nitrone **635**, which illustrates the matched pair, the extra stereogenic center improves upon the selectivity seen in **629** in Scheme 153.[374]

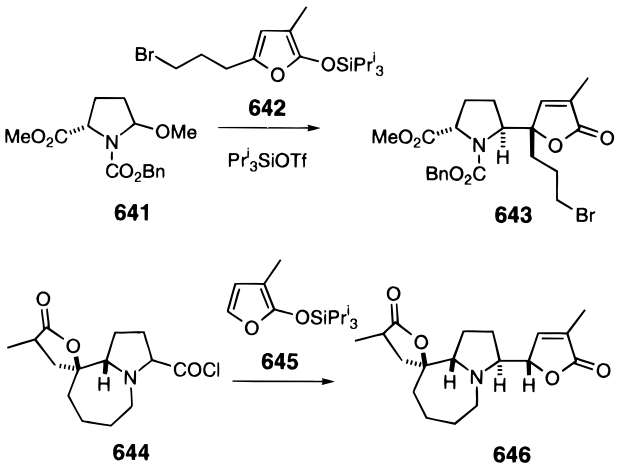
Simple diastereocontrol is also seen with imines, generally, but not always,[380] in favor of the *anti* isomer, as with the silylated imine **636**,[381] which can be used *in situ* for making *trans* disubstituted β-lactams **637**, and with the cyclic acyliminium ion **639** derived from the aza acetal **638** (Scheme 155).[382]

Scheme 155



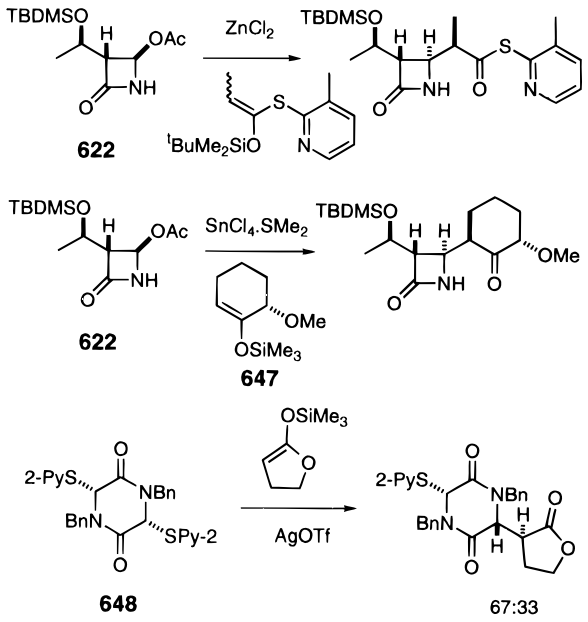
The latter reaction, setting up the substituents at the ring junction with an *anti* relationship, as drawn **640**, can be combined with diastereocontrol from the electrophile. The siloxyfuran **642** reacted with the aza acetal **641** to give largely the diastereoisomer **643** with the same relationship at the ring junction, and with attack *anti* to the methoxycarbonyl group. This type of reaction was then used a second time by combining an imine derived by decarbonylation of the unstable acid chloride **644** with the siloxyfuran **645** to give largely the dilactone **646**, a late intermediate in a remarkably short synthesis of (+)-croomine (Scheme 156).[383]

Scheme 156



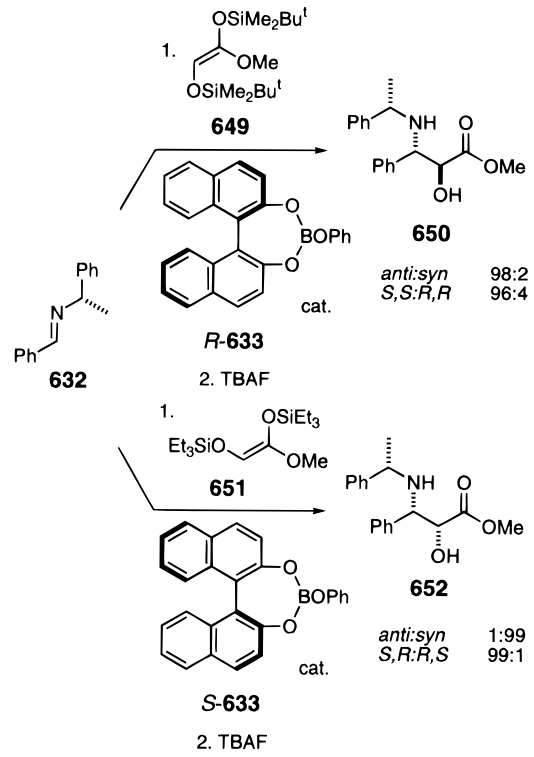
Simple diastereocontrol has been combined with attack on the less-hindered side of the iminium ion derived from the β-lactam **622** in a synthesis of a 1β-methylcarbapenem,[384] and has been extended to a homochiral silyl enol ether **647** matched to the homochiral iminium ion derived from the lactam **622**.[385] A different homochiral acyliminium ion derived from the glycine anhydride **648** also showed simple diastereocontrol in a synthesis of bicyclomycin (Scheme 157).[386]

Scheme 157



The reaction of the imine **632** in Scheme 154 can be extended to include simple diastereo- and enantioselectivity. The reactions (Scheme 158) are unusual in being stereospecific—giving the *anti* aldol **650** from the (*E*)-silyl enol ether **649**, and the *syn* aldol **652** from a (*Z*)-silyl enol ether **651**. The matched pairs in each case, (*R*)-**633** with the (*E*)-silyl

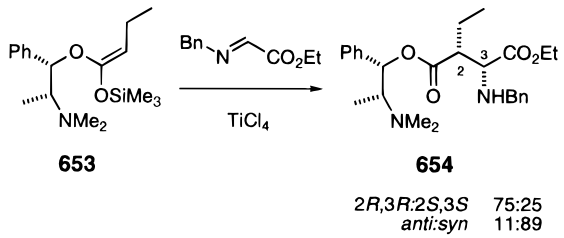
Scheme 158



enol ether **649**, and (*S*)-**633** with the (*Z*)-silyl enol ether **651**, give the diastereoisomers **650** and **652** with high enantio- and diastereoselectivity.[379]

The ephedrine-based chiral auxiliary has also been used in reactions with imines **653** → **654** (Scheme 159) in a synthesis of β-lactams,[387] with selectivity somewhat lower but in the opposite sense, giving the *syn* adduct, to the corresponding aldol reaction in Scheme 147.

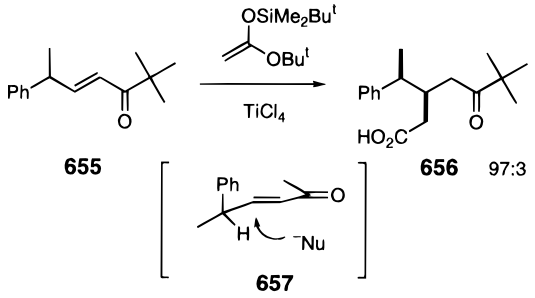
Scheme 159



D. Intermolecular Attack on Enones[388]

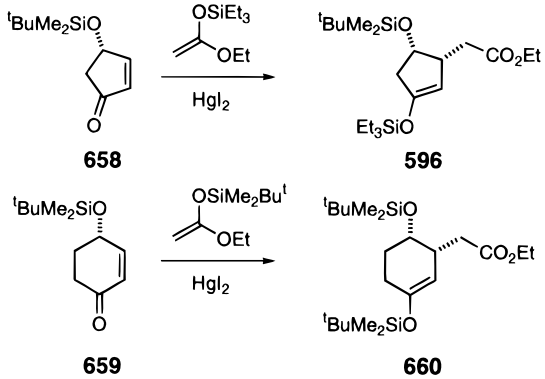
Silyl enol ethers react with α,β-unsaturated ketones to give 1,5-dicarbonyl products in a reaction known as the Mukaiyama−Michael reaction. The neighboring stereogenic center in the enone **655** gives a product **656** with selectivity controlled by a modified Felkin−Anh rule **657** in which the hydrogen atom on the stereogenic center, rather than the medium-sized group, is inside (Scheme 160).[389]

Scheme 160



An oxygen substituent adjacent to the electrophilic carbon in a five-[350,390] or six-membered[391] ring, as in the enones **658** and **659**, induces unhindered silyl enol ethers to attack highly selectively *syn* in contrast to organometallic nucleophiles, and the product silyl enol ethers **596** and **660** (Scheme 161) are set up for

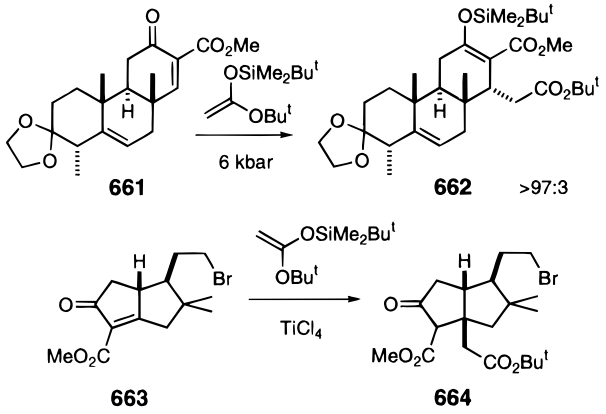
Scheme 161



further stereoselective reactions of the type already seen in Scheme 142. However, with a silyl enol ether having a fully substituted nucleophilic atom, where steric effects can be expected to become more important, the reaction is selective for attack *anti* to a (*tert*-butyldimethylsilyl)oxy group.[390]

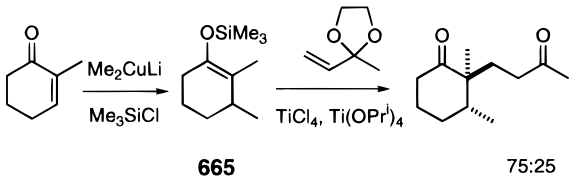
On the other hand, silyl enol ethers, just like other nucleophiles, attack bicyclic enones **661**[392] and **663**[393] from the less hindered side, with the product **662** used in an approach to the synthesis of bruceantin and the product **664** used in a synthesis of quadrone (Scheme 162).

Scheme 162



Conjugate addition to a cyclohexenone and trapping with a silyl chloride sets up a biased silyl enol ether **665**, which can be attacked *anti* to the recently introduced substituent in the acetal version of a Mukaiyama−Michael reaction (Scheme 163),[394] just as it was in the aldol reaction in Scheme 142.

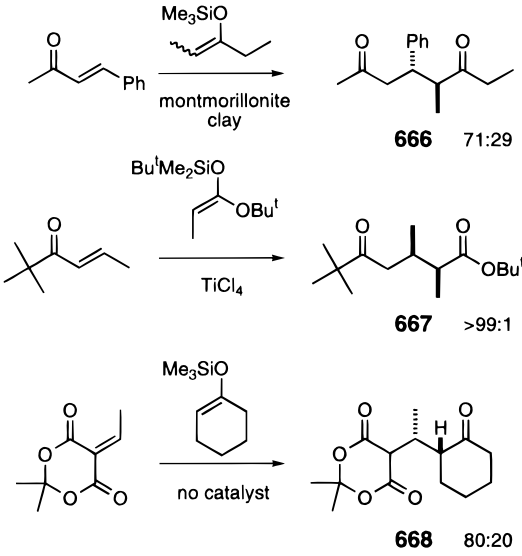
Scheme 163



Simple diastereoselectivity in the reactions of open-chain silyl enol ethers having a substituent on the nucleophilic carbon and open-chain enones having a substituent on the electrophilic carbon have been found rather to favor the *anti* isomer **666** in most situations,[395] but there are examples, such as the product **667**[396] from reaction with a *tert*-butyl ketone, and the product **668**[397] from a doubly activated enone requiring no catalyst, of highly selective reactions in favor of the *syn* isomers (Scheme 164). There is another example of the usual preference for the *anti* relationship in the 1,5-diketone **1027** in Scheme 256.

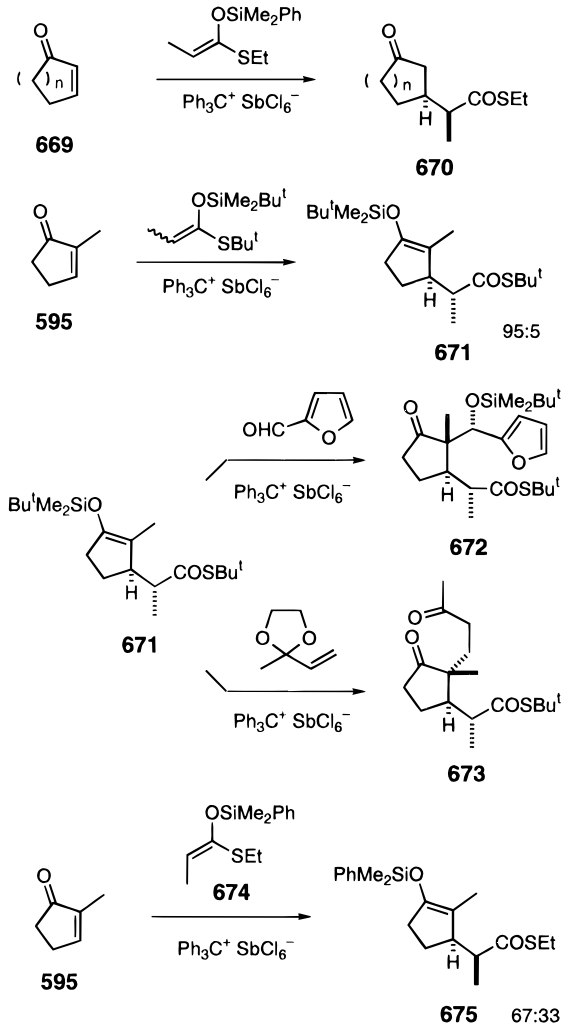
Cyclopentenone and cyclohexenone **669** usually give the *anti* diastereoisomer **670** ($n = 1, 2$), of which the former was used in a synthesis of dehydroiridodiol, as the major product from most silyl enol ethers.[395] Again, however, there are some reports of good diastereocontrol in favor of the *syn* isomer, such as that from 2-methylcyclopentenone **595**, giving the silyl enol ether **671**, independent of the geometry of the silyl enol ether.[398] The silyl enol ether **671** can subsequently react in a Mukaiyama aldol reaction, setting up the four stereocenters of the aldol **672** used in a synthesis of fasitigilin C.[399] Only two diastereoisomers in an 86:14 ratio were detected, the minor isomer being a consequence of a small loss of *anti* selectivity in the aldol step. Alternatively the Mukaiyama−Michael product **671** can be used in a second Mukaiyama−Michael reaction with the acetal

Scheme 164



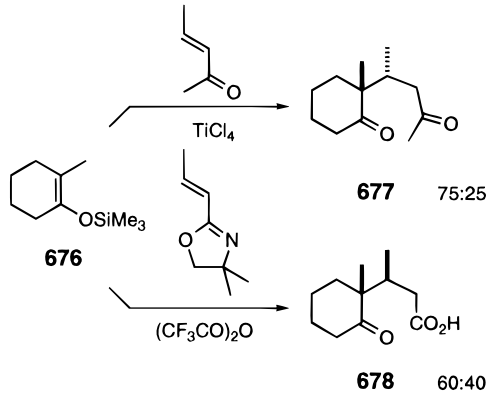
of methyl vinyl ketone setting up the three stereocenters of the diketone **673** having the three stereogenic centers of the CD ring of a steroid.[400] In both cases the attack is *anti* to the resident chain, and the reactions can be carried out in one pot from achiral starting materials. The diastereoisomer **675** can be made to be the major product by changing to the (*Z*)-phenyldimethylsilyl enol ether **674** of the ethylthio ester (Scheme 165).

Scheme 165



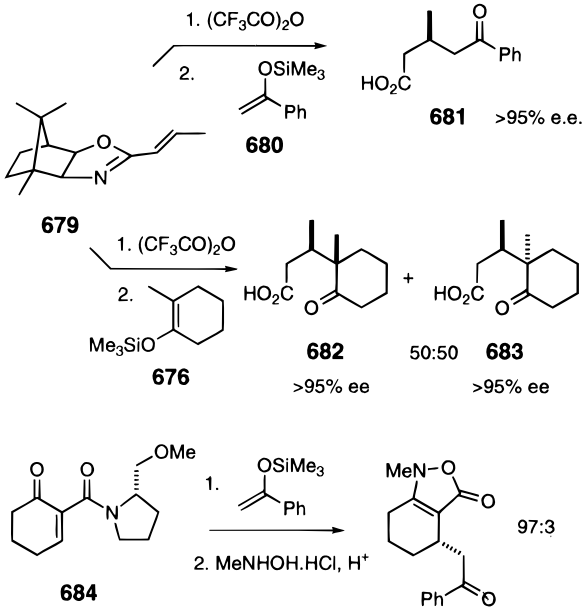
The thermodynamic silyl enol ether **676** from 2-methylcyclohexanone can be induced to give as the major product either stereochemical relationship **677** or **678** by changing the enone to an enone masked as a 2-vinyloxazoline[401,402] (Scheme 166).

Scheme 166



The Mukaiyama−Michael reaction can be made to give enantiomerically enriched product by attaching a chiral auxiliary to the electrophile. The reaction of the silyl enol ether **680** derived from acetophenone with a camphor-derived auxiliary attached to crotonate **679** gave the *S* product **681** (Scheme 167).

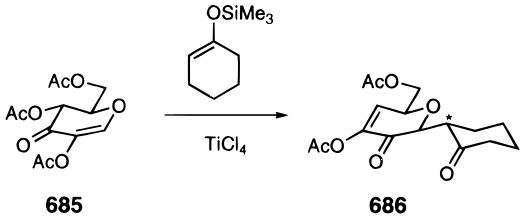
Scheme 167



Although the small amount of simple diastereoselectivity seen in Scheme 166 with the silyl enol ether **676** was lost, the enantiocontrol in the reaction between the same silyl enol ether and the chiral crotonate **679** was high for both diastereoisomers **682** and **683** (although the sense illustrated has not been proved) (Scheme 167). A complementary chiral auxiliary based on phenylglycinol gave nearly as good results.[403] Other chiral auxiliaries include one **684** derived from proline, which can be attached to cyclohexenones (Scheme 167),[404] another derived from camphor, which has been used as part of the catalyst in a reaction of silyl nitronates,[405] another derived from BINAP used on open-chain enones,[406] and another (TADDOL) derived from tartaric acid, which has been used in a reaction on cyclopentenones.[407]

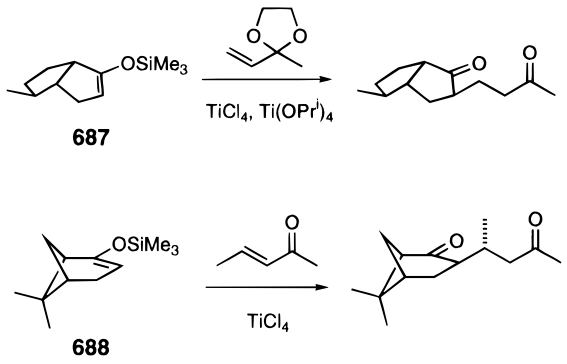
The ketoglycal **685** gave the ketone **686** with both high anomeric and high simple diastereocontrol, although the configuration at C* was not proved (Scheme 168).[408]

Scheme 168



Among silyl enol ethers having a stereochemical bias, bicyclic systems are apt to give reliable stereoselectivity for attack on the convex surface or the surface with the smaller bridge, as in the reactions of the silyl enol ethers **687**[409] and **688**[410] with the latter showing simple diastereoselectivity as well as enantioface selectivity (Scheme 169).

Scheme 169



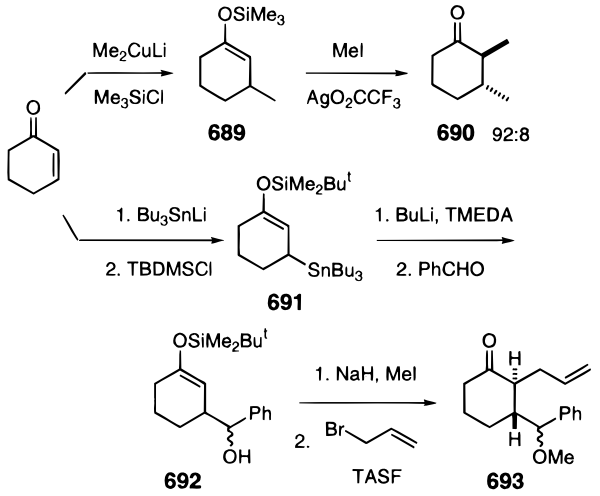
The ephedrine-based chiral auxiliary has also been used in Mukaiyama−Michael reactions.[360]

E. Intermolecular Attack by Other Electrophiles

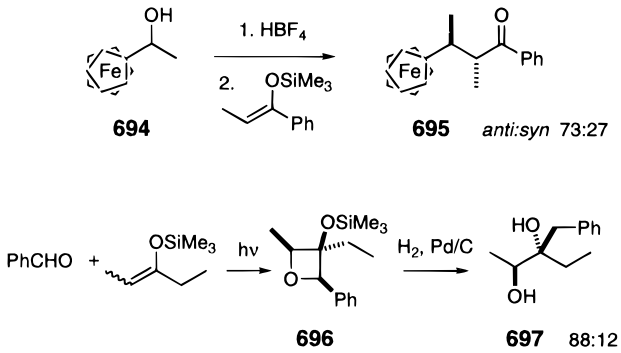
Silyl enol ethers are not normally alkylated directly with alkyl halides, but alkylation with Lewis acid catalysis is possible with tertiary and secondary benzyl halides or acetates, and even methylation has been achieved using silver ion as a Lewis acid with stereoselectivity **689** → **690** for the introduction of the alkyl group *anti* to the resident center (Scheme 170).[411] A tributylstannyl group in the silyl enol ether **691** can be replaced by an electrophilic group without disturbing the silyl enol ether function, and subsequent alkylation of the silyl enol ether **692**, catalyzed by fluoride ion, sets up the usual *trans* arrangement in the ring **693** (Scheme 170).[412] The Mukaiyama−Michael reaction can also be followed by alkylation.[413]

A ferrocenylethyl cation derived from the alcohol **694** is attacked with simple diastereocontrol in favor of the *anti* isomer **695** (Scheme 171).[414] Photocycloaddition of benzaldehyde to a silyl enol ether is stereoselective in favor of the isomer **696**, whatever the geometry of the silyl enol ether but with opposite regiochemistry to the usual reaction with an alde hyde. Hydrogenolysis gives overall the product **697** of addition by a hydroxy and a benzyl group (Scheme 171).[415]

Scheme 170

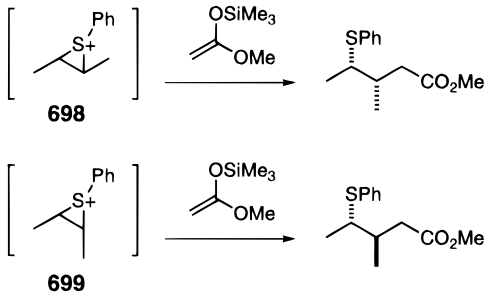


Scheme 171



Episulfonium ions **698** and **699** are attacked by silyl enol ethers stereospecifically with inversion of configuration at the electrophilic carbon (Scheme 172),[416] even when that carbon is tertiary,[417] and episelenenium ions are similarly opened by silyl enol ethers in a reaction exactly parallel to that illustrated in Scheme 172.[418]

Scheme 172

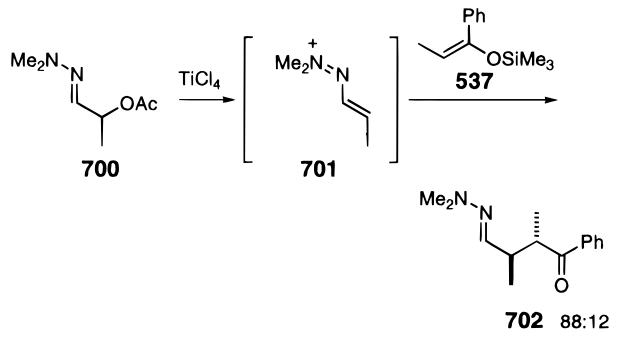


The reaction between the α-acetoxy *N*,*N*-dimethylhydrazone **700** and silyl enol ethers **537** probably takes place by way of the cation **701**, and gives the *N*,*N*-dimethylhydrazone **702** of a 1,4-dicarbonyl compound. The stereochemistry was largely *anti* (Scheme 173).[419]

Silyl dienol ethers with stereogenic centers adjacent to the diene system are selective in their Diels−Alder reactions.[420]

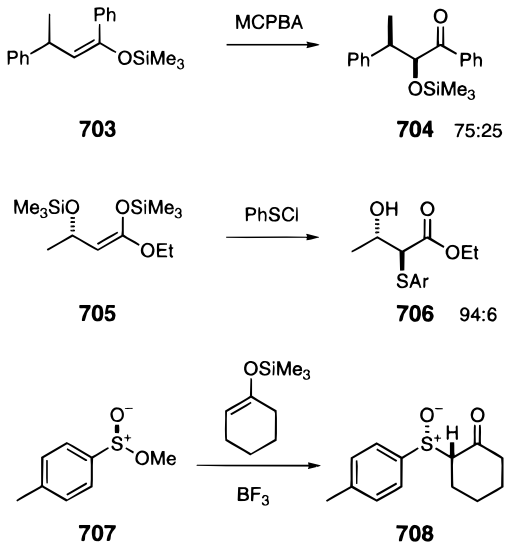
With respect to heteroatom electrophiles, open-chain silyl enol ethers having a stereogenic center adjacent to the nucleophilic carbon can show selectivity in epoxidation opening **703** → **704** and in sulfenylation **705** → **706** (Scheme 174).[421,422] Electrophilic

Scheme 173



sulfenylation **707** → **708** is also stereospecific with inversion at sulfur (Scheme 174).[423]

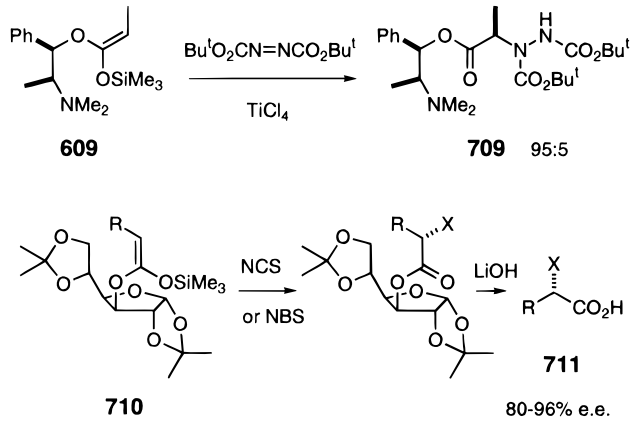
Scheme 174



Homochiral catalysts have been used to hydroxylate silyl enol ethers to give enantiomerically enriched α-hydroxy ketones,[424] with the Sharpless asymmetric dihydroxylation catalyst notably successful.[425]

The silyl enol ether **609** with the ephedrine-based chiral auxiliary has also been used in a reaction with a nitrogen electrophile to give the ester **709** (Scheme 175), which could be used to synthesize alanine, and

Scheme 175



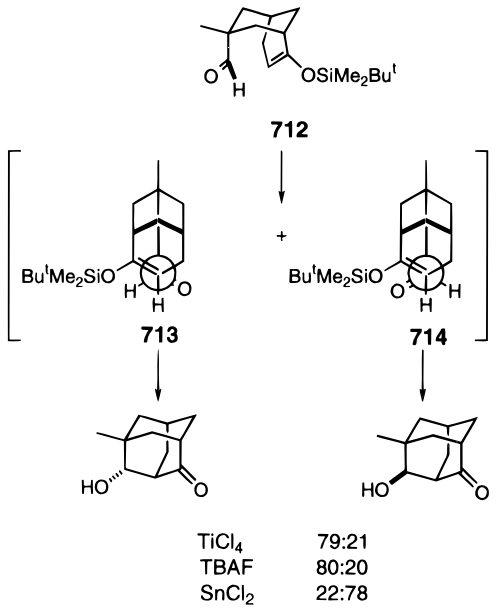
the method was suitable for the synthesis of other α-amino acids.[426] Sugar-derived silyl enol ethers **710** can be halogenated to give largely one diastereoisomer and hence largely one enantiomer of the corresponding α-halo carboxylic acids **711** (Scheme 175).[427]

F. Intramolecular Electrophilic Attack on Silyl Enol Ethers

Intramolecular reactions are rather less common with silyl enol ethers than they are with allylsilanes. The silyl enol ether function is so easily hydrolyzed that it can be a little more difficult to set up the regio- and stereoisomer of the silyl enol ether and an appropriate electrophilic group in the same molecule. The stereochemistry is controlled more by the folding of the connecting chain, and the influence of resident stereogenic centers in the chain, with the result that the role of the silyl group in controlling stereochemistry, is minimal. The various categories of intramolecular reactions are treated below in the same order as their intermolecular counterparts: reactions with carbonyl groups and their acetals, iminium ions, enones, and other electrophiles.

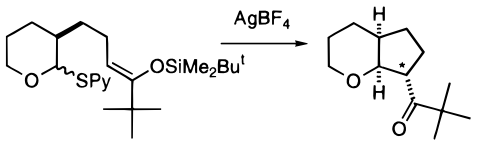
Intramolecular reactions with aldehydes are rare, because of the constraints of setting up the silyl enol ether of one carbonyl group in the presence of another. The nonenolizable aldehyde **712** is one such example, designed specifically to test the geometry of approach of the two double bonds, antiperiplanar **713** or synclinal **714**.[428] The antiperiplanar transition structure **713** proved to be favored when the reaction was catalyzed by most Lewis acids and by fluoride ion, whereas the synclinal transition structure **714** was favored with the highly chelating Lewis acid tin(II) chloride (Scheme 176).

Scheme 176



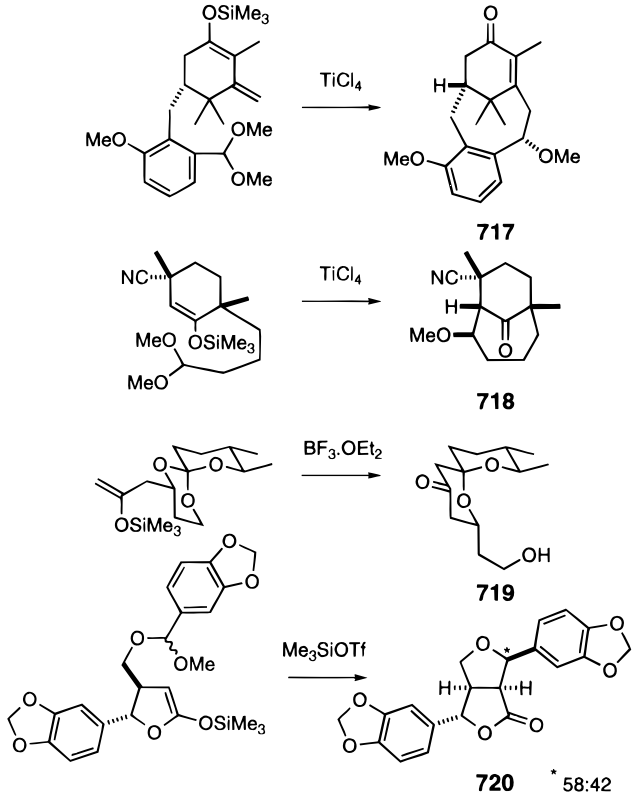
Similar reactions with acetals are relatively easy to set up. Synclinal transition structures seem to be unavoidable for the cyclization to a five-membered ring **715** → **716**,[429] which was more selective when the β-phenylthio anomer was used, because the α-anomer can react with more S_N2 character (Scheme 177). A similar reaction is available for forming a four-membered ring.[430]

Scheme 177



These intramolecular reactions have both double bonds exocyclic to the ring being formed, or at least to one of them in the case of **712**, but having one double bond endocyclic is more common. In these, both synclinal and antiperiplanar approaches appear to be common, and one can only note the sense of the stereoselectivity. There are examples, all with acetals as the electrophilic function, of eight- (**717**),[431] seven- (**718**),[432] six- (**719**),[433] and five-membered (**720**)[434] ring formation, the last of these being used in a synthesis of asarinin (Scheme 178).

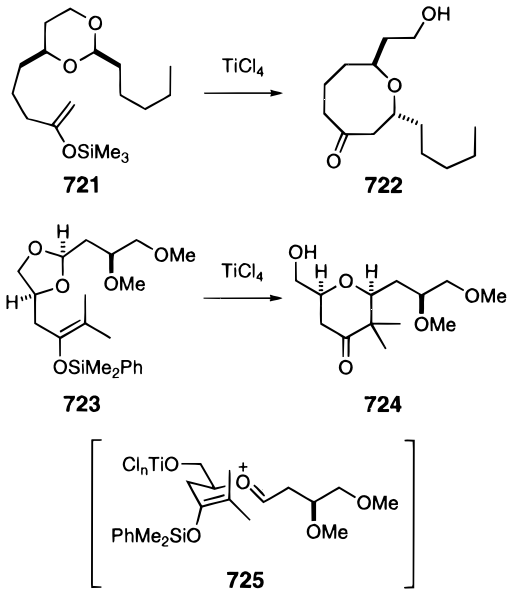
Scheme 178



There are other examples of eight-[435] and six-membered[266] ring formation, the former **721** → **722** in a synthesis of ψ-gloeosporone, and the latter **723** → **724** tested for a synthesis of pederin. The transition structure **725**, with both double bonds endocyclic, synclinal, and in a chair conformation explains the formation of the *syn* isomer **724**, and not the *anti* isomer that was wanted for the synthesis (Scheme 179). One way round this difficulty, already referred to in Scheme 113, was to carry out an open-chain Mukaiyama aldol reaction on the aldehyde **493**. The other solution was to use the axial delivery of cyanide discussed in connection with Scheme 332.

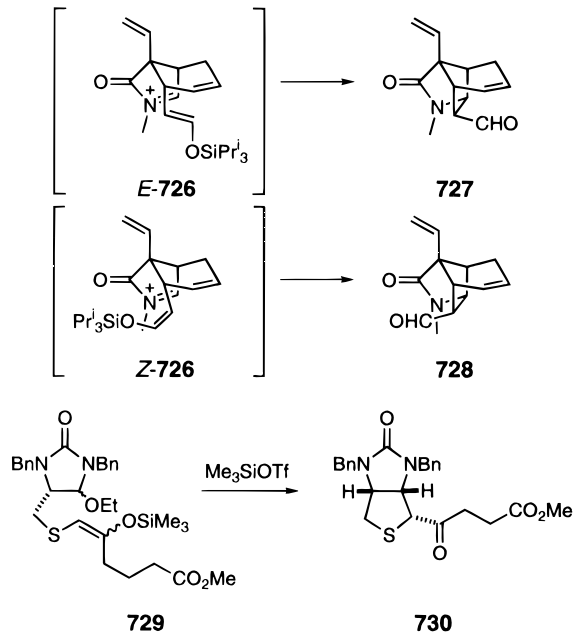
An intramolecular reaction of an aldehyde-derived silyl enol ether with an acyliminium ion proved to be stereospecific, with the *E* isomer (*E*)-**726**, giving

Scheme 179



the aldehyde **727** needed for a synthesis of gelsemine, and the *Z* isomer (*Z*)-**726**, giving its diastereoisomer **728** (Scheme 180).[436] Another intramolecular reac-

Scheme 180

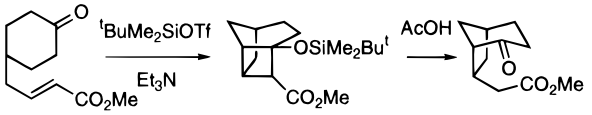


tion with an iminium ion **729** → **730** was not affected by the geometry of a ketone-derived silyl enol ether, but selectively gave the *cis* ring fusion, and both diastereoisomers at the center adjacent to the sulfur atom in a ratio of 67:33 (Scheme 180). Both diastereoisomers were used in a synthesis of biotin.[437]

Intramolecular reactions with α,β-unsaturated esters **731** have given cyclobutanes **732**, which can be opened by a retro-aldol reaction, achieving overall a Michael reaction in which the ester group is *endo* in the bicyclic system **733** (Scheme 181).[438] A similar reaction has been used in syntheses of anthoplalone and lepidozene.[439]

Other electrophiles that reacted intramolecularly with silyl enol ethers with stereochemical consequences were an alkyl halide **734** in a synthesis of calonectrin,[440] the propargyl ethers **735**, which gave

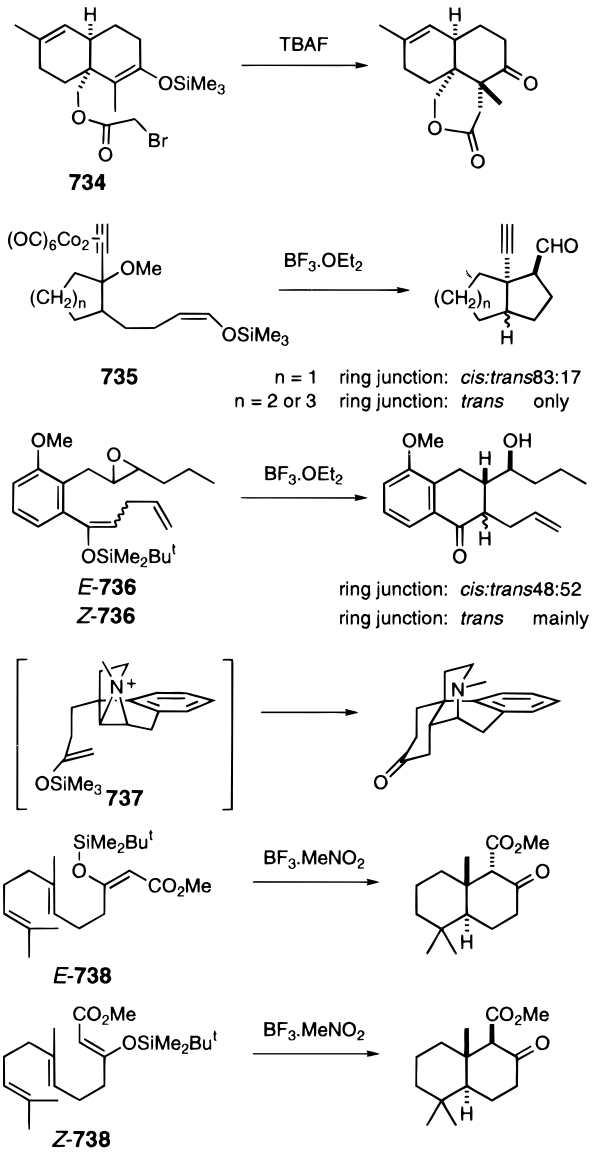
Scheme 181



731 732 733

largely the *trans* ring junction, except when the five-membered ring was being fused to another five-membered ring,[441] a stereoisomeric pair of epoxides **736**,[442] an aziridinium ion **737** in a synthesis of the morphine skeleton,[443] and polyene cyclizations from a stereoisomeric pair of silyl enol ethers **738**[444] (Scheme 182).

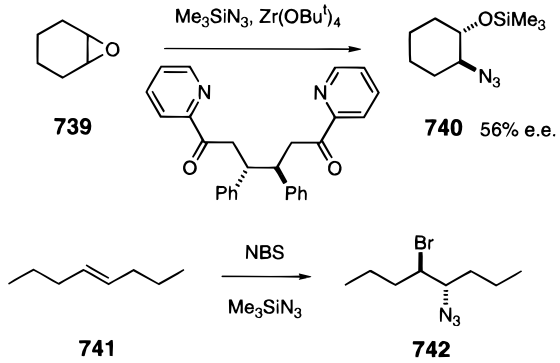
Scheme 182



VII. Silyl Azides[445,446]

Trimethylsilyl azide is commonly used, in conjunction with a variety of Lewis acids, to open epoxides, with the usual inversion of configuration at the carbon atom suffering nucleophilic attack.[447] With a homochiral Lewis acid, the reaction can be made enantioselective, as in the reaction **739** → **740** (Scheme 183).[448] A similar reaction on alkenes **741** using *N*-bromosuccinimide and trimethylsilyl azide

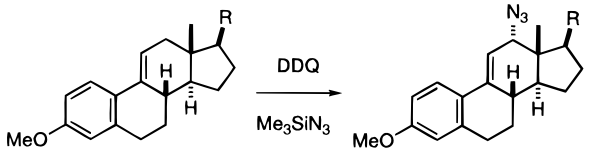
Scheme 183



sets up adjacent azido and bromine functions **742** with the usual stereochemistry from *anti* opening of an epibromonium ion intermediate (Scheme 183).[449]

Trimethylsilyl azide delivers azide ion axially to the steroidal allylic cation created from the alkene **743** with DDQ, giving the azide **744** (Scheme 184).[450]

Scheme 184



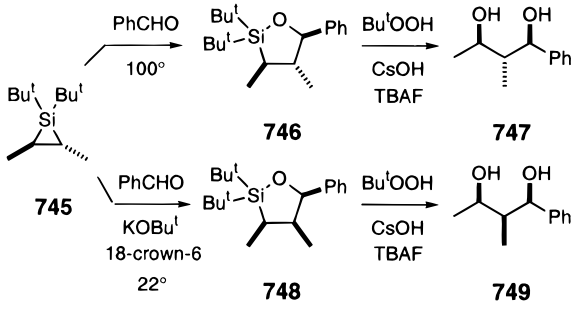
743 744

VIII. Silicon–Carbon Bonds as Carbon Nucleophiles

Most silicon-containing carbon nucleophiles like vinylsilanes and allylsilanes use a π-bond as the site of attack by the electrophile, and the silicon−carbon bond is broken in a second step. A silicon−carbon bond on its own, unconnected to a π-bond, is not usually reactive enough to make the carbon atom usefully nucleophilic, and when a simple silane does react with an electrophile, it is usually a methyl or primary alkyl group that is attacked. Protodesilylation of such unactivated silanes is the most frequently encountered reaction in this class. It is usually carried out using fluoride ion or *tert*-butoxide ion, it is useful for removing silyl groups from unfunctionalized primary or secondary alkyl positions,[451−454] but it has no stereochemical consequences. Two reactions in which a carbon electrophile attacks a secondary silane, and where there might be some stereochemistry, are not stereochemically defined,[455] but one stereochemically interesting type of reaction, the attack of benzaldehyde on the silacyclopropane **745**, with or without catalysis by *tert*-butoxide ion, has been reported. Reaction presumably takes place because of the strain in the ring, and it is stereochemically defined. Although the reactions are not completely stereospecific, the major product without catalysis **746** shows retention of configuration, while that from the catalyzed reaction **748** shows inversion of configuration. Whatever the mechanism in detail, the stereochemistry bears some resemblance to that of the opening of cyclopropanols—where the electrophile is a proton and the nucleophile a carbon−carbon bond—which take place in acid with retention of configuration, and in base with inversion.[456] The silyl groups in the ethers **746**

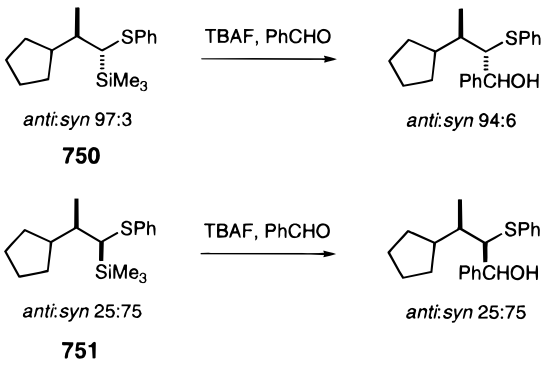
and **748** were subjected to silyl-to-hydroxy conversion under new conditions, using *tert*-butyl hydroperoxide, cesium hydroxide, and tetrabutylammonium fluoride in dimethylformamide, and oxidation took place in spite of the hindering *tert*-butyl groups (Scheme 185).[457]

Scheme 185



When anion-stabilizing groups are present, the silyl group can be easily displaced, but the stereochemistry is usually lost, as with α-silyl ketones and esters, which give trigonal enols or enolate ions. The same loss of configuration appears also to take place when a silyl group is removed from α-silyl sulfones,[458] but the sulfide groups in the alcohols **750** and **751** allow the configuration to be retained (Scheme 186),[459] and

Scheme 186

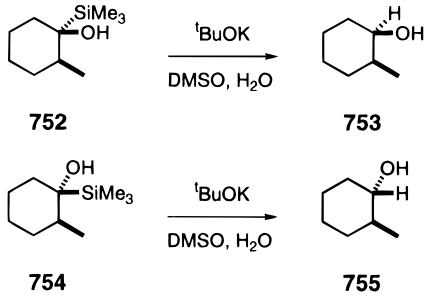


protodesilylation usefully takes place with retention of configuration from α-silyl epoxides, as in the reaction **274** → **272** in Scheme 62, and this reaction has been much used in synthesis, with or without the Sharpless asymmetric epoxidation.[460]

A neighboring oxyanion can remove a silyl group in what is usually seen as the first step of a Brook rearrangement. The usual consequence is a stereoselective β-elimination, as in the reaction in Scheme 2, but the intermediate can pick up a proton with retention of configuration when there is no β-nucleofugal group, as in the reactions demonstrating the stereospecificity **752** → **753** and **754** → **755** (Scheme 187).[13] Further examples of stereospecific protonation after Brook rearrangement are discussed in section XVI, as useful reactions following nucleophilic attack on acylsilanes.

The other reaction in which an otherwise unfunctionalized C−Si bond is replaced by something else is the oxidation using peroxides or peracid already discussed in section IV and elsewhere. Whatever the method, the overall conversion of a silyl into a hydroxyl takes place stereospecifically with retention of configuration.

Scheme 187



IX. Allylsilanes

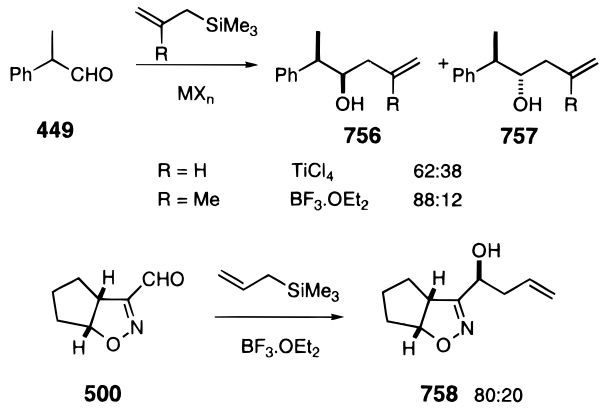
Allylsilanes have proved to be one of the most versatile of the silicon-containing carbon nucleophiles, often showing high levels of stereocontrol in their attack on cationic electrophiles.[2,76] In general, allylsilanes react with the same types of electrophiles that silyl enol ethers react with, and the topics will be taken here in the same order—carbonyl electrophiles (section A), iminium ions (section B), enones (section C), and other (section D), with control from the electrophile covered first, followed by simple diastereoselection, and then the combined effects of both. This is followed by two sections on stereocontrol from features within the allylsilane, first the reactions that have a parallel in silyl enol ether chemistry, where the stereocenter is not the silicon-bearing carbon atom (section E), and then a much larger section where the stereocontrol stems from the silicon-bearing carbon—the S_E2' reaction and related reactions in which the silyl group is not actually replaced, but stays in the molecule (section F). Because of the importance of this subject, this section includes a summary of the stereocontrolled methods by which allylsilanes with three-dimensional stereochemical features can be synthesized. Intramolecular versions of all these reactions are covered separately in section G. Some related systems—pentadienylsilanes, allenylsilanes and propargylsilanes—are covered in sections H and I. As with silyl enol ethers, those intramolecular allylsilane reactions in which the components are linked through the silyl group are discussed, entirely separately, later in the review, in section XVIII. Finally, those allylsilane reactions where the silyl group itself is the stereogenic center, or where the silyl group carries stereochemical features in its nonfunctional side chains, are discussed in section XIX.

A. Intermolecular Attack on Carbonyl Groups and Acetals

1. Stereocontrol Only from the Electrophile

Neighboring stereogenic centers exert the expected influence based on Cram's rule or its chelation counterpart, with the paradigm being the reaction of 2-phenylpropanal (**449**) with allyltrimethylsilane giving largely the homoallylic alcohol **756**, but with indifferent selectivity (62:38) (Scheme 188). By changing the variables by having a C-2 methyl group on the allylsilane and boron trifluoride as the Lewis acid, better selectivity up to 88:12 could be achieved, one of the highest for this stereogenic center.[461] Equivalent reactions of the thioacetal giving the

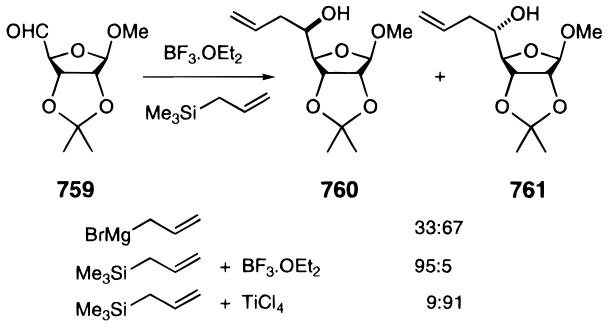
Scheme 188



corresponding thioethers have also been performed.[257] Unusually good stereoselectivity has also been seen from more distant stereocenters in attack by allyltrimethylsilane on the aldehyde **500** (Scheme 188), just as it was with silyl enol ethers (Scheme 115).[462]

Neighboring oxygen and sulfur groups do not necessarily give rise to chelation control, especially if trimethylsilyl triflate or boron trifluoride etherate, which cannot chelate, are used as the Lewis acid,[463] or the oxygen atom is tied up with a hindered silyl group. Cram control with aldehydes has been used several times in synthesis[464] and has been found specifically to give better stereochemical control than the Grignard reagent in the selective (95:5) formation of the alcohol **760** from the aldehyde **759** (Scheme 189).[465]

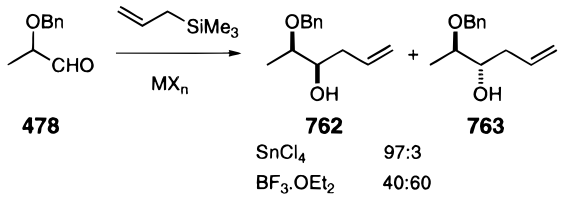
Scheme 189



Chelation control is more usual when there is a coordination site like a neighboring oxygen function, as in the ethers **759** and **478**, and indeed it is quite common to find that changing the Lewis acid changes the diastereoselectivity dramatically. In the reaction in Scheme 189, allyltrimethylsilane and a chelating Lewis acid, titanium tetrachloride, gave largely (91:9) the alcohol **761**, in contrast to the result with boron trifluoride. Although the examples in Scheme 189 have Cram and chelation control nearly equally effective, chelation control is generally more selective, as usual with reactions having a ring system in the substrate or transition structure. Thus the aldehyde **478** gave the product **762** of chelation control with high selectivity (97:3) using tin(IV) chloride, but the Cram product **763** with low selectivity (60:40) using the nonchelating boron trifluoride (Scheme 190).[461,466]

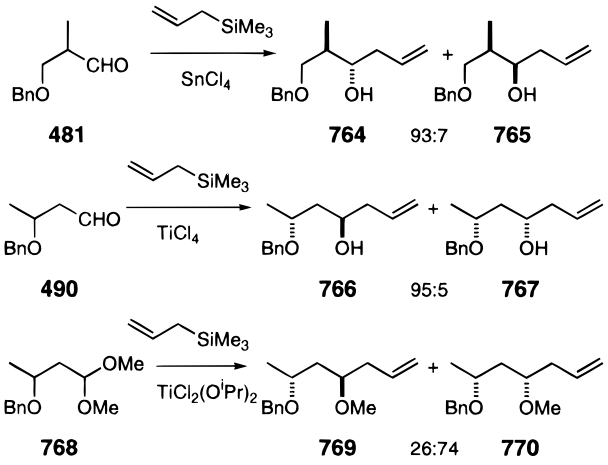
The Lewis acids most commonly used for chelation control are, in order of popularity, titanium tetrachloride, tin(IV) chloride, and magnesium bromide. Chelation-controlled attack on aldehydes has been

Scheme 190



used in synthesis, both with 2-benzyloxy[467] and protected 2-amino substituents.[468] Chelation can also control diastereoselectivity when the coordinating substituent is on C-3, or even further away, and the group, although typically an ether, can be an alcohol,[174] an ester,[469] or an amide group.[470] Thus the aldehydes **481** and **490** gave the alcohols **764** and **766** with high levels of diastereocontrol (Scheme 191).[461,471,472] Somewhat mysteriously, the reaction

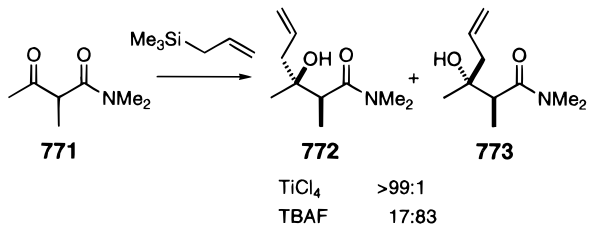
Scheme 191



with the aldehyde **490** gave stereocontrol in the same sense with boron trifluoride as the Lewis acid. The opposite sense of selectivity in this case was achieved by using the corresponding acetal **768** in place of the aldehyde, although the selectivity in favor of the diastereoisomer **770** was lower.[473] The order in which the reagents are mixed with any of these reactions can be important,[471] and so, it appears, is the amount of Lewis acid with aldehydes like **490**, but not with aldehydes like **478**.[474]

Chelation can also be avoided by using fluoride-catalyzed reactions, as in the contrasting results with the ketone **771**, which gives the alcohol **772** with a chelating Lewis acids, and the alcohol **773** with fluoride ion (Scheme 192).[470]

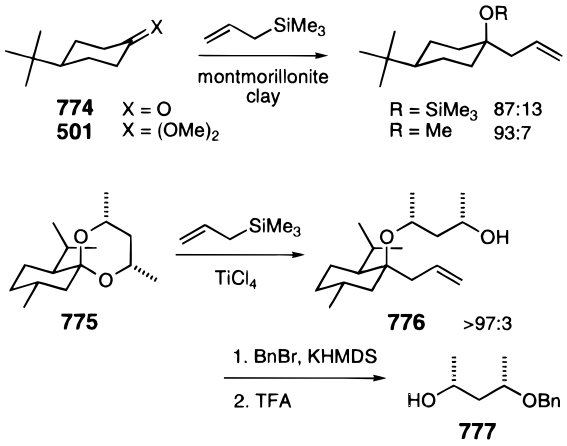
Scheme 192



In attacking ring systems, allylsilanes inevitably comply with the constraints imparted by the ring system. Unlike the relatively small nucleophiles, silicon hydrides and silyl cyanides, allylsilanes, like silyl enol ethers (Scheme 116), attack cyclohexanes

like 4-*tert*-butylcyclohexanone (**774**) and its acetal **501** equatorially (Scheme 193).[475] This preference

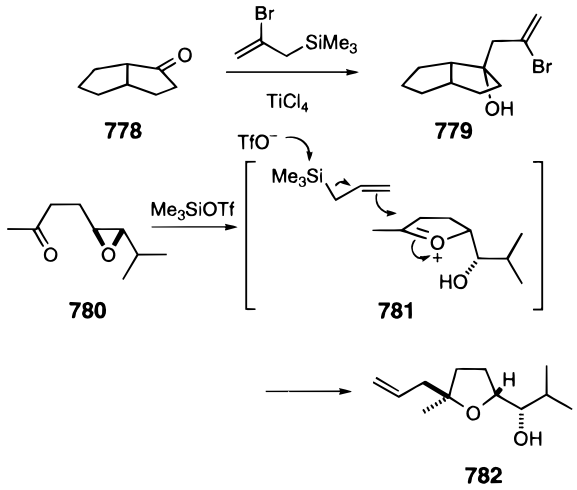
Scheme 193



was used on the more complex acetal **775** to prepare the tertiary homoallylic ether **776** subtly to differentiate in the final product **777** the enantiotopic 1,3-diol functions.[476]

Similar attack on other straightforward rings, like the bicyclic ketone **778**[477] and the intermediate **781**,[478] took place unexceptionably from the less hindered direction (Scheme 194). In reactions on

Scheme 194

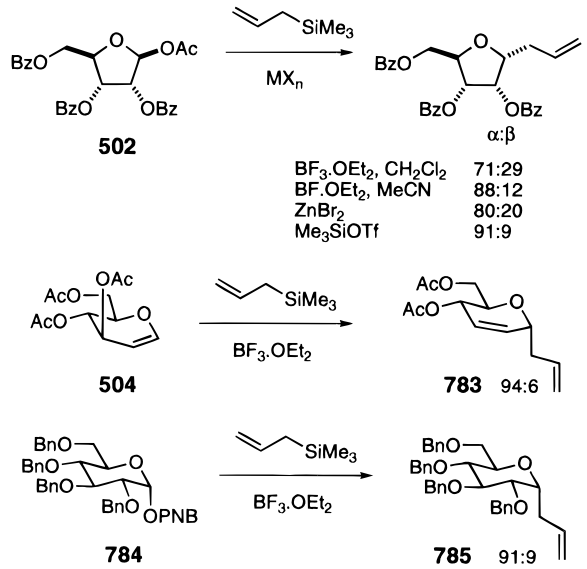


oxygen-functionalized ketones, chelation can play a role in defining the less hindered direction.[479]

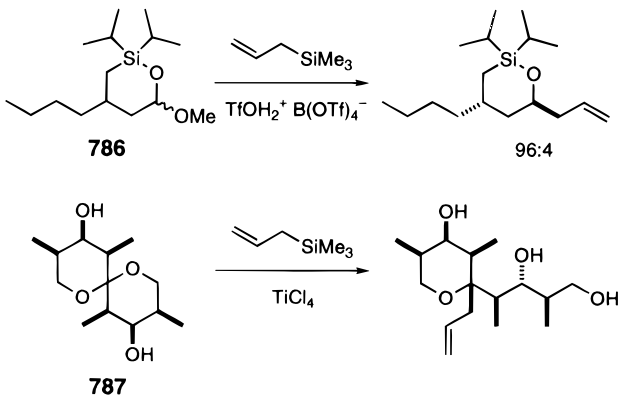
However, the most fruitful application of diastereoselective attack on rings by allylsilanes is not governed simply by attack from the less hindered direction. Allylsilanes selectively attack axially at the anomeric position of tetrahydrofuranyl **502**,[480] dihydropyranyl **504**,[481] and tetrahydropyranyl **784**[482] systems to make *C*-glycosides[483] (Scheme 195), presumably for stereoelectronic reasons. The configuration at the anomeric position of starting materials like **502** and **784** makes little difference to the stereoselectivity, and the C-3 diastereoisomer of **504** gives the axial anomer **783**, with a selectivity (86:14) in the same sense and only a little less than that shown by **504** (94:6).

Reactions of this type have been used many times in organic synthesis to make more or less sugar-like tetrahydrofurans,[272,484] dihydropyranes,[330,485] and tetrahydropyranes,[274,275,486] and an axially allylated 1,3-dioxan.[487] The reaction, of course, does not need the number of hydroxyl groups characteristic of sugars—the anomeric effect still controlled the stereochemistry both for the minimally substituted tetrahydropyran-like system **786**[488] and the heavily substituted spiro system **787** that is also a tetrahydropyran[489] (Scheme 196).

Scheme 195

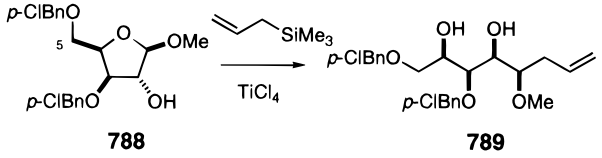


Scheme 196



No protection was needed for the hydroxyl groups in the spiroacetal **787**, and this has also been observed with a more sugar-like dihydropyran substrate.[490] The one area where the ring system failed to give a *C*-glycoside was when there was chelation between a C-5 substituent and the ring oxygen atom. For example, the C-5 ether group caused the furanoside **788** to give the ring-cleaved product **789** instead of displacing the methoxy group at the anomeric position of the intact ring (Scheme 197).[491]

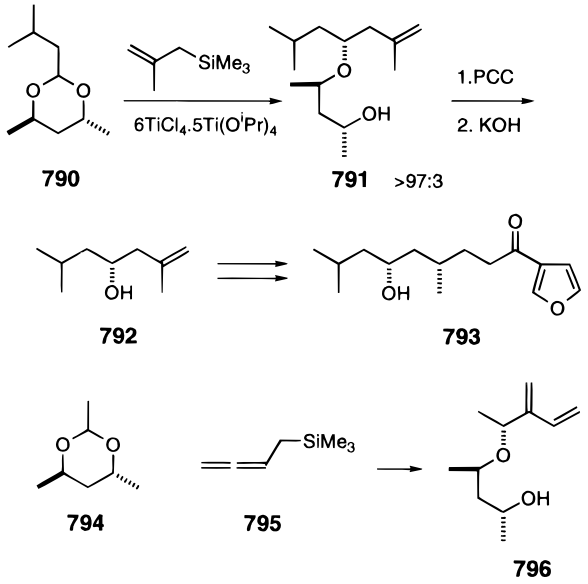
Scheme 197



Allylsilanes, like silyl enol ethers, ethynyl, and cyanosilanes, react with chiral acetals of the type **508** and **513** with high stereoselectivity and in the same

sense as the other nucleophiles. Thus, the acetal **790** gave the homoallylic ether **791** in a diastereoisomeric excess of better than 98%. The chiral auxiliary was easily removed by oxidation and β-elimination to give the homoallylic alcohol **792**, which was used in a synthesis of dihydromyoporone (**793**), thereby establishing the absolute configuration (Scheme 198).[492]

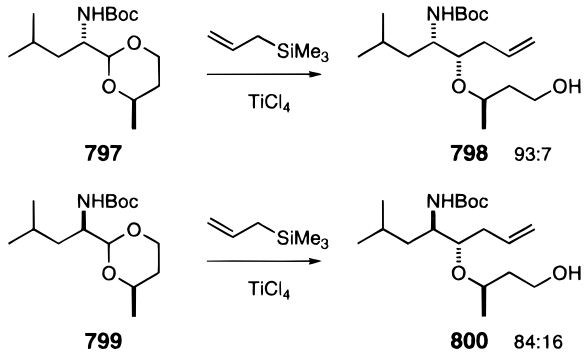
Scheme 198



4-(Trimethylsilyl)buta-1,2-diene (**795**) reacted similarly with the acetal **794** to give a homochiral 2-(1-alkoxyethyl)butadiene (**796**) for a synthesis of anthracyclinones (Scheme 198).[493]

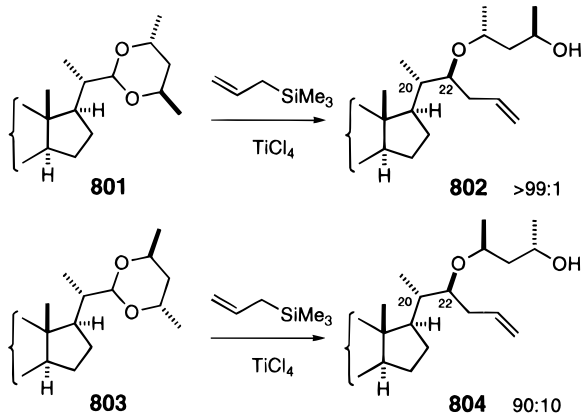
The mechanism by which the stereochemistry is transmitted from the acetal to the product has been discussed briefly in the section on silyl enol ethers. It has also been extensively investigated for allylsilanes and allylstannanes, with the latter both more nucleophilic and more stereoselective.[494] Whatever the details of the mechanism, the selectivity in this type of reaction can be powerful enough to override the effect of a neighboring stereogenic center, as in the reactions with the acetals **797** and **799** giving mainly the homoallylic ethers **798** and **800** in syntheses of statine and its diastereoisomer (Scheme 199).[495]

Scheme 199



In contrast, the acetals **801** and **803** gave products **802** and **804** with the same stereochemistry at C-22, showing that the resident center at C-20 controlled stereochemistry in the Cram sense, not the acetal stereochemistry (Scheme 200).[496,497] The corresponding allylstannane, however, gave products controlled mainly by the acetal stereochemistry, specifically **802** from **801**, and **804** and its diastereoisomer at C-22 in a ratio of 30:70 from **803**. Not surprisingly, when the C-20 resident center has the much less effective 1,3-relationship to a developing center at C-23, the acetal controls the stereochemistry unimpeded, as in a synthesis of calcitrol lactone.[498]

Scheme 200

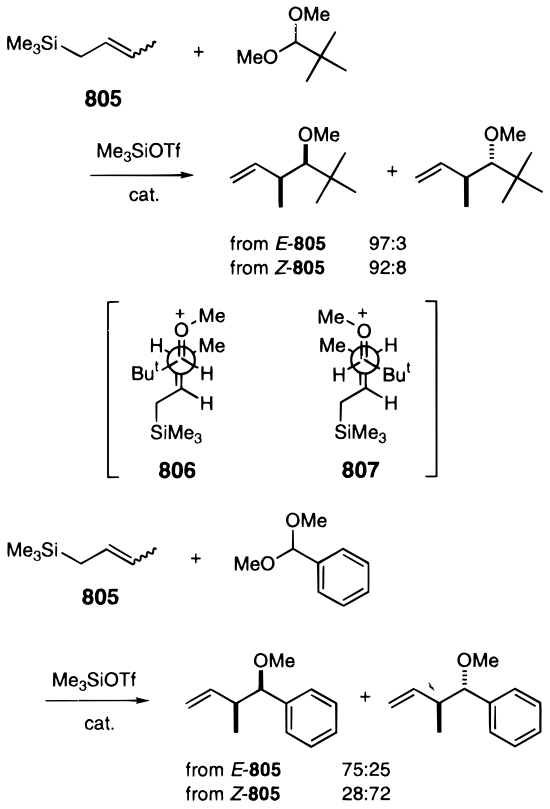


Diastereocontrol in reactions with aldehydes and ketones can be changed to enantiocontrol when a chiral auxiliary is attached by a temporary linkage, as in the reaction of allylsilanes on glyoxalates and pyruvates. A wide range of chiral auxiliaries has been tried, including those based on menthol,[499] phenylmenthol,[500] 2-phenylcyclohexanol,[501] norephedrine,[502] proline,[288,503] inositol,[504] and 2,5-dihydroxymethylpyrrolidine,[505] several of them with very high levels of selectivity. The homochiral auxiliary can also be an alcohol that generates an acetal *in situ*.[506] The other major way of solving the problem of bringing together two achiral substrates and getting a homochiral product is to use a homochiral catalyst. This works with allylsilanes and aldehydes or ketones, especially methyl glyoxylate, and with catalysts based on tartaric acid,[507] BINAP,[508] *trans*-1,2-diaminocyclohexane,[509] and norephedrine.[510]

2. Simple Diastereoselection

All the reactions described above have a methylene group, or a *gem*-dimethyl group, at the nucleophilic terminus C-3 of the allylsilane, and the discussion has been concerned only with the stereochemistry generated at the electrophilic carbon atom of the substrate. When the allylsilane has a C-3 substituent, two new stereogenic centers are set up. There is a preference for the formation of the *syn* relationship between the oxygen substituent and the substituent originally on C-3, as illustrated in the simple reaction between the allylsilane **805** and the acetal of pivalaldehyde (Scheme 201).[511,512] Both the (*E*)- and the (*Z*)-allylsilane show a marked preference for the *syn* relationship, with that from the *E* isomer slightly higher. The straightforward explanation for the geometry of the double bond having little influence is a linear transition structure, usually called antiperiplanar, with a 180° torsional angle between the two π-bonds. In this case the transition structures **806** and **807** leading to the *syn* product are favored because the *tert*-butyl group of the aldehyde is placed in the less hindered sector between the

Scheme 201



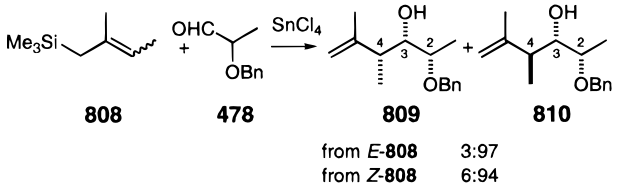
hydrogen atom and the double bond of the allylsilane, rather than between the methyl group and the double bond. The corresponding reactions of silyl enol ethers are less reliably selective, although analogous transition structures **535** and **536** have been suggested for them. In contrast, the reaction of the same allylsilanes (*E*)- and (*Z*)-**805** with the acetal of benzaldehyde, or of benzaldehyde carrying electron-withdrawing substituents, gave the *syn* relationship from the (*E*)-allylsilane but the *anti* relationship from the (*Z*)-allylsilane (Scheme 201).[511]

3. Simple Diastereoselection Combined with Stereoselectivity from the Electrophile

Which of the two *syn* relationships that will be set up can be controlled by the aldehyde or acetal component, but the story is complicated, because the preference for the *syn* relationship often disappears or is seriously muted, especially in reactions with aldehydes under chelation control. The allylsilane **808** and 2-(benzyloxy)propanal (**478**) react in the presence of chelating Lewis acids to give, as expected by analogy with the reaction in Scheme 190, the two possible products **809** and **810** having the *syn* relationship between C-2 and C-3 as a result of chelation control, but the major isomer **810** was that with an *anti* relationship between C-3 and C-4, and this was true for both the (*E*)- and the (*Z*)-allylsilanes (Scheme 202).[513]

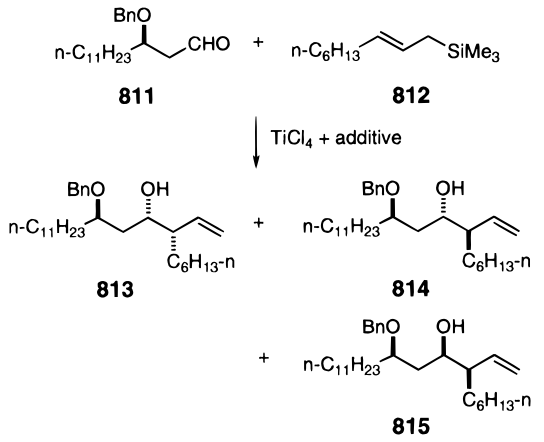
In a less extreme example, chelation control from C-3 in the aldehyde **811** gave comparable amounts of both chelation-control products **813** and **814** and also some of a third diastereoisomer **815** where the chelation control had failed. The ratios of the three compounds varied with the Lewis acid used, with the presence or absence of various additives, and with the order of mixing of the reagents. The highest

Scheme 202



proportion (70:30) of the *syn* diastereoisomer **813** relative to the other two was given by titanium tetrachloride with the addition of zirconocene dichloride, and the highest proportion (57:43) of the *anti*-**814** by titanium tetrachloride with the addition of titanocene dichloride (Scheme 203).[514] This work,

Scheme 203

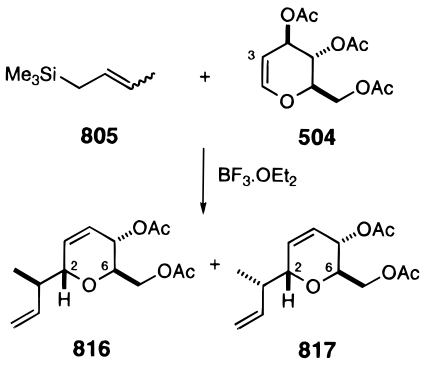


additive	813:814:815
none	28:44:28
$TiCp_2Cl_2$	38:57:5
$ZrCp_2Cl_2$	70:21:9

part of a synthesis of tetrahydrolipstatin, shows that it is possible to adjust the proportions of the diastereoisomers in order to optimize the preparation of one of them. In this case, the *anti* isomer **814** had the desired relative stereochemistry, but the apparently unavoidable formation of the *syn* isomer **813** was compensated for later in the synthesis by enolate formation and reprotonation at C-2 to give the correct relative stereochemistry. The *Z*-allylsilane corresponding to **812** gave largely (64:23:13) the *syn* diastereoisomer **813**, and so this was no help in the synthesis.

The most extensive study of *syn*,*anti* selectivity, and the factors that affect it, has been carried out for the special case of the reaction of allylsilanes with glycal acetates typified by the glucal **504**. In all cases, the anomeric selectivity was very high, giving the *anti* relationship between C-2 and C-6, as in the earlier work (Scheme 195) with allylsilanes having no substituent at C-3. The main conclusion of this study is that (*E*)-crotylsilanes are selective for the formation of the *anti* relationship **816**, while (*Z*)-crotylsilanes are selective for the formation of the *syn*-**817** (Scheme 204).[515] Other factors that affect the ratio are the leaving group, the substituents on the silyl group, and the presence or absence of a substituent at C-3 of the sugar, with a substituent like methyl or phenylthio raising the proportion of the *anti* isomer. In the optimized state, the proportion of the isomer with the *anti* relationship could

Scheme 204

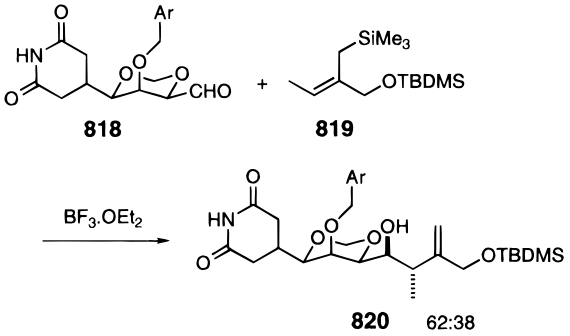


allylsilane	816:817
E-**805**	75:25
Z-**805**	25:75

be made very high, and this was used in syntheses of indanomycin[515] and zincophorin.[330] The less complete, but often more than adequate, selectivity for the *syn* isomer from a (*Z*)-crotylsilane was used in a synthesis of avermectin A_{1a}.[516]

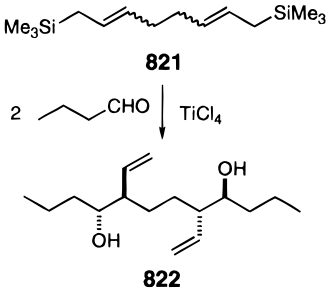
The ready formation of the *anti* isomer was also observed in a reaction with the aldehyde **818** in a synthesis of sesbanimide using the (*Z*)-allylsilane **819**, which gave a mixture of two adducts, both of which were Cram controlled, with the *anti*-**820** as slightly (62:38) the major product (Scheme 205).[517]

Scheme 205



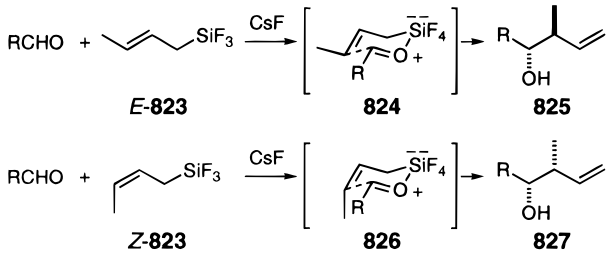
Normal *syn* selectivity from a mixture of geometrical isomers in the bis-allylsilane **821** was coupled with even more remarkable 1,4-stereoselectivity in the formation largely (90:10) of the *meso*-diol **822** (Scheme 206).[518]

Scheme 206



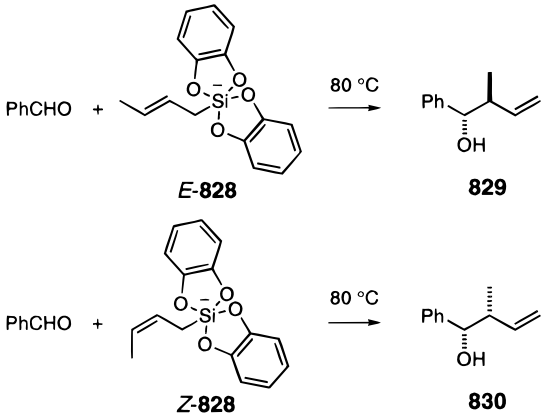
Much more reliably high levels of diastereocontrol are achieved when the reaction is made effectively intramolecular by coordination of the aldehyde to the silyl group, which is easy when the silyl group carries several electronegative substituents, making it a stronger Lewis acid. Because of the preference in the cyclic transition structure for chairlike conformations **824** and **826**, there is a high level of stereospecificity, with the (*E*)-allylsilane (*E*)-**823** giving, with a wide range of aldehydes, the *anti* product **825**, and the (*Z*)-allylsilane *Z*-**823** giving the *syn*-**827** (Scheme 207).[519]

Scheme 207



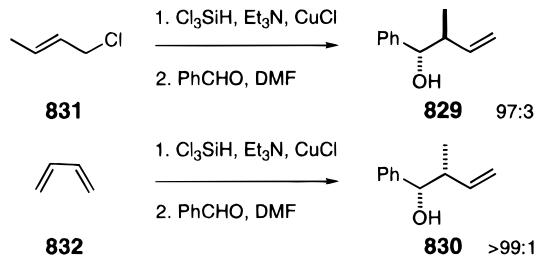
The silicon appears to be hexacoordinated in the transition structures, needing catalysis by fluoride ion or by internal coordination by an α-hydroxy group in the electrophile.[520] Catechol-based pentacovalent silanes (*E*)-**828** and (*Z*)-**828** react without catalysis with aromatic aldehydes and show the same stereospecificity indicative of cyclic transition structures (Scheme 208).[521]

Scheme 208



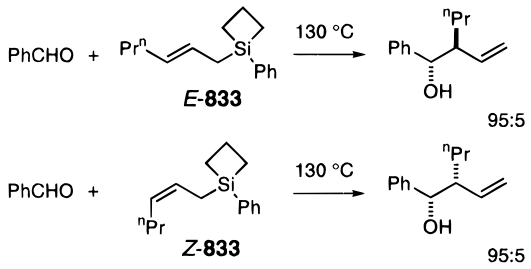
(*E*)-Crotyltrifluorosilane [(*E*)-**823**] can be made by the reaction of trichlorosilane and triethylamine on (*E*)-crotyl chloride (**831**) followed by halide exchange, and (*Z*)-crotyltrifluorosilane [(*Z*)-**823**] by hydrosilylation of butadiene **832** followed by halide exchange.[522] However, the intermediate chlorosilanes are also able to coordinate to an aldehyde, and the whole operation, synthesis and allylsilane reaction, can be carried out in one pot, with the solvent, dimethylformamide, providing the sixth ligand in the transition structure (Scheme 209). This method also works for setting up quaternary centers.[523]

Scheme 209



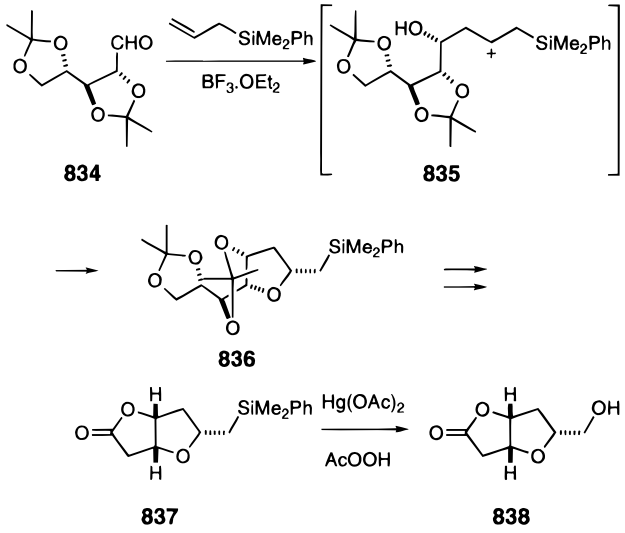
Coordination to the silicon atom in the silacyclobutanes (*E*)-**833** and (*Z*)-**833** relieves some of the strain in the small ring, making the silicon atom significantly more Lewis acidic, and indeed Lewis acidic enough to participate in a thermal reaction with aldehydes. Although there is a penalty in the need for a high temperature, these showed the stereospecificity indicative of a cyclic transition structure, and also required no catalysis (Scheme 210).[524]

Scheme 210



Although substitution is the usual outcome of the reaction between an allylsilane and an aldehyde, the silyl group can remain in the product when the aldehyde carries a suitably disposed nucleophilic center with which to capture the intermediate cation. Thus the aldehyde **834** reacts with the allylsilane with Cram control to give as the major product a ring-expanded acetal **836**, with the C-2 oxygen atom in a neighboring acetal group capturing the cation **835**. Subsequent manipulation, and silyl-to-hydroxy conversion[218] gave the lactone **838** used in a synthesis of *trans*-kumausyne (Scheme 211).[525]

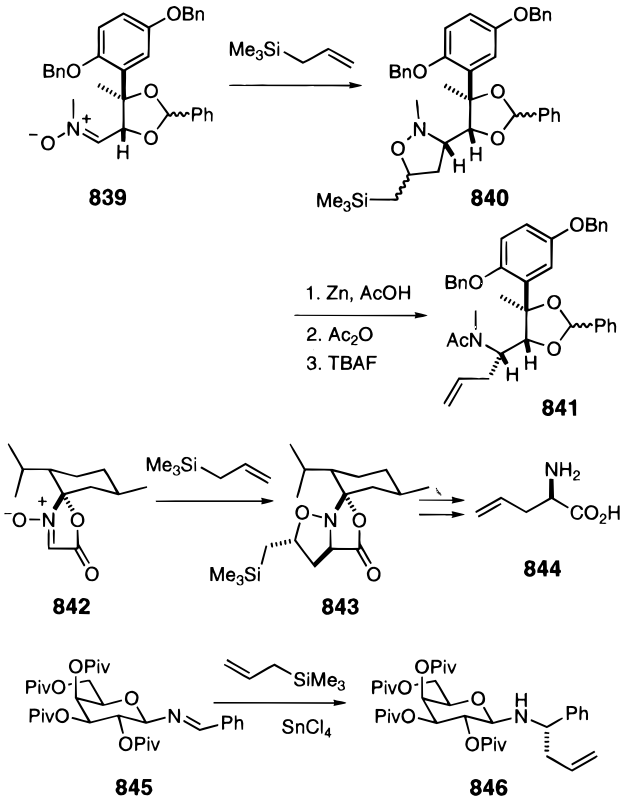
Scheme 211



B. Intermolecular Attack on Iminium Ions

Paralleling their reactions with carbonyl compounds and their acetals, allylsilanes selectively attack iminium ions from the less hindered side, although the rules for identifying the less hindered side are not as well categorized as for carbonyl groups. Examples in open-chain systems include the nitrile oxide cycloadditions **839** → **840**,[526] and **842** → **843**,[527] and the Lewis acid-catalyzed attack on the imine **845** attached to a protected sugar (Scheme 212).[528] The cycloadditions can effectively be made

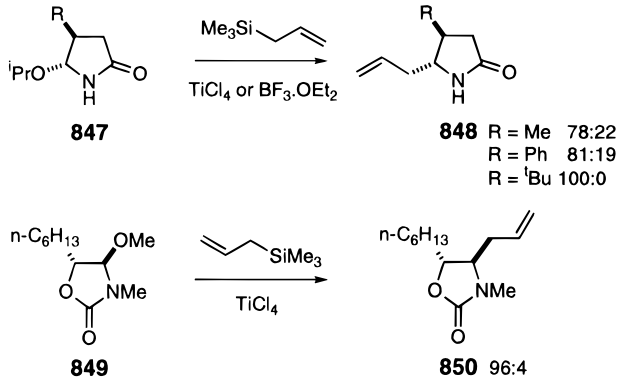
Scheme 212



into electrophilic substitutions by reductive cleavage of the N−O bond and desilylative elimination **840** → **841** and **843** → **844**.

The attack of allylsilanes on cyclic acyliminium ions is also predictably from the less hindered side, as in the reactions **847** → **848**[529] and **849** → **850**[530] (Scheme 213), and several other examples are known

Scheme 213

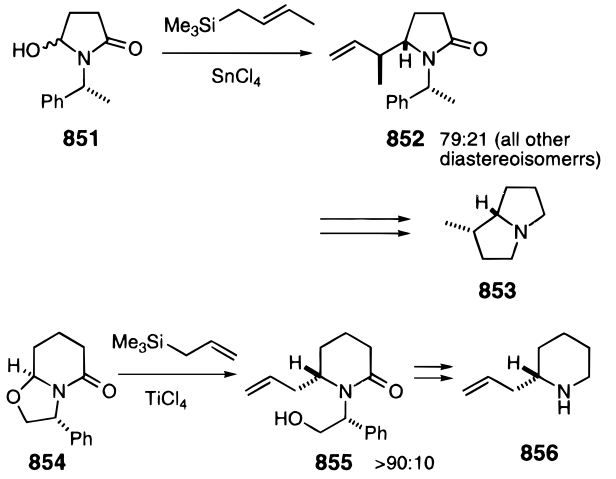


having four-[531,532] five-,[452,533,534] and six-membered rings,[534,535] although in the five- and six-membered rings the major products may be the result of attack *cis* or *trans* to the existing substituent, depending upon its 1,2-, 1,3-, or 1,4-relationship to the atom undergoing attack.

Diastereoselective attack on cyclic acyliminium ions can also be controlled by a chiral auxiliary outside the ring,[536] as in the pyrrolidone **851** and the piperidone **854**, rather than by having a substituent in the ring. The benzylic chiral auxiliaries in the products **852** and **855** can be removed afterward by hydrogenolysis, leaving the allyl group as the only substituent in the ring, as in the syntheses of (−)-

heliotridane (**853**)[537] and of (−)-coniine (**856**)[538] (Scheme 214).

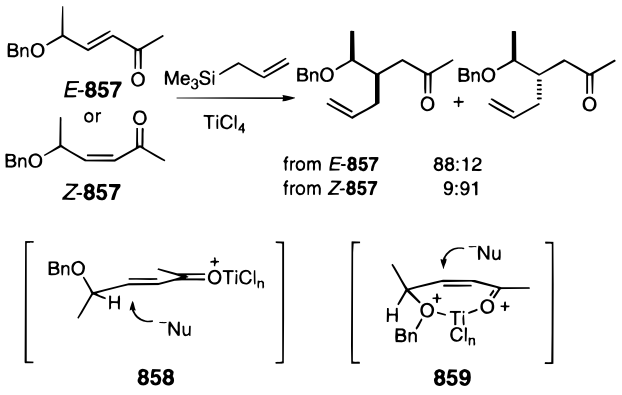
Scheme 214



C. Intermolecular Attack on Enones

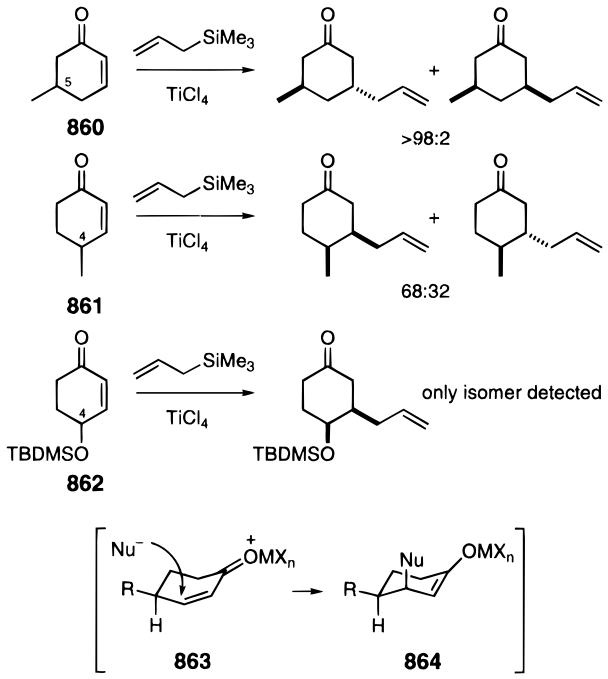
Allylsilanes are much used in conjugate addition reactions to enone systems. The reaction is known as the Sakurai reaction. With open-chain enones, the addition of simple allylsilanes follows the modified Felkin−Anh-like rule for the *trans*-enone (*E*)-**857**, with a transition structure something like **858** similar to **657** for silyl enol ethers in Scheme 151. However the *cis*-enone (*Z*)-**857** gives the opposite result, perhaps through some kind of chelation control **859**, which only fits if the incoming nucleophile attacks *syn* to the methyl group (Scheme 215).[461]

Scheme 215



Allylsilanes attack *anti* to the 5-substituent in 5-substituted cyclohexenones **860** and cycloheptenones, with higher selectivity (>98:2) than that shown by the *n*-propylcuprate (80:20), but they attack 4-substituted cyclohexenones **861** and 4- and 6-substituted cycloheptenones with selectivity for attack *syn* to the substituent,[539] especially if it is electronegative, as with the enone **862**[540] (Scheme 216). Attack *syn* to a neighboring substituent can be explained as axial attack in the conformation **863** with the substituent pseudoequatorial, leading to a chairlike conformation **864**. The mystery then is why allylsilanes follow this picture, while cuprates and other nucleophiles usually attack *anti* to the substituent. Presumably there is a subtle balance between attack in the sense illustrated as **863** and

Scheme 216

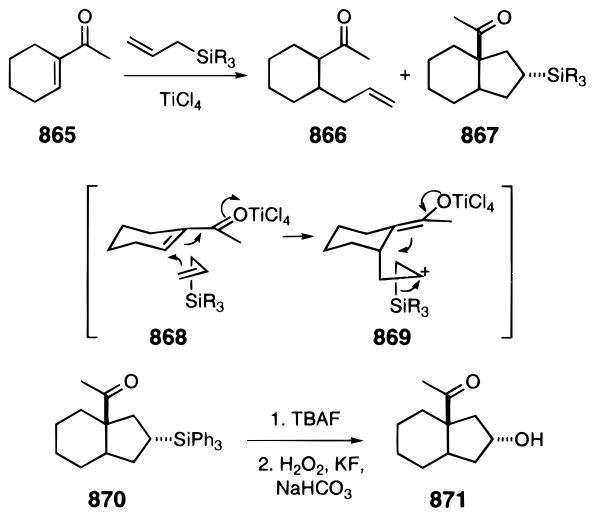


axial attack on the lower surface of the alternative conformation with the substituent R pseudoaxial. That 4-substituted cycloalkenones are attacked *syn* to the substituent adds some weight to the idea that chelation **859** is involved in the reaction with the enone (*Z*)-**857**.

Conjugate addition of allylsilanes to 5-substituted cyclohexenones has been used in syntheses of lycopodine,[541] ptilocaulin,[542] and fawcettimine[543] and in approaches to the synthesis of coriolin,[544] a model for calicheamicin,[545] and strychnine.[546]

While all these reactions are straightforward substitution reactions as far as the allylsilane is concerned, rearrangement and ring closure can take place in competition with the usual loss of the silyl group. With acetylcyclohexene **865** reacting with allyltrimethylsilane the major product is the usual ketone **866**, but a minor product **867** (R = Me) retains the silyl group (Scheme 217).[547] With hindered silyl

Scheme 217

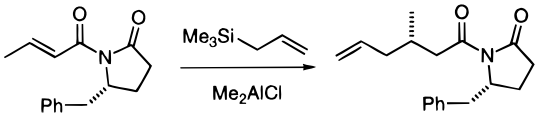


groups, like *tert*-butyldimethylsilyl, triisopropylsilyl, triphenylsilyl, or especially *tert*-butyldiphenylsilyl,

the cyclopentane **867** becomes the major product, and in every case the major stereoisomer has the silyl group *anti* to the acetyl group.[548] An *anti* stereospecific attack on the allylsilane could be taking place in the *synclinal* arrangement **868**, with the allyl system oriented *endo* to the ketone. Other conformations are possible, as long as they retain the topology of **868**, which has the merit of being already in the correct conformation for the next step. The resulting cation **869** either loses the silyl group to give the conjugate addition product **866**, or undergoes a suprafacial 1,2-silyl shift and ring closure to give the cyclopentane **867**. Such products can be used in synthesis by taking advantage of the silyl-to-hydroxy conversion as in **870** → **871**, where the triphenylsilyl group is a good compromise between selectivity for the annelation product **867** (51%) and the ease of the silyl-to-hydroxy conversion, since it has not proved possible to oxidize the *tert*-butyldiphenylsilyl group (Scheme 217).[549] In this silyl-to-hydroxy conversion, one of the phenyl groups on the triphenylsilyl group could, unusually, be removed by fluoride ion attack. A better solution to the same problem uses the trityldimethylsilyl group, which is hindered, and therefore stays efficiently in the molecule, giving the ketone **867** in 78% yield, and has a highly stabilized benzylic group easily cleaved by nucleophilic attack on silicon using fluoride ion as the first step in the silyl-to-hydroxy conversion **870** → **871**.[550]

Allylsilanes have been added to an α,β-unsaturated carbonyl system **872** attached to a chiral auxiliary prepared from phenylalanine (Scheme 218),[551] where

Scheme 218

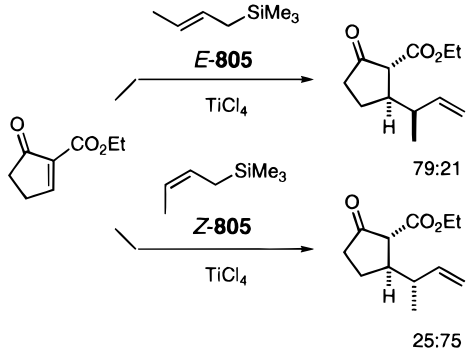


872 67:33

a fairly substantial minor product was a similar silylcyclopentane. Other chiral auxiliaries based on proline,[404] phenylglycine,[552] and Oppolzer's sultam[552] have been used.

When the allylsilane carries a C-3 substituent, as with the allylsilanes **805**, the diastereoselectivity is affected by the geometry of the allylsilane (Scheme 219).[553] The relative stereochemistry is not easily

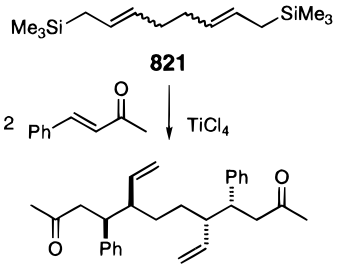
Scheme 219



explained as being a consequence of an antiperiplanar transition structure, since that explanation works best when the (*Z*)- and (*E*)-allylsilanes give the same relative stereochemistry. Whatever the explanation, reactions of this type have been used in syntheses of neonepetalactone,[553] nootkatone,[410] juvabione and its epimer,[554] and the steroidal CD ring system.[555]

The allylsilane **821**, in spite of being a mixture of *E* and *Z* isomers, is remarkable in giving mainly one diastereoisomer **873**, just as it was in its reaction with an aldehyde (Scheme 206), not only by being selectively *syn* with respect to the 1,2-relationship, possibly from an antiperiplanar transition structure making it independent of the geometry of the allylsilane, but also *anti* with respect to the 1,4 relationship (Scheme 220).[556]

Scheme 220

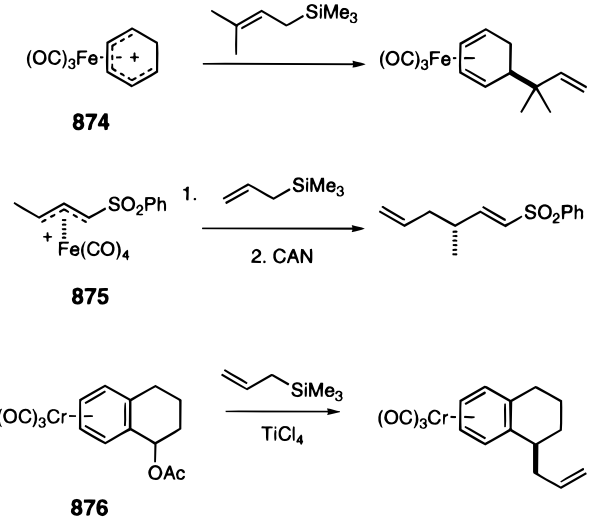


873

D. Intermolecular Attack by Other Electrophiles

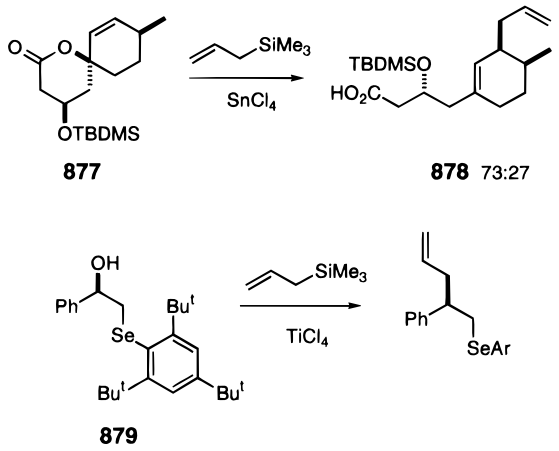
A few other electrophiles, not covered by sections A−C above, react with allylsilanes, mostly with unsurprising stereochemical control. Thus the irontricarbonyl cationic complex **874**,[557] the homochiral irontetracarbonyl cationic complex **875**,[558] and the chromiumtricarbonyl complex **876**[559] are all attacked *anti* to the metal (Scheme 221).

Scheme 221



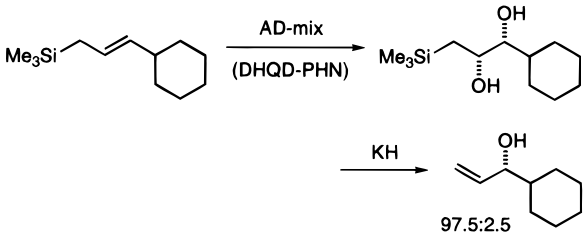
The tertiary ester **877** is attacked *syn* and adjacent to the ring substituent giving the cyclohexene **878** with similar selectivity (73:27) (Scheme 222)[560] to that shown in conjugate addition to 4-substituted cyclohexenones (Scheme 216). The alcohol **879** is displaced by an allyl group with retention of configuration, presumably by way of an intermediate selenonium ion (Scheme 222).[418]

Scheme 222



Allylsilanes are substrates for Sharpless asymmetric dihydroxylation, providing access to allylic alcohols with high enantiomeric purity in favorable cases (Scheme 223).[69] However, the silyl group

Scheme 223



appears to be a bit too bulky to fit easily into the cleft in the current Sharpless catalysts, and terminal allylsilanes are therefore notably poor substrates. Nevertheless, the reaction is good enough to have been used with a nonterminal allylsilane for kinetic resolution (Scheme 267).

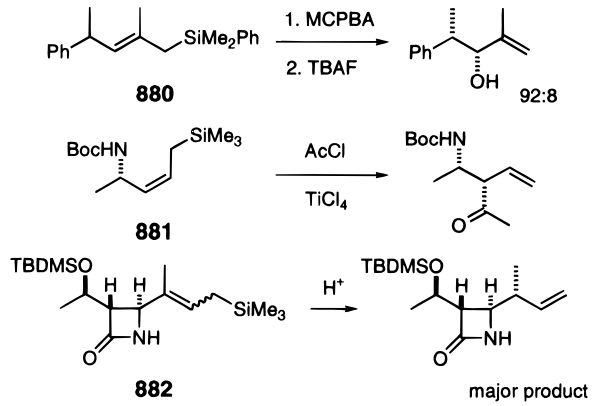
E. Intermolecular Attack Controlled by Stereogenic Centers Resident in the Allylsilane Except at the Si-Bearing Center

Allylsilanes having resident stereogenic centers at the silicon-bearing carbon will be discussed in the next section. This section is concerned with the intermolecular reactions of allylsilanes having resident stereogenic centers elsewhere in the carbon framework, but excluding those where the stereogenic center is the silyl group itself, or is on one of the substituents on the silyl group, categories which are covered in section XIX.

The resident stereogenic centers adjacent to the nucleophilic carbon of the allylsilanes **880**,[561] **881**,[562] and **882**,[532] govern the diastereoselectivity of attack by a wide range of electrophiles (Scheme 224).

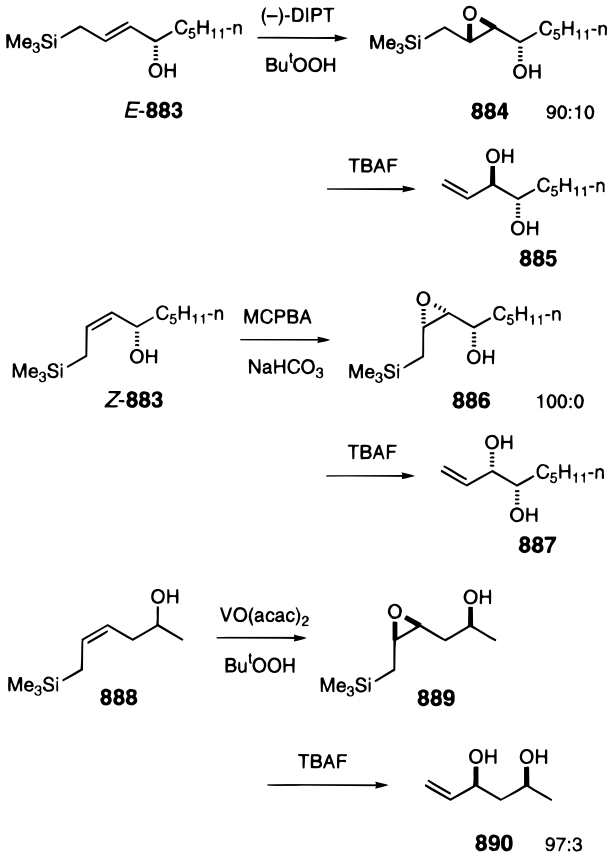
Although only nominally intermolecular reactions, the epoxidation of the homochiral allylsilanes (*E*)-**883** and (*Z*)-**883** can be controlled by intramolecular delivery of the reagent. With the *trans*-allylic alcohol (*E*)-**883**, enantioselective epoxidation under Sharpless conditions, coupled with matched intramolecular diastereoselection, gave largely the epoxide **884**, and

Scheme 224



hence the *anti*-1,2-diol **885**. With the *cis*-allylic alcohol (*Z*)-**883**, double stereodifferentiation was not necessary, and epoxidation with peracid gave only the epoxide **886**, and hence the *syn*-1,2-diol **887** (Scheme 225).[563] Similarly the homoallylic alcohol **888** gave the epoxide **889**, and hence the 1,3-diol **890**.[564]

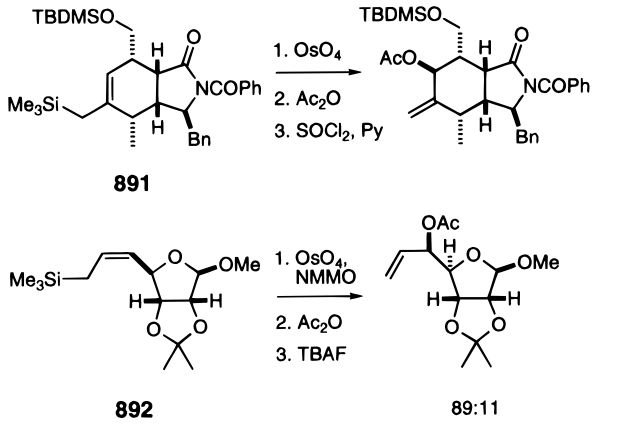
Scheme 225



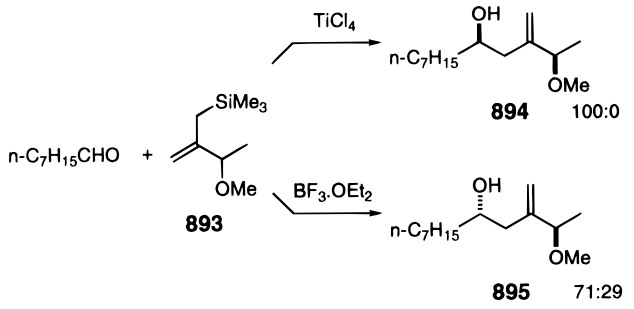
In some rather more complicated systems, osmium tetraoxide dihydroxylations are stereoselective with respect to the bicyclic ring system in the allylsilane **891**,[565] and to the neighboring stereogenic center in the allylsilane **892**, a representative of several sugar-derived systems[566] (Scheme 226).

With the resident stereogenic center cross-conjugated with the silyl group, the allylsilane **893** controls the stereochemistry well (100:0) with chelation control **893** → **894**, and rather less well (71:29) in the opposite sense with an open-chain transition structure in the reaction **893** → **895** (Scheme 227).[567]

Scheme 226



Scheme 227



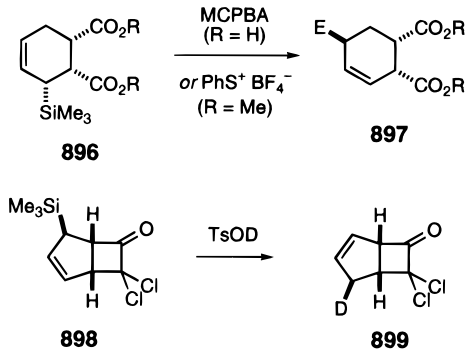
F. The Stereochemistry of the S_E2' Reaction of Allylsilanes

In most of the reactions of allylsilanes described so far, the allylsilanes were racemic, and the configuration at the newly created stereogenic center at C-3 was necessarily uncontrolled. However, the argument that electrophilic attack is *anti* to the silyl group in either conformation **188** or **200** implies that electrophilic attack on allylsilanes should lead to an S_E2' reaction with overall *anti* stereospecificity, as is indeed the case. In acyclic systems, the reactions are clean and potentially most useful when the structure of the starting allylsilane is such that it can be relied upon to react largely in the conformation **188**, and give, therefore, products with a *trans* double bond. If attack is also taking place in the sense **200**, to give a *cis* double bond, the overall result is still *anti* stereospecific, but the control of the absolute stereochemistry is compromised, because it is opposite at the newly created stereogenic center to that when the attack takes place in the sense **188**. It is therefore important to know which allylsilane structures react in which conformation, and which electrophiles are the best behaved.

1. Exploratory Reactions with Racemic Allylsilanes

The first stereochemically defined reactions of allylsilanes, still racemic, were in cyclic systems, as in the epoxidation and sulfenylation of the allylsilanes **896**, which were selective for the formation of the allylic alcohol **897** (E = OH, R = H) and sulfide **897** (E = SPh, R = Me), respectively (Scheme 228).[34] However, the constraints of the cyclic system might well have been controlling the stereochemistry, with electrophilic attack taking place *anti* to the carboxyl substituents, and the allylsilane system having little influence. In a bicyclic system **898**, with stronger

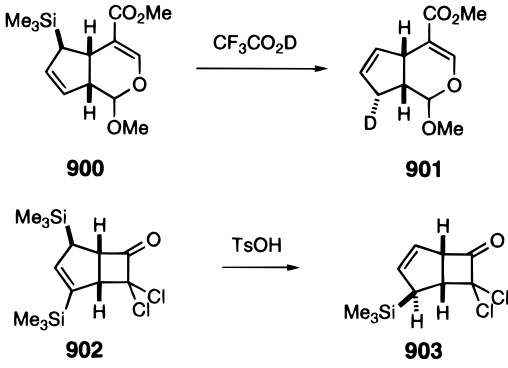
Scheme 228



stereochemical imperatives, the inherent *anti* stereospecificity of the allylsilane system was overcome in the deuteriodesilylation, giving the alkene **899**, a process which was *syn* with respect to the allylsilane, but *exo* as usual for this bicyclic system (Scheme 228).[568]

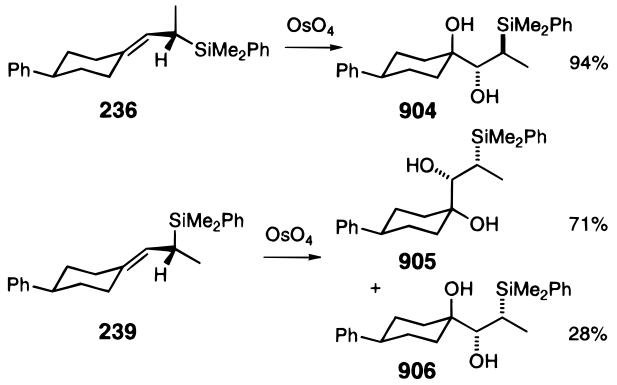
Even a small change in the bicyclic system allows *anti* attack sometimes to override the natural steric preference of the bicyclic system, as in the allylsilanes **900** and **902**, which react *anti* with respect to the allylsilane stereochemistry but *endo* in the bicyclic systems, to give the alkenes **901** and **903** (Scheme 229).[569,570]

Scheme 229



With the open-chain allylsilane **236**, still racemic, the *anti* attack to the silyl group matches the preference for axial attack on the ring system by the osmium tetraoxide, and the product is cleanly the diol **904** (Scheme 230).[571] With the diastereoisomeric

Scheme 230

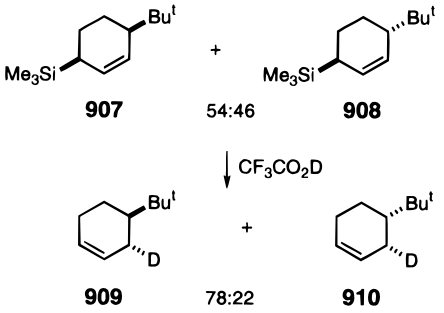


allylsilane **239**, the *anti* attack to the silyl group is set against the preference for axial attack on the ring system, and the allylsilane stereochemistry wins, with more of the product **905** of equatorial attack *anti*

to the silyl group, than of the product **906** of axial attack, *syn* to the silyl group. This problem did not surface in the corresponding Simmons−Smith reactions (Scheme 54), which appear to have been controlled entirely by the stereogenic centers carrying the silyl group.

A similar competition in the cyclohexenylsilanes **907** and **908** also showed some loss of *anti* stereospecificity. The results indicated that the allylsilane **907** reacted cleanly *anti*, giving the alkene **909**, but the large substituent in the allylsilane **908** interfered substantially, since attack *anti* to the silyl group involved the electrophiles being *syn* to the large substituent. Both alkenes **909** and **910** were produced, the former by *anti* attack on the allylsilane **907** and by *syn* attack on the allylsilane **908** (Scheme 231).[572] With less-hindering substituents, and with other cyclohexenyl and cycloheptenylsilanes, there was virtually no erosion of the *anti* stereospecificity.[572,573]

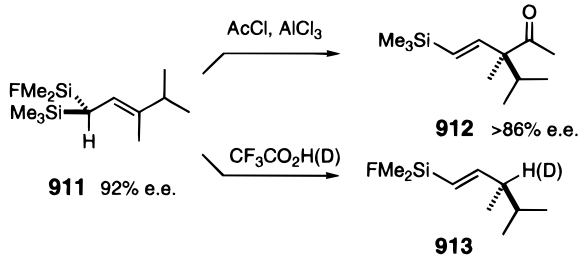
Scheme 231



2. Exploratory Reactions with Homochiral Allylsilanes

The first open-chain system with an enantiomerically enriched allylsilane to be studied proved to be anomalous. Acetylation of the allylsilane **911** gave the ketone **912**, which was the result overall of a *syn* substitution (Scheme 232).[574] It is possible in this

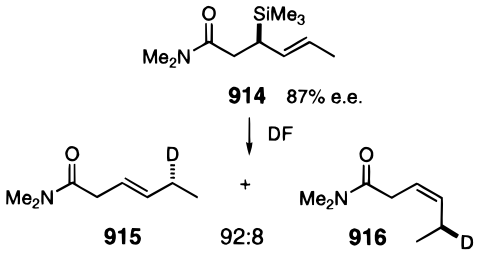
Scheme 232



reaction that the trimethylsilyl group is the more powerful group in directing the stereochemistry of attack by the electrophile, while the fluorodimethylsilyl group is the better electrofugal group.[575] The same allylsilane was normal in being *anti* stereospecific in proto- or deuterodesilylation, giving the vinylsilane **913**, with loss of the trimethylsilyl group. What has not been established is why the nature of the nucleophile should change the chemoselectivity in the removal of the silyl groups.

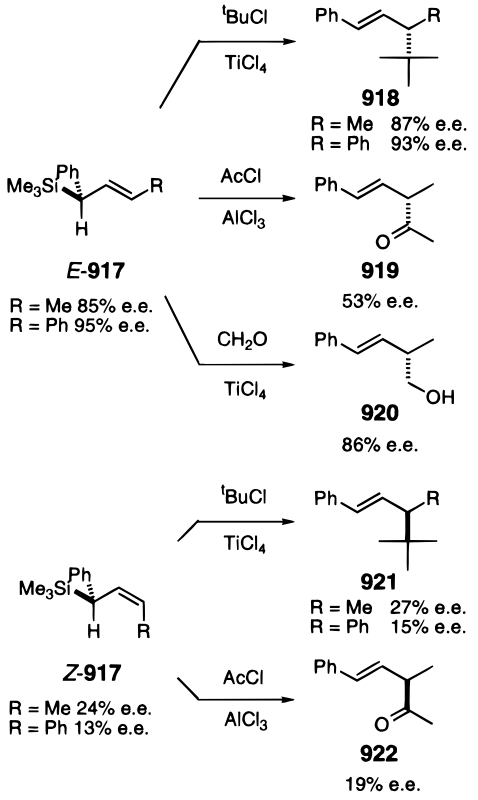
The first straightforward *anti* stereospecific reaction with an enantiomerically enriched open-chain allylsilane was the deuteriodesilylation **914** → **915** + **916**, in which the enantiomeric purity of the α-deuteriopropionic acid derived from the mixture corresponded, after allowing for the incomplete enantiomeric purity of the starting material and for the fact that *anti* stereospecificity gives opposite absolute configurations at the deuterium bearing carbon in each product, with that expected for a completely *anti* stereospecific reaction (Scheme 233).[576]

Scheme 233



The most wide-ranging results were carried out with the homochiral allylsilanes (*E*)-**917** and (*Z*)-**917**. These allylsilane reacted with a wide range of carbon electrophiles with, as far as could be measured by rotations, complete *anti* stereospecificity (Scheme 234).[577] The analysis was helped by the fact that,

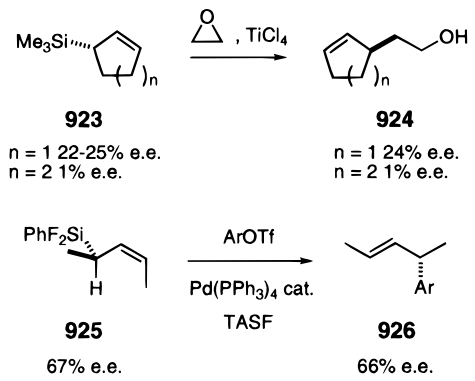
Scheme 234



with a phenyl group on the stereogenic center, and with a *cis* double bond in the allylsilanes (*Z*)-**917**, all the products **918**-**922**, cleanly had *trans* double bonds (>99%) as a consequence of reactions taking place only in the conformation **188** with hydrogen on the inside.

Other carbon electrophiles that have been shown in similar model reactions to give straightforward *anti* reactions are several aldehydes and their acetals, discussed separately below, ethylene oxide with the cyclic allylsilanes **923** giving the alcohols **924**,[578] and aryl triflates in cross-coupling with the allylsilane **925**[579] (Scheme 235). The last reaction however is

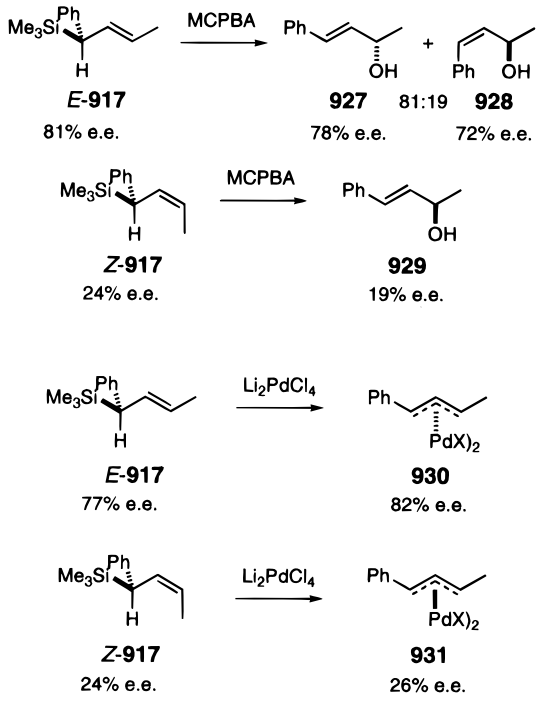
Scheme 235



susceptible to manipulation, giving overall *syn* substitution when cesium or potassium fluoride is used as the catalyst in THF in place of TASF in DMF.

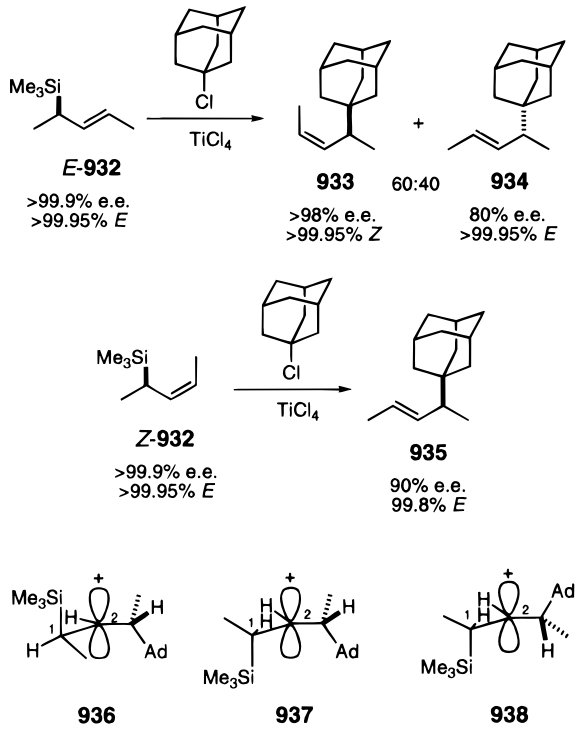
Heteroatom electrophiles also react stereospecifically *anti*, as shown by deuteriodesilylation of the allylsilanes (*E*)- and (*Z*)-**917**.[580] Peracid epoxidation of *trans* allylsilanes is rather more apt to show some reaction in conformation **200** rather than only in conformation **188**, even when there is a phenyl group on the stereogenic center, as established in Scheme 52. Thus epoxidation of the allylsilane (*E*)-**917** gave some of the *cis*-allylic alcohol **928** as well as the *trans*-alcohol **927**, whereas the *cis* isomer (*Z*)-**917** gave only the *trans*-alcohol **929**, but now all the products are enantiomerically enriched and the reactions are shown to be *anti* stereospecific (Scheme 236).[581] Reaction of palladium(II) chloride with the same allylsilanes (*E*)- and (*Z*)-**917** gave the π-allylpalladium complex **930** and its enantiomer **931**, respectively (Scheme 236).[582]

Scheme 236



In almost all of these reactions, the degree of *anti* stereospecificity appears to be essentially complete. However, using optical activity to measure the level of enantiomeric purity is inherently not susceptible to high accuracy or reliability, especially when the allylsilanes are themselves far from enantiomerically pure. Given that other constraints are known to be able to override the *anti* preference (Schemes 52 and 228−231), it seemed likely that small amounts of *syn* reaction were going undetected. To deal with this problem, the reactions in Scheme 47 were repeated with enantiomerically pure allylsilane (*E*)-**932**, with measurements of enantiomeric and geometric purity by chiral GC for the starting material and by the attachment of a chiral auxiliary to degradation products for the products. The *cis* product **933** was enantiomerically pure, but the *trans* product **934** did show some loss of the *anti* stereospecificity (Scheme 237). The *cis*-allylsilane (*Z*)-**932** gave only the *trans*

Scheme 237

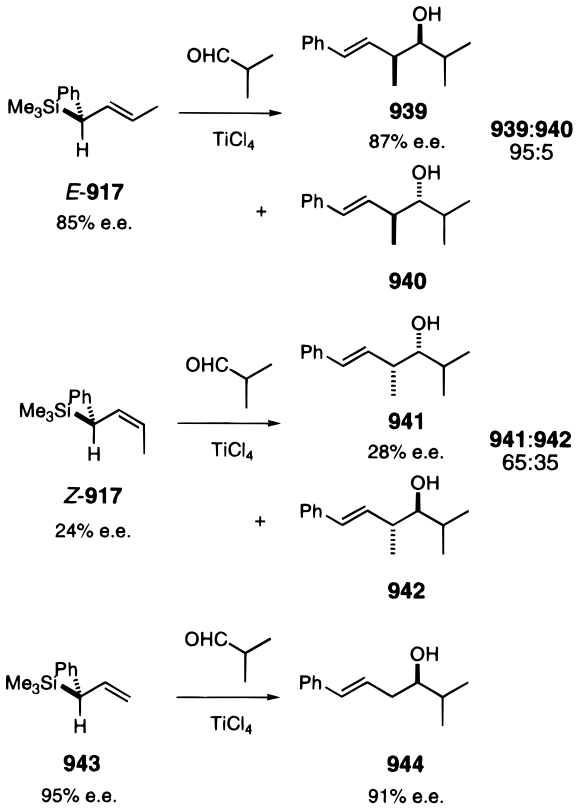


product **935**, which was also contaminated with some of the product of *syn* reaction, although to a lesser extent.[138] The most likely explanation for most of the loss of stereospecificity is that attack in conformation **200** takes place entirely *anti* to the silyl group, but that the intermediate cation **936** does not completely maintain its configurational identity. Most of it simply loses the silyl group and gives directly the *cis* product **933**, but some of it undergoes rotation about the bond between C-1 and C-2, giving the cation **937**, and hence the enantiomer **935** of the major *trans* product **934**. Attack in the conformation **188** *anti* to the silyl group leads to the intermediate **938**, which should have less propensity to undergo rotation about the bond between C-1 and C-2, and should simply lose the silyl group to give the major enantiomer **934**.

The Lewis acid-catalyzed reactions of allylsilanes with aldehydes are somewhat more complicated. As usual, they are *anti* with respect to the allylsilane component, as shown in the most simple case by the formation of the alcohol **920** in the reaction of the allylsilane (*E*)-**917** with formaldehyde. But they are also selective at the second stereocenter created in the reaction, typically giving more of the *syn* arrangement of substituents on the backbone than of

the *anti*. The selectivity is high (95:5) for the *trans* allylsilane, as in the example (*E*)-**917** → **939** + **940**, but less (65:35) for the *cis*, as in the example (*Z*)-**917** → **941** + **942** (Scheme 238).[583] This pattern is the

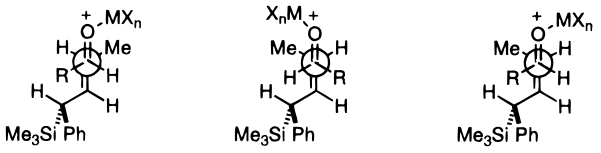
Scheme 238



same as that found for achiral allylsilanes, like crotyltrimethylsilane (Scheme 201).[584] The selectivity for the *anti* arrangement is higher when the aldehyde is more hindered, as with pivalaldehyde, and is similar when the C-3 substituent is phenyl in place of methyl. A consequence of this coupling of the stereochemistry at both centers is that, when there is no substituent on C-3, as in the allylsilane **943**, and there is no way of detecting the *anti* stereospecificity in the allylsilane fragment, the selectivity at the only new stereogenic center created in the product **944** is still high, although when the aldehyde is unbranched the selectivity is less (Scheme 238).[585,586]

Antiperiplanar transition structures **945**−**947**, enlarged from the drawings used earlier **806** and **807** to include the orientation of the silyl group, are usually drawn for this type of reaction (Scheme 239).

Scheme 239

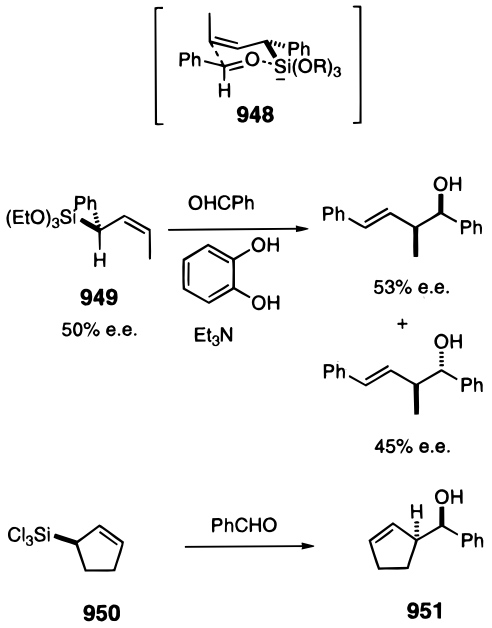


945 **946** **947**

The aldehyde substituent R is in the clearly less hindered sector **945** when the allylsilane is *trans*, but has a less obvious preference, when the allylsilane is *cis*, between the arrangement **946**, where there is a gauche interaction between R and the phenyl group, and the alternative **947**, where it is close to the methyl group.[583] The greater selectivity for the *syn* arrangement was evident in the reactions discussed earlier in Scheme 201, but was less extreme, because there was no substituent where the phenyl group is in the transition structure **946**.

When the allylsilane has electron-withdrawing ligands, the aldehyde coordinates to the silyl group, and the reaction is intramolecular **948**, with a synclinal approach of the two π-bonds, making a *cis*-allylsilane (**949**) give more (90:10) of the *syn* homoallylic alcohol than of the *anti*, but now the S_E2' reaction is stereospecifically *syn* for both diastereoisomers (Scheme 240).[587] The same combination of absolute and relative stereocontrol works in the reaction of a cyclic allylsilane with benzaldehyde **950** → **951** (Scheme 240).[588]

Scheme 240

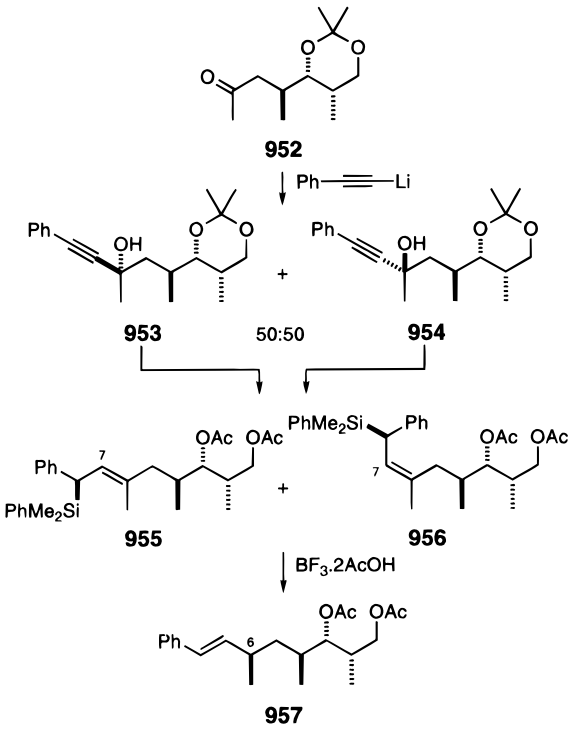


3. Stereospecific S_E2' Reactions of Allylsilanes in Synthesis[5]

a. Protodesilylation. The pair of allylsilanes **955** and **956**, prepared by a three-step stereoconvergent route from each of the separated propargylic alcohols **953** and **954**, underwent stereospecific protodesilylation to give the alkene **957**, in a synthesis of the Prelog−Djerassi lactone. The protodesilylation step set up the stereocenter C-6, remote from the influence of the other stereogenic centers C-2, C-3, and C-4, with the stereoconvergence overcoming the unsurprising lack of selectivity in the step **952** → **953** + **954** (Scheme 241).[589]

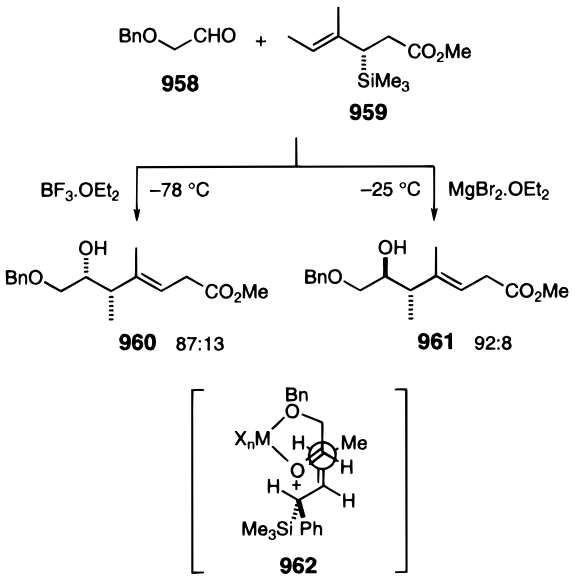
In the protodesilylation step in Scheme 241, the stereospecificity was eroded somewhat. Although both allylsilanes **955** and **956** were free of the other pair of diastereoisomers, the product **957** was contaminated with 17% of its diastereoisomer at C-6, probably because some of the protonation initially took place at C-7, with a subsequent, and incompletely stereoselective, hydrogen shift to C-6. This is a pitfall in protodesilylation reactions of allylsilanes having two substituents at the allylic terminus stabilizing the formation of a cation at that site.[590]

Scheme 241



b. Reactions with Carbonyl Groups and Acetals. The allylsilane **959** reacts with the aldehyde **958** in the presence of boron trifluoride etherate to give the homoallylic alcohol **960** with the usual *syn* disposition of substituents on the backbone. In the presence of magnesium bromide, the extra functionality in the aldehyde allowed an alternative pathway, with chelation between the benzyloxy group and the aldehyde by the Lewis acid, giving the *anti* product **961** (Scheme 242). The explanation for the change

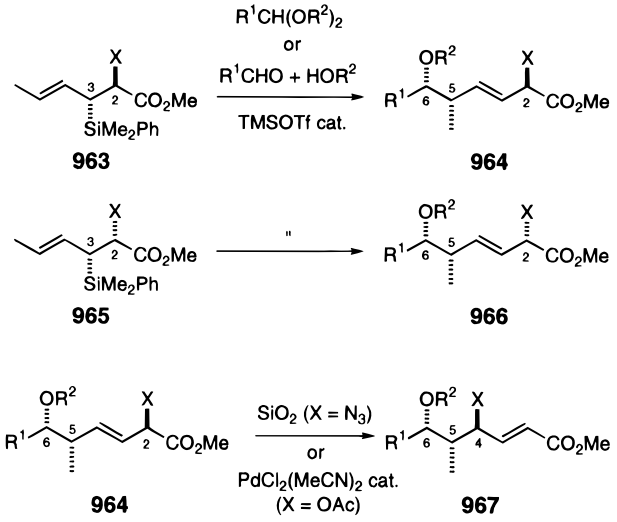
Scheme 242



in the relative configuration of the substituents on the carbon backbone from *syn* to *anti* is that the transition structure changes from the usual *anti-periplanar* **945** to the *synclinal* **962**. Because of the chelation, the Lewis acid is *cis* to the carbon chain, and the aldehyde oxygen is effectively smaller. In consequence, it sits in the more crowded sector adjacent to the stereogenic center of the allylsilane instead of adjacent to the terminal methyl group, and the vinylic hydrogen atom still sits in the most crowded sector.[591]

In Lewis acid-catalyzed reactions, allylsilanes usually react more cleanly with acetals than with aldehydes, avoiding the formation of tetrahydrofurans that are major byproducts in the reactions in Scheme 242, as discussed below. Thus several allylsilanes of general structure **963** react with acetals to give largely the products **964** with the *syn* arrangement of substituents on C-5 and C-6 and a stereospecifically *anti* substitution in the transfer of chiral information from C-3 of the allylsilane **963** to C-5 of the product **964** (Scheme 243). The substituent X in

Scheme 243

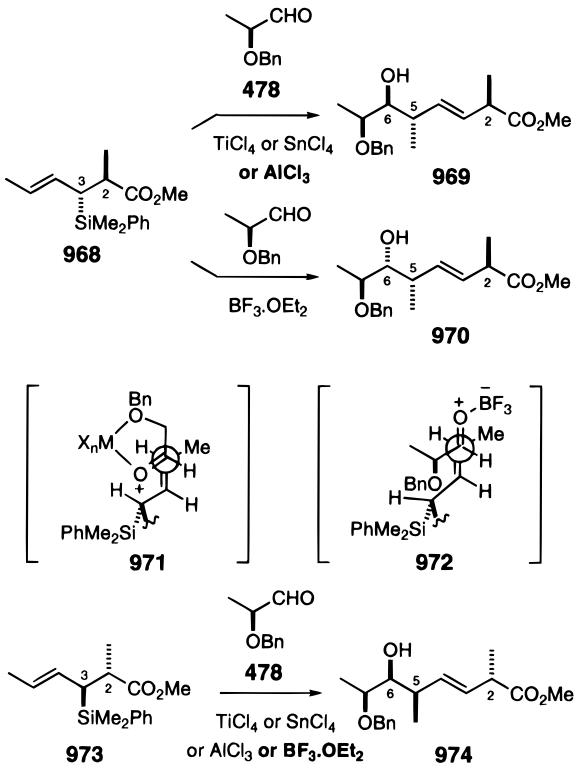


the allylsilanes **963** has been hydrogen,[592] methyl, methoxy,[593,594] acetoxy,[595] and azido,[596] and it has in most cases been available in either relative configuration **963** or **965** between the substituents on C-2 and C-3, and also in either absolute sense. In consequence the relative configurations between C-2 and C-5 can be controlled to be either **964** or **966**, respectively, or their enantiomers. The acetal can be aryl, alkyl and functionalized alkyl, like the aldehyde **958**, and it does not always need to be prepared beforehand—it can be prepared *in situ*[597] by mixing the aldehyde and the trimethylsilyl ether of the alcohol with trimethylsilyl triflate before adding the allylsilane.[598] When the substituent X is an acetoxy group[595] or an azido group,[596] the product **964** can easily rearrange, or be caused to rearrange, suprafacially to give products **967** with the three stereogenic centers contiguous.

When the aldehyde is also chiral, matched and mismatched pairs can be combined. The pair **968** and **478** are matched for reaction in the presence of a chelating Lewis acid. The *synclinal* transition structure **971**, similar to **962**, places the methyl group on the opposite side of the carbonyl group from the attacking nucleophile, and the product is the homoallylic alcohol **969** with the *anti* relative configuration between C-5 and C-6. The only unusual feature here is that aluminum chloride appears, somewhat unusually, to be a chelating Lewis acid. The same pair **968** and **478** are also matched for reaction using a nonchelating Lewis acid like boron trifluoride. The

usual *antiperiplanar* transition structure **972**, similar to **945**, has the benzyloxy group on the opposite side of the carbonyl group from the attacking nucleophile in the Cornforth−Felkin−Anh model, and the product is cleanly the homoallylic alcohol **970** with the *syn* relative configuration between C-5 and C-6. With the mismatched pair **973** and **478**, the stereospecifically *anti* S_E2' process still controls the stereochemistry at C-5, but the configuration created at C-6 in the major product **974** is that of chelation control with an *antiperiplanar* transition structure, whether the Lewis acid is chelating or not (Scheme 244).

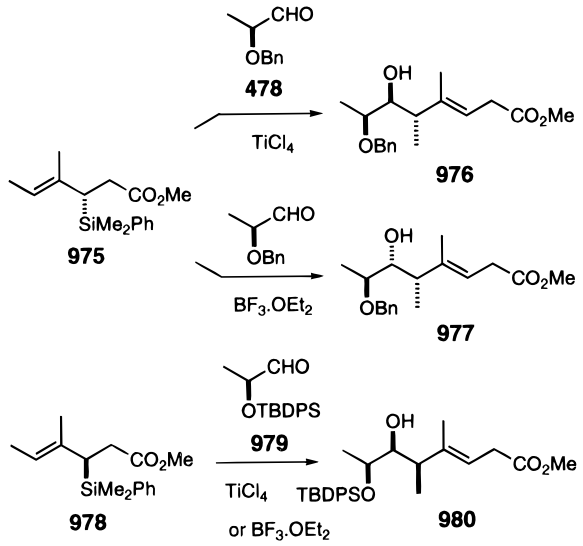
Scheme 244



Thus it appears that the chelated electrophile gives up its preference for a *synclinal* transition structure, and the nonchelated electrophile gives up its preference for the Cornforth−Felkin−Anh model. However, most of these reactions do not give in good yield directly the open-chain products of an S_E2' reaction. The open-chain products are the major products only with the more aggressive Lewis acids like aluminum chloride in the mismatched pairing. The major products with the other Lewis acids and with the matched pair, whatever the Lewis acid, are tetrahydrofurans, as discussed below, but with the same stereochemical relationships as those in the reactions in Scheme 244.[599]

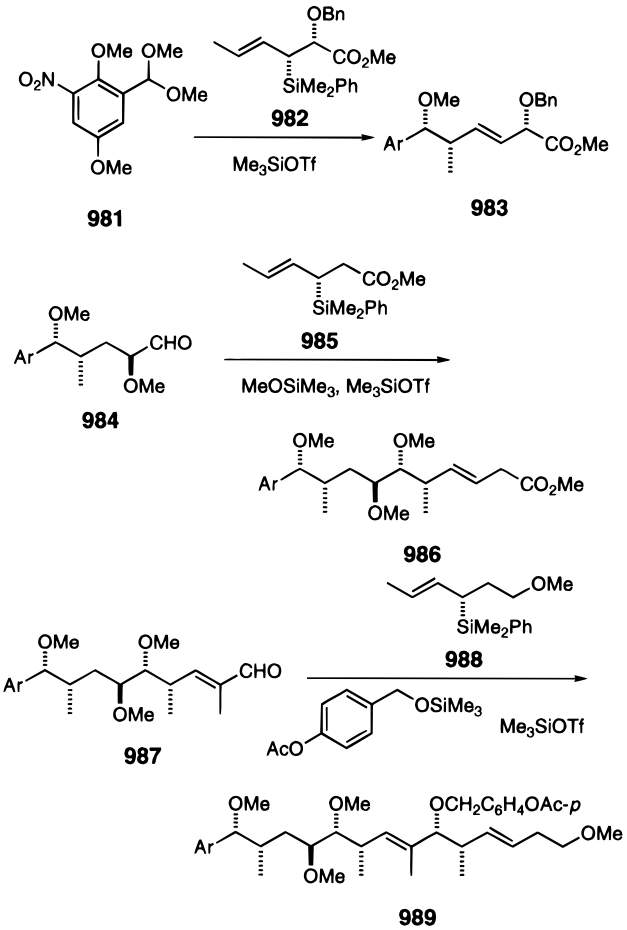
The same pattern of an *anti* relationship between the two new stereocenters from a titanium tetrachloride reaction, and a *syn* relationship from the boron trifluoride reaction, was seen when C-4 carried a substituent, as in the reactions of the allylsilane **975** with the aldehyde **478** leading to the stereotriads **976** and **977** (Scheme 245). Chelation could be prevented by using a *tert*-butyldiphenylsilyl group in place of the benzyl, so that the enantiomeric allylsilane **978** reacted with the aldehyde **979** to give the *all-syn* isomer **980** whatever the Lewis acid (Scheme 245).[600]

Scheme 245



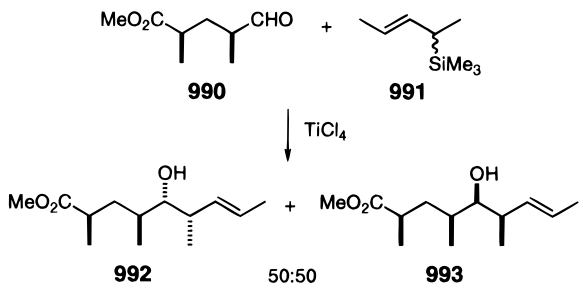
In the most substantial application of this methodology, the allylsilane **982** was treated with the acetal **981**, and successively the allylsilanes **985** and **988** with the acetals derived from the aldehydes **984** and **987**, respectively, in the course of a synthesis of (+)-macbecin I (Scheme 246).[601]

Scheme 246



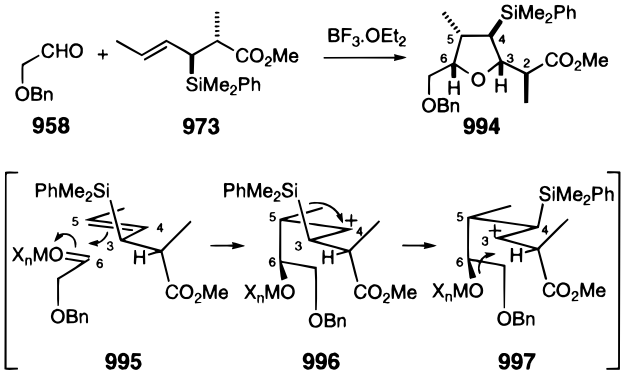
The same powerful constraint, that the S_E2' reaction be stereospecifically *anti*, makes the enantiomerically pure aldehyde **990** combine with the racemic allylsilane **991** with little selectivity, giving equal amounts of the two products **992** and **993** (Scheme 247).[602]

Scheme 247



In the reactions with aldehydes, discussed above, tetrahydrofuran rearrangement products were mentioned as being major byproducts in the synthesis of the open-chain products like **960** and **961** in Scheme 242; **969**, **970**, and **974** in Scheme 244; and **976**, **977**, and **980** in Scheme 245. Thus the aldehyde **958** reacts with the allylsilane **973** in the presence of a nonchelating Lewis acid to give, as the major product, the tetrahydrofuran **994**. The initial attack can take place in the *antiperiplanar* approach **995**, the first-formed cation **996** undergoes a 1,2-silyl shift, with the resultant cation **997** being captured by the oxygen of the original aldehyde group, with rotation about the C-5 to C-6 bond at some stage to bring the oxygen atom into position to attack the cation (Scheme 248).

Scheme 248

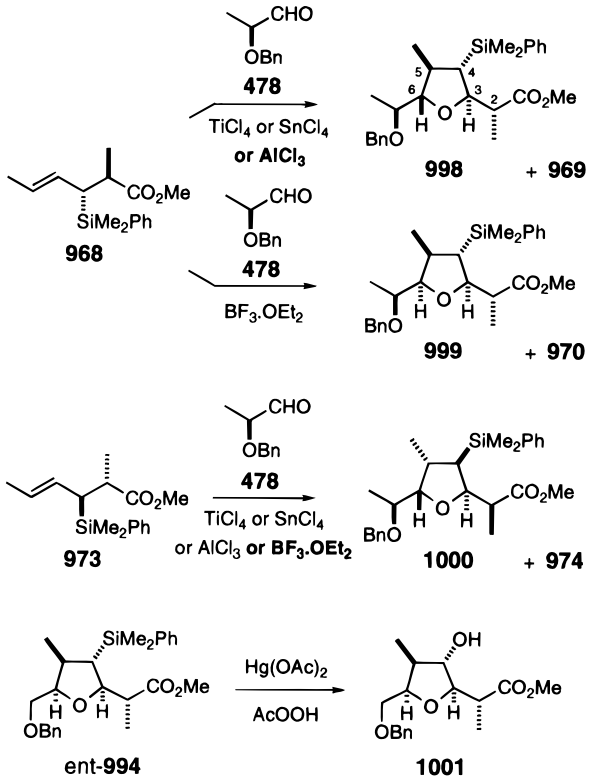


The stereochemical constraints are the same as before: the stereochemistry at C-5 in the product **994** is controlled by the *anti* S_E2' reaction, the relationship between C-5 and C-6, corresponding to the *syn* arrangement in **960**, is explained by the *antiperiplanar* transition structure, and the two additional centers, C-3 and C-4, are controlled by the suprafacial shift of the silyl group in the first-formed cation **996** and the capture of the resultant cation **997** with inversion of configuration at C-3.[603]

The pair of cations **996** and **997** illustrated here are often subsumed in a drawing with a single bridging silyl group. However, bridging is not necessarily the best representation,[604] although it is certainly a good representation of the transition structure of this easy rearrangement. Calculations for the gas phase suggest that the bridged structure is only a minimum for the parent β-trimethylsilylethyl cation, and that secondary cations are more likely to be hyperconjugating β-silyl cations as drawn here.[605] Bridging is likely to be more important in the absence of solvation, and so the transfer from the gas phase to solution is only likely to make the hyperconjugating structures more favorable. Certainly bridging is not needed to explain the maintenance of stereochemistry—all that is needed to account for the graceful stereochemical displacements in the steps **996** → **997** → **994** is the knowledge that the intermediate cations do not appear to rotate freely around the bond between C-3 and C-4, and nucleophiles will selectively attack such cations *anti* to the silyl group.

Similarly, when the aldehyde is chiral, the choice of Lewis acid affects the relative stereochemistry in the same way as in the reactions illustrated in Scheme 244, with the matched pair **968** and **478** giving different tetrahydrofurans **998** and **999** with different Lewis acids, and the mismatched pair **973** and **498** giving the tetrahydrofuran **1000** with all Lewis acids (Scheme 249). Again, all the stereo-

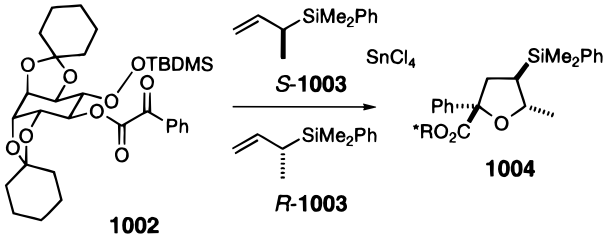
Scheme 249



chemical constraints are the same as for the open-chain products but two additional stereogenic centers are controlled.[599] The additional stereocenters are again potentially useful, because the phenyldimethylsilyl group can be converted with retention of configuration into a hydroxy group,[218] as in the conversion of the tetrahydrofuran *ent*-**994** into the alcohol **1001** (Scheme 249).[603]

The homochiral α-keto ester **1002** controlled the face of the carbonyl group being attacked, and the chiral but racemic allylsilane **1003** reacted with it to give one product **1004**, in which the silyl group had again been retained (Scheme 250).[606] Because of the uncertainty which conformation, methyl inside, like **169**, or hydrogen inside, like **157**, it is not easy to predict which enantiomer of the allylsilane **1003**, with only a methyl group as the carbon substituent on the stereogenic center, will make the matched pair

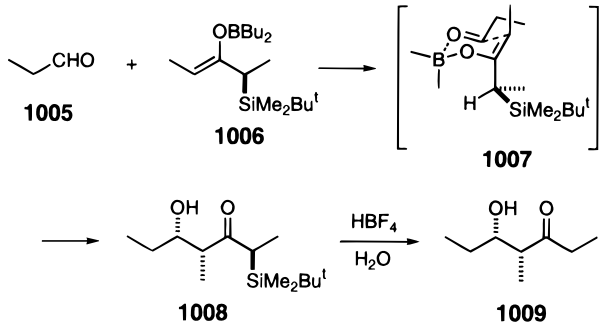
Scheme 250



with the ketone **1002**. In the event, the product **1004** corresponds to attack by the *S* isomer, with the hydrogen atom inside like **188**, the more unusual conformation for this type of allylsilane. Two equivalents of the racemic allylsilane were used, so that there would be one full equivalent of each enantiomer available, but it is not clear in this case whether the *R* enantiomer could have been isolated enantiomerically enriched, or whether it would have suffered protodesilylation, a frequent cause of byproducts in this type of reaction. With achiral dicarbonyl compounds in place of the α-keto ester **1002**, the same diastereoselectivity is observed, and presumably both enantiomers of the allyl silane are consumed.[607]

In all the reactions described above in which the silyl group is not lost, there remains the possibility of removing it by some kind of *β*-elimination. In a few other reactions, that possibility does not arise. Thus the enantiomerically enriched allylsilane **1006** is also a boron enolate and its reaction with aldehydes **1005** is an aldol reaction giving the aldol **1008**, in which the silyl group remains in the molecule, helped by the fact that it is hindered and slow to be electrofugal. The absolute stereochemistry, however, is controlled by the presence of the silyl group, with the *anti* attack on the allylsilane taking place **1007** with the methyl group inside, like **200**. Because it is adjacent to a carbonyl group, the silyl group can easily be removed, and in this case doing so gave the pheromone sitophilure **1009** (Scheme 251).[608]

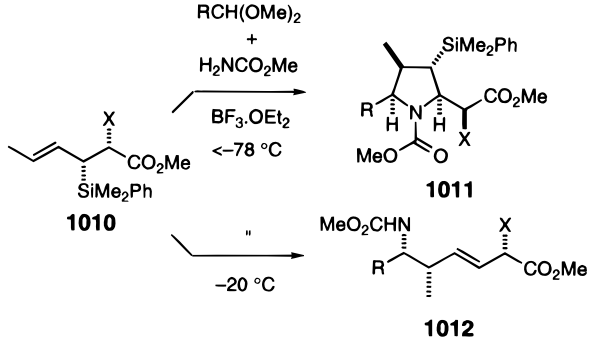
Scheme 251



c. Reactions with Iminium Ions. An iminium ion is similar to an aldehyde, or the oxenium ion intermediate in acetal reactions. Thus imines, prepared *in situ* from an aldehyde or its acetal and methyl carbamate, react with the family of allylsilanes **1010** in the same way as the aldehydes and their acetals did with the closely similar allylsilanes **965**, and with the same feature that cyclization and 1,2-silyl shift giving the pyrrolidine **1011** are major pathways to begin with, but warming the mixture gives the open-chain product **1012** (Scheme 252).[609]

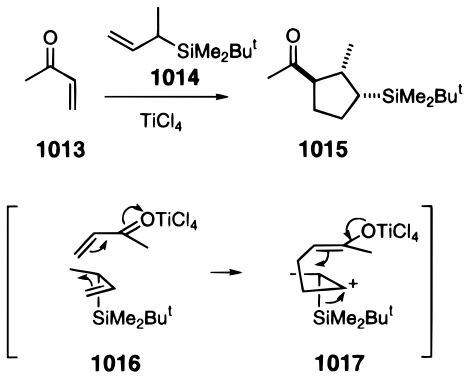
d. Reactions with Enones. Most of the reactions of enones with allylsilanes having an S_E2'

Scheme 252



stereochemistry are intramolecular and covered in section IX.G. In those intermolecular reactions in which the silyl group is retained, as with methyl vinyl ketone **1013** and the chiral allylsilane **1014**, having a hindered silyl group, the major product is the cyclopentane **1015**, which still has the silyl and acyl groups *trans*, as in the reaction in Scheme 217, but in addition has the methyl group *cis* to the silyl, showing that attack on the double bond probably takes place in the *synclinal* conformation **1016**, rearranging with silyl shift **1017**, with the allyl system *endo* and the methyl group inside, similar to the conformation **200** common with allylsilanes with a small group on the stereogenic center (Scheme 253).

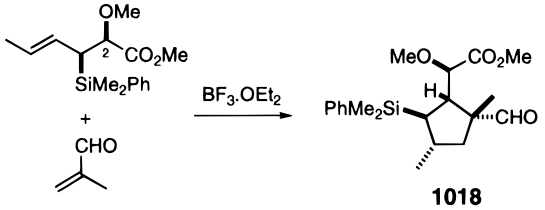
Scheme 253



The various minor products can be identified as coming from a similar *endo* conformation, but with the methyl group outside, and from attack with the allyl system *exo* and with the methyl group either inside or outside.[610]

The [3+2] cycloaddition pathway even takes place with α,*β*-unsaturated aldehydes, giving control of the stereochemistry of four or five contiguous centers in products like **1018**. The stereochemistry is that expected of attack on the allylsilane *anti* to the silyl group in a conformation with the branched carbon, C-2, outside, like **188** (Scheme 254).[611]

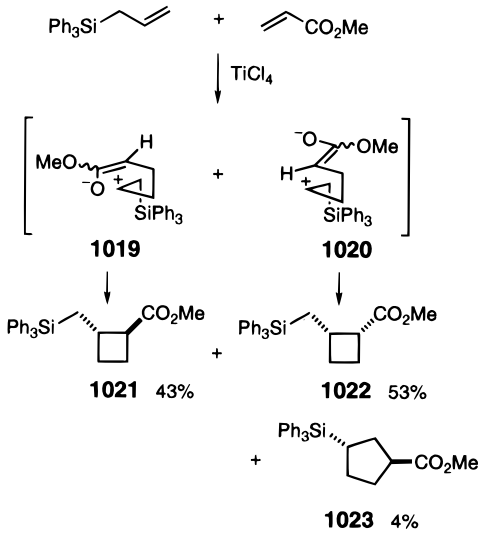
Scheme 254



The same type of reaction with α,*β*-unsaturated esters, however, gives largely cyclobutane products

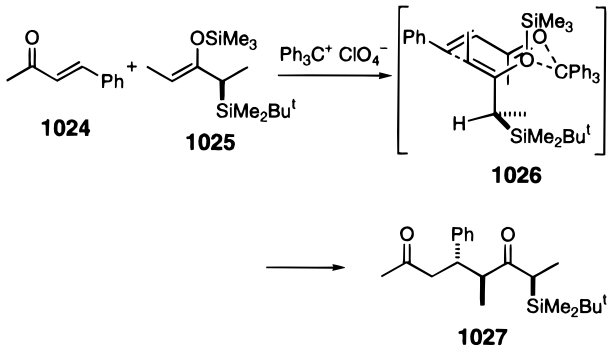
1021 and **1022** without silyl shift, and with little control of the relative stereochemistry in the two new stereogenic centers. Presumably there is little to choose between the conformations **1019** and **1020**, since the silyl group will be oriented on the opposite side from the ester group (Scheme 255).[612]

Scheme 255



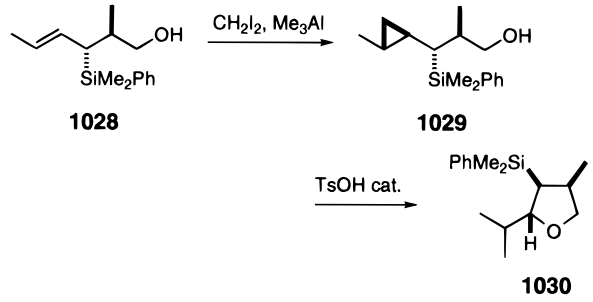
The allylsilane **1025** is also a silyl enol ether, related to the boron enolate in Scheme 251. Its reaction with enones like **1024**, catalyzed by trityl perchlorate, is a Mukaiyama−Michael reaction, giving the 1,5-diketone **1027**, but the absolute stereochemistry is again controlled by the presence of the silyl group. The allylsilane is attacked *anti*, from the conformation with the hydrogen atom inside like **188**, and the relative configuration is *anti* between the two newly created stereogenic centers in a chairlike transition structure **1026** (Scheme 256).[613]

Scheme 256



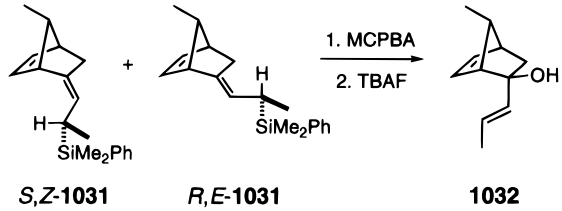
e. Reactions with Other Carbon Electrophiles. Simmons−Smith reactions on chiral allylsilanes, or better the Yamamoto version,[614] give cyclopropylmethylsilanes with high diastereoselectivity when the carbon substituent on the stereogenic center is branched.[143,146] Thus the allylsilane **1028** gives the cyclopropane **1029**, and this can be opened without loss of the silyl group to give the tetrahydrofuran **1030** (Scheme 257).[615] As already seen in Scheme 54, the silyl group may also be removed by electrophilic opening of the cyclopropane ring, giving overall an S_E2' reaction.

Scheme 257



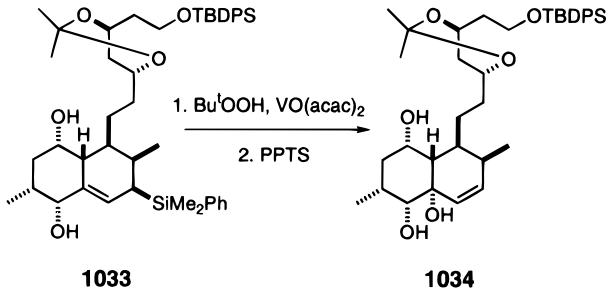
f. Reactions with Oxygen and Selenium Electrophiles. Stereospecific epoxidation of an allylsilane, and its desilylative opening, has been used in a synthesis of (±)-dihydronepetalactone, where the epoxidation of the mixture of allylsilanes **1031** was designed to have the *exo* preference for attack on the bicyclic system matched to the preference for attack *anti* to the silyl group in *both* allylsilanes. The only product was the allylic alcohol **1032** with the propenyl group *endo*, ready for an oxy-Cope rearrangement (Scheme 258).[616]

Scheme 258



It has also been used in a synthesis in the mevinolin field to make the diol **1034** from the allylsilane **1033** (Scheme 259).[617]

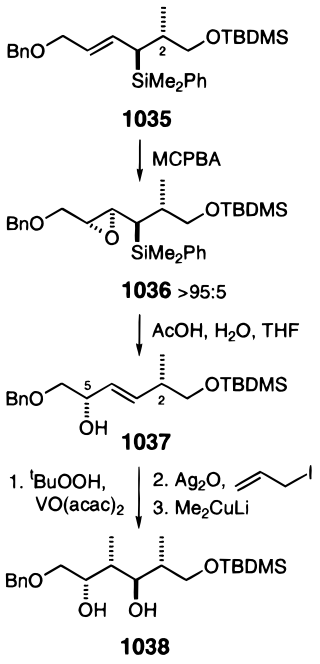
Scheme 259



In open-chain systems, the epoxidation of an allylsilane like **1035** is relatively straightforward, with high (>95:5) stereoselectivity when C-2 is branched, but lower (80:20 or worse), when it is not, as expected from the results in Scheme 52. The epoxide **1036** can easily be opened with loss of the silyl group to give the *trans* allylic alcohol **1037**, establishing the 1,4-relationship between C-2 and C-5. This allylic alcohol is then set up for stereoselective epoxidation and further manipulation to give an intermediate **1038** for polyketide synthesis (Scheme 260).[618]

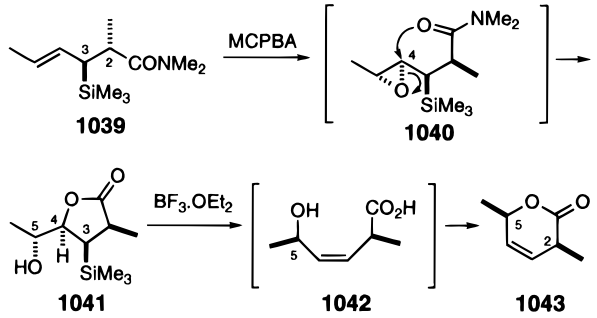
However, the presence of nucleophilic substituents in functionalized allylsilanes like these can lead to opening of the epoxide without loss of the silyl group. Thus the amide **1039** stereoselectively gives the lactone **1041** by carbonyl participation in the opening of the epoxide **1040**. Such intermediates still have a silyl group β to a nucleofugal group, and are easily

Scheme 260



opened stereospecifically *anti* to give a *cis* allylic alcohol **1042** that creates overall the new stereocenter at C-5 with the expected relationship with that at C-3 for an *anti* S_E2' reaction. Curiously, the inversion of configuration at C-4 in the step **1040** → **1041**, followed by the *anti* elimination giving a *cis* double bond in **1042**, makes the reaction **1039** → **1042** formally a *syn* S_E2' reaction. The alcohol **1042** forms the lactone **1043**, which was hydrogenated to give the carpenter bee pheromone with the correct relative stereochemistry between C-2 and C-5 (Scheme 261).[619]

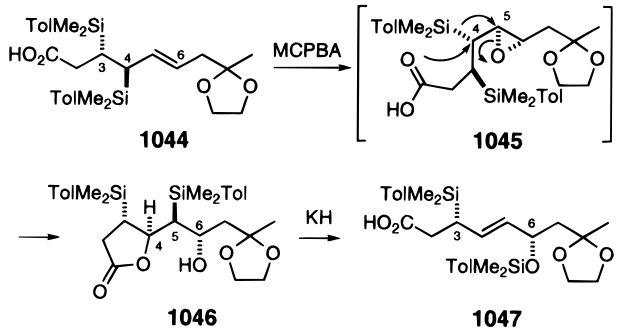
Scheme 261



Carboxylic acids are even better than amides in giving high yields of lactones like **1041**, whereas esters are more likely to lead to an epoxide that can be isolated, and to its direct opening to give a *trans* allylic alcohol.[620] If the ester is reduced to an alcohol before the epoxidation, that too can open the epoxide and give a tetrahydrofuran.[621]

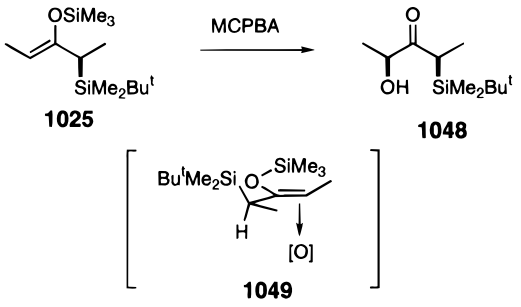
In the allylsilane **1044** the nucleophilic carboxylic acid group is one further atom away from the epoxide, but participation still occurred with the formation of a γ-lactone by way of a C-4 to C-5 silyl shift **1045** → **1046**. The new stereocenter at C-6 was correctly set up, and the subsequent elimination, which this time, with good precedent,[622] was merely stereoselective for the formation of a *trans* double bond, rather than stereospecifically *anti*, gave the allylic silyl ether **1047** that is the overall result of an *anti* S_E2' reaction on the allylsilane (Scheme 262). The silyl ether **1047**, having had stereochemical information stereospecifically moved from C-4 to C-6, had the desired 1,4-relationship between C-3 and C-6 for a synthesis of nonactin.[623]

Scheme 262



Epoxidation of the allylsilane **1025** gave largely the alcohol **1048**, the result of reaction in the conformation **1049** with the methyl group inside (Scheme 263), in contrast to the reactions in Schemes 251 and 256.[624]

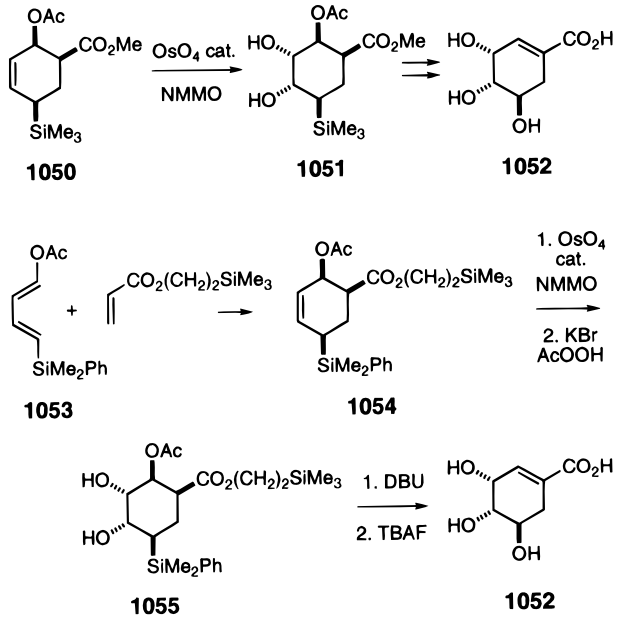
Scheme 263



Osmium tetraoxide, discussed earlier (see Scheme 50), has a useful complementary selectivity to that of epoxidation, and again the elimination step may or may not be carried out. Dihydroxylation *anti* to the silyl group in the cyclic allylsilane **1050** gave only the one diol **1051**, which was used in a synthesis of (±)-shikimic acid (**1052**, Scheme 264).[625] A later synthesis of shikimic acid, based on a similar dihydroxylation **1054** → **1055**, was followed by silyl-to-hydroxy conversion[218] to give the intermediate **1055** (Scheme 264), an improvement over the earlier route, where the silyl group had to be removed and oxygen reinstated.[626]

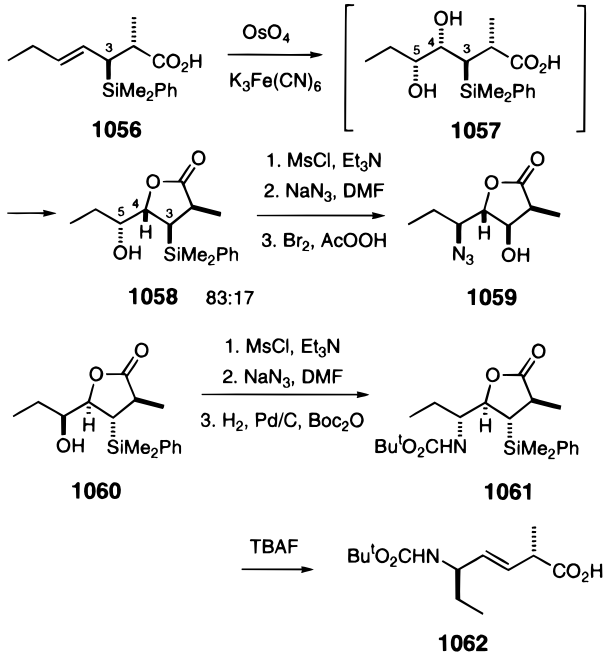
In an open-chain system, the reaction of osmium tetraoxide on the allylsilane **1056** gave, with an *anti* to *syn* selectivity of 83:17, the diol **1057**, which lactonized to give the lactone **1058**. Because there was no inversion of configuration at C-4 the relationship between C-3 and C-4 is opposite to that in the lactone **1041** obtained by epoxidation, but the relationship between C-3 and C-5 is the same (Scheme 265).[627] The free hydroxyl group in the lactone **1058** can be used to introduce nitrogen functionality, and silyl-to-hydroxy conversion[218] then gives the highly functionalized lactone **1059**.[628] The same sequence

Scheme 264



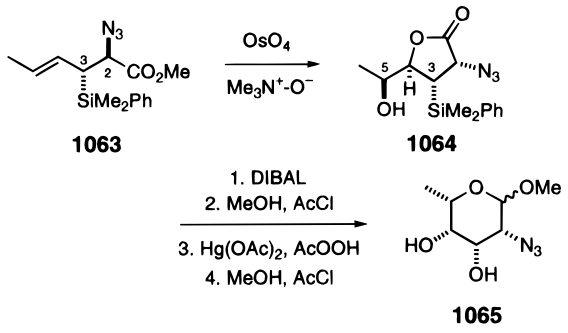
from the diastereoisomeric lactone **1060** also introduced nitrogen functionality into the lactone **1061**, which was induced to undergo elimination to give the protected amino acid **1062**, suitable for the synthesis of peptide isosteres (Scheme 265).[629]

Scheme 265



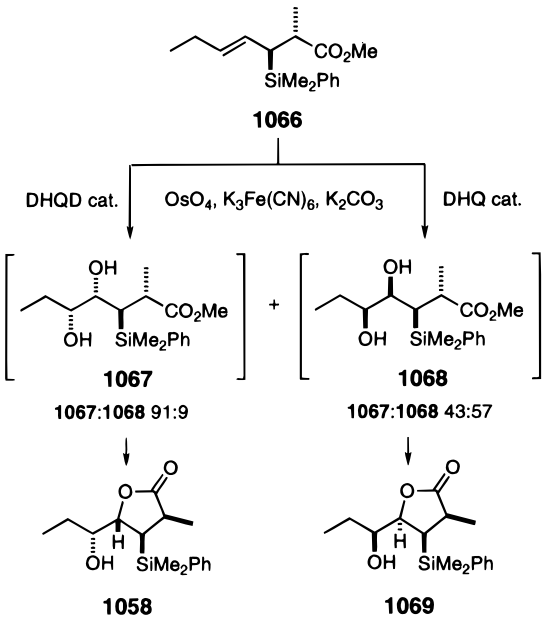
Similarly, osmium tetraoxide and the allylsilane **1063** gave, with 94:6 selectivity, the γ-lactone **1064**. Reduction of the lactone, acetal formation, silyl-to-hydroxy conversion[218] and acetal exchange gave the 2-azidodeoxytaloside (**1065**, Scheme 266).[630] Since both the absolute configuration and the relationship between C-2 and C-3, can be controlled in either sense, and since a *cis* double bond used in place of the *trans* would change the relative stereochemistry between C-3 and C-5, every possible enantiomer and diastereoisomer of this kind of molecule can in principle be created by epoxidation or osmium tetraoxide reactions.

Scheme 266



Asymmetric dihydroxylation can be superimposed to enhance the diastereoselectivity stemming from the allylsilane. A dihydroquinidine-derived catalyst matches the sense for attack *anti* to the silyl group in the enantiomer **1066**, and the lactone **1067** is produced with higher selectivity (91:9) than with the achiral reagent (85:15, similar to the 87:13 ratio from the corresponding acid in Scheme 264). In contrast, the dihydroquinine-derived catalyst is a mismatch (Scheme 267).[628] Asymmetric dihydroxylation can also be used for kinetic resolution in this series, but the degree of kinetic resolution is not yet high.

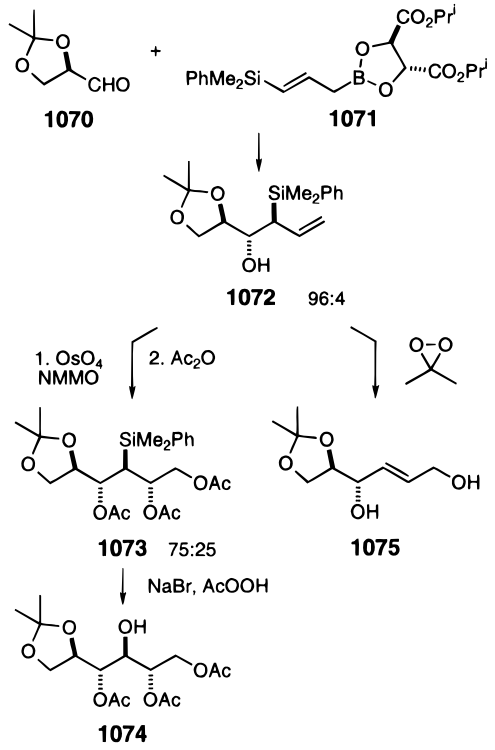
Scheme 267



For sugar synthesis, the dihydroxylation of an allylsilane followed by silyl-to-hydroxy conversion[218] gives a 1,2,3-triol derivative. Thus the reaction of the allylsilane **1072** with osmium tetraoxide followed by acetylation gave the triacetate **1073**, and silyl-to-hydroxy conversion gave the hexitol derivative **1074** (Scheme 268).[631] Epoxidation−elimination gave the allylic diol **1075**, which could be dihydroxylated to give other diastereoisomers.

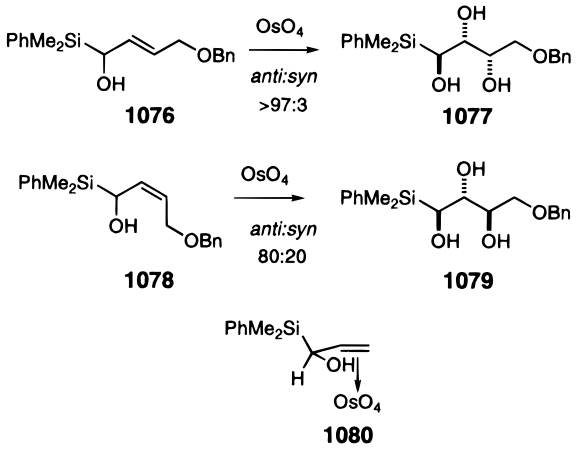
In another approach to sugar systems, the osmium tetraoxide reaction was carried out on the allylsilanes **1076** and **1078** having hydroxyl groups on the stereogenic centers. Because the hydroxyl group is not large and because a C−O bond conjugated to the allyl system would reduce the nucleophilicity of the double bond, the conformation adopted is relatively cleanly that in which the oxygen group is inside **1080**. In

Scheme 268



this arrangement, the C−O bond is not conjugated with the π-system, and, especially when the substituent on the double bond *cis* to the stereogenic center is hydrogen, the $A^{1,3}$ interaction is small. In consequence the *trans*-allylsilane **1076** was highly selective (>97:3) in favor of the triol **1077**, but the *cis*-allylsilane **1078** was less so (80:20), although still in the same sense, in favor of the triol **1079** (Scheme 269).[632] Similar work, with a terminal double bond

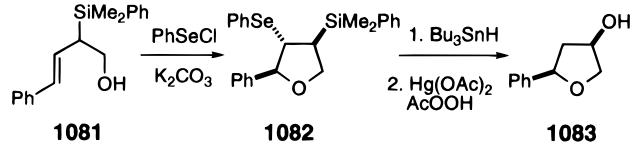
Scheme 269



and an acetoxy group on the stereogenic center, also showed that the major product came from the conformation with the acetoxy group inside, and added that the degree of selectivity was affected by the electronic donor capacity of the substituents on the silyl group.[633]

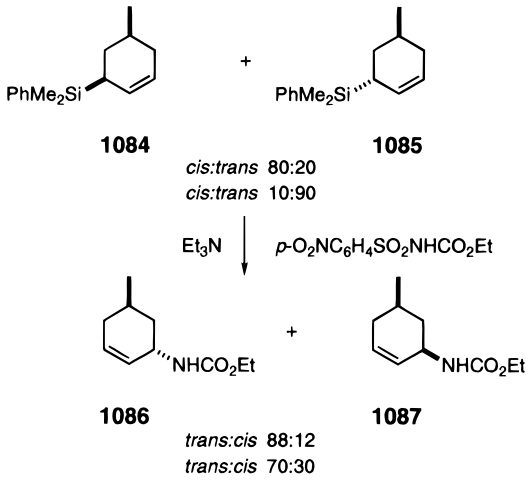
Selenoetherification was moderately selective for the selenium electrophile attacking *anti* to the silyl group in the allylsilane **1081** giving the *trans,trans*-tetrahydrofuran **1082**. The selenium was removed by tin hydride reduction and the silyl group converted into a hydroxyl,[218] to make the *cis*-alcohol **1083** with the opposite relative configuration to that of the major product (73:27) obtained directly from the alcohol corresponding to the allylsilane (Scheme 270).[634]

Scheme 270



g. Reactions with Nitrogen Electrophiles. A mixture of the cyclic allylsilanes **1084** and **1085** reacted with ethoxycarbonylnitrene to give the allylic carbamates **1086** and **1087**, presumably by way of the aziridines. The mixture rich in the *cis* isomer **1084** reacts with what appears to be high *anti* stereospecificity, but the mixture rich in the *trans* isomer **1085** gives the same major product, the *trans* isomer **1086**, but with lower stereoselectivity (Scheme 271).[635] This result is in line with the lower ste-

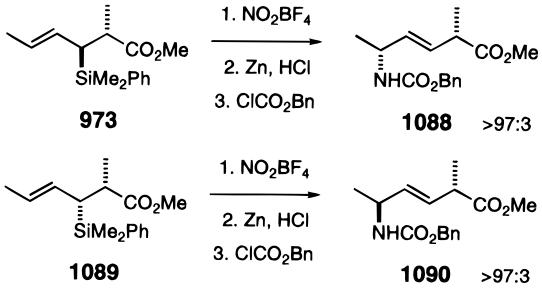
Scheme 271



reospecificity found for cyclic allylsilanes in protodesilylation (Scheme 231), and is probably caused by the incoming electrophile meeting a 1,3-diaxial interaction with the methyl group were it to attack *anti* to the silyl group. The electrophile in this case is larger, and the loss of stereospecificity may well be greater, but direct comparisons have not been made.

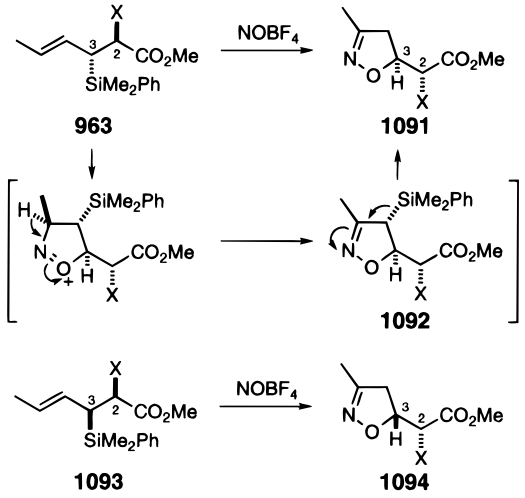
Nitrodesilylation of an open-chain allylsilane is better behaved stereochemically, with the allylsilanes **973** and **1089**, giving the allylic nitro compounds, stereospecifically *anti*, and hence, after reduction and protection the peptide isosteres **1088** and **1090** (Scheme 272).[636]

Scheme 272



Nitrosation of an allylsilane also has the feature of a nucleophilic atom in what was originally the electrophile being poised to capture a rearranged cation. The eventual products from nitrosation of the allylsilanes **963** (X = Me, OMe, OBn, or OAc) are the isoxazolines **1091**, from which the silyl group has actually been lost. The first intermediates after the oxygen atom coordinates to C-3 must lose a proton to give the silicon-containing isoxazolines **1092**. These are set up to lose a silyl group and then regain a proton. The relative configuration between C-2 and C-3, meanwhile, has been set up stereospecifically with a high level of control (≥95:5) from the original relationship between C-2 and C-3, as shown by the fact that the diastereoisomers **1093** give diastereoisomeric isoxazolines **1094** (Scheme 273).[637]

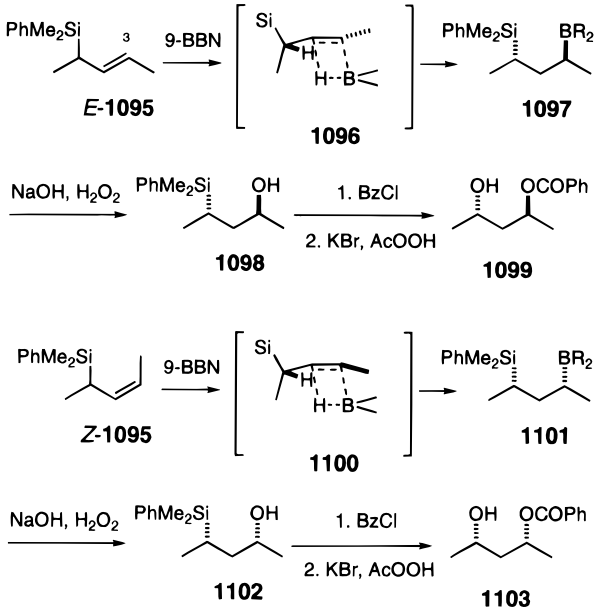
Scheme 273



h. Hydroboration of Allylsilanes. Hydroboration of allylsilanes is only marginally an electrophilic attack, but once again it is substantially affected by the silyl group. The selectivity for the boron to attach itself to C-3 of the allyl system is higher than for the corresponding alkenes lacking the silyl group, and the stereoselectivity is that expected for *anti* attack. For those allylsilanes like (*E*)-**1095** with a methyl group on the stereogenic center and a *trans* double bond, the stereoselectivity is greatly affected by the hydroborating agent, with hindered boranes like 9-BBN usually reacting with the allylsilane in conformation **1096**, with the hydrogen atom inside. With those allylsilanes having a branched substituent on the stereogenic center and/or having a *cis* double bond like (*Z*)-**1095**, the conformation is, as usual, reliably that with the hydrogen atom inside, and reaction takes place in the sense **1100** with most hydroborating agents. Both the regioselectivity and the stereoselectivity in these two reactions are >95:5. The products of hydroboration, **1097** and **1101**, can then be oxidized in the usual way to give the alcohols **1098** and **1102**, and then oxidized again by the related silyl-to-hydroxy conversion[218] to give the differentiated 1,3-diols **1099** and **1103** (Scheme 274).[150]

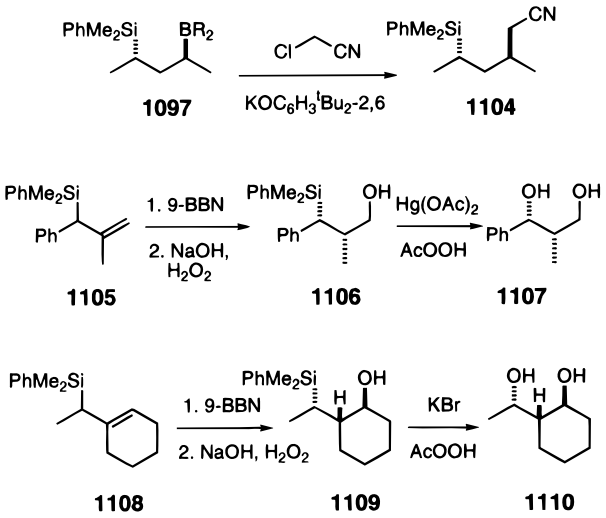
The intermediate boranes like **1097** can be used in stereospecific C−C bond formation, as in the formation of the 3,5-disubstituted nitrile **1104**, and with suitable substrates like the allylsilanes **1105**

Scheme 274



and **1108**, the same stereoselectivity in the hydroboration can, be used to set up 1,2-related centers and 1,2,3-related centers in silyl alcohols **1106** and **1109** and in the corresponding diols **1107** and **1110** (Scheme 275).[150] The stereochemical relationship in the 1,3-diol **1107** is the opposite of that produced by hydroboration of the corresponding allylic alcohol derivative.[638]

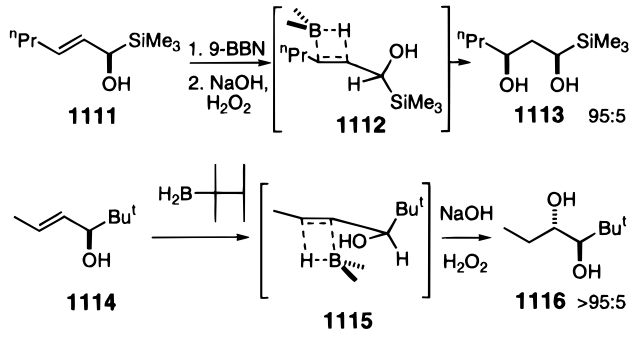
Scheme 275



When the allylsilane has an oxygen substituent on the stereogenic center, as in **1111**, the silicon still controls the regiochemistry, and the stereochemistry is, somewhat surprisingly, that in which the hydrogen atom is inside **1112**, giving as the major product the 1,3-diol derivative **1113**. Replacing the silyl group with a *tert*-butyl group, as in **1114**, results in a change both of regiochemistry and in the sense of the stereochemistry **1115**, with the major product being the 1,2-diol derivative **1116** (Scheme 276).[639]

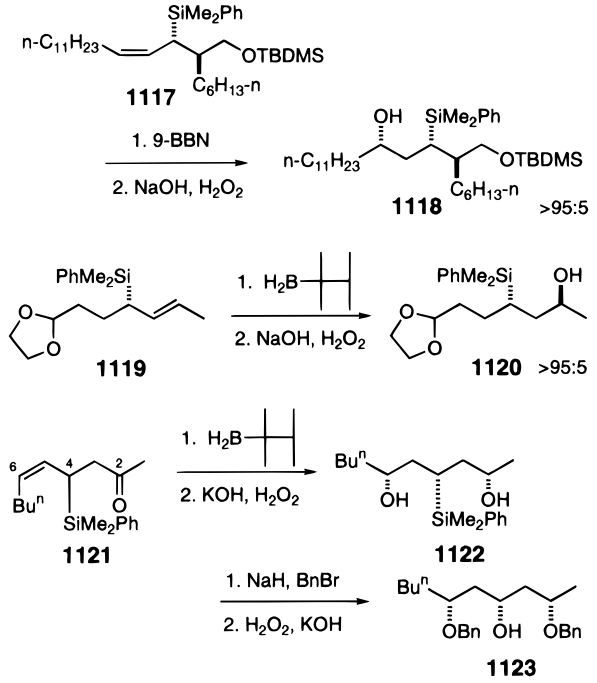
The hydroboration of the allylsilanes **1117** and **1119** has been used to set up the 1,3-relationships in **1118** and **1120** in syntheses of tetrahydrolipstatin[111] and nonactic acid,[640] respectively, and the hydroboration of the allylsilane **1121** in the synthesis

Scheme 276



of the selectively protected triol **1123**, in which the ketone group at C-2 was reduced, intramolecularly and stereoselectively, by the borane attached at C-6 in the precursor to the silanediol **1122** (Scheme 277).[641]

Scheme 277

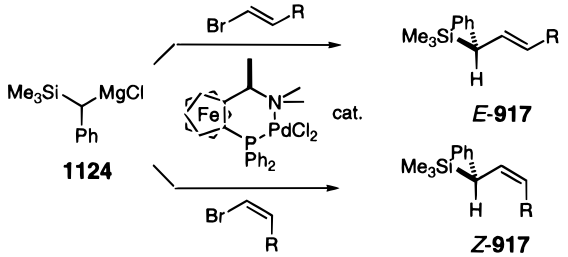


4. Stereocontrolled Syntheses of Allylsilanes

Of all the methods for the synthesis of allylsilanes,[642] only a few are suitable for the synthesis of stereodefined, and usually homochiral, allylsilanes.

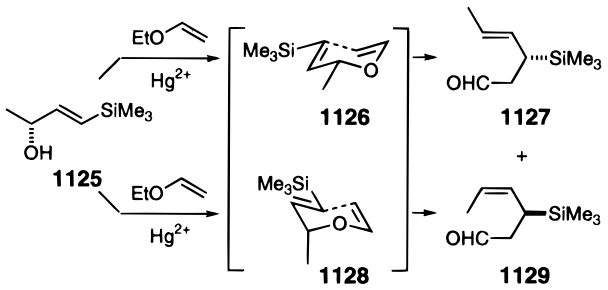
The allylsilanes (*E*)- and (*Z*)-**917** were prepared by cross-coupling, catalyzed by a ferrocene-based homochiral palladium catalyst, of the α-silylbenzyl Grignard reagent **1124** and *trans*- or *cis*-vinyl bromides, respectively (Scheme 278).[643] The enantiomeric excesses are much better for the *trans*-allylsilanes.

Scheme 278



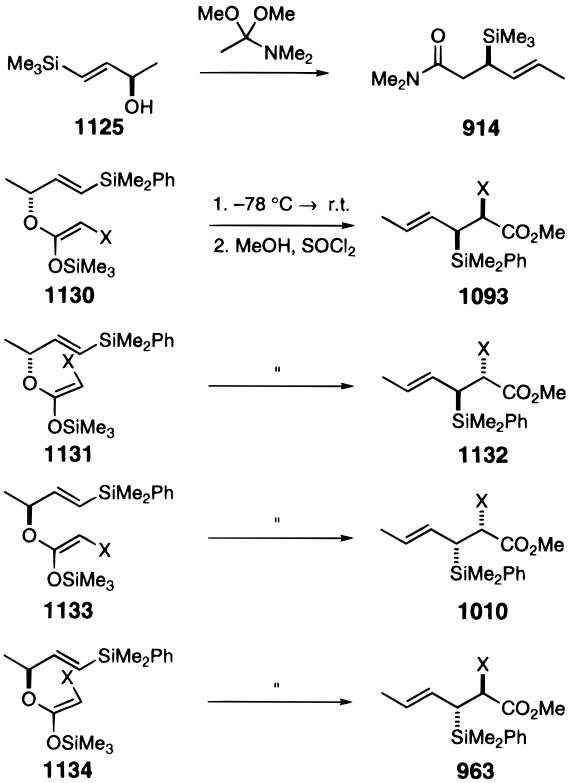
A widely used route is based on Claisen rearrangements of one kind or another. These include the normal[644] allyl vinyl ether rearrangement used in the synthesis of the allylsilanes **1127**, **1129**, and **1163**. A single enantiomer of the allylic alcohol **1125** can undergo Claisen rearrangement with the methyl group equatorial **1126**, the major pathway, or axial **1128**, giving the pair of allylsilanes **1127** and **1129** (Scheme 279). These allylsilanes differ in *two* respects, double-bond geometry and absolute configuration at the silicon center. This seeming stereochemical divergence is therefore corrected in the next step (Scheme 288), with a stereospecifically *anti* process converging on a single alcohol **1162**.

Scheme 279



The Eschenmoser variant using *N*,*N*-dimethylacetamide dimethyl acetal on the same allylic alcohol **1125** gave the allylsilane **914** (Scheme 280).[576] The

Scheme 280

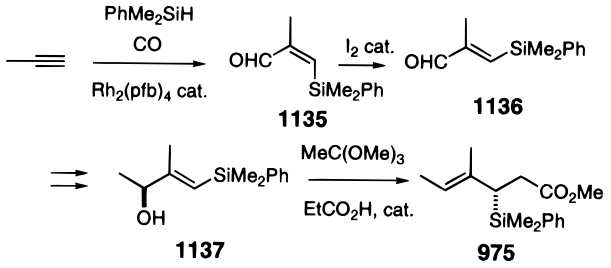


Ireland−Claisen version was used for the synthesis of the allylsilanes **959**, **963**, **965**, **968**, **973**, **1010**, and **1093**, with both absolute configurations of the allylic oxygen and of the enolate geometry **1130**, **1131**, **1133**, and **1134**, giving access to all four possible isomers **1093**, **1132**, **1010**, and **963** (Scheme 280).[645]

Another variant is the *ortho* ester rearrangement, which was used to synthesize the allylsilane **975**

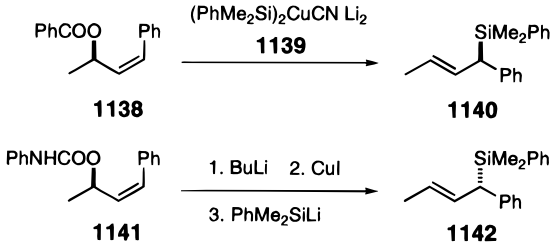
(from Scheme 245), with the trisubstituted double bond set up by a silylformylation reaction of propyne followed by vinylsilane equilibration **1135** → **1136** and an enzymatic resolution to give the allylic alcohol **1137** (Scheme 281).[646]

Scheme 281



A different method using stereodefined allylic alcohols is the stereospecifically *anti* displacement of an allylic acetate or benzoate by the phenyldimethylsilyl-cuprate reagent **1139**. This reaction is highly stereospecific, and regioselectivity is complete when the acetate group is on a tertiary carbon.[571] Regiocontrol is not complete when the acetate or benzoate is on a secondary carbon, but it is often good if the double bond is *cis*, when the silyl group selectively attaches itself with allylic shift, as in the reaction **1138** → **1140**. A complementary procedure is to assemble the cuprate on a carbamate group, when the reaction is intramolecular, stereospecifically *syn*, and takes place with high regiocontrol with allylic shift **1141** → **1142** (Scheme 282).[647]

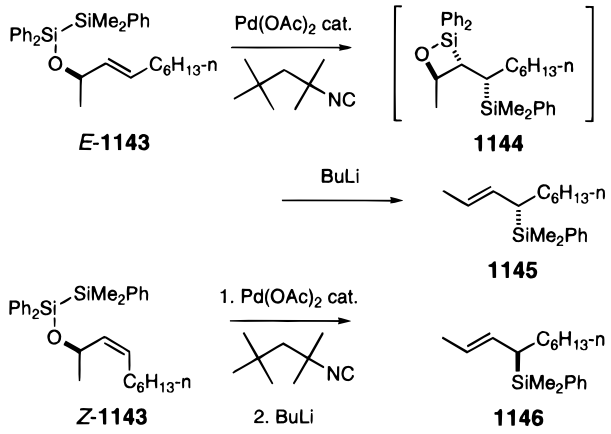
Scheme 282



Procedures like these were used in the syntheses of the allylsilanes **236**, **239**, **955**, **956**, **1031**, **1033**, **1210**, **1241**, and **1256**. It is a highly adaptable procedure for convergent synthesis, as in the example in Scheme 241, where a diastereoisomeric pair of propargylic alcohols, after separation, could be made to converge on a pair of allylsilanes that, differing in two respects, are both set up to give a single stereoisomer in the protodesilylation step. Convergence was achieved in this case by reducing one acetylene to a *trans* double bond and the other to a *cis*. Reaction of the silyl cuprate reagent on the acetates then gave the same pair of allylsilanes from each. For the allenylsilane **1299**, another complementary procedure used a propargylic sulfonate with the silyl group attached to the terminal acetylene, and lithium dimethylcuprate. The case of **1033** is actually a reaction of the silyllithium reagent on an allylic epoxide, a reaction that was much affected in its regiochemistry by the nature of the silylmetal species.[648]

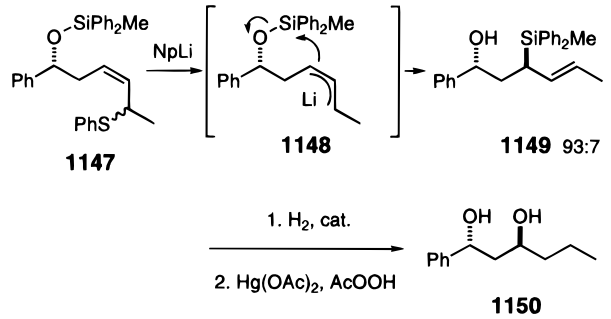
A better method starting from an allylic alcohol uses intramolecular silylsilylation (discussed in section XVIII.3.A) of the silyl ether (*E*)-**1143** to set up three adjacent stereocenters in the silyl ether **1144**. Peterson elimination then establishes the allylsilane **1145** with a *trans* double bond, cleanly the result of allylic shift, and the same sequence, but using the silyl ether (*Z*)-**1143** stereoisomeric at the double bond, gives the enantiomeric allylsilane **1146** (Scheme 283).[649]

Scheme 283



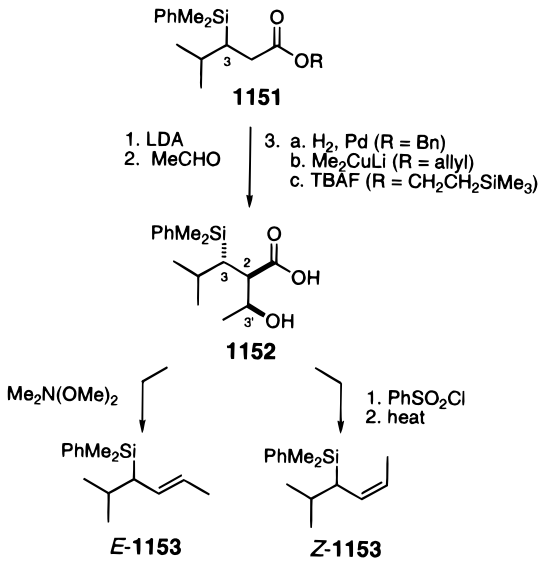
Another method based on an intramolecular reaction uses the resident carbinol stereocenter in the homoallylic alcohol **1147** to deliver the silylating agent to an allylic anion **1148** to give selectively the *anti*-(*E*)-allylsilane **1149** (Scheme 284).[650] This allylsilane was converted[218] to the diol **1150**, after the double bond had been removed by hydrogenation.

Scheme 284



A rather long route to homochiral allylsilanes has the advantages that the regiochemistry is completely controlled, that the double bond can be controlled as either *cis* or *trans*, and that the intermediates give an opportunity for enriching the enantiomeric purity. A β-silyl ester **1151** is subjected to an aldol reaction to give as the major diastereoisomer, typically 70%, the alcohol **1152**. The relative stereochemistry between C-2 and C-3 is controlled by the stereoselectivity of β-silyl enolate alkylations, discussed in section XIV.B, and the stereochemistry between C-2 and C-3′ is controlled by the constraints of the aldol transition structure. For good stereocontrol in this step, the group R must be fairly small, with benzyl, allyl, and (trimethylsilyl)ethyl as usually effective. The decarboxylative elimination of the β-hydroxy acid can be *anti* stereospecific giving the *trans*-allylsilane (*E*)-**1153**, or it can be *syn* stereospecific, by way of the β-lactone, giving the *cis*-allylsilane (*Z*)-**1153** (Scheme 285).[651] The carbon group on C-3 of the

Scheme 285



ester and the aldehyde can be interchanged, so that the regioisomers of the allylsilanes are equally easy to make. The esters can be set up with high levels of enantiomeric purity by conjugate addition of the silylcuprate reagent to α,β-unsaturated imides carrying chiral auxiliaries,[652] or by adding carbon cuprates to β-silyl-α,β-unsaturated *N*-acylsultams.[653] The various intermediates in this synthesis give several opportunities for enriching the major enantiomer. This method was used to make the enantiomerically pure allylsilanes (*E*)- and (*Z*)-**932**, and the racemic allylsilanes (*E*)- and (*Z*)-**1095**. To optimize the yields, the other diastereoisomers of the aldol intermediate like **1152** can be separated and treated appropriately to make the whole mixture of aldols converge on either the *cis* or the *trans* allylsilane. This was the method used to make the allylsilane **1044**.

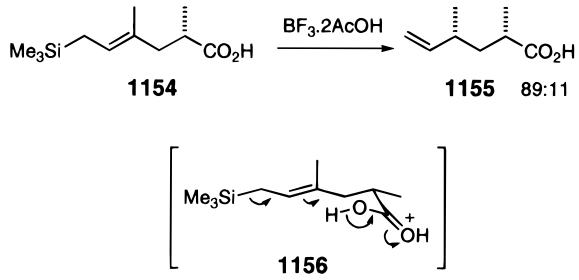
Another effective method is the combination of an allylmetal species that is also a vinylsilane with an electrophile, as illustrated by the combination of the aldehyde **1070** with the allylborane **1071** giving the allylsilane **1072** in Scheme 268. Other methods of synthesis include the hydrosilylation of dienes catalyzed by homochiral catalysts, as used in the synthesis of the allylsilanes **925**,[579] **949**, and **950**,[588] and illustrated in Scheme 407. The reduction of 3-silylated allylic carbonates,[586] catalyzed by a homochiral binaphthyl-derived catalyst, was used in the synthesis of the allylsilane (*Z*)-**917**. The allylsilane **1243** was enantiomerically enriched by resolving an intermediate in its preparation, the 3-silylcyclohexene-2-carboxylic acid. The allylsilanes **1076** and **1078** were prepared by adding (phenyldimethylsilyl)-lithium to the (benzyloxy)crotonaldehydes. The allylsilanes **896** and **1050** were prepared by Diels–Alder reactions, as illustrated **1053** → **1054** in Scheme 264. The allylsilanes **1117** and **1121** were prepared by adding the appropriate *cis*-vinylcuprate to the enone system carrying the phenyldimethylsilyl group in the β-position. Finally, a homochiral susbtituent on an allylsilane anion allows stereoselective alkylation, as illustrated in Scheme 461 with the synthesis of the homochiral allylsilane **1917**.

G. Intramolecular Electrophilic Attack on Allylsilanes

Intramolecular reactions are so much controlled by the folding of the connecting chain, and the influence of resident stereogenic centers in the chain, that the role of the silyl group in controlling stereochemistry is often subordinate, except in those cases where the silyl group is attached to a stereogenic center. The various categories of intramolecular reactions are treated below in the same order as their intermolecular counterparts above: reactions with protons, carbonyl groups, and acetals, iminium ions, enones, and other electrophiles.

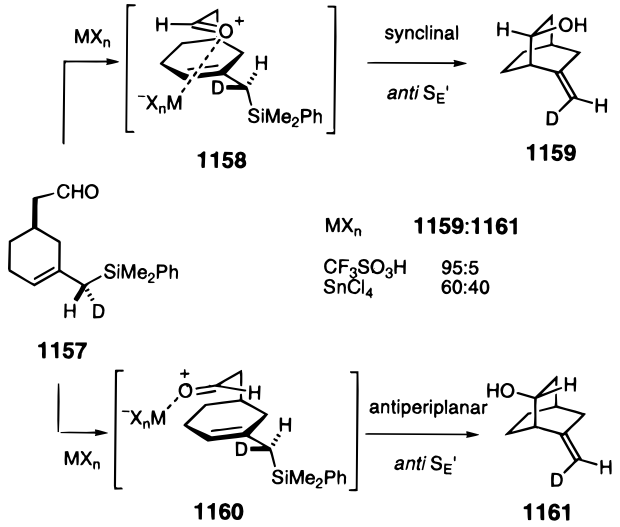
Protodesilylation of the allylsilane **1154** gave largely the product **1155** with the *syn*-1,3-related centers by intramolecular delivery of the proton in a chairlike transition structure **1156** (Scheme 286).[654]

Scheme 286



In reactions with aldehydes and their acetals, the preference for antiperiplanar over synclinal transition structures was used to explain the relative stereochemistry in the reactions discussed in connection with Schemes 201 and 239, but there was no proof that antiperiplanar transition structures were actually involved. In a test of this aspect of stereochemistry in a constrained system **1157**, the preference proved to be for synclinal transition structures **1158**, with a 60° torsional angle, leading to the bicyclic alcohol **1159** to a greater extent than the antiperiplanar transition structure **1160**, leading to its diastereoisomer **1161** (Scheme 287).[655] Changes

Scheme 287



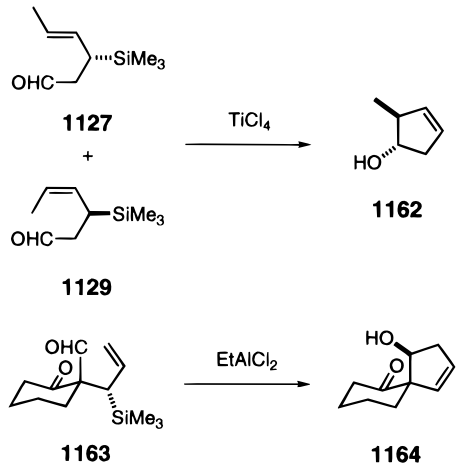
in the Lewis acid used to catalyze the reaction did not change the *anti* selectivity in the allylsilane fragment, which was essentially complete, but they did influence the preference for the synclinal over the

antiperiplanar orientation of the double bonds in the transition structure, probably because of the differing steric demands of the Lewis acids. The largest preference was shown with a proton (95:5) and the lowest with tin(IV) chloride (60:40), and other Lewis acids gave ratios in between. The *Z* orientation of the deuterium atom in the products showed that the S_E2' attack by the electrophile took place *anti* to the silyl group, but the synclinal and antiperiplanar preferences controlling the relative stereochemistry of the new tetrahedral carbon atoms in the diastereoisomeric alcohols **1159** and **1161** were, of course, independent of that feature and showed up without the deuterium atom.[656]

It is also possible to catalyze the reaction of allylsilanes with aldehydes using base or fluoride ion. The normal consequence is to lose regiospecificity, but in a constrained case, like that in Scheme 287, the regiochemistry is fixed by the system, and the effect on the stereochemistry can be followed. The reaction using tetrabutylammonium fluoride is still stereospecifically *anti*, but no longer to as high a degree, and it is much more selective for the *antiperiplanar* route than the *synclinal*. Thus the substrate **1157** gave largely the same products **1159** and **1161**, but in a ratio of 20:80, and the double-bond geometry was only 80:20 in favor of the *Z* isomer illustrated. The diastereoisomer of **1157**, with the H and D interchanged, gave the same two diastereoisomers, but largely the *E* isomer, with the same 80:20 selectivity, showing that the reaction did not take place by way of a free allylic anion.[655]

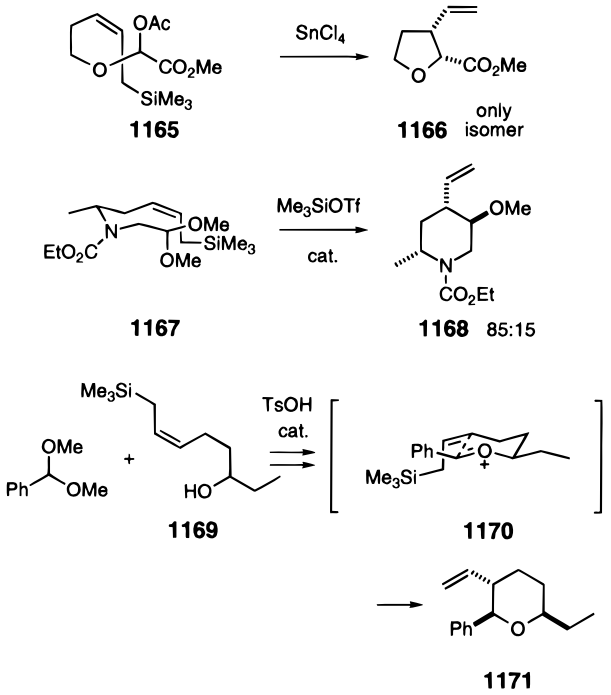
Some intramolecular reactions are even more constrained. The mixture of *R*,*trans*-**1127** and *S*,-*cis*-**1129** allylsilanes converge on the alcohol **1162**. This result is compatible with an antiperiplanar transition structure for the *trans* isomer and a synclinal transition structure for the *cis*, both reacting stereospecifically *anti* with respect to the allylsilane fragment (Scheme 288).[657] The similar intramolecular reaction between the allylsilane and aldehyde groups in the ketoaldehyde **1163** was used to prepare the alcohol **1164** in a synthesis of secokaurenes (Scheme 288).[658] This reaction was chemoselective for attack at the aldehyde group, apparently following the synclinal stereochemistry of the allylsilane **1129**, with the aldehyde group oriented away from the ring.

Scheme 288



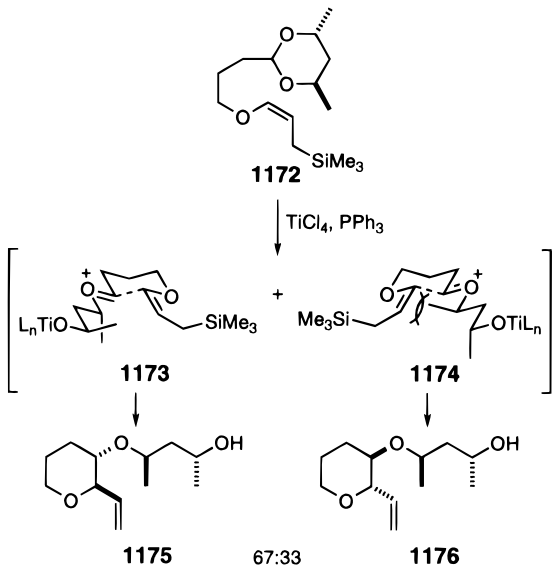
Synclinal transition structures, although not proved for less rigid structures, would explain why the cyclization of the allylsilane **1165** is selective for the formation of a *cis* arrangement of the substituents in the tetrahydrofuran **1166**,[659] and why the cyclization of the allylsilane **1167** to a piperidine **1168** is selective for the formation of a *trans* arrangement across the newly formed bond (Scheme 289).[660] On the other hand, in a reaction in which the electrophilic double bond is endo, the cyclization of the intermediate **1170** derived in situ from the alcohol **1169** acetal of benzaldehyde appears to be antiperiplanar, with all the substituents in the product **1171** equatorial on the ring (Scheme 289).[661]

Scheme 289



As in the reactions in Schemes 118, 119, and 198−200, acetal stereochemistry can control the creation of a new stereocenter. In the cyclization of the allylsilane **1172**, this type of control is again accompanied by the formation of a *trans* arrangement of the substituents on the tetrahydropyran ring of the products **1175** and **1176** (Scheme 290). Although

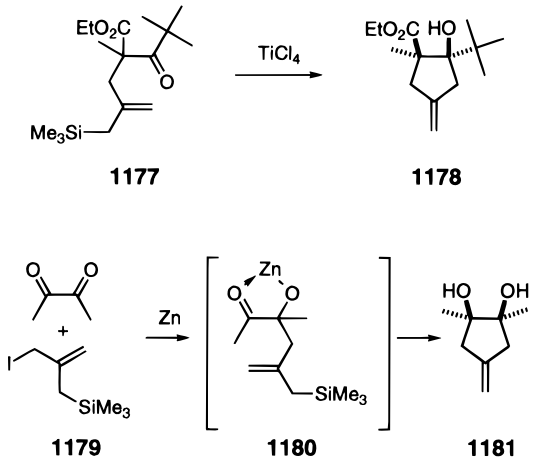
Scheme 290



the enantioselectivity is low, this reaction has strong mechanistic implications, because the reaction of the corresponding allylstannane remarkably gives as the major product (93:7) the diastereoisomer **1176**, with the enantiomeric relationship at the two new stereogenic centers. The explanation offered is that the allylsilane **1172**, as the less nucleophilic reagent, reacts with cationic, S_N1-like transition structures **1173** and **1174**, and not by an S_N2-like transition structure. Of the two reasonable transition structures of this type, the one **1173** leading to the major product **1175** has a smaller steric interaction between the side chains than the alternative **1174**. The allylstannane, being more nucleophilic, reacts with an S_N2-like transition structure, with the Lewis acid coordinated to the oxygen atom adjacent to the axial methyl group.[278]

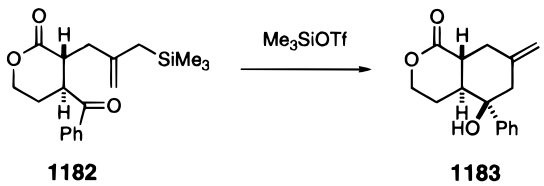
The possibility of using chelating Lewis acids opens up possibilities of stereocontrol peculiarly suited to the use of allylsilanes. Thus the cyclization onto the ketone group in the β-keto ester **1177** is controlled by chelation with the ester carbonyl group to give only one product **1178**,[662] and a ring **1181** can be formed in one pot from 2,3-butanedione and the doubly nucleophilic allylzincate derived from the (iodoallyl)silane **1179**, with better than 75:1 stereocontrol from the chelated intermediate **1180** (Scheme 291).[663]

Scheme 291



The allylsilane **1182** also has the resident stereogenic center adjacent to the electrophilic carbon, which is attacked in a conformation with the phenyl group more or less eclipsing the hydrogen atom to give the homoallylic alcohol **1183** (Scheme 292).[664]

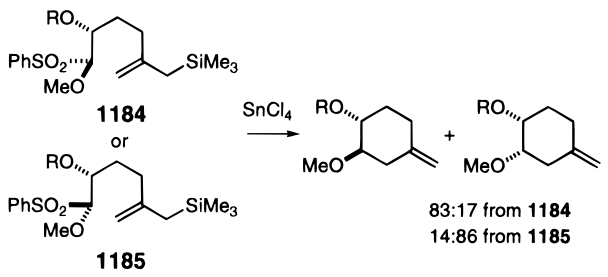
Scheme 292



In contrast, the allylsilanes **1184** and **1185** appear to react with stereospecific inversion of configuration at the acetal-like electrophilic center rather than by control from the resident stereogenic center (Scheme 293).[665]

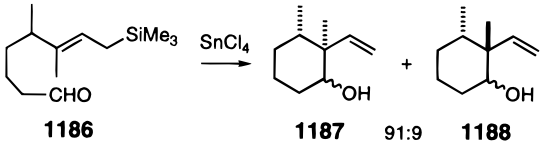
The allylsilane **1186**, which has the resident stereogenic center adjacent to the nucleophilic instead

Scheme 293



of the electrophilic carbon, and no possibility of chelation, gives largely the pair of isomers **1187** from reaction, which is best explained with the methyl group equatorial in a chairlike, synclinal transition structure (Scheme 294).[666] An antiperiplanar transi-

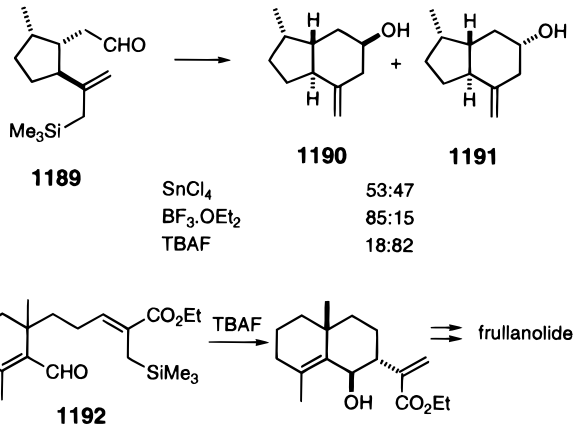
Scheme 294



tion structure with the methyl group equatorial would give the minor isomer **1188**.

In systems with more distant stereogenic centers, stereocontrol can be achieved by tailoring the Lewis acid or by using fluoride ion catalysis instead. Thus the cyclization of the allylsilane **1189** was controllable within limits for the formation of either diastereoisomer **1190** or **1191** by the right choice of Lewis acid or fluoride ion as the catalyst (Scheme 295).[667]

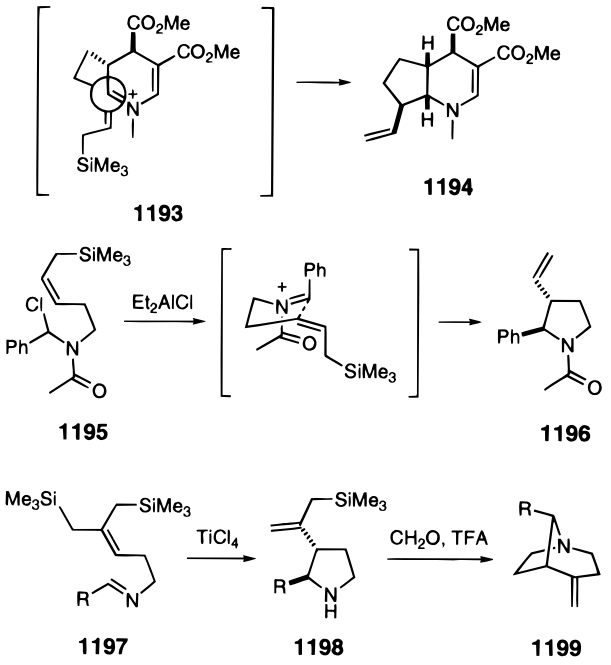
Scheme 295



This flexibility, together with additional stereocontrol from the geometry of the double bond, and from the use of protic acid as well, has been exploited with the allylsilane **1192**, and several similar allylsilanes, in syntheses of sesquiterpene lactones like frullanolide (Scheme 295).[668]

In the cyclization to iminium ions, useful selectivity compatible with synclinal transition structures has been found for the formation of five-membered rings, when either both double bonds are exocyclic to the ring being formed **1193** → **1194**[669] or when one of them is endocyclic **1195** → **1196** (Scheme 296).[670] The same selectivity in the cyclization of the double allylsilane **1197** onto an imine with the formation of the *trans* disubstituted pyrrolidine **1198** gave a new

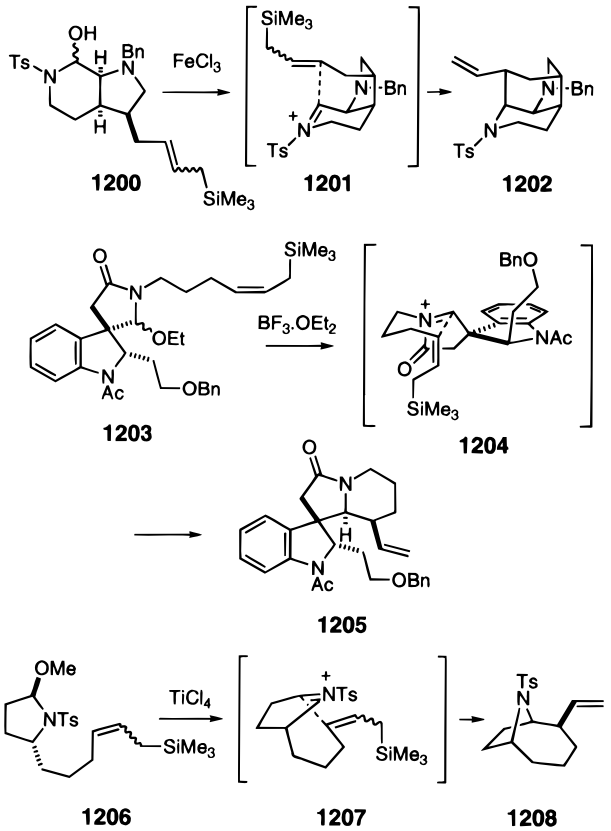
Scheme 296



allylsilane for a second iminium ion cyclization to give the bridgehead amine **1199** (Scheme 296).[671]

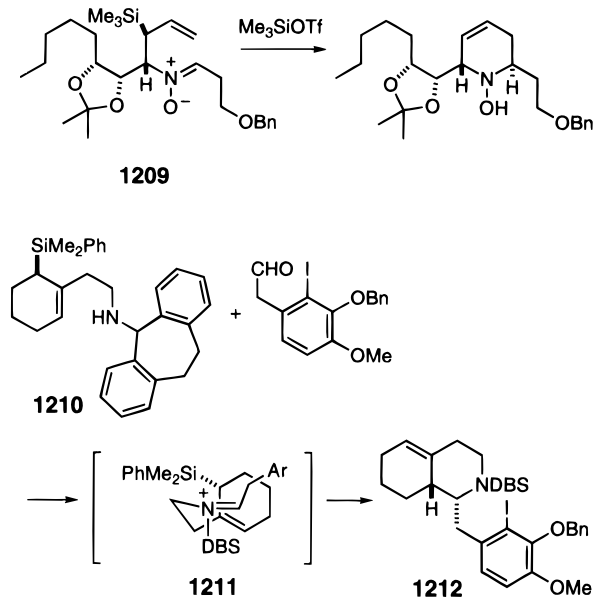
The same is true in the formation of six-membered rings with both double bonds exocyclic **1200** → **1202**[672] and with one endocyclic **1203** → **1205**,[673] showing a preference for synclinal transition structures **1201** and **1204**. The only seven-membered ring-forming reaction is one with an endocyclic double bond **1206** → **1208**,[674] showing the same preference for a synclinal transition structure **1207** (Scheme 297).

Scheme 297



With the silyl group attached to a stereogenic center, the allylsilane **1209** reacted *anti* to the silyl group with the iminium ion system of the nitrone to give the *trans* arrangement at C-2 and C-6 of the piperidine ring for a synthesis of cannabisativine (Scheme 298).[675] The iminium ion **1211**, prepared *in*

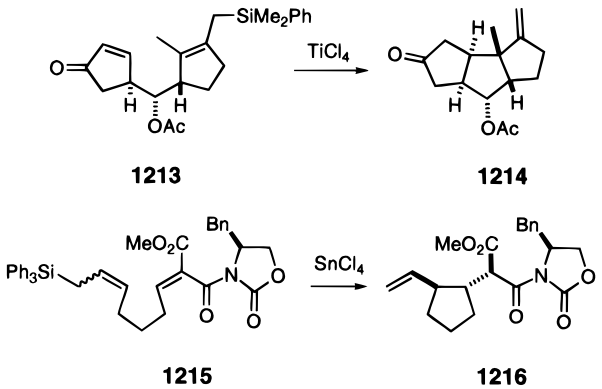
Scheme 298



situ from a secondary amine **1210** and an aldehyde, also reacted intramolecularly to give the piperidine **1212**, an intermediate in a synthesis of (−)-morphine (Scheme 298). The relative stereochemistry between the two newly created stereogenic centers was controlled by the preference for the conformation **1211** to be better than 20:1, and the absolute control appeared to be nearly completely *anti*, with the precursor of the allylsilane **1210** having an e.e. of 96% and the product **1212** having an e.e. of 91%.[676]

Many factors affect the stereochemistry in cyclizations to enones.[677] The product structure can have an influence, with the formation of the triquinane **1214** from the allylsilane **1213** being the result of a natural preference for both ring fusions to be *cis* (Scheme 299).[678] Similarly the formation of very largely one diastereoisomer of the cyclopentane **1216** may simply be a result of a preference for the two substituents to be *trans* with the absolute control stemming from the chiral auxiliary (Scheme 299).[679]

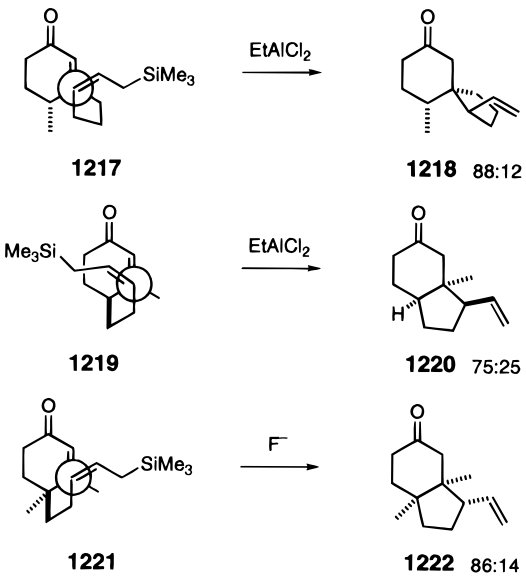
Scheme 299



As with carbonyl compounds and iminium ions, the preference for synclinal or antiperiplanar transition structures affects the relative stereochemistry when both the nucleophilic and electrophilic carbons carry substituents. The evidence from intermolecular reactions with enones (Schemes 219 and 220) is ambiguous, and the preferred folding of the chain in intramolecular reactions will constrain whatever natural preference allylsilanes may have. The folding will also be different when both double bonds involved are exocyclic to the ring being formed, and when one or both of them is endocyclic.

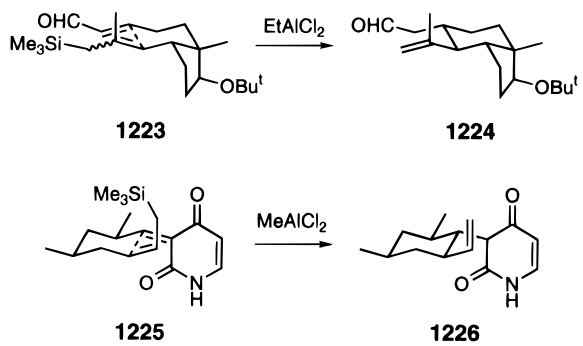
The usual result in the formation of five-membered rings when both double bonds are exocyclic appears to be a preference for one or another synclinal approach. Thus the Lewis acid-catalyzed cyclizations of the allylsilanes **1217** and **1219** gave the cyclopentanes **1218** and **1220**, but fluoride ion catalysis with a similar substrate **1221** to the latter gave the product **1222** expected from an antiperiplanar transition structure or from a different synclinal transition structure **1221** (Scheme 300).[680,681]

Scheme 300



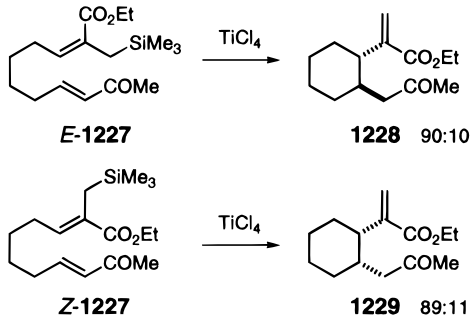
Similarly in the formation of six-membered rings when both double bonds are exocyclic, there is a preference for the substituents to come out *trans*, with control also from the substituents on the carbon atoms forming the ring adopting equatorial orientations, whether they are adjacent to the nucleophilic carbon **1223** → **1224** or the electrophilic carbon **1225** → **1226** (Scheme 301).[682,683]

Scheme 301



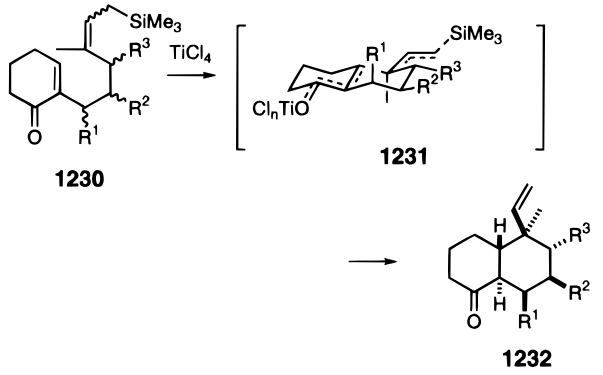
On the other hand, the allylsilanes (*E*)- and (*Z*)-**1227** having no controlling stereogenic centers, are stereospecific, the stereochemistry of the two side chains in the products **1228** and **1229** depending upon the stereochemistry of the allylsilane (Scheme 302).[684]

Scheme 302



In the cyclization of the enones **1230**, where one of the double bonds is endocyclic, the major products **1232** have the vinyl group and the hydrogen atom at the ring junction *cis*, with the sense in which they are *cis* stemming from the substituents R^1−R^3 around the ring being formed. The substituent R^1 favors a transition structure, summarized as **1231**, in which it is axial, and R^2 and R^3 favor transition structures in which either or both are equatorial; when they are in competition, R^3 is the more important influence (Scheme 303).[685] This chemistry has been used in a synthesis of linaridial.[686]

Scheme 303

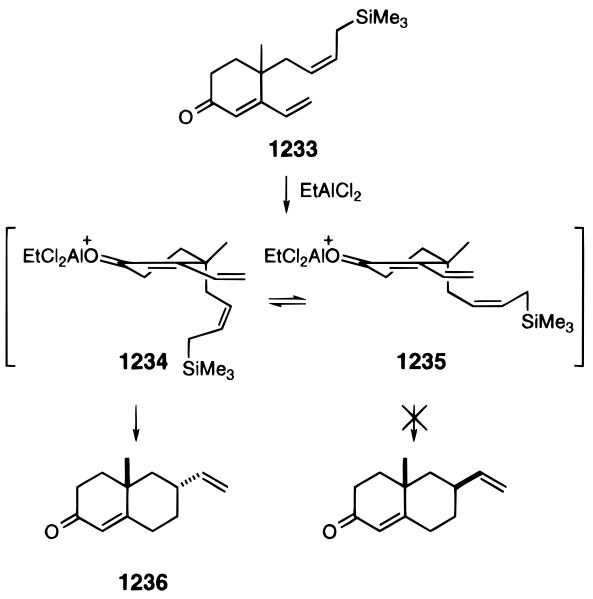


The cyclization of the dienone **1233**, where again there is one endo- and one exocyclic double bond, shows a preference for the product **1236** of the synclinal transition structure **1234** rather than the antiperiplanar transition structure **1235** (Scheme 304). This chemistry has been used in a synthesis of nootkatone.[687]

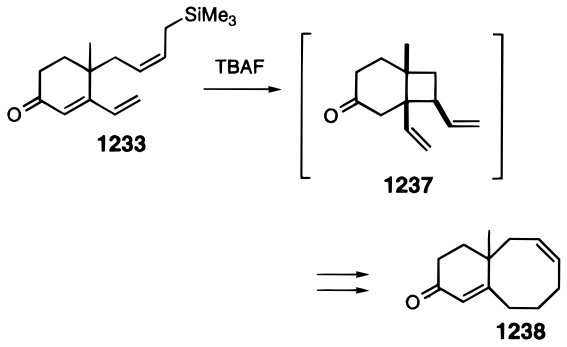
The fluoride ion-catalyzed reaction on the same dienone, however, gave a different regioisomer, the cyclooctene **1238**, by way of the cyclobutane **1237** and a Cope rearrangement. The intermediate **1237** can be trapped, and its stereochemistry, with the two vinyl groups *cis*, proved (Scheme 305).[687]

A seven-membered ring can be formed when both double bonds are endocyclic, but when the silyl group is not on a stereogenic center, the stereochemistry created at the nucleophilic carbon is relatively uncontrolled as in the cyclization of the allylsilane **1239** to a mixture of diastereoisomers **1240** in a synthesis

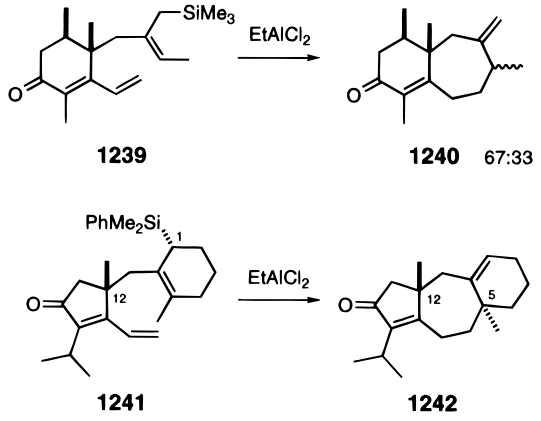
Scheme 304



Scheme 305



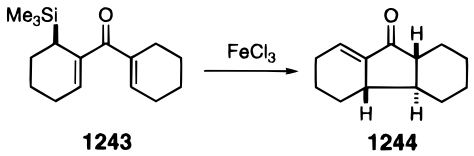
Scheme 306



of three perforenes (Scheme 306).[688] There has been no work when both participating *endo* double bonds carry substituents. However , with the stereospecific *anti* reaction of the allylsilane to control the new stereogenic center, the allylsilane **1241** gave the hydroazulene **1242** in a synthesis of (±)-14-deoxyisoamijiol (Scheme 306). The relative stereochemistry between C-1 and C-12 in the allylsilane controlled the relative stereochemistry between C-5 and C-12 in the product, because the diastereoisomer at C-1 gave the product diastereoisomeric at C-5.[689]

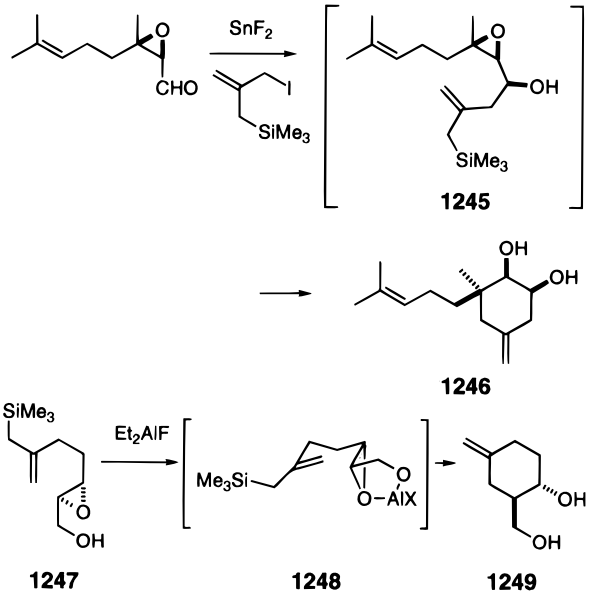
The absolute stereochemistry of the allylsilane fragment in the dienone **1243** completely controlled the torquoselectivity in the conrotatory Nazarov cyclization, giving the enone **1244**, in a reaction that is both pericyclic and a stereospecifically *anti* reaction of an allylsilane with an enone electrophile (Scheme 307). In this case the enantiomer of the allylsilane **1243** gave the enantiomer of the enone **1244**.[690]

Scheme 307



Epoxides are so apt to rearrange in the presence of Lewis acids that their reaction with allylsilanes is usually only possible in intramolecular reactions, but these have been used several times in synthesis. The electrophilic carbon is attacked with inversion of configuration, as in the cyclization of the intermediates **1245** and **1247** giving the alcohols **1246** and **1249**, with the regioselectivity for the latter being a function of the chelated transition structure **1248** (Scheme 308).[691,692]

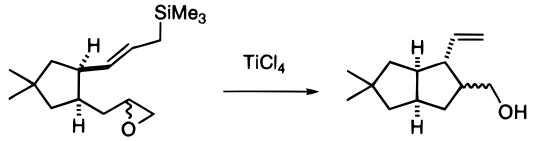
Scheme 308



There is also some stereoselectivity at the new stereocenter set up at the nucleophilic carbon, as in the reaction of the presumed 50:50 mixture of epoxides **1250** used in the synthesis of hirsutene. Although the stereochemistry was not proved, the product mixture **1251** showed three diastereoisomers in a ratio of 50:42:8. It is probable that the two major isomers have the same stereochemistry at the vinyl-bearing carbon, and differ at the carbinol-bearing carbon. Control stems from the stereogenic center adjacent to the nucleophilic carbon, with the conformation of the transition structure having the C−H bond inside. The selectivity in this reaction can then be expected to be higher than in the intermolecular reactions of allylsilanes **880** and **881** with a stereogenic center next to the nucleophilic carbon in Scheme 224, because the intramolecularity determines which face of the double bond is attacked (Scheme 309).[693]

Control at both the nucleophilic and the electrophilic carbon is seen in the cyclization of the epoxide **1252** to give the alcohol **1253**, used in a synthesis of

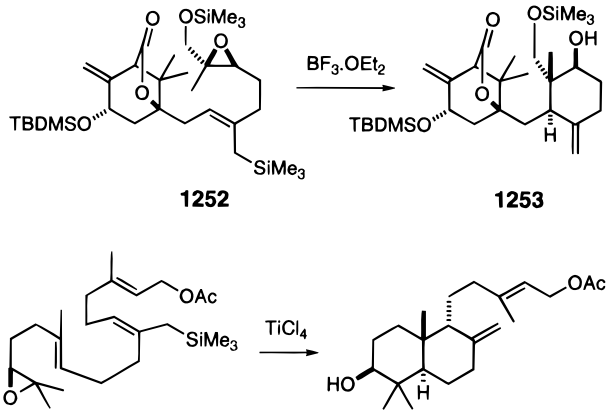
Scheme 309



1250 **1251**

the taxol skeleton,[694] and in the polyene cyclization of the epoxide **1254** terminated by the allylsilane unit to give the alcohol **1255** in a diterpene synthesis[695] (Scheme 310).

Scheme 310

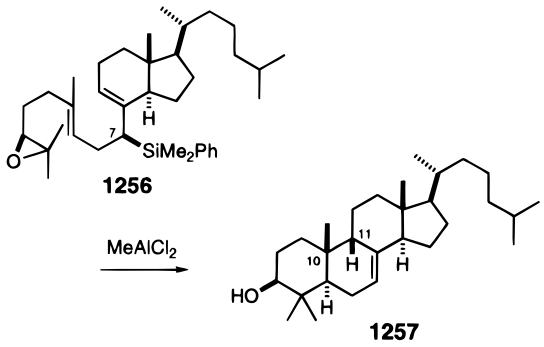


1252 **1253**

1254 **1255**

The allylsilane **1256** showed the usual attack *anti* to the silyl group in the epoxide-initiated and allylsilane-terminated diene cyclization giving the intermediate **1257** controlling the stereochemistry at C-10 and C-11 (Scheme 311) in a synthesis of (+)-lanos-

Scheme 311



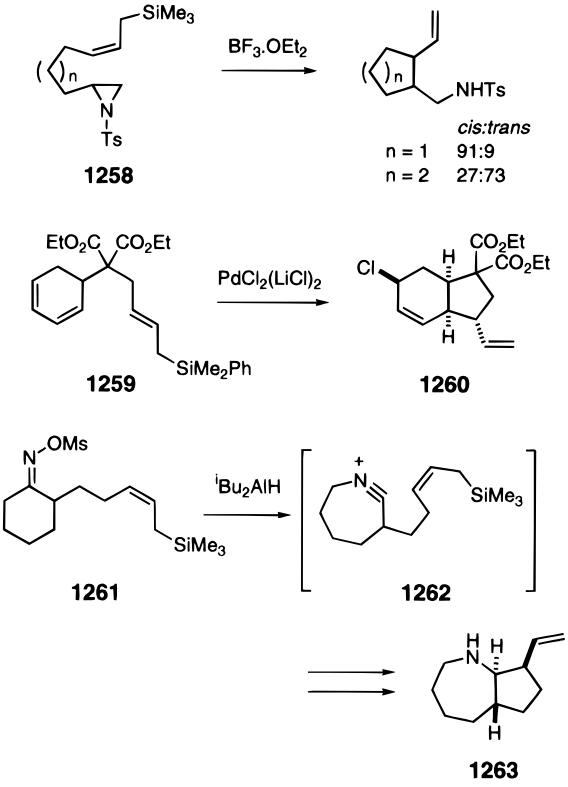
1256

1257

tenol, with the diastereoisomer at C-7, giving the diastereoisomer at C-10 and C-11.[696]

A few other electrophilic groups induce cyclizations of allylsilanes. Among those with stereochemical consequences, an *N*-tosylaziridine **1258** reacts intramolecularly with a preference for the *cis* arrangement of substituents when a five-membered ring is being formed, but for the *trans* arrangement when it is a six-membered ring,[697] the palladium(II)-activated diene **1259** gives a tetrahydroindan **1260** with a *cis* ring fusion and moderate (75:25) selectivity in favor of the *exo* vinyl group,[698] and the oxime mesylate **1261**, presumably reacting by way of the cation **1262**, similarly sets up the vinyl group *cis* to the ring junction, and reduction then gives a *trans*-fused perhydroazaazulene **1263** (Scheme 312).[699]

Scheme 312



1258

1259 **1260**

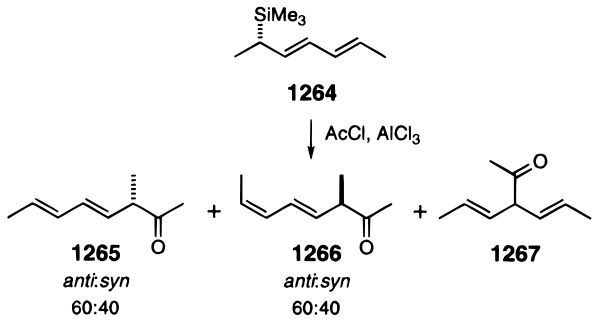
1261 **1262**

1263

H. Pentadienylsilanes

The S_E2'' reactions of aldehydes and their acetals with pentadienylsilanes having a substituent at the double-bond terminus show the same simple diastereoselectivity in favor of the *syn* diastereoisomer, as shown in the corresponding reaction of allylsilanes.[700] The reaction, a vinylogous version of the S_E2' reaction, is also stereospecifically *anti*. With a homochiral *trans*,*trans*-pentadienylsilane **1264**, the degree of selectivity with acetyl chloride is not high (*anti*:*syn* 60:40), and both a *trans*,*trans*-diene **1265** and a *cis*,*trans*-diene **1266** are obtained, as a result of reactions taking place in both conformations, with the hydrogen atom inside and with the methyl group inside (Scheme 313). The achiral product **1267** of the S_E2' reaction is also obtained.[701]

Scheme 313



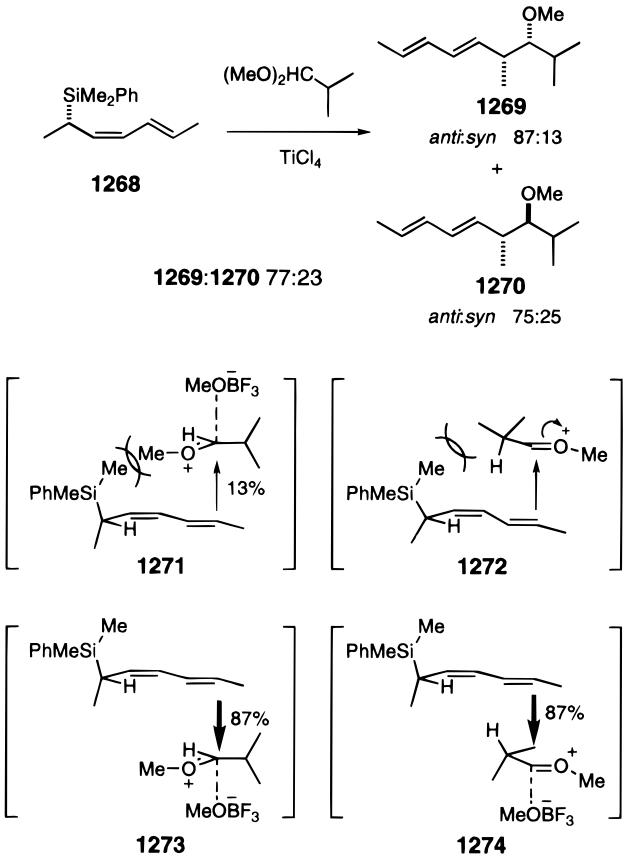
1264

1265 **1266** **1267**

With the *cis*,*trans*-pentadienylsilane **1268**, only the conformation with the hydrogen atom inside is significantly populated, as usual with (*Z*)-allylsilanes, giving only *trans*,*trans*-dienes as products of the reaction with isobutanal dimethyl acetal. The two diastereoisomers **1269** and **1270** were present in a ratio of 77:23, the major **1269** had the usual *syn*

arrangement of the substituents on the backbone, and the minor **1270** had the *anti* arrangement. The stereoselectivity with respect to the S_E2'' process was remarkably high (*anti*:*syn* 87:13 for the major product **1269**), apparently because the electrophile was large enough to experience a direct steric interaction with the silyl group in the transition structure for attack *syn* to the silyl group, whether that is *synclinal* **1271** or *antiperiplanar* **1272**. Attack on the *anti* surface, **1273** or **1274**, is not so hindered (Scheme 314).[702]

Scheme 314

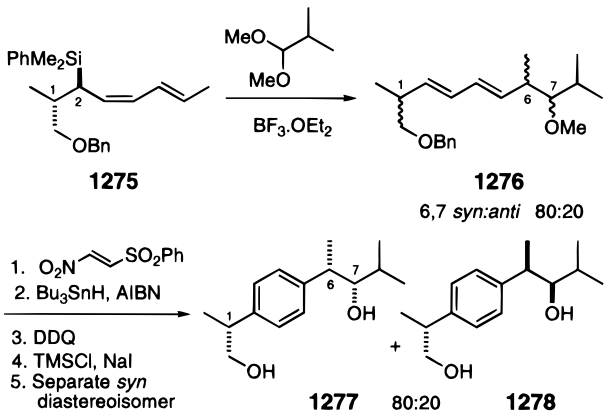


Several similar reactions all showed a comparably high level of stereoselectivity, unaffected by changes in the carbon group on the stereogenic center or in the size of the silyl group. The products of S_E2' reaction were not observed in this series; it seems that acylation is more apt to take this path than attack by other carbon electrophiles.

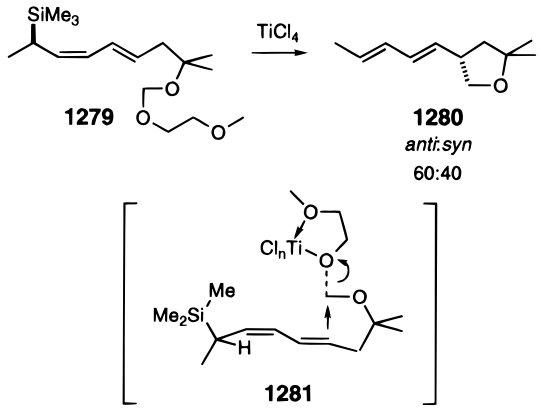
A similar S_E2'' reaction **1275** → **1276** has been used to control the relative configuration of two substituents with a 1,6-relationship *para* across a benzene ring, with a level of control a little less (**1277**:**1278** 80:20) than that seen in the model reactions in Scheme 314 (Scheme 315).[703]

However, when the electrophile is small enough not to experience any steric interaction with the silyl group, as with a deuteron or the methylene group in the intramolecular reaction **1279** → **1280**, the selectivity reverts to the low level (*anti*:*syn* 60:40) seen with the *trans*,*trans*-pentadienylsilane **1264**, where even a transition structure **1281** for *syn* attack in an S_N2-like reaction on the acetal is relatively unproblematic, and the S_N1 version even less so (Scheme 316).[702]

Scheme 315

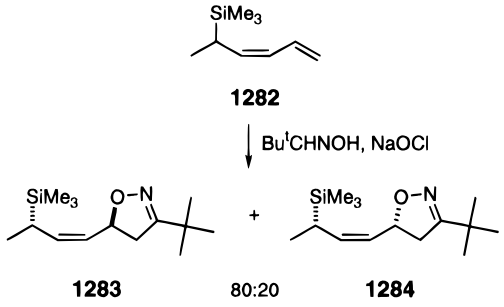


Scheme 316



Pentadienylsilanes such as **1282** undergo cycloaddition reactions with nitrile oxides across the terminal double bond with moderately high levels (typically 3:1) of stereocontrol, with the isoxazolines **1283** and **1284** present in this case, the best, in a ratio of 80:20. The major product is in the *anti* sense, if we assume that reaction takes place in the usual conformation for an allylsilane unit with a *cis* double bond, with the hydrogen atom on the stereogenic center inside. The ratios are only a little affected by the carbon group on the stereogenic center or by the size of the silyl group (Scheme 317).[702]

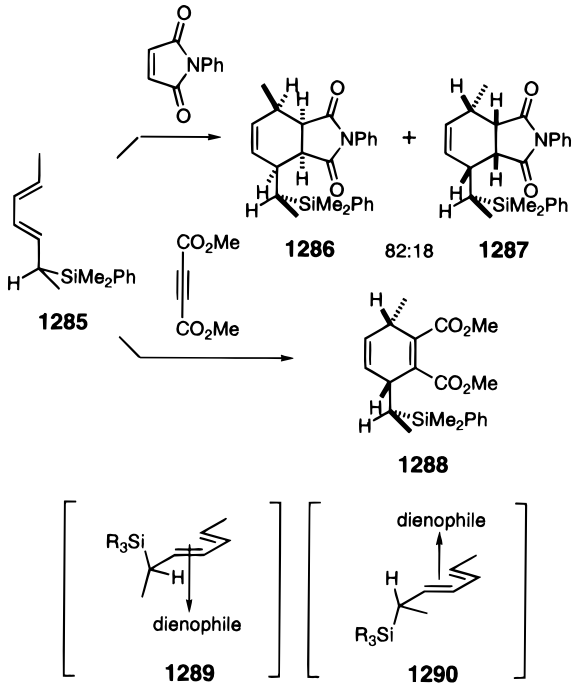
Scheme 317



Diels−Alder reactions on the (*E*,*E*)-pentadienylsilane **1285** are if anything a little more selective, but give adducts which cannot so easily be identified as *syn* or *anti*, because the conformation at the time of reaction is not preserved in the double-bond geometry, as it is in S_E2' and S_E2'' reactions. Furthermore, a *cis* double bond adjacent to the silyl group cannot be used more or less to fix the conformation, as it was in the reactions in Schemes 314−317, because

only *trans,trans*-dienes easily take part in Diels–Alder reactions. The sense of selectivity proves to be dramatically dependent upon the dienophile, with *N*-phenylmaleimide selectively (82:18) giving the adduct **1286** that is *anti* if the hydrogen atom on the stereogenic center is inside **1289**, and dimethyl acetylenedicarboxylate giving only the adduct **1288** that is *anti* if the methyl group is inside **1290** (Scheme 318).[704] Perhaps more significantly, the

Scheme 318

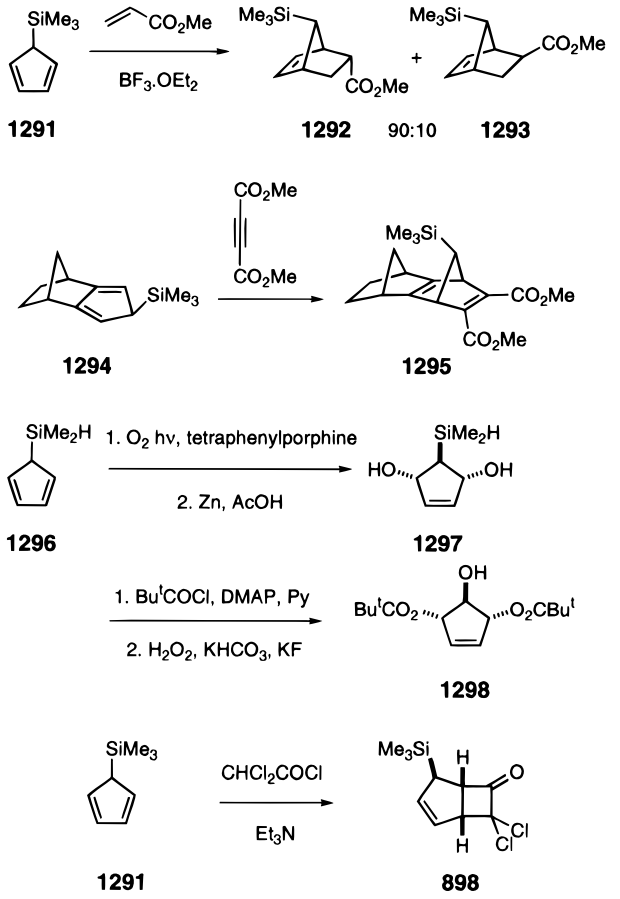


stereochemical sense of both of these reactions is the opposite to that found[705] for the corresponding dienes with oxygen substituents in place of the silyl.

The selectivity of a 1-[1-(trimethylsilyl)ethyl]naphthalene in a Diels–Alder reaction with singlet oxygen has been found to be even higher (95:5), but the sense of the selectivity was not determined.[706]

5-Silylated cyclopentadienes are a rather different type of pentadienylsilane. Because of rapid 1,5-hydrogen shift,[707] they are in equilibrium with the 1- and 2-silylated isomers, and Diels–Alder reactions often give mixtures because of the mixture of dienes present. However, they react with powerful dienophiles,[708] and with methyl acrylate in the presence of Lewis acids,[709] to give largely 7-silylated norbornenes, with attack taking place both for the major *endo* **1292** and the minor *exo* isomer **1293** exclusively *anti* to the silyl group (Scheme 319). The high selectivity for attack *anti* to the silyl group allows the diene **1294** to overcome the normal preference for attack by dienophiles on the *exo* surface, and give instead the adduct **1295** of attack on the *endo* surface.[710] The cyclopentadienylsilane **1296** similarly underwent a cycloaddition with singlet oxygen *anti* to the silyl group to give, after reduction, the diol **1297**.[711] Protection and silyl-to-hydroxy conversion[217] then gave the differentially protected triol **1298** (Scheme 319). The corresponding cyclopentadienylsilane with a phenyldimethylsilyl group in place of the dimethylsilyl group would not have been suitable for the oxidation step **1297** → **1298**, because of the presence of the alkene double bond, and did not in fact work in the singlet oxidation step either. Dichloroketene also adds to the cyclopentadiene **1291** to give the [2 + 2] adduct **898** (Scheme 319).[568,712]

Scheme 319

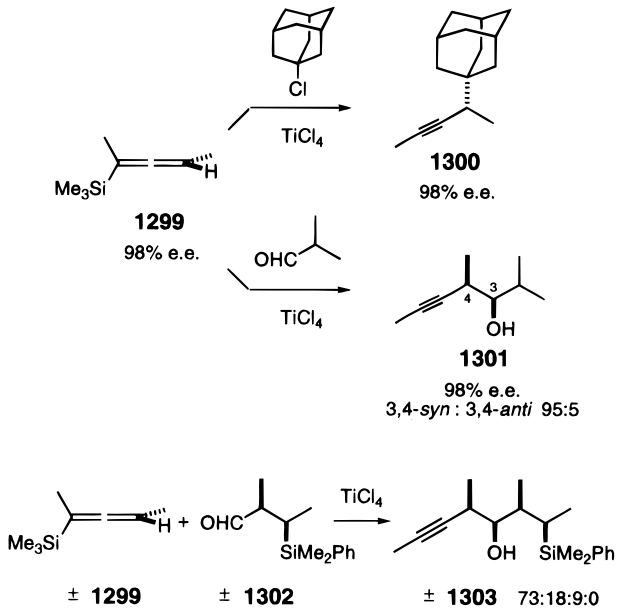


I. Allenylsilanes and Propargylsilanes

The S_E2' reaction of allenylsilanes is stereospecifically *anti* like the corresponding reaction of allylsilanes, with the homochiral allenylsilane **1299** giving the alkyne **1300** with the same high level of enantiomeric purity as the starting material (Scheme 320).[713] In simple diastereoselectivity, allenylsilanes having a substituent at the double-bond terminus show the same preference for the formation of the *syn* diastereoisomer as shown by allylsilanes and pentadienylsilanes.[714] In consequence, the reaction of the same homochiral allenylsilane **1299** with isobutanal gave largely (95:5) the *syn* arrangement of the substituents on the backbone **1301** and essentially enantiomerically pure product (Scheme 320).[713] With a chiral but racemic aldehyde **1302** having no capacity to chelate and the same chiral allenylsilane **1299**, but this time racemic, the reaction was similar, in giving the *syn* arrangement of substituents, *anti* S_E2' reaction, and Cram control, thereby giving the major product **1303** as a result of a high level of chiral recognition between the matched enantiomers (Scheme 320).[715]

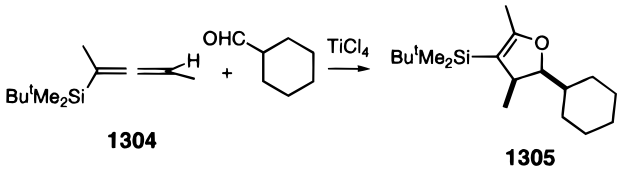
Since all of these reactions used a trimethylsilyl group, the major products were open-chain acety-

Scheme 320



lenes, which had lost the silyl group. When the allenylsilanes have a hindered silyl group they react with aldehydes to give the [3 + 2] annelation products retaining the silyl group. The major product using the racemic allenylsilane **1304** is typically a dihydrofuran **1305** with the usual *syn* arrangement of the substituents (Scheme 321).[716] With an α-ben-

Scheme 321



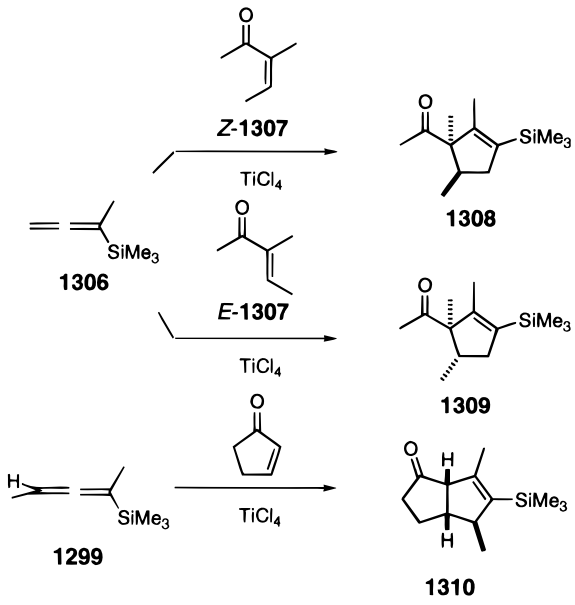
zyloxy aldehyde, however, the major product (78:22) using a chelating Lewis acid, titanium tetrachloride, and the same allenylsilane **1304** appeared to have the *anti* arrangement, although the experiment was only carried out when both partners were racemic.[716]

In the reaction of allenylsilanes with enones, even the trimethylsilyl group stays in the molecule, rearranging in the same way as for the allylsilanes in Schemes 217 and 253. Thus the allenylsilane **1306** reacts with the (*Z*)- and (*E*)-3-methyl-3-penten-2-ones **1307** to give the diastereoisomeric cyclopentenes **1308** and **1309**, proving that these reactions are stereospecifically suprafacial on the enone partner. Also the allenylsilane **1299** reacts with cyclopentenone to give a cyclopentene **1310** with the equivalent of a *syn* arrangement of substituents (Scheme 322).[717]

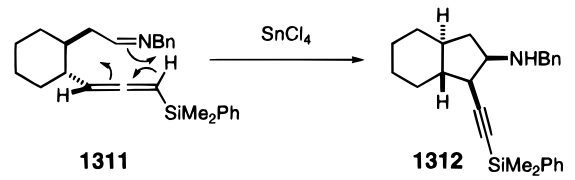
In an intramolecular reaction with an imine **1311**, the stereospecificity was that expected for attack *anti* to the silyl group, but the proton transfer of an ene reaction **1311** → **1312** took place rather than loss of the silyl group. The removal of the silyl group from the acetylene was no problem, and the intermediate **1312** was used in a synthesis of (−)-papuamine (Scheme 323).[718]

A propargylsilane has been shown to give an *anti* stereospecific reaction with a *tert*-butyl cation but the degree of selectivity is unknown (Scheme 324).[719]

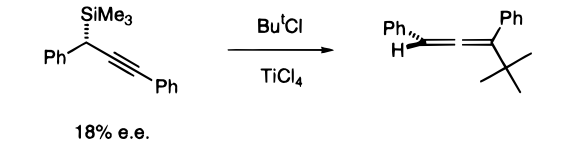
Scheme 322



Scheme 323



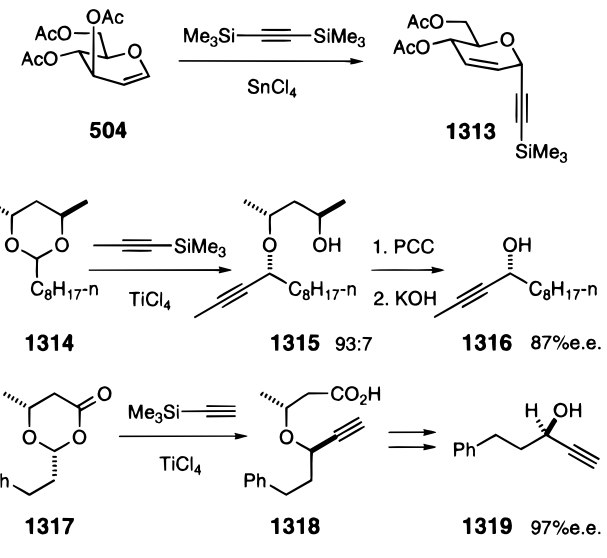
Scheme 324



X. Ethynylsilanes

Like allylsilanes, ethynylsilanes can attack axially at the anomeric position of glucals, making *C*-glycosides **1313** with a versatile ethynyl group (Scheme 325).[720] Ethynylsilanes also attack acetals of the type **1314** (the enantiomer of **508**) and **1317**, with the same high stereoselectivity as silyl enol ethers and allylsilanes, to give propargylic ethers

Scheme 325

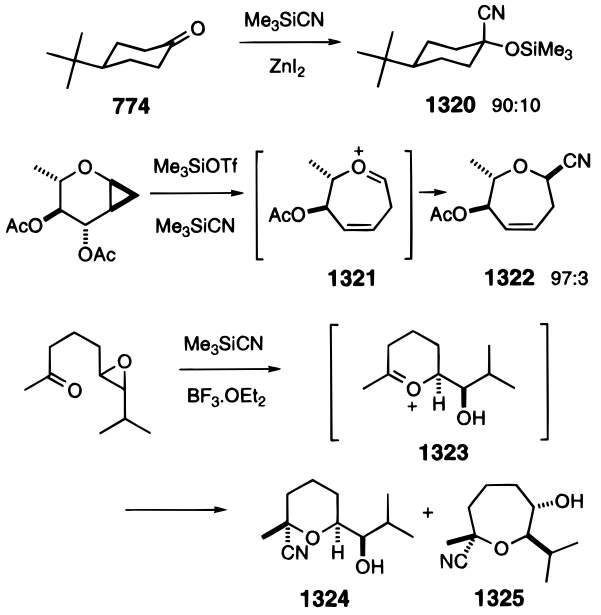


1315 and **1318**, from which the homochiral propargylic alcohols **1316** and **1319** can be released by oxidation and base-catalyzed elimination (Scheme 325).[721,722]

XI. Cyanosilanes[445]

Trimethylsilyl cyanide is another of the silicon-containing nucleophiles suitable for delivering a carbon nucleophile, typically to a cationic electrophile, with the special feature that it is a one-carbon nucleophile. 4-*tert*-Butylcyclohexanone (**774**), for example, is attacked under kinetic control to give largely the cyanohydrin silyl ether **1320** with an axial cyano group,[723] and the oxenium ions **1321** and **1323** give, by axial attack, the nitriles **1322** and a mixture of **1324** and **1325** (Scheme 326).[724,725] In contrast, a

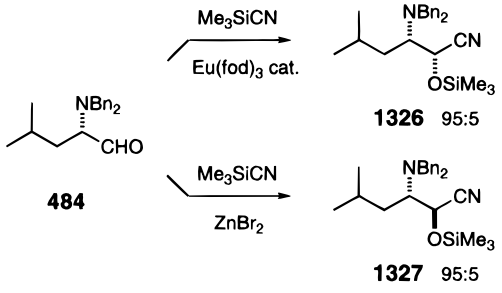
Scheme 326



cyclic imine with a five-membered ring was unselective, because of epimerization of the α-cyanopyrrolidine product.[726]

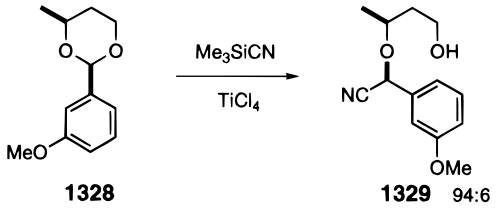
The aldehyde **484** gives the product **1326** of chelation control, suitable for a synthesis of norstatine, when a europium-based, chelating Lewis acid is used but the opposite stereochemistry **1327** with zinc bromide (Scheme 327).[727]

Scheme 327



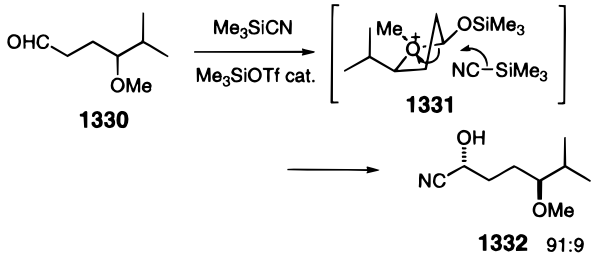
The Lewis acid-catalyzed reaction with acetals is stereoselective in the same sense as for the other carbon nucleophiles in Schemes 118, 119, 198−200, and 325, with the cyclic acetal **1328** effectively giving inversion of configuration in the acetal opening and hence the cyanohydrin ether **1329** suitable for a synthesis of deltamethrin (Scheme 328).[728] Scandium(III) triflate is a good Lewis acid for this type of reaction.[729]

Scheme 328



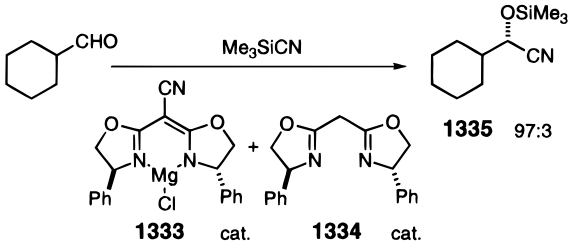
The opening of a cyclic acetal **1331** is an intermediate step in the reaction of the aldehyde **1330** giving the cyanohydrin **1332** in what looks like 1,4 open-chain stereocontrol (Scheme 329).[730]

Scheme 329



The use of homochiral Lewis acids in the reaction of trimethylsilyl cyanide with aldehydes has been much tested, and has given high levels of control in the formation of one enantiomer of a cyanohydrin with several catalysts.[731] The example illustrated with cyclohexancarboxaldehyde giving the cyanohydrin **1335** is one of the best, probably because it has been designed with a Lewis acid ligand **1333** to bind the aldehyde and another **1334** to bind by hydrogen bonding to hydrogen cyanide (Scheme 330).[732]

Scheme 330

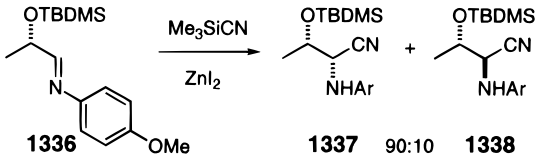


Both the imine **1336** and the nitrone **1339** are attacked selectively in the sense expected from a modified version of Felkin−Anh rule in which the hydrogen atom is inside to give mainly the *syn* diastereoisomers **1337** and **1340**, respectively (Scheme 331).[733,734]

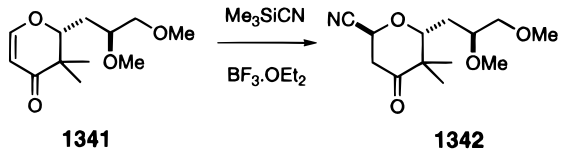
Trimethylsilyl cyanide adds to enones and is axially selective in the case of the dihydropyrone **1341**, giving only the ketone **1342** (Scheme 332).[266] This was the second, and better solution to a stereochemical problem in a synthesis of pederin already referred to in Schemes 113 and 179.

The delivery of the cyano group from dicyanodimethylsilane to the β-hydroxy ketone **1343** may at the critical stage be intramolecular, but it is more probable that the silicon holds the molecule in a ring **1344** like that of a cyclohexenone, so that attack by

Scheme 331

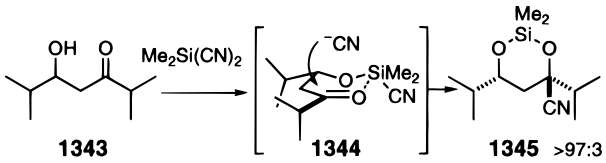


Scheme 332



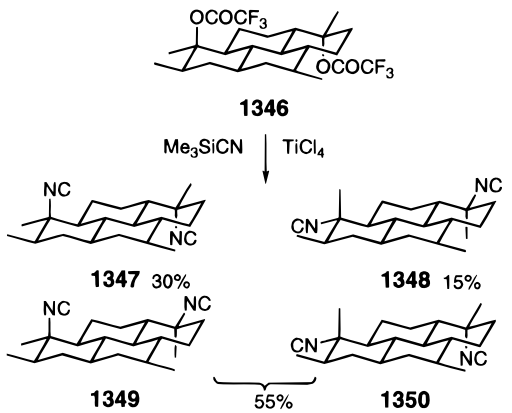
the cyanide is actually intermolecular and occurs axially to give the β-hydroxycyanohydrin **1345** (Scheme 333).[735]

Scheme 333



The steroidal allylic cation created from the alkene **743** with DDQ gives the axial nitrile corresponding to the azide **744** illustrated in Scheme 184.[450] Trimethylsilyl cyanide is similarly axially selective toward cyclohexyl carbocations, but with simple tertiary carbocations gives isonitrile products, attacking at the nitrogen end of the ambident nucleophile. The one-step reaction on the bis-trifluoroacetate **1346**, gave in 70% yield a mixture of all four possible diastereoisomers, consisting of 30% of diaxial product **1347**, 15% of diequatorial **1348**, and 55% of the mixture of axial−equatorial isomers **1349** and **1350**, from which the target molecule, 7,20-diisocyanoadociane **1349**, was separated (Scheme 334).[736]

Scheme 334



XII. Vinylsilanes

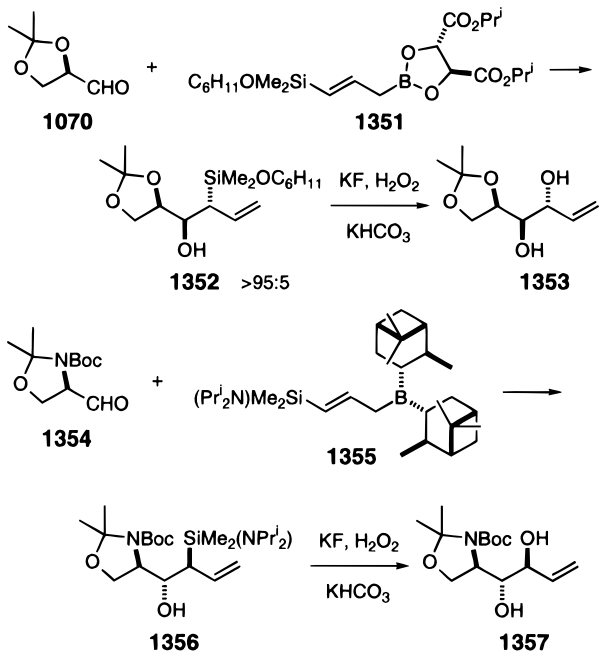
Vinylsilanes undergo electrophilic substitution with retention or inversion of configuration, controlling the double-bond geometry, as discussed in section II.C. Stereochemical consequences elsewhere in the molecule are rare, because vinylsilanes are not as powerfully nucleophilic as silyl enol ethers, allylsilanes, or silyl cyanides, and they are not as often used as carbon nucleophiles in carbon−carbon bond formation. However, there are several reactions of vinylsilanes not of this type, in which reaction takes place on a double bond to which a silyl group is attached, and the presence of the silyl group has stereochemical consequences.

A. Nucleophilic Attack by Vinylsilanes

When the vinylsilane carries, at an allylic position, another and more electropositive metal, the reaction with an electrophile creates an allylsilane, as in the reactions in Schemes 7−10, where the stereoselectivity setting up the β-silyl alcohols was used for the stereospecific formation of alkenes of controlled geometry. Similarly, in Scheme 268, the β-silyl alcohol **1072** was also an allylsilane that could be used to make a tetrol by dihydroxylation, followed by silyl-to-hydroxy conversion. In principle, the β-silyl alcohol intermediates like **1072** can also be used to make 1,2-diols when the silyl group carries substituents allowing easy silyl-to-hydroxy conversion. However, the phenyldimethylsilyl group present in this molecule cannot be used directly—any attempt to remove the phenyl group by aromatic electrophilic substitution is prevented by the allylsilane group acting as a better nucleophile than the arylsilane. Three solutions have been developed to solve this problem. One is the Birch reduction followed by fluoride ion-catalyzed protodesilylation (Scheme 341), useful so long as there are no functional groups easily reduced by electron transfer. A second uses previously functionalized silyl groups,[737] as in the parallel reaction between the allylborane **1351** and the same aldehyde **1070**, which, as a matched pair, gave the allylsilane **1352** with good stereoselectivity. Silyl-to-hydroxy conversion no longer needed the electrophilic step, and gave the *anti*-diol **1353** (Scheme 335).[631] A similarly matched pair, the serinal derivative **1354** and the allylborane **1355** derived from a different chiral auxiliary, gave only the *anti*-β-silyl alcohol **1356** and hence the *anti*-diol **1357** (Scheme 335).[738]

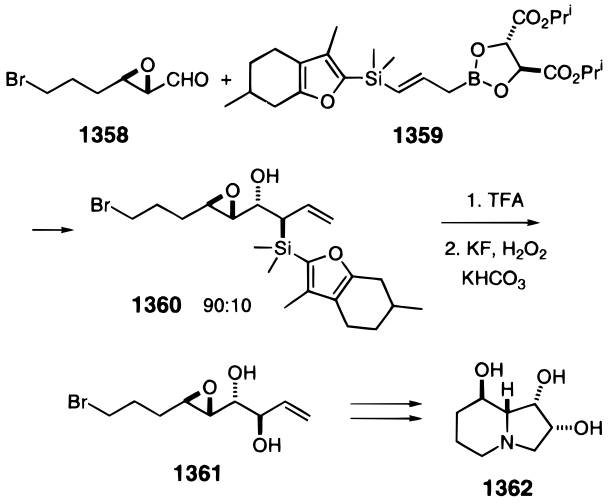
A third solution, if a hydrolytically more robust silyl group is needed, is to design a substituent on the silyl group that is attacked more easily than the double bond of allylsilanes like **1072**, **1352**, and **1356**. Candidates are the 2-methylbut-2-enyl group used in Scheme 95, the 2-furyl groups used in Schemes 339 and 345, and the even more substituted furyl group in the allylborane **1359**, which gave the β-silyl alcohol **1360**. Trifluoroacetic acid now attacked the furyl ring more rapidly than the double bond, and the oxidation step[217] therefore gave the *anti*-diol **1361**, but with more opportunity to carry out modifications of the intermediate **1360**. This route was

Scheme 335



used in a synthesis of swainsonine (**1362**, Scheme 336).[739]

Scheme 336

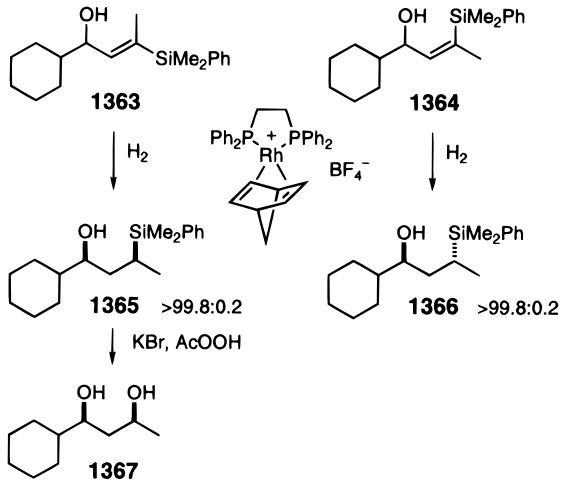


B. Additions, Cycloadditions, and Other Pericyclic Reactions

Stereoselective or stereospecific reactions, such as ionic additions and pericyclic cycloadditions, taking place on a double bond to which a silyl group is attached, give products still carrying the silyl group. The stereochemical relationship of the silyl group to the rest of the structure stems from the geometry of the double bond or other constraints, and subsequent silyl-to-hydroxy conversion gives an alcohol with the same relationship. Thus the double bond has proved to be the structural equivalent of an enol, which would not itself have been able to participate in many of these reactions.

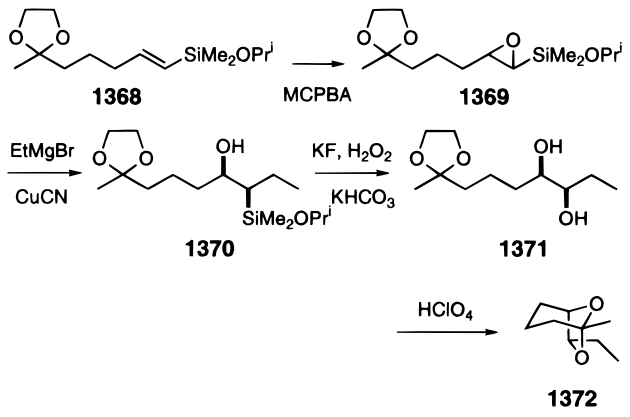
The hydrogenation of allylic alcohols having a silyl group on the double bond is *syn* stereospecific in the usual way, with the geometry of the double bond in the starting materials **1363** and **1364** controlling the relative stereochemistry in the products **1365** and **1366**. In these reactions, the catalyst is coordinated to the hydroxyl group, and delivers the hydrogen intramolecularly. The presence of the two substituents on the double bond ensures that the favored conformation has the hydrogen inside, and the hydroxy group then delivers the hydrogenated catalyst to the *syn* surface. In section III.B, the presence of silicon had a similar effect on several other kinds of double bond reaction, but served its turn only to be removed. In the present context, removal would leave no stereochemistry to be proud of, but silyl-to-hydroxy conversion[218] **1365** → **1367** makes the method a stereocontrolled synthesis of 1,3-diols (Scheme 337).[740]

Scheme 337



A different kind of addition to a vinylsilane, this time *anti* overall, is the sequence epoxidation and nucleophilic opening of the epoxide. The *trans*-vinylsilane **1368** gave an epoxide **1369**, evidently without silyl-to-hydroxy conversion, presumably because no base was present. The epoxide was then opened in a copper-catalyzed Grignard reaction to give the *syn*-*β*-silyl alcohol **1370**, and hence the *syn*-1,2-diol **1371** used in a synthesis of (±)-brevicomin (**1372**, Scheme 338).[741] Another way in which the

Scheme 338

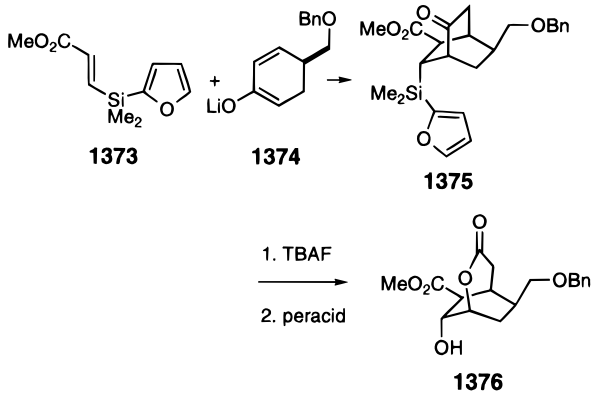


epoxidation of a vinylsilane can effectively give a 1,2-diol is recorded in Scheme 454.

Cycloadditions on vinylsilanes have been used, most conspicuously in an extraordinarily efficient synthesis of reserpine, where the key step was the suprafacial double-Michael cycloaddition, possibly a Diels−Alder reaction, of the (furyldimethylsilyl)-acrylic ester **1373** to the dienolate **1374** to give the

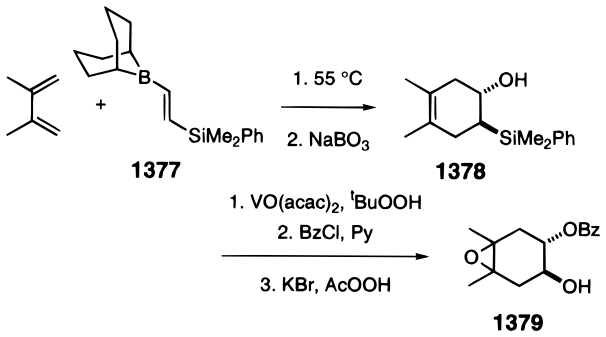
adduct **1375** with four new stereogenic centers correctly set up relative to the single center in the starting diene. Silyl-to-hydroxy conversion, where the furyl group was critically easier to remove from the silicon than the more usual phenyl group, was coupled with a Baeyer−Villiger reaction to give the lactone **1376** with all the required functionality (Scheme 339).[742]

Scheme 339



A true Diels−Alder addition to a vinylsilane is that between 2,3-dimethylbutadiene and the vinylsilane **1377** that is also a vinylborane. This reaction is suprafacial on the dienophile, giving the *trans* arrangement of substituents **1378**, and with unsymmetrical dienes takes place with moderately good regiocontrol. The successive, mechanistically related boron-to-hydroxyl and silyl-to-hydroxyl conversions,[218] with the former easier than the latter, gave the cyclohexanediol **1379** with differentiated hydroxyl groups (Scheme 340).[743]

Scheme 340

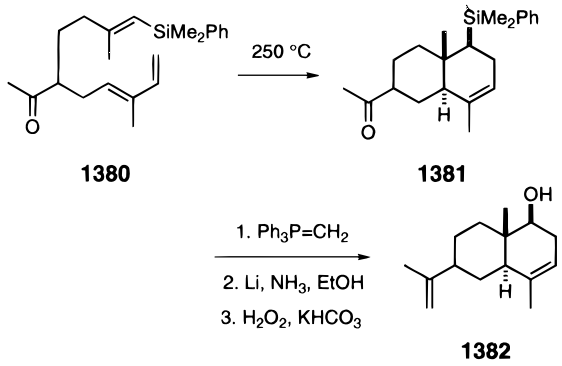


A vinylsilane without further activation can be the dienophile in an intramolecular Diels−Alder reaction, as in the cycloaddition of the vinylsilane **1380** giving the *trans*-octalin **1381**. The conversion of the silyl group to a hydroxy was not possible directly because of the presence of the double bond. This problem was solved by a new method,[744] Birch reduction of the benzene ring, and fluoride ion-catalyzed removal of the cyclohexadienyl anion, which gave, after oxidation, α-dictyopterol (**1382**, Scheme 341).[745]

Diels−Alder reactions can also take place with the silyl group on the diene, as in the reaction in Scheme 264, with the diene **1053** giving the adduct **1054**.

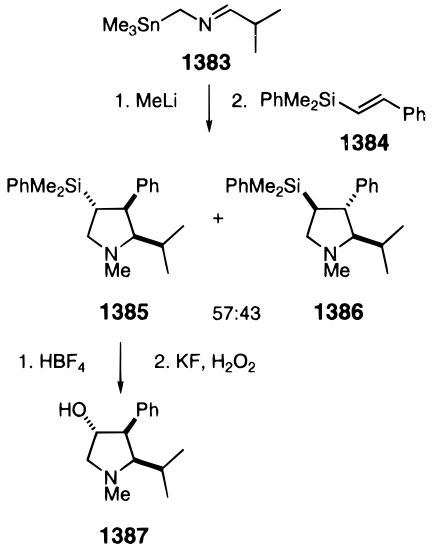
A different six-electron cycloaddition is the cleanly suprafacial reaction between the 2-azaallyl anion

Scheme 341



derived from the stannane **1383** and the vinylsilane **1384**, giving the pyrrolidines **1385** and **1386** with good regiocontrol but low stereoselectivity. Silyl-to-hydroxy conversion[218] of the former gave the alcohol **1387**, which would not have been available by cycloaddition to an enol (Scheme 342).[746]

Scheme 342

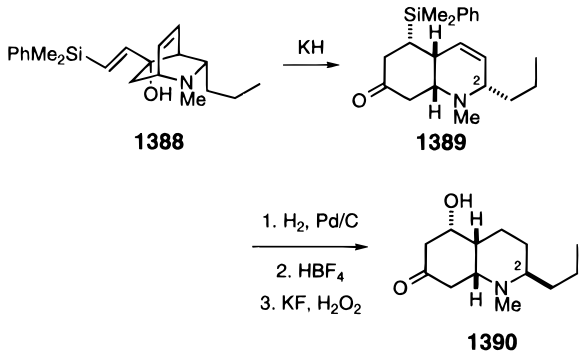


Other pericyclic processes taking place with the double bond of a vinylsilane as one of the components include [3.3] Cope and Claisen sigmatropic rearrangements, and [2.3] Wittig rearrangements. Some of these have been discussed already in section III.B, where the silyl group made a perceptible contribution to the stereochemistry observed. Here we discuss a few more reactions, where the silyl group is merely carried through the sequence, with its attendant stereochemical consequences.

The oxy-Cope rearrangement of the vinylsilane **1388** set up the β-silyl ketone **1389**, and hence the β-hydroxy ketone **1390** (Scheme 343). The configuration at C-2 inverted during the hydrogenation step, with the silyl group probably playing a part in this event by helping to fix the conformation so that the change was energetically favorable.[747]

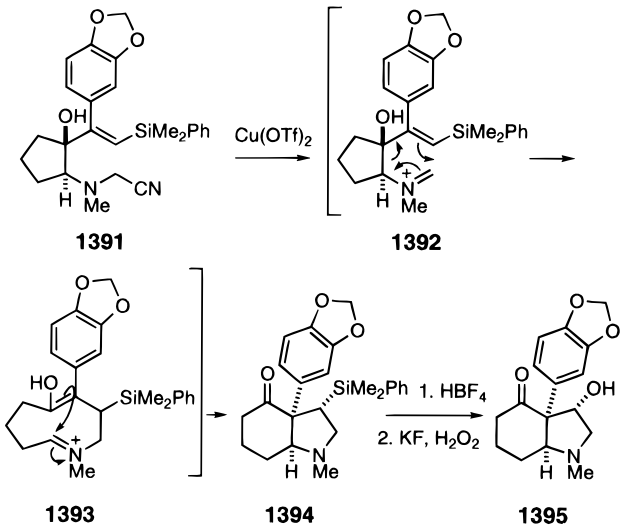
The Cope rearrangement of the iminium ion **1392** derived from the vinylsilane **1391** gave the enol **1393**, and this undergoes the usual Mannich reaction to set up the pyrrolidine ring **1394**. Silyl-to-hydroxy conversion[218] then gave the alcohol **1395** used in a synthesis of (±)-epipretazzetine (Scheme 344),[748] although in a similar system rather more prone to

Scheme 343



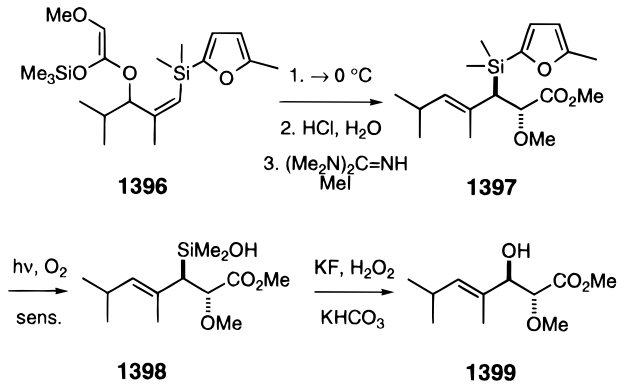
rearrangement, this reaction proved to be troublesome in the acid-catalyzed step.[749]

Scheme 344



Ireland−Claisen rearrangement of the vinylsilane **1396** gave the allylsilane **1397** with the *anti* arrangement of the silyl and methoxy groups following from a chair-transition structure with a (*Z*)-silyl enol ether. The silyl-to-hydroxy conversion[217] in this case used new conditions based on singlet oxygen for the removal of the furyl ring to give the silanol **1398**, necessary because of the extreme sensitivity of an allylsilane function with this substitution pattern to the electrophilic attack usually needed to cleave off the furyl ring. The allyl alcohol produced **1399** was the C-26 to C-32 component of rapamycin (Scheme 345).[750]

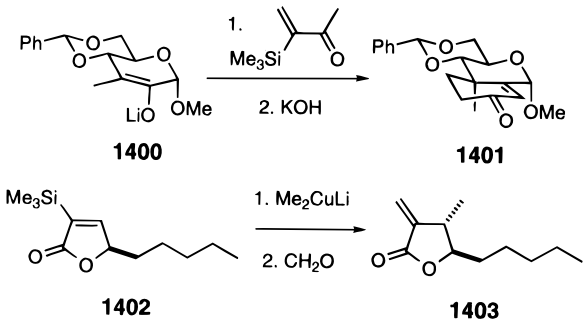
Scheme 345



C. Nucleophilic Attack on Vinylsilanes

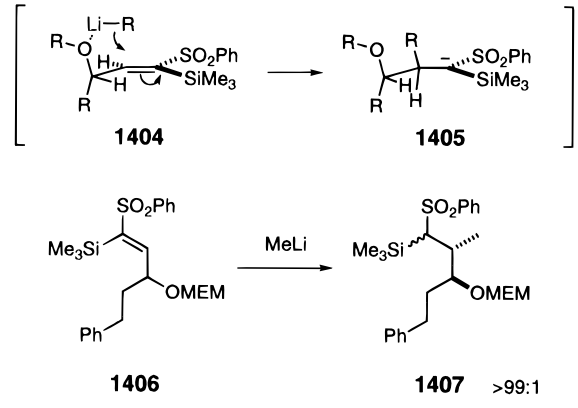
A silyl group stabilizes an anion adjacent to it, and in consequence makes nucleophilic attack on a vinylsilane easier than it is on the corresponding C=C double bond without the silyl group, but another anion-stabilizing substituent is usually needed in addition to the silyl group. Although this device has been used many times since the introduction of an α-silyl group to methyl vinyl ketone to make Robinson annelations easier,[751] stereochemical consequences are not usually in evidence—the silyl group is there to make the reaction work rather than to affect the stereochemistry. This Michael acceptor simply attacks from whichever side of the nucleophile is less hindered,[752] as in the example **1400** → **1401**, which is unusual in that it is not obvious which side would be the less hindered (Scheme 346).[753] More obvious is the clean selectivity for attack *anti* to the resident substituent in the cuprate addition **1402** → **1403** to a silylated butenolide (Scheme 346).[754]

Scheme 346



The most fruitful aspect of nucleophilic addition to a vinylsilane has come from vinylsilanes which are also vinyl sulfones. With two substituents at the terminus of the vinylsilane, the neighboring stereogenic center at the other end can be relied upon to adopt a conformation with the hydrogen atom inside. The organometallic nucleophile is then delivered **1404**, effectively intramolecularly, *syn* from the oxygen function, to give the sulfur- and silicon-stabilized anion **1405**. The reaction proves to be highly stereoselective, as in the example **1406** → **1407**,[755] used as a model reaction for a synthesis of maytansinol[756] (Scheme 347).

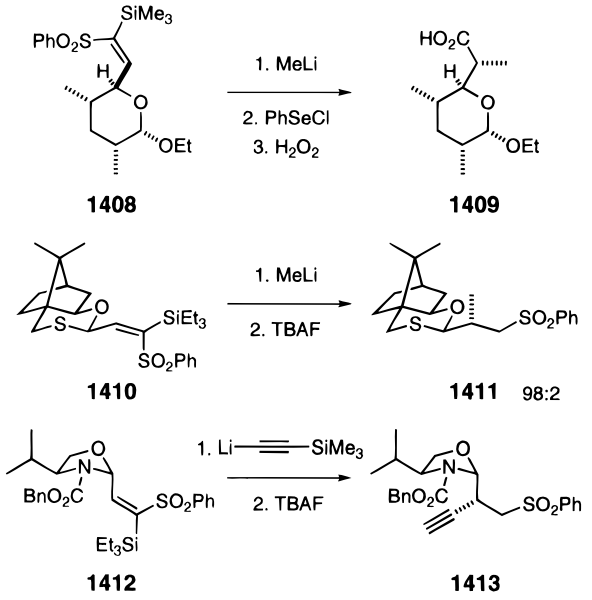
Scheme 347



High levels of control have been found for many other reactions of this type based on chiral auxiliaries taken from a sugar in the addition **1408** → **1409**, and

used in a synthesis of the Prelog−Djerassi lactone,[757] from camphor in the addition **1410** → **1411**,[758] showing that specifically oxygen, rather than sulfur, delivers the nucleophile, and used in a synthesis of citronellal, and from valine in the addition **1412** → **1413**,[759] which was anomalous, with most nucleophiles in this system being delivered *cis* to the carbobenzyloxy function (Scheme 348). In all these

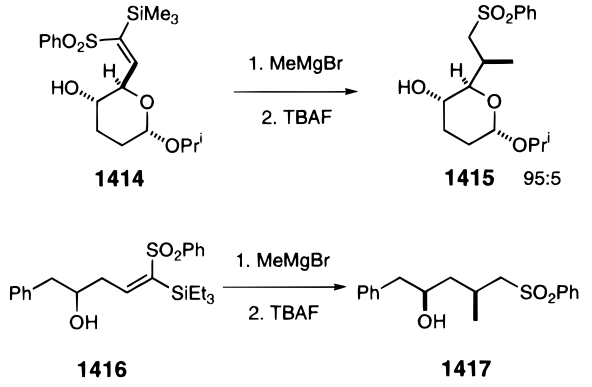
Scheme 348



reactions, the silyl group is easily removed after the conjugate addition, either oxidatively, as in the first of these examples, or by protodesilylation.

The oxygen function still delivered the nucleophile from one atom further away, as in the addition **1414** → **1415**,[760] where the C-5 oxygen function, rather than the ring oxygen, directed the attack, and hence gave the opposite stereochemistry to that of **1408** → **1409**. The addition **1416** → **1417** showed that good 1,3-control was possible by delivery from a *β*-oxygen with no other stereochemical constraint (Scheme 349).[761]

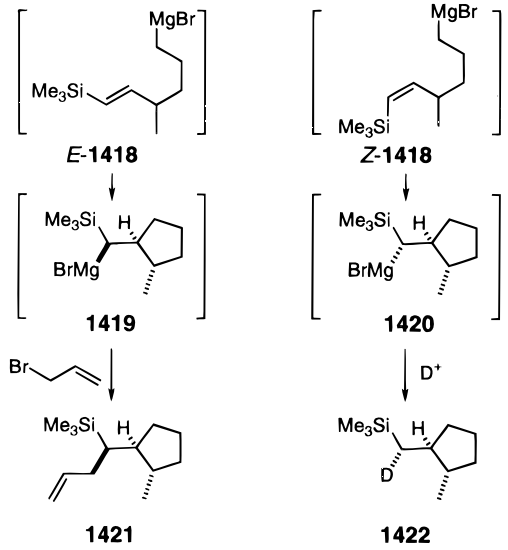
Scheme 349



Among other natural products synthesized using this powerful method are okadaic acid,[762] where the device was used twice,[763] and segment C of tautomycin.[764]

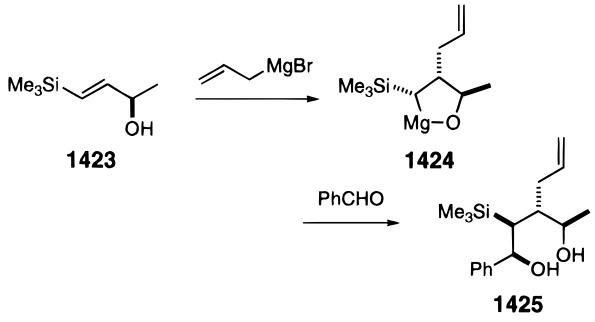
The silyl groups in the simple vinylsilanes (*E*)- and (*Z*)-**1418** do have a stereochemical role to play, in that they identify the stereochemistry of the nucleophilic attack. They are also the only anion-stabilizing group present. The isomeric vinylsilanes each undergo stereospecifically *syn* intramolecular addition to give the intermediates **1419** and **1420**, respectively, followed by electrophilic substitution with retention of configuration both for alkylation giving the silane **1421** and for deuteronation giving the silane **1422** (Scheme 350).[765]

Scheme 350



Some loss of stereochemistry appears to be a risk in any application of this type of reaction. The delivery of the allylmagnesium reagent in the first step **1423** → **1424** is most probably intramolecular with delivery from the hydroxy group, and ought to take place by analogy *syn* stereospecifically. Quenching with deuterium oxide confirms stereospecificity, giving very largely one diastereoisomer, but of unproved configuration. The only product **1425** that gave any indication about stereochemistry was from a reaction with benzaldehyde; it was isolated only in low yield from a mixture of several diols, indicating perhaps that the intermediate **1424** had suffered some epimerization (Scheme 351).[766] The silyl group,

Scheme 351



like other anion-stabilizing groups, makes epimerization easier.[767]

These reactions, in which an "anion" is created adjacent to the silyl group, could as easily have belonged in the next section.

XIII. α-Silyl Anions

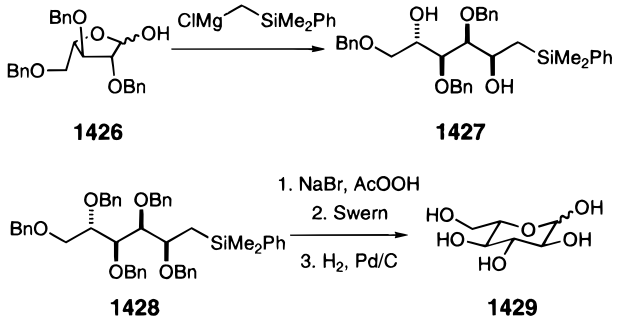
We necessarily adopt here an unsophisticated use of the word "anion", since the nature of the intermediates is barely known in any of these reactions.

What we include here are those reactions of stereochemical interest where the carbon atom attached to the silicon exhibits nucleophilic character stemming from some other feature than the silicon−carbon bond itself. These intermediates have been mentioned already in section II.A.3 in connection with Peterson olefination.

A. Silylmethyl Nucleophiles as Hydroxymethyl Synthons

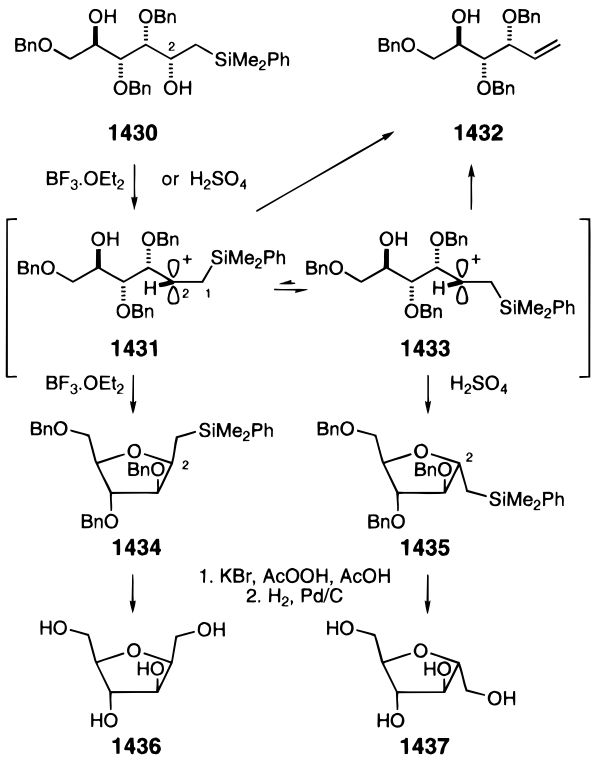
The Grignard reagents derived from (isopropoxydimethylsilyl)methyl chloride,[768] or from (allyldimethylsilyl)methyl chloride,[769] or from (phenyldimethylsilyl)methyl chloride[770] react like any other Grignard reagents, typically with aldehydes to give β-silyl alcohols. In each case silyl-to-hydroxy conversion shows that these reagents are hydroxymethyl anion synthons. Cram control in these reactions has been used several times for the homologation of sugars.[770,771] Thus, the most robust of these reagents, [(phenyldimethylsilyl)methyl]magnesium chloride, reacts with the aldehyde derived from the pentose **1426** giving only the alcohol **1427**. The silyl group in this compound is stable to the benzylation conditions necessary to protect the free hydroxyl groups giving the perbenzylated silasugar **1428**, and then silyl-to-hydroxy conversion,[218] oxidation and deprotection gave the L-glucose homologue **1429** of the original sugar, uncontaminated by any mannose diastereoisomer (Scheme 352).[772]

Scheme 352



The enantiomer **1430** of the adduct **1427** underwent cyclization in acid to give tetrahydrofurans as well as the expected elimination product **1432**. Remarkably, the choice of acid determined the stereochemical sense at C-2, with boron trifluoride etherate giving the tetrahydrofuran **1434**, and sulfuric acid giving the tetrahydrofuran **1435**. The former is the product of retention of configuration, with the silyl group presumably remaining *anti* to the leaving group and the incoming nucleophilic atom. The latter is probably the thermodynamic product that is formed from the same intermediate **1431** after rotation about the bond between C-1 and C-2 giving the intermediate **1433**, a rotation that can normally be relied upon not to take place (Scheme 353).[773] Silyl-to-hydroxy conversion[218] and debenzylation were then used to give the anhydrohexitols **1436** and **1437**, and the proportion of elimination product can be reduced by using a hindered silyl group. An alternative sequence leading to diastereoisomeric 2,5-anhydrohexitols uses inversion at C-4 in the cyclic sulfates,[774]

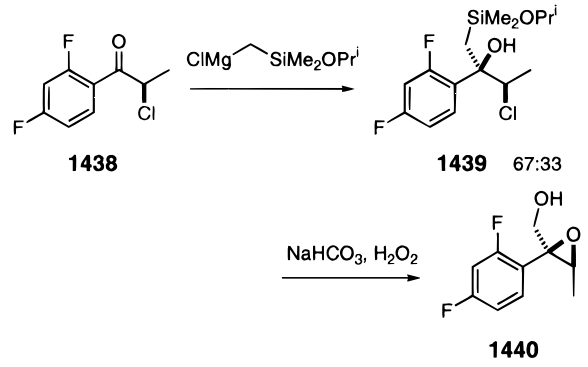
Scheme 353



and an alternative Grignard reagent has been developed using [[[(phenylthio)methyl]dimethylsilyl]-methyl]magnesium chloride, which has the advantage that the silyl-to-hydroxy conversion can be carried out with hydrogen peroxide without needing peracetic acid.[775]

Similarly, the least robust of these reagents, [(isopropoxydimethylsilyl)methyl]magnesium chloride, reacted with the homochiral ketone **1438** to give the intermediate **1439**, which had to be oxidized immediately[217] and concurrently with the epoxide-forming reaction, to give the alcohol **1440** (Scheme 354).[776]

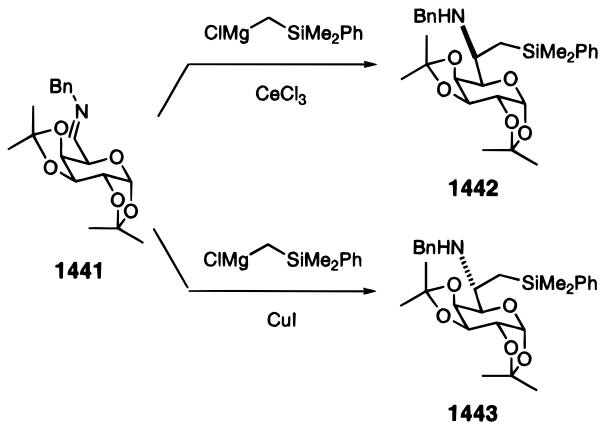
Scheme 354



[(Phenyldimethylsilyl)methyl]magnesium chloride adds with high selectivity to the imine **1441**, with the stereochemical sense of attack controlled by adding cerium(III) chloride to get the amine **1442**, a precursor of destomic acid, and by adding copper(I) iodide to get the amine **1443**, a precursor of lincosamine (Scheme 355).[777]

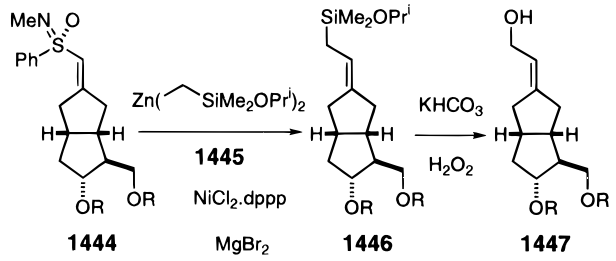
A related zinc reagent **1445** in the presence of a nickel(II) catalyst replaced the sulfoximine group on the exocyclic double bond of the alkene **1444** to give,

Scheme 355



after immediate silyl-to-hydroxy conversion,[217] the allylic alcohol **1447** ready for a synthesis of a 3-oxacarbacyclin (Scheme 356).[778]

Scheme 356

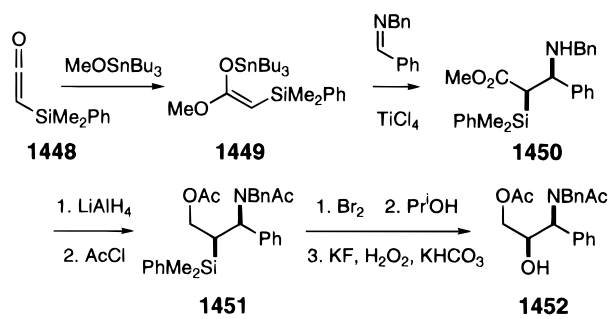


[(Allyldimethylsilyl)methyl]magnesium chloride and [(phenyldimethylsilyl)methyl]magnesium chloride have also been used in copper-catalyzed conjugate addition reactions, with the expected stereoselectivity, depending upon the substrate.[769,779]

B. α-Silylalkyl Anions with more than one Carbon

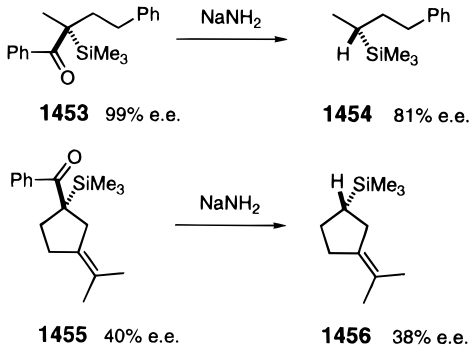
Enolates having an α-silyl group create two stereogenic centers when they attack trigonal electrophiles like aldehydes, setting up *β*-hydroxy silanes ready for Peterson eliminations as in Scheme 7. Similarly, the tin enolate **1449** derived by nucleophilic attack on the silylketene **1448** reacts with aldimines to give, with high *syn* selectivity, *β*-amino silanes **1450**, which can be reduced and protected to give the amide **1451**, and the silyl group converted into a hydroxyl group[218] to give the alcohol **1452** (Scheme 357).[39]

Scheme 357



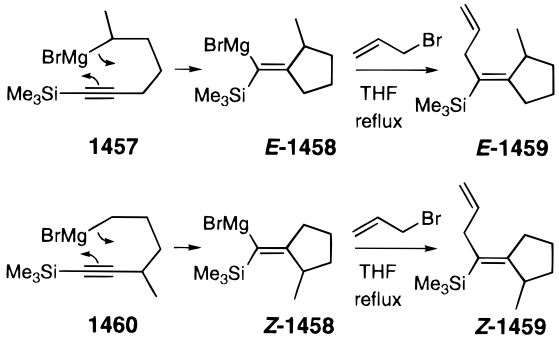
With enolates the nucleophilic carbon is trigonal, but α-silyl groups can also be attached to tetrahedral nucleophilic centers, since they stabilize "anions". Such anions can retain their configuration and have therefore an intrinsic stereochemistry. However, this stereochemistry is not easily set up with absolute control, and so this aspect of organosilicon chemistry has not yet received much attention, except with intramolecularly coordinated anions, as described in section XIX.D and Schemes 460−462. Evidence for some configurational stability, even without coordinating groups in the molecule, comes from Haller−Bauer cleavage of α-silyl ketones, both open chain and in a ring, which take place **1453** → **1454** and **1455** → **1456** with retention of configuration (Scheme 358).[780]

Scheme 358



Nucleophilic attack on the vinylsilane **1418** gave a Grignard reagent **1419**, which could be trapped with electrophiles to give overall the product **1421** of *syn* addition to a double bond, as illustrated earlier in Scheme 350.[765] The corresponding reactions on the regioisomeric ethynylsilanes **1457** and **1460** proved also to be stereospecifically *syn*, giving the vinylsilanes (*E*)- and (*Z*)-**1459**, respectively, with less than 10% loss of stereospecificity (Scheme 359).[781]

Scheme 359

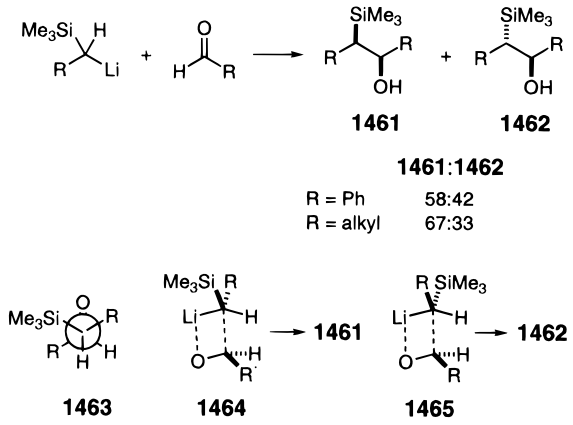


In contrast to the configurational stability in refluxing THF of the vinylmagnesium reagents **1458**, vinyllithium reagents carrying a neighboring silyl group are configurationally unstable even at 0 °C, although reasonably stable at −70 °C.[782] Activation parameters for the equilibration have been measured in several solvents.[783]

Racemic α-silylated carbon nucleophiles react with trigonal electrophiles with some diastereochemical preferences, but the story is complicated by the great variety of substituents and their effects on the stereochemistry. The most common of these reactions is the first step of the Peterson olefination process,[12] where it is usually possible to isolate the mixture of *β*-silyl alcohol diastereoisomers, and to

identify the stereochemistry by the elimination step, whether it is carried out with base or acid. The stereoselectivity in this step has already been mentioned in section II.A.3. It is usually rather low and, in simple systems, is in favor of the *syn* diastereoisomer **1461** over the *anti*-**1462** (Scheme 360).[28,27]

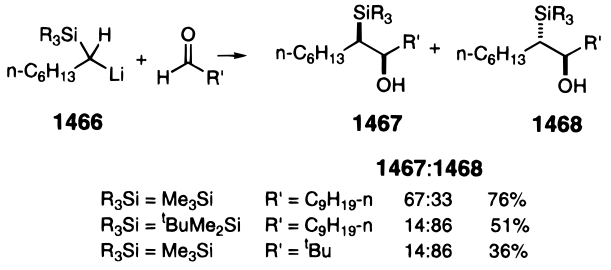
Scheme 360



Such selectivity has been explained as a consequence of approach in the sense of the Newman projection **1463**.[28] It is perhaps better to include the metal, but its detailed role is hardly well settled. In the transition structures **1464** and **1465**, with the metal reasonably placed over the carbonyl oxygen atom, one of the substituents on the nucleophile must be tilted down toward the back of the carbonyl group, and the smallest substituent, the hydrogen atom, should therefore take this role. Of the other two substituents, the larger should be placed between the hydrogen of the aldehyde group and the oxygen, and the smaller in the remaining segment between the R group and the oxygen. Both substituents are likely to be oriented well away from the carbonyl group, which explains why low selectivity is usually observed, but it is not easy to classify the silyl and R groups on the nucleophilic component. If the long silicon−carbon bond effectively makes the silyl group the less hindering, it will occupy the segment between the R group on the aldehyde and the oxygen, and the R group on the nucleophile will occupy the remaining segment, as in the drawings **1463** and **1464**, leading to the major diastereoisomers **1461**.

This picture is supported by the observation that increasing the size of the silyl group on the lithium reagent **1466** inverted the stereochemical preference. A trimethylsilyl group made the major adduct the *syn* isomer **1467**, but a *tert*-butyldimethylsilyl group gave the *anti* diastereoisomer **1468** (Scheme 361).[27] In-

Scheme 361

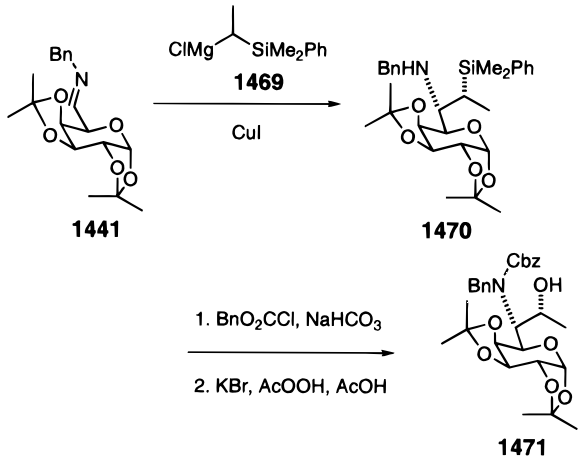


creasing the size of the alkyl group on the aldehyde also increased the selectivity in favor of the *anti* diastereoisomer, even with the trimethylsilyl group, which is not straightforwardly consistent with the picture **1463**. In any case, the problem with this approach to stereocontrol was that the yield fell off as the steric hindrance increased.

Most of the results in this field indicate that the major diastereoisomer, whether the intermediate is isolated or not, is the one that gives the (*Z*)-alkene on completion of the Peterson olefination, which fits the general picture in **1465** where we count the silyl as usually the "large" group. The low stereoselectivity, and uncertainty about the extent of thermodynamic control when an anion-stabilizing group is present, make further speculation unripe.

The Grignard reagent **1469** reacts with the imine **1441**, remarkably giving only the amine **1470** in the presence of copper ions, and with selectivity in favor of the *anti* isomer at the silicon-bearing carbon. Silyl-to-hydroxy conversion[218] gave the lincosamine precursor **1471** (Scheme 362).[784]

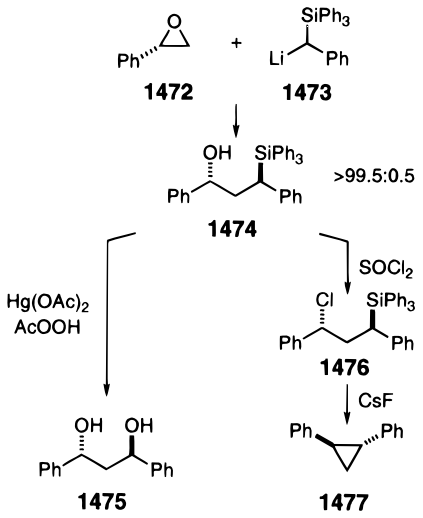
Scheme 362



Moving from 1,2-control to 1,3-control, enantiomerically enriched styrene oxide **1472** reacted with the α-silylorganolithium reagent **1473** with high selectivity for the formation of the 1,3-*anti* (hydroxypropyl)silane **1474**, with a plausible transition structure favoring the formation of this diastereoisomer, but with evidence of equilibration also having taken place under the reaction conditions, giving the thermodynamically more favorable product. This class of compound, already seen in the section on the hydroboration of allylsilanes (Schemes 274−277), can be used to synthesize 1,3-diols **1475**, with retention of configuration at both centers. Alternatively, they can be used by way of the chloride **1476** to make cyclopropanes **1477**, with inversion of configuration at both centers, a pathway and a stereochemistry with strong parallels in tin chemistry[785] but relatively little precedent[786] hitherto in silicon chemistry (Scheme 363).[787]

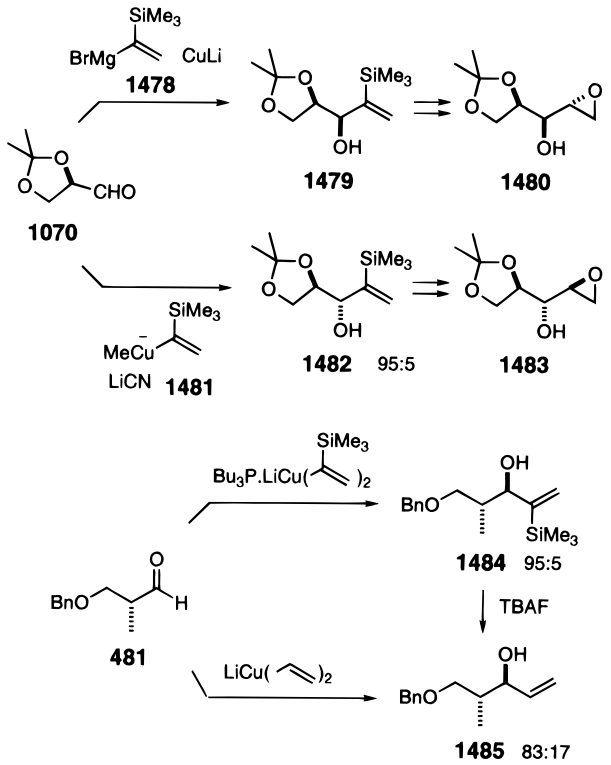
The presence of a silyl group on the double bond of the Grignard reagent **1478** makes the attack on the aldehyde **1070** more diastereoselective in the formation of the chelation product **1479** than it is without the silyl group, and changing the nucleophilic species from copper-catalyzed Grignard to the vinyl cuprate **1481** inverts the stereoselectivity giving the Cram product **1482**. The silyl group was removed from the vinylsilane epoxides, to give the pentose precursors

Scheme 363



1480 and **1483** (Scheme 364).[788] Likewise, the addition of a silylated vinyl cuprate to the α-chiral *β*-alkoxy aldehyde **481** gave the alcohol **1484** more selectively (95:5) with chelation control than the same reaction without the silyl group (83:17). The silyl group was easily removed from the vinylsilane **1484** by protodesilylation to give the alkene **1485** (Scheme 364).[789]

Scheme 364



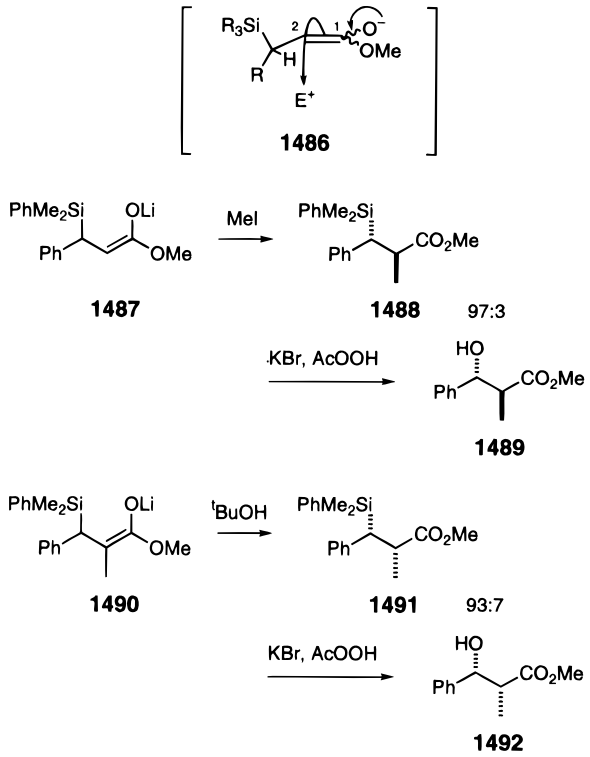
XIV. β-Silyl Enolates

In contrast to the material in the preceding section on α-silylalkyl nucleophiles, there has been little work on simple *β*-silylalkyl carbon nucleophiles, and none with stereochemical features. However, one functionalized member of this class of carbon nucleophiles, *β*-silyl enolates does have considerable usefulness and much of stereochemical interest. A *β*-silyl enolate has essentially the same framework as an allylsilane, and hence the same stereochemical imperatives, but with a change of substituents that makes C-2 the nucleophilic atom. The almost invariable presence of a substituent on C-1 *cis* to the stereogenic center makes the conformation reasonably certain to be that with the hydrogen atom inside **1486**, and attack is often cleanly *anti* to the silyl group.

A. Alkylation and Protonation of *β*-Silyl Enolates

For example, the highly stereoselective methylation **1487** → **1488**, and the nearly as selective protonation **1490** → **1491** make both diastereoisomers of the *β*-silyl esters almost equally available with high levels of stereocontrol.[790] Such products are useful in synthesis because of the possibility of converting the phenyldimethylsilyl group into a hydroxyl **1488** → **1489** and **1491** → **1492** (Scheme 365).[218,791,792]

Scheme 365



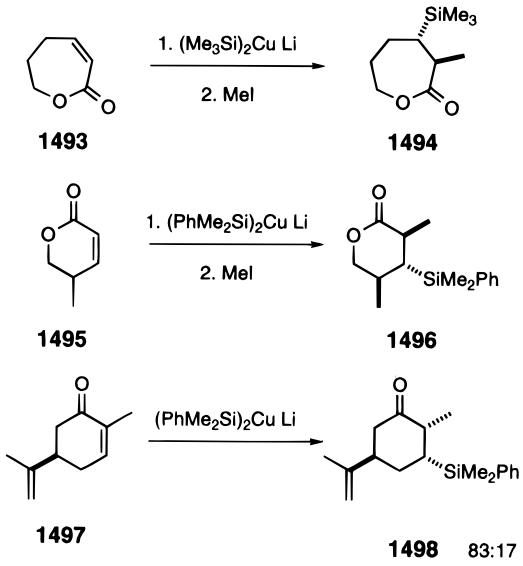
The alkylation reaction is selective in a wide variety of situations. The enolate can be that of an ester, a ketone, an aldehyde, or an amide, and it can be a silyl enol ether as well as a lithium enolate. The stereogenic center can carry other groups in place of the phenyl, although a phenyl or alkenyl group at this position does seem to lead to the best levels of stereoselectivity. The stereoselectivity, although reduced to 2:1 by large groups like *tert*-butyl, is still in the same sense with them all. The electrophile can be a primary or secondary alkyl halide, and the selectivity is still available for making quaternary centers by the alkylation of α-substituted enolates, provided that the α-substituent is not much larger than a methyl group.

The selectivity for *anti* attack extends to the anions of phosphine oxides[651] and sulfoxides, with matched and mismatched possibilities with the latter.[793]

Cyclic enolates are similarly selective in the *anti* sense with complete selectivity in the conjugate

addition−alkylation on the lactones **1493**[794] and **1495**,[795] giving only the lactones **1494** and **1496** perhaps less surprisingly in view of the usual control possible in rings, and with high control in the conjugate addition−protonation **1497** → **1498** (Scheme 366).[796] The comparable phenylselenenylation of a

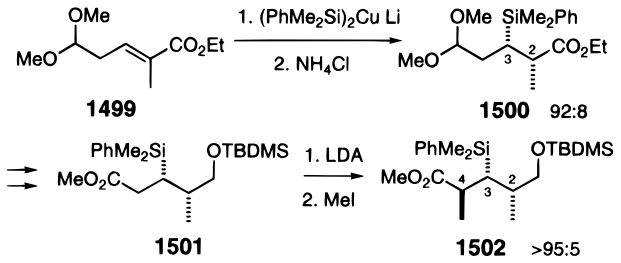
Scheme 366



β-silylcyclopentanone is *anti* selective, but equilibration takes place easily by deselenenylation−reselenenylation.[797]

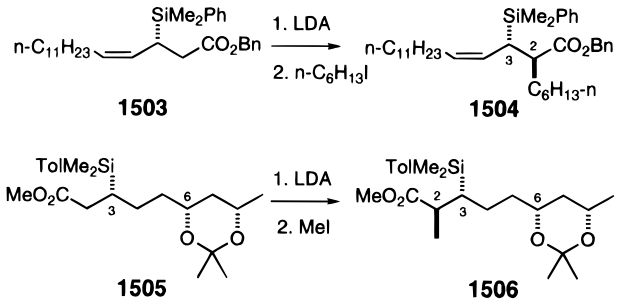
The protonation **1499** → **1500** and methylation **1501** → **1502** of β-silyl enolates were used successively to control the stereochemistry of C-2 and C-4 relative to C-3 of a β-silyl enolate in a synthesis of the Prelog−Djerassi lactone, so that all the relative stereochemistry, both that shown in Scheme 241 and that shown here (Scheme 367), was controlled by silicon.[589]

Scheme 367



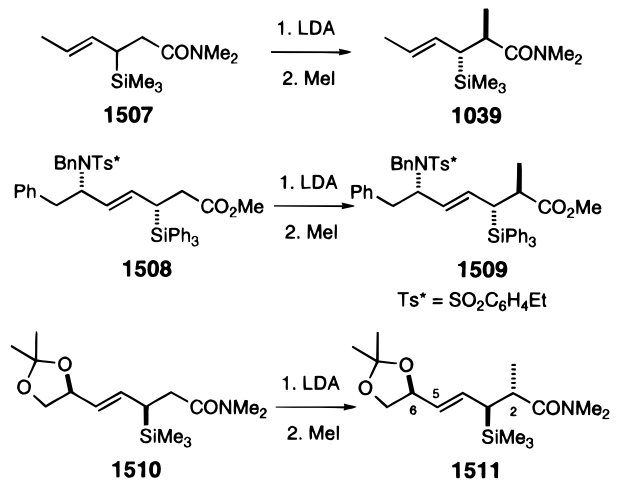
Likewise, the alkylation of the ester **1503** with hexyl iodide to give the ester **1504** was used with essentially complete control of the relative stereochemistry between C-2 and C-3 in a synthesis of tetrahydrolipstatin, so that again all the relative stereochemistry, both the 1,3-relationship in the hydroboration (Scheme 277) and the 1,2-relationship in the alkylation, was controlled by silicon (Scheme 368).[111] The open-chain methylation **1505** → **1506** was used to control the relative stereochemistry between C-2 and C-3 in a synthesis of benzyl (−)-nonactate (Scheme 368), where silicon had already been used earlier in the synthesis to control the relative stereochemistry between C-3 and C-6 (Scheme 262).[623] A closely similar methylation was also used in a different synthesis of methyl (+)-nonactate.[640]

Scheme 368



Methylation of the amide **1507** gave the amide **1039** used in the allylsilane work in Scheme 261.[619] Similarly, alkylation, and azidation with trisyl azide, were used to make the *anti* diastereoisomers **963**, **968**, **973**, and **1063** used in Schemes 243, 244, 248, 249, 265, and 273, more easily in several cases than by the Claisen rearrangement in Scheme 280.[798] In more functionalized examples, the ester **1508** and the amide **1510** have also been methylated to give, respectively, the ester **1509**, designed as precursor for an analog of bestatin,[799] and the amide **1511**, which was used to demonstrate the efficient moving of stereochemical information from C-5 four atoms along the chain to C-2 by successive enzymatic, Eschenmoser−Claisen and enolate alkylation reactions.[800] All three methylations took place with a high level of control (>95:5), typical for substrates having an alkene group on the stereogenic center (Scheme 369).

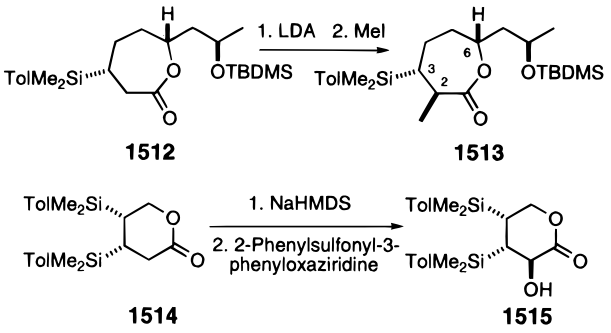
Scheme 369



In cyclic systems, enolate methylation of the lactone **1512** giving the lactone **1513** was used in a synthesis of methyl (+)-nonactate parallel to that of the (−)-nonactate in Scheme 368,[623] and the enolate oxidation **1514** → **1515** was used in a synthesis of arabonolactone (Scheme 370).[801]

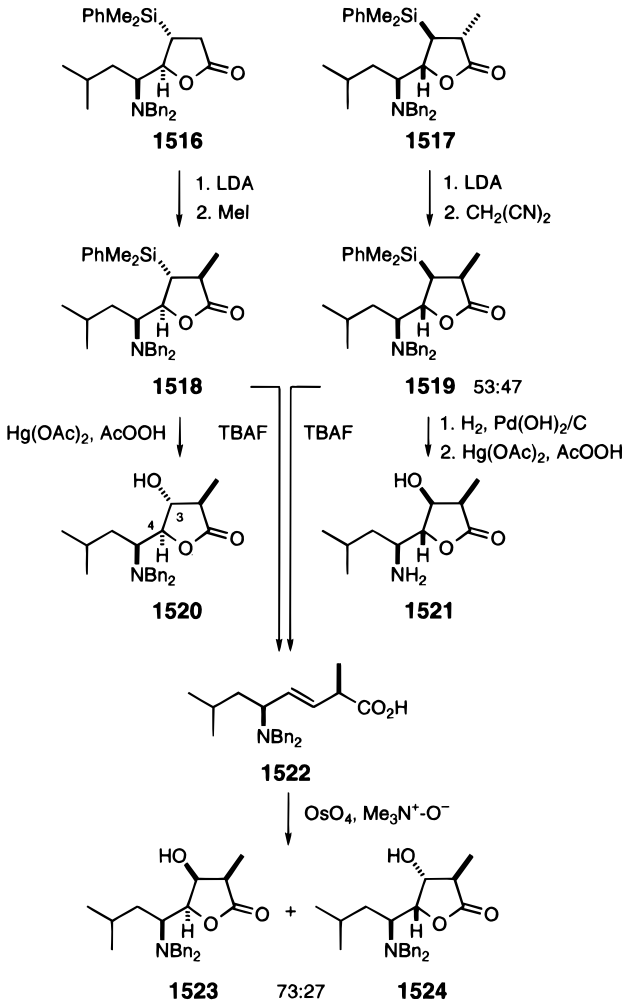
Enolate alkylation of the lactone **1516** and enolate protonation of the lactone **1517** were used in syntheses of the diastereoisomeric lactones **1518** and **1519**, with malononitrile significantly better than other proton sources for the synthesis of the latter, although not actually good.[50] These compounds could be precursors either by silyl-to-hydroxyl conversion[218] to the alcohols **1520** and **1521**, respectively, or by *anti* elimination to the alkene **1522**, which could be oxidized with osmium tetraoxide to give the lactones

Scheme 370



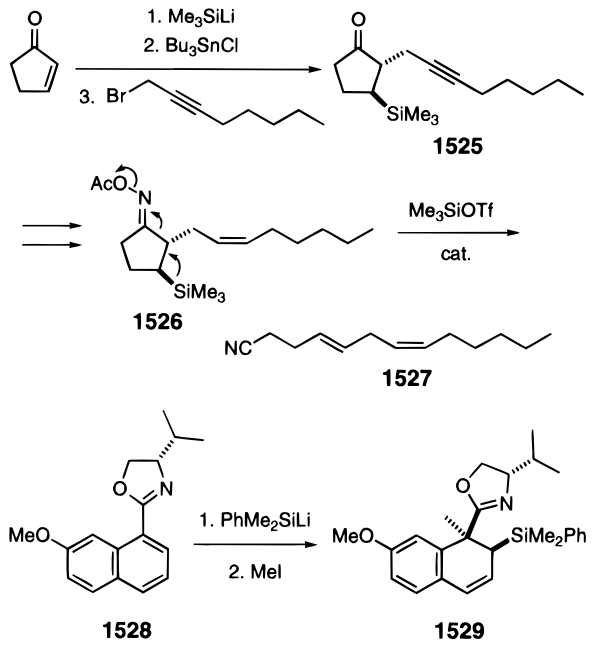
1523 and **1524**, making available all four of the diastereoisomers at C-3 and C-4 of this system of peptide surrogates (Scheme 371).[50]

Scheme 371



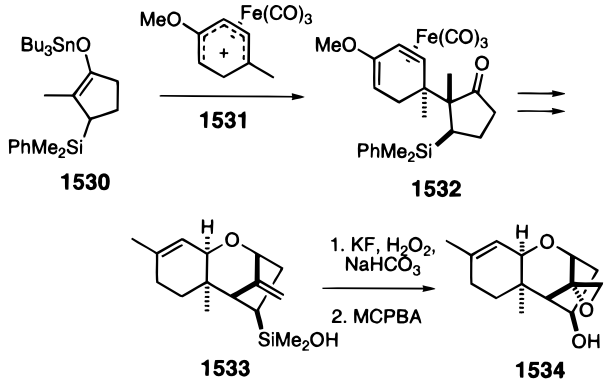
The conjugate addition−alkylation sequence on cyclopentenone gave the ketone **1525**, which was used to set up an oxime acetate for an *anti* fragmentation reaction **1526** → **1527**, where the *trans* disposition of the silyl and alkyl groups produces the *trans* double bond in a synthesis of the pheromone of the potato tuberworm moth (Scheme 372).[802] A similar conjugate addition−ethylation gave the ketone **74** used in the synthesis of brevicomin. The conjugate addition−methylation of the oxazoline **1528** was used to set up the quaternary center in the intermediate **1529**, which was used in syntheses of (−)-aphanorphine and (−)-eptazocine (Scheme 372).[803]

Scheme 372



Alkylation of the tin enolate **1530** with the cationic iron complex **1531** gave largely the adduct **1532**, and this after many steps gave the tricyclic ether **1533**. Silyl-to-hydroxy conversion,[218] followed by epoxidation, was then used to give trichodermol **1534** (Scheme 373).[804] The removal of the phenyl group from the

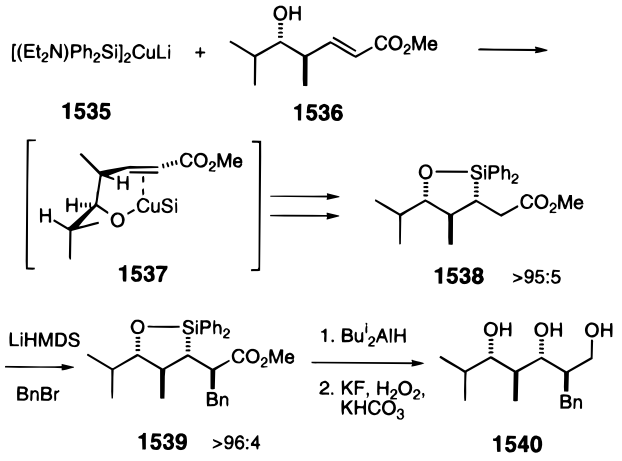
Scheme 373



silane, in order to functionalize it for the rearrangement step, had to be carried out by protodesilylation with fluoroboric acid at an earlier stage, to avoid acid-catalyzed reactions of the double bonds.

The functionalized silyl−nucleophile **1535** was specifically designed to overcome the problem of having to remove the phenyl group at some stage by aromatic electrophilic substitution—it is a cuprate carrying an amino group allowing direct oxidation by alkaline hydrogen peroxide.[805] The aminosilane however is very hydrolytically labile, and the oxidation step cannot be delayed for many steps. Thus conjugate addition to the α,β-unsaturated ester **1536** proved to be diastereoselective with respect to the resident stereogenic centers, by virtue of intramolecular delivery from the hydroxy group with the hydrogen atom inside **1537**. The intermediate **1538** was alkylated with the usual diastereocontrol to give the ester **1539**. Reduction of the ester and silyl-to-hydroxy conversion[217] then gave the triol **1540** with the *all-anti* arrangement (Scheme 374).[806]

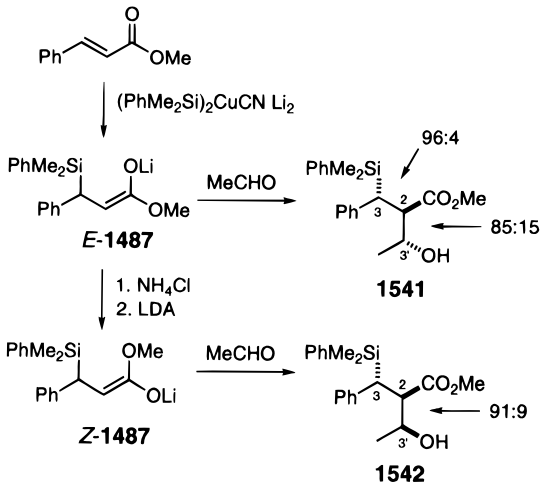
Scheme 374



B. Aldol Reaction of β-Silyl Enolates

β-Silyl enolates also react stereoselectively, and in the same sense, with trigonal carbon electrophiles, of which aldehydes are the most important. They react, as mentioned already and illustrated with one example in Scheme 285, with high diastereoselectivity, not only with respect to the relationship between C-2 and C-3, but also with respect to the centers C-2 and C-3′. The former relationship is determined by the attack *anti* to the silyl group, as usual, and the latter is controlled by the constraints of the aldol transition structure, with the geometry of the enolates translated into relative stereochemistry, as in the reactions (*E*)-**1487** → **1541** and (*Z*)-**1487**→ **1542** (using here the strict *E* and *Z* nomenclature, not that commonly used in connection with aldol chemistry). Both geometrical isomers of the enolates are readily available, the isomer (*E*)-**1487** by direct reaction of the silylcuprate reagent on methyl cinnamate, and the isomer (*Z*)-**1487** by regeneration of an enolate from the ester produced by protonation of the (*E*)-enolate (Scheme 375).[807]

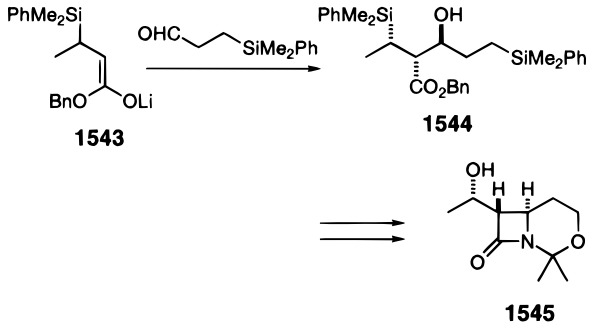
Scheme 375



The stereocontrol between C-2 and C-3′ is well controlled only when the alcohol component of the ester is relatively small, the opposite of the usual requirement in aldol reactions of lithium enolates, most of which use the ester of a large alcohol or phenol and have a small group, typically methyl, at C-3. Changing both constraints in the reactions illustrated in Scheme 375, restores good stereocontrol, which is in the opposite sense to the usual. This type of reaction has been most used as a prelude to the synthesis of allylsilanes, where the relative stereochemistry between C-2 and C-3′ is used to control the double-bond geometry, as illustrated in Scheme 285. For this purpose the high level of control is not strictly necessary—all that is needed is to be able to separate the diastereoisomers and use the appropriate method for the decarboxylative elimination.

However, the reaction has been used in synthesis. The reaction **1543** → **1544** was used to control the relative stereochemistry of all three stereogenic centers in one pot in a synthesis of the (±)-thienamycin precursor **1545**, where the phenyldimethylsilyl group was used twice over as a masked hydroxyl group (Scheme 376).[808] An approach to the synthesis

Scheme 376

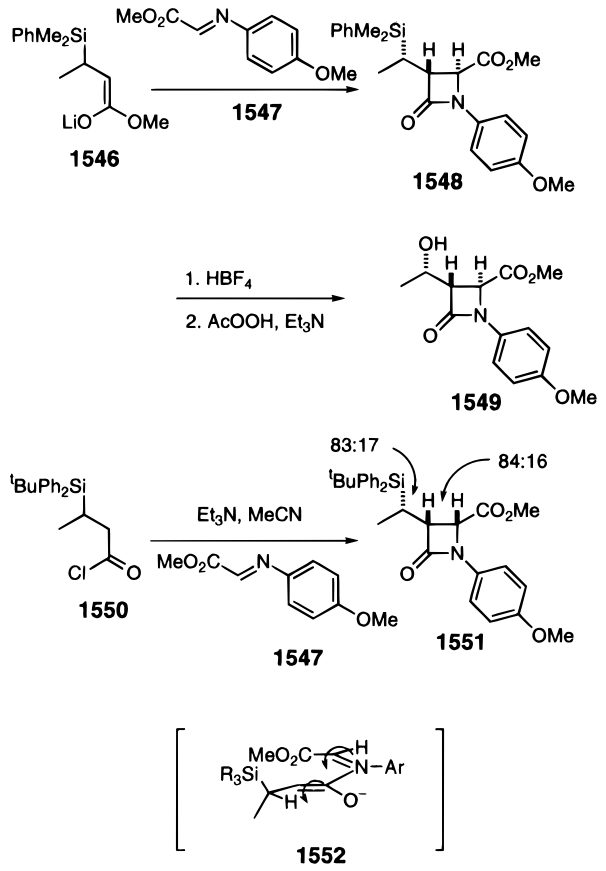


of chrysanthemic acid used the addition of lithium bis(trimethylsilyl)cuprate to an α,β-unsaturated ester followed by trapping the enolate with acetone with high diastereoselectivity in the usual sense, but the silyl group proved to be insufficiently electrofugal for the next step and the synthesis had to be repeated with tin in place of silicon.[809]

Even better, trapping a β-silyl enolate with an aldimine gives directly a β-lactam.[810] Thus, conjugate addition of the silyl cuprate to methyl crotonate, and trapping the intermediate enolate **1546** with the aldimine **1547**, gave directly the β-lactam **1548**, and hence the (±)-thienamycin precursor **1549**. In an alternative approach, the same aldimine **1547** combined in a Staudinger reaction with the ketene derived from the acid chloride **1550** to set up the stereocenters of the alternative diastereoisomer **1551**. In this reaction, the silyl group controls the torquoselectivity of the conrotatory electrocyclic ring closure **1552**, which is still in the usual sense that the side of the enolate double bond *anti* to the silyl group is being attacked by the iminium ion, with the size of the silyl group on this occasion adding significantly to the stereoselectivity (Scheme 377).[811]

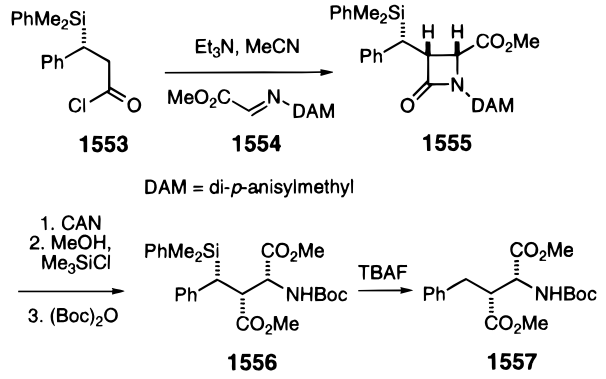
The Staudinger reaction has also been used in the homochiral series to make the β-lactam **1555**, where the change of N-protecting group in the aldimine **1554** and the change to a phenyl group on the stereogenic center **1553** improved the stereoselectivity so that even the phenyldimethylsilyl group was effective. The β-lactam was opened to give the diester **1556**, and the silyl group, having done its job,

Scheme 377



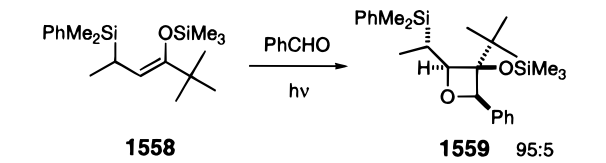
was removed from the benzylic position to give the β-alkyl aspartate derivative **1557** (Scheme 378).[812]

Scheme 378



The silyl enol ether **1558** of a β-silyl carbonyl compound undergoes a Paterno−Büchi type of reaction with aldehydes to give the regioisomer **1559** of an aldol reaction, but with the same high level of stereoselectivity with respect to the resident stereogenic center (Scheme 379).[813]

Scheme 379



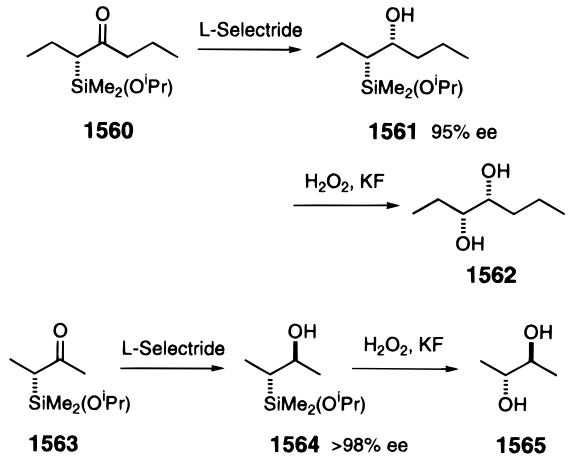
The β-silyl carbonyl compounds used in all this work can be prepared: (i) by conjugate addition of a silylcuprate[814] or zincate[815] to enone systems, with or without chiral auxiliaries;[652,814] (ii) by conjugate addition of a carbon cuprate to β-silyl enones, with or without chiral auxiliaries;[652,653] (iii) by Claisen rearrangement, as described for the synthesis of chiral allylsilanes (Schemes 279 and 280); and (iv) palladium-catalyzed asymmetric 1,4-disilylation of α,β-unsaturated ketones.[792]

XV. α-Silyl Carbonyl Compounds

The reduction of an α-silyl ketone under Cram control has already been discussed in section II.A.4, as one of the means of setting up adjacent stereocenters preparatory to β-elimination, and α-silyl carbonyl compounds were also the precursors of the enol derivatives in Schemes 251 and 256. However, they do have other uses of stereochemical interest that do not belong in those sections.

The same Cram selectivity **56** can also be used preparatory to the conversion of the silyl group to a hydroxyl[217] for setting up 1,2-diols. Thus the ketone **1560** undergoes highly selective hydride reduction in the same sense leading to the *syn*-β-silyl alcohol **1561**, and hence to the *syn*-diol **1562**. However, the transition structure based on the Felkin−Anh model appears to be surprisingly sensitive to the length of the carbon chains on the ketone, with the α-silyl ketone **1563** giving, with just as good selectivity, the *anti* alcohol **1564**, and hence the *anti* diol **1565**. The temperature and the reducing agent have a large effect on the degree of selectivity, and the presence or absence of Lewis acids also affects its sense (Scheme 380).[816]

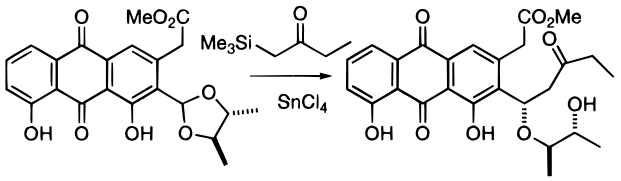
Scheme 380



α-Silyl carbonyl compounds can sometimes be used in place of silyl enol ethers, since they are rapidly converted regiospecifically into silyl enol ethers in the presence of a variety of Lewis acids. A stereochemically controlled reaction that might be taking this path is the reaction between (trimethylsilyl)-2-butanone and the acetal **1566** (Scheme 381), used in a synthesis of aklavinone,[817] and a similar reaction used in the synthesis of 11-deoxydaunomycinone.[818] However, stannic chloride-catalyzed reactions like this may simply take place by way of a tin enolate.

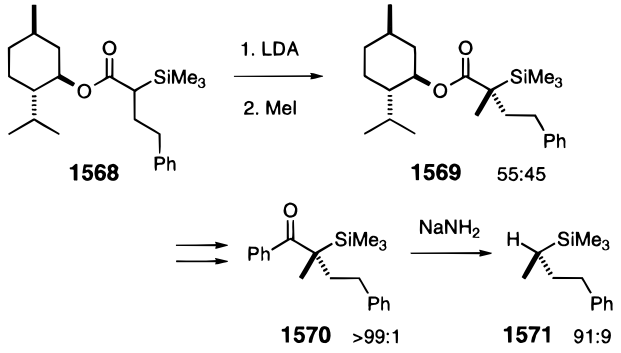
It is easily possible selectively to remove a proton from an α-silyl ketone or ester by using a nitrogen base, and then to alkylate the enolate. With a chiral auxiliary, the alkylation steps can be diastereoselec-

Scheme 381



tive **1568** → **1569**, but the diastereoisomers could be separated to enhance the diastereoisomeric purity. Perhaps most remarkably, a Haller−Bauer cleavage of the derived ketone **1570**, largely with retention of configuration, can then be used to create an otherwise unfunctionalized homochiral alkylsilane **1571** (Scheme 382).[819] Other routes to homochiral α-silyl ketones

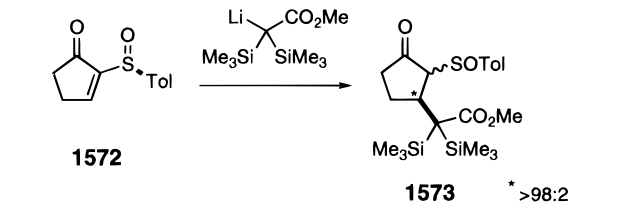
Scheme 382



and esters include diazo ester-derived carbenoid insertion into an Si−H bond,[820] and SAMP/RAMP methodology.[821]

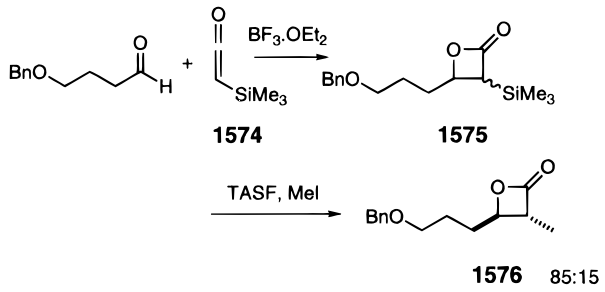
α-Silyl enolates have often been used in Michael reactions, with the silyl group contributing to the selectivity for conjugate addition over direct attack on the carbonyl group,[822] and sometimes perhaps providing extra bulk to affect the stereochemistry of attack on the resultant enolate.[823] It is not usually possible to identify any stereochemical consequences, but the sheer size of the nucleophile in the reaction **1572** → **1573** may well be contributing to the high enantiomeric excess found in this reaction, which was part of a synthesis of methyl jasmonate (Scheme 383).[824]

Scheme 383



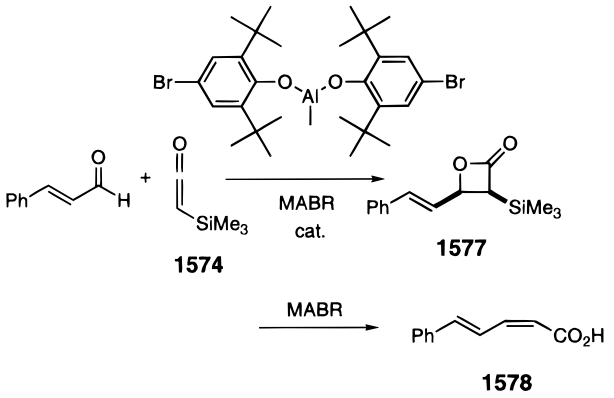
A special example of an α-silyl ketone is (trimethylsilyl)ketene **1574**, which undergoes cycloaddition to aldehydes in the presence of Lewis acids to give *β*-lactones **1575**. With boron trifluoride as the catalyst, the stereoselectivity is poor (*cis*:*trans* 55:45),[825] but this was immaterial for the main use of these compounds—the fluoride ion-catalyzed desilylative alkylation, which gave largely the *trans* *β*-lactone **1576** (Scheme 384).[826]

Scheme 384



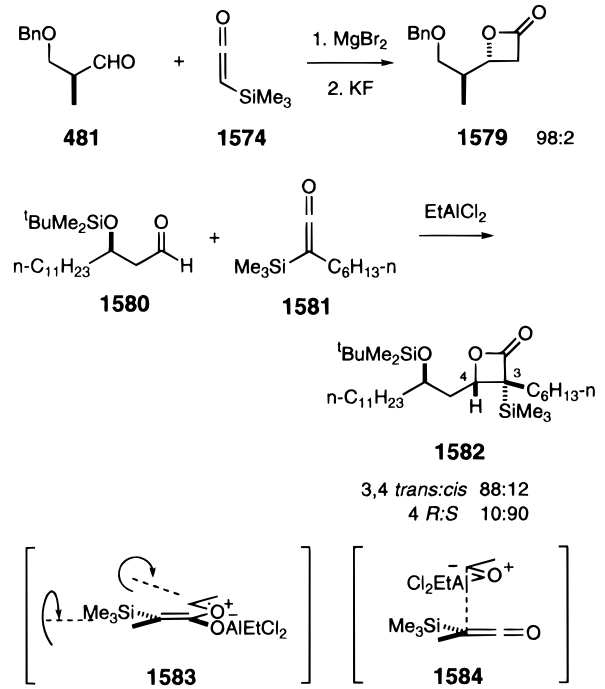
However, the Lewis acid MABR induces much better selectivity for the *cis* isomer **1577**, as long as the aldehyde is not highly hindered. The adducts from aromatic and α,*β*-unsaturated aldehydes decompose stereospecifically in the presence of stoichiometric amounts of Lewis acid to give only the α,*β*-*cis* unsaturated acids **1578** (Scheme 385).[827]

Scheme 385



(Trimethylsilyl)ketene reacts with the chiral aldehyde **481** in the presence of magnesium bromide with a high level of chelation control to give, after protodesilylation, the *β*-lactone **1579** (Scheme 386).[828]

Scheme 386

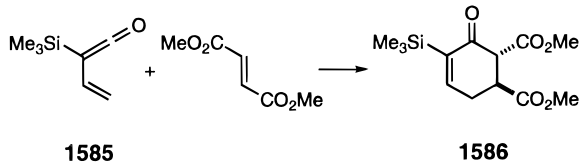


The aldehyde **1580** reacted with the substituted silylketene **1581** with a high level of selectivity for the silyl group to be *cis* to the alkyl chain, but also with a remarkable level of 1,3-control from the resident center in the aldehyde, so that the β-lactone **1582** was 80% of the product mixture in this synthesis of (−)-tetrahydrolipstatin (Scheme 386).[829] Only the 1,3-control was actually important, since the next step was protodesilylation, which was stereoselective for setting up the two chains *trans* on the β-lactone. A very similar route was used, but with two double bonds in the long side chain, for the synthesis of the natural product lipstatin itself.[830]

In all these reactions of silylketenes, one function of the silyl group is to make the silylketene a stable molecule that can be handled. Another is that it may be controlling the stereochemistry by determining either the sense of the torquoselectivity **1583**, if the reaction begins with nucleophilic attack by the aldehyde on the ketene, or the sense of synclinal attack **1584**, if, instead, the reaction begins with nucleophilic attack by the ketene on the aldehyde.[829]

Whereas vinylketene itself is apt to undergo [2+2] cycloadditions rather than Diels−Alder reactions, (trimethylsilyl)vinylketene **1585** does undergo Diels−Alder reactions, which take place suprafacially on the dienophile in the usual way giving a cyclohexenone **1586** (Scheme 387).[831] The stabilizing overlap of the

Scheme 387



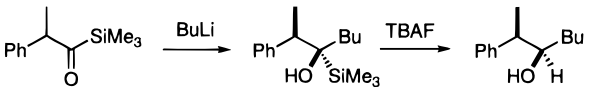
1585 **1586**

Si−C bond with the carbonyl π-orbitals makes a silyl ketene less reactive in [2+2] cycloadditions and leaves the lone pair on the oxygen atom to overlap with the diene orbitals, in turn making these orbitals more reactive toward the usual dienophiles.

XVI. Acylsilanes[832]

Acylsilanes, like ketones, show higher Cram selectivity than the corresponding aldehydes, long understood to be because the presence of a large substituent on the carbonyl group encourages the medium-sized group on the stereogenic center to be oriented away from it and *syn* to the carbonyl group in the usual Felkin−Anh conformation. The acylsilane **1587** gave the alcohol **1588** with high selectivity (>99:1), whereas the corresponding aldehyde gave a ratio of only 83:17. Again, the silyl group can be removed to give the Cram alcohol **1589** (Scheme 388).[833] This reaction could therefore have equally well been discussed in section III.B.

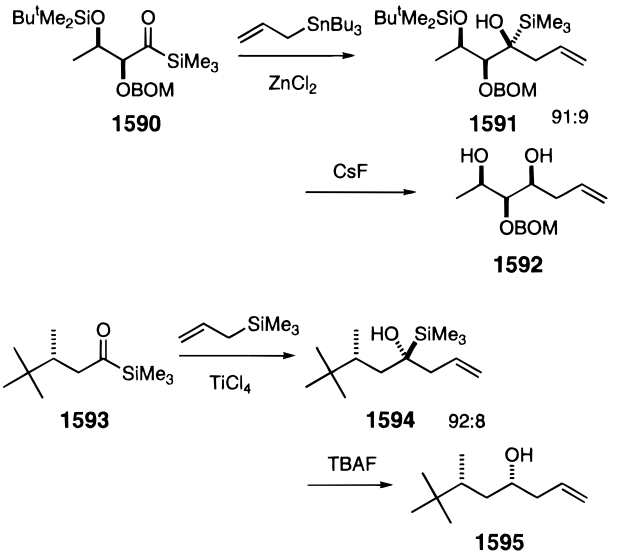
Scheme 388



1587 **1588** >99:1 **1589**

High levels of stereocontrol in attack on acylsilanes have also been found in chelation control **1590** → **1591**,[834] stemming from the neighboring BOM ether not the silyl ether (section III.A), and in open-chain 1,3-control **1593** → **1594** (Scheme 389).[835] In both

Scheme 389



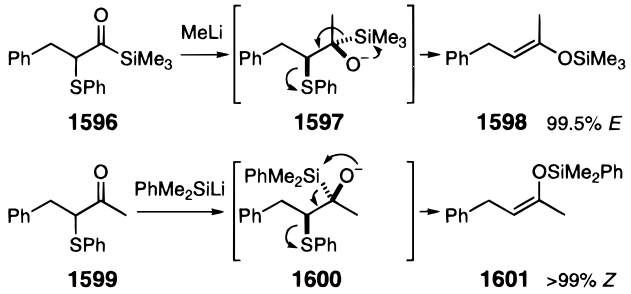
1590 **1591** **1592**

1593 **1594** **1595**

cases the sequence was consummated by a Brook rearrangement and protonation with retention of configuration, to give the silicon-free secondary alcohols **1592**, used in a synthesis of β-D-boivinose, and **1595**.

The selectivity of attack on a chiral acylsilane can be used for a different purpose when the acylsilane carries an α-nucleofugal group. Nucleophilic attack on the [α-(phenylthio)acyl]silane **1596** took place with Cram control to give largely the intermediate **1597**, which underwent a Brook rearrangement, but this time coupled to loss of the phenylthio group stereospecifically *anti*, to give the (*E*)-silyl enol ether **1598** (Scheme 390).[836] A similar sequence with Cram

Scheme 390



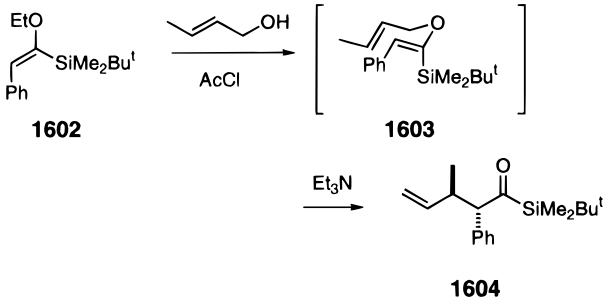
1596 **1597** **1598** 99.5% *E*

1599 **1600** **1601** >99% *Z*

control and *anti* elimination **1600**, but using a silyllithium reagent on the methyl ketone **1599**, gave the opposite geometry in the silyl enol ether **1601**. A wide variety of carbon nucleophiles and hydride ion can be used as the nucleophiles, and also a variety of nucleofugal groups.

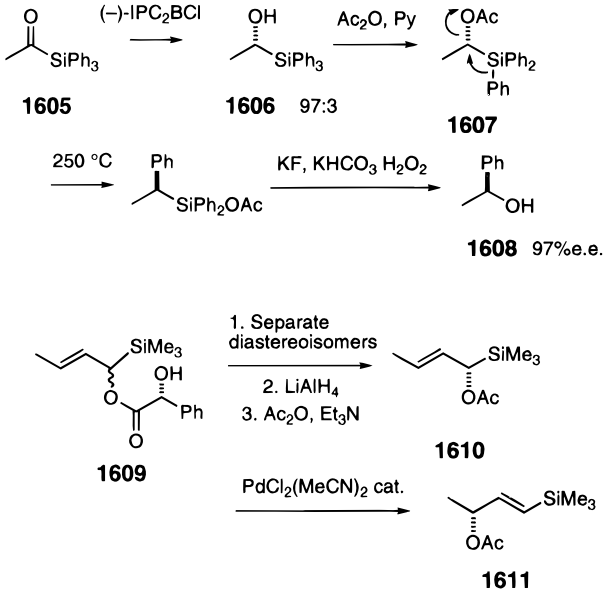
Claisen rearrangements take place on the enol ethers **1602** of acylsilanes and the new stereogenic centers **1604** appear to be set up as a consequence of a *Z* geometry of the double bond and the usual chair transition structure **1603** (Scheme 391).[837] Evidently the silyl group can be *cis* to the phenyl group without a serious energetic penalty.

Scheme 391



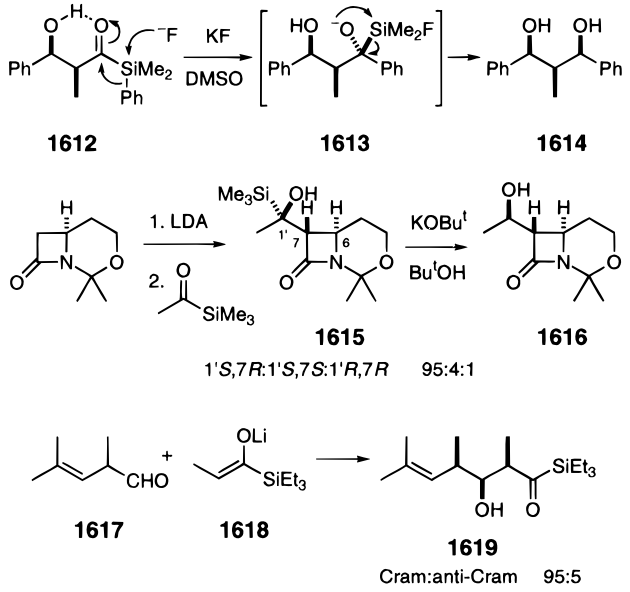
Enantiomerically enriched α-silyl alcohols can be made by reduction of acylsilanes chemically **1605** → **1606**[838,839] or enzymatically,[840] by chiral-catalyzed nucleophilic attack by carbon nucleophiles on acylsilanes,[841,842] by resolution **1609** → **1610**,[843] and by silylation of enantiomerically enriched α-metalated ethers.[844] In principle many of these compounds can be used to make homochiral alcohols by Brook rearrangement. Alternatively, 1,2-shift of a group from the silicon **1607** takes place with inversion of configuration, and this can be followed by silyl-to-hydroxy conversion,[217] as in the synthesis of the benzylic alcohol **1608**,[838] or, in the case of allylic silyl alcohols **1610**, by suprafacial palladium-catalyzed 1,3-transfer to give homochiral allylic alcohols **1611**[845] (Scheme 392).

Scheme 392



1,2-Shift from the silyl group can also take place to the carbonyl group of an acylsilane **1612**, and this too can be stereoselective if the carbonyl group has diastereotopic faces. The product can then undergo a stereospecific Brook rearrangement−protonation **1613**, with inversion of configuration when the silyl group is benzylic, to give a secondary alcohol **1614** (Scheme 393).[846] Simple intermolecular diastereoselectivity of attack by a β-lactam enolate upon acetyltrimethylsilane, with attack selectively taking place on the *exo* surface, gave very largely one aldol product **1615**. Brook rearrangement−protonation, with retention of configuration in this non-benzylic case, then set up the side-chain stereochemistry in this synthesis of the thienamycin precursor **1616**

Scheme 393



(Scheme 393).[847] Similar diastereoselectivity highly in favor of the *syn* product was also observed from an enolate derived from an acylsilane, provided that the silyl group carried large substituents. The *syn* selectivity could be combined with higher Cram selectivity toward chiral aldehydes than is usual with lithium enolates, as in the reaction between the aldehyde **1617** and the acylsilane enolate **1618** giving the aldol product **1619** (Scheme 393).[848] The corresponding reaction with the usual LDA-derived ester enolate would have been selective for the *anti* isomer, following the usual Zimmerman−Traxler transition structure, from which we can deduce that the acylsilane enolate is the *E* isomer. The acylsilane was easily oxidized to the corresponding carboxylic acid, which could be esterified, so that the overall result was different from that most easily achieved using esters themselves.

Nucleophilic attack on an acylsilane with stereochemical consequences is also seen in the Wittig reaction in Scheme 44. Photocycloaddition of electrophilic alkenes to thioacylsilanes shows a preference for the electron-withdrawing substituent on the alkene to be *cis* to the silyl group.[849]

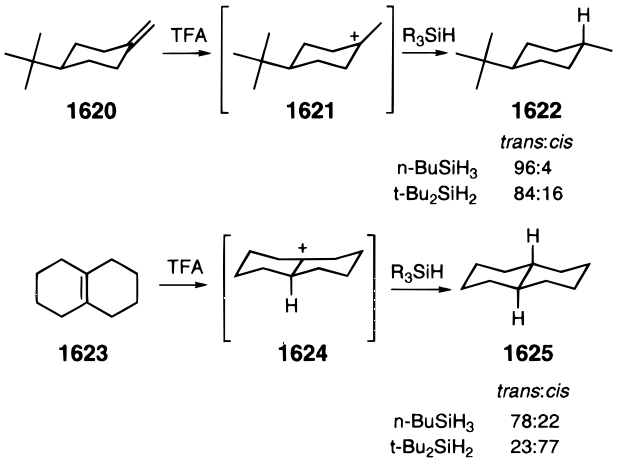
XVII. Silicon Hydrides

A. Hydride Delivery

Silicon hydrides deliver hydride to strong electrophiles like carbocations, protonated carbonyl groups, and iminium ions, and they deliver hydrogen atoms to carbon radicals. In substrates with a stereochemical bias, the outcome is usually controlled by hydride delivery from the sterically or stereoelectronically favored direction, and silicon hydrides are only different in detail from other hydride sources, and often being more stereoselective than trimethylsilyl cyanide, for example. Thus the stereochemically defined cyclohexyl cations **1621** and **1624**, derived by protonation of the alkenes **1620** and **1623**, are predominantly attacked axially to give the hydrocarbons **1622** and **1625**, but with more hindered silanes the selec-

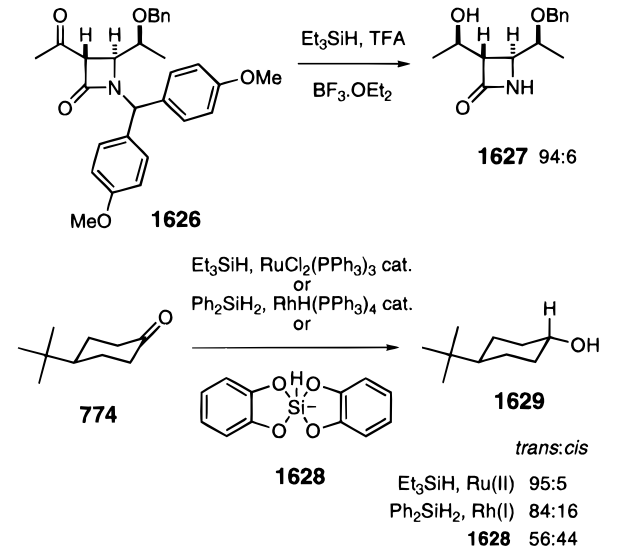
tivity is eroded or inverted in favor of attack from the less hindered direction (Scheme 394).[850]

Scheme 394



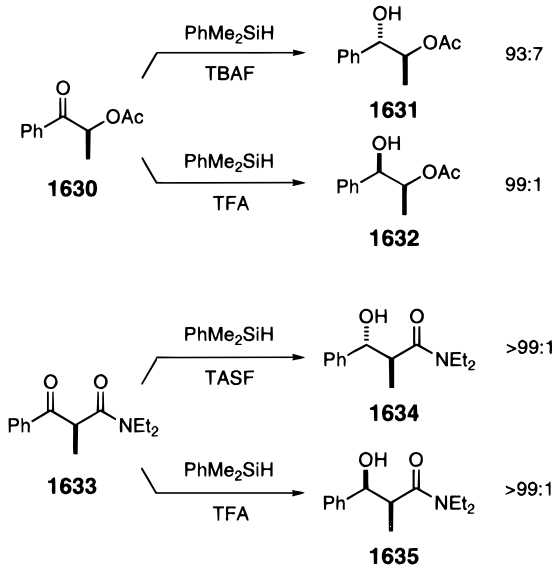
Silicon hydride reduction of ketones in the presence of acids is apt to give overreduction, but a mixture of trifluoroacetic acid, boron trifluoride, and triethylsilane with the functionalized ketone **1626** is highly Cram selective (94:6) in favor of the β alcohol **1627**, as are other hydride reagents, but this mixture is significantly cheaper.[851] Rhodium- or ruthenium-catalyzed silicon hydride reduction is selective for attack from the *endo* surface of camphor and from the axial surface of cyclohexanones **774** → **1629**,[852] but the pentacovalent silicon hydride **1628** is only just selective for axial attack on the same ketone (Scheme 395).[853]

Scheme 395



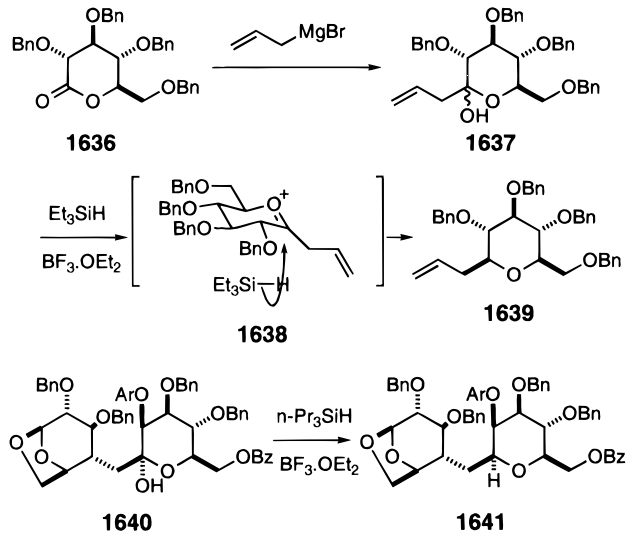
Hydride delivery from silicon can also be catalyzed by fluoride ion, without the need to protonate the carbonyl group. Intriguingly, the reduction of α- or β-functionalized carbonyl groups catalyzed by acid and fluoride ion can show complementary stereochemistry. Thus the reduction of the α-acetoxy ketone **1630** or β-keto amide **1633** with phenyldimethylsilane in the presence of fluoride ion gave the *threo* alcohols **1631** and **1634**, whereas the diastereoisomeric *erythro* alcohols **1632** and **1635** were produced in the presence of acid (Scheme 396).[854]

Scheme 396



Cyclic acetals in six-membered rings are reduced with high selectivity, as in the formation of only the tetrahydropyran **1639** from the hemiacetal **1637**, with axial attack in the sense **1638** making the *C*-glycoside with an equatorial allyl group (Scheme 397).[482] This result is complementary to that in

Scheme 397

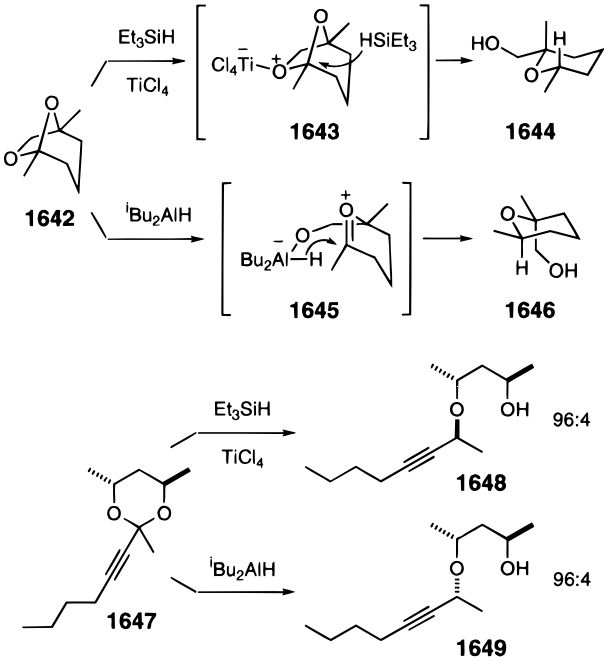


Scheme 195, giving the diastereoisomer **785** by axial attack of the allyl group. Similar anomerically axial selectivity is observed when the resident group is aryl rather than allyl.[855] Similarly, the more complex *C*-disaccharide **1641** was produced from the hemiacetal **1640** (Scheme 397).[856] Pentoses, with substituents at the anomeric position, can, in different systems, be reduced with attack by hydride from the α-direction, to give the β-configuration for the C-1 substituent,[857] or from the β-direction, to give the α configuration for the C-1 substituent.[858] There is another example of anomeric hydride delivery in Scheme 413, where it is placed in contrast to its complementary intermolecular counterpart.

Significantly, silicon hydrides, which are coordinatively saturated and have no easy coordination site, deliver hydride without intramolecular chelation to resident Lewis basic groups like hydroxyls, as in

the reduction of the acetal **1642** to give the tetrahydropyran **1644** with overall inversion at the site of substitution, effectively as drawn in **1643**, regardless of the detailed mechanism. In contrast, reduction by an aluminum hydride reagent, which is a Lewis acid, gives the diastereoisomer **1646** as a consequence of intramolecular hydride delivery **1645**, and hence overall retention of configuration (Scheme 398).[859]

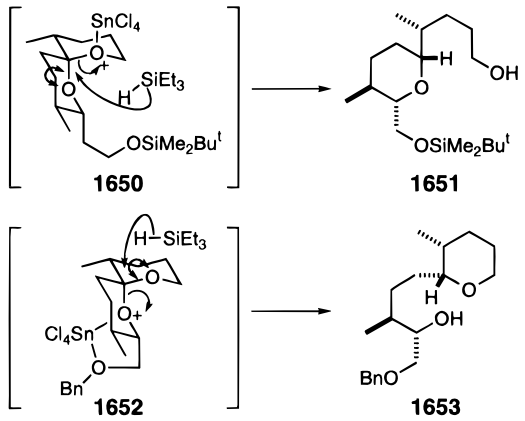
Scheme 398



Similarly, reductive cleavage of the alkynyl acetal **1647** with triethylsilane gave the alcohol **1648** as the major product, whereas the organoaluminum reagent gave its diastereoisomer **1649** (Scheme 398).[860]

The stereochemistry of reduction of spiroacetals is governed by some of the same constraints, but coordination by the Lewis acid only to the more accessible oxygen **1650** or with intramolecular coordination **1652** to the less accessible oxygen, can override other factors and make two otherwise similar compounds, differing only in the protecting group on a primary hydroxyl, behave substantially differently (Scheme 399). These reactions, which also

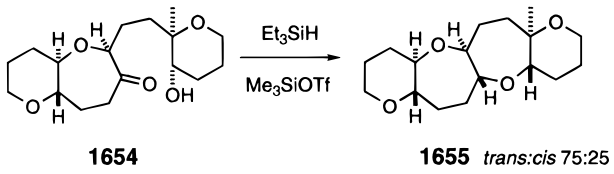
Scheme 399



illustrate stereocontrol from having a silyl group on oxygen (section III.A), were used in a synthesis of tautomycin.[861]

The oxenium ion intermediate can be set up by ionization of a hemiacetal formed in situ by intramolecular combination of an alcohol and a ketone, with the stereochemistry of the reduction controlled by the resident stereogenic centers. This device was significantly explored for a synthesis of brevetoxin B, where the reaction **1654** → **1655** is one example of many successful model studies giving fair selectivity for axial attack by the hydride with the formation of a *trans* ring junction (Scheme 400). In the real

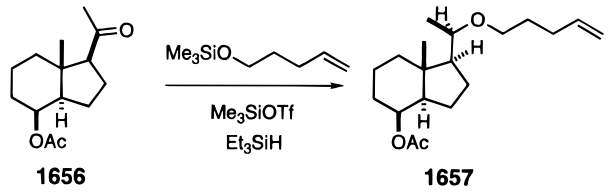
Scheme 400



synthesis, however, with significantly more elaborate structures present, the acidic conditions set off rearrangements that limited its applicability.[862]

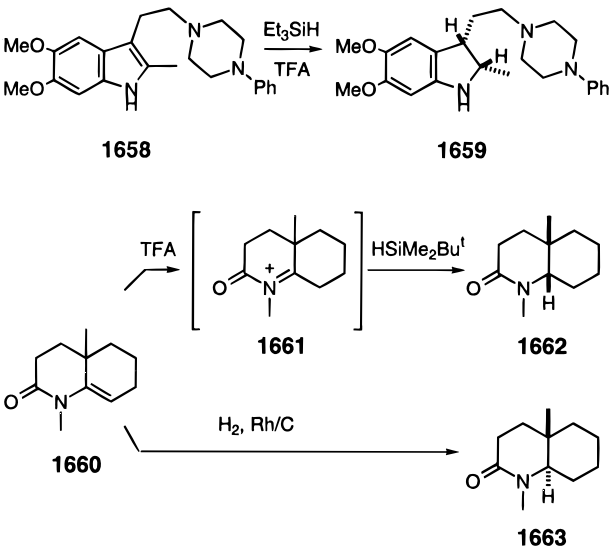
The reduction of the oxenium ion intermediate in acetal synthesis can also be carried out in one pot from the separate components, by treating a ketone with the trimethylsilyl ether of an alcohol, trimethylsilyl triflate, and triethylsilane. This reaction can give some stereocontrol in the Cram sense in the reaction **1656** → **1657** (Scheme 401).[863]

Scheme 401



Silicon hydrides also reduce iminium ions stereoselectively, with triethylsilane being the best of many metal hydride and other reducing agents for reducing the 2,3-dialkylindole **1658** to the *cis*-dialkyldihydroindole **1659**. Hydride attack takes place on the opposite side from the 3-alkyl group in the intermediate 3-protonated indole (Scheme 402).[864] Reduction of the bridgehead acyliminium intermediate **1661**

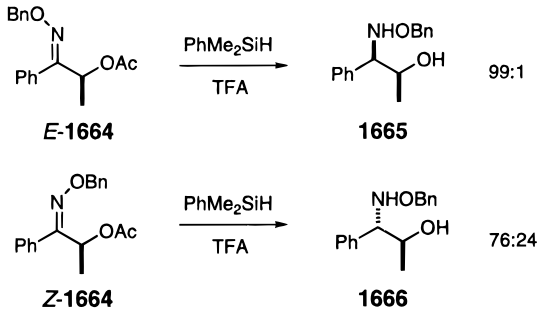
Scheme 402



derived from the enamide **1660** gives, with a silicon hydride, the *cis* ring junction **1662**, but with hydrogenation over rhodium on carbon the *trans* ring junction **1663** (Scheme 402).[865]

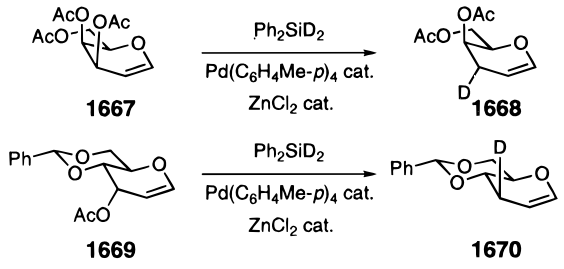
The *erythro*- and *threo*-alcohols **1665** and **1666** are obtained through reductive hydrosilylation of the (*E*)- and (*Z*)-oxime ethers **1664**, respectively. The former is the result of attack *anti* to the methyl group in a proton-chelated intermediate, and the latter, where a proton cannot sit between the two groups, is the result of straightforward, but not very good, Cram control (Scheme 403).[866]

Scheme 403



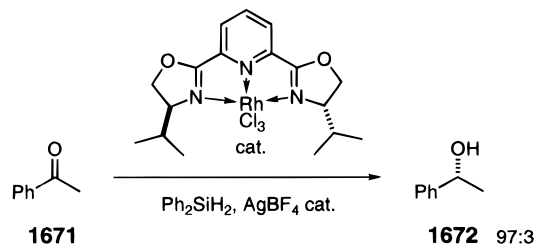
Silicon hydrides are convenient sources of reducing power in cooperation with many transition metals. The transition metal must undergo at some stage oxidative insertion into the Si−H bond to create an intermediate transition metal hydride, which in its turn transfers the hydrogen to the substrate. Thus the combination of a palladium(0) complex, diphenylsilane, and a catalytic amount of zinc chloride reduces the allylic acetates **1667** and **1669** stereospecifically with inversion of configuration as shown by the configuration of the deuterium in the products **1668** and **1670** (Scheme 404).[867]

Scheme 404



The opportunity to attach homochiral ligands to the transition metal has stimulated many reports of substantial asymmetric induction in the reduction of ketones and imines using silicon hydrides as the source of the hydrogen. The example **1671** → **1672** (Scheme 405)[868] is only one of many.[869]

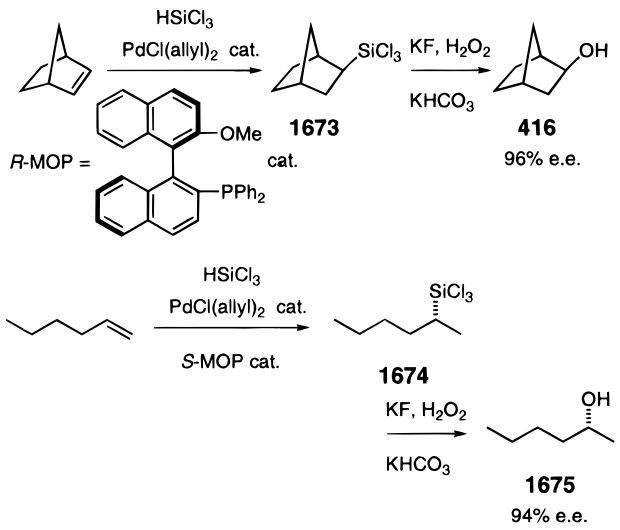
Scheme 405



B. Hydrosilylation–Oxidation[870]

Intermolecular hydrosilylation of alkenes usually takes place with the silyl group attaching itself to the primary terminus, and even moving down a carbon chain by reversible hydrosilylation and elimination in order to arrive at a primary terminus far away from the original alkene group. Such reactions usually have no stereochemical consequences, but a few alkenes have no such propensity, as in the hydrosilylation of norbornene with a homochiral catalyst, giving the silane **1673** and eventually enantiomerically enriched norbornanol **416** (Scheme 406).[871]

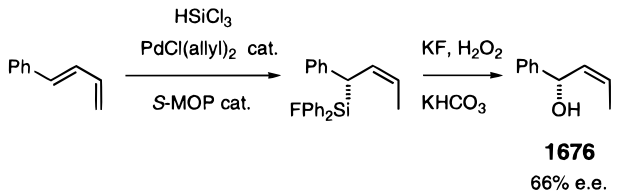
Scheme 406



More recently catalysts have been found that, in addition to being themselves homochiral, place the silyl group mainly at the secondary carbon. The result is catalytic asymmetric induction in the formation of the silane **1674**, and the silyl-to-hydroxy conversion[217] then gives homochiral secondary alcohols **1675** (Scheme 406).[872]

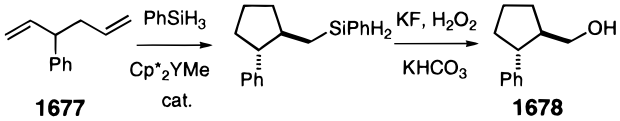
Similar selectivity in the hydrosilylation of dienes makes homochiral allylsilanes and hence allyl alcohols **1676** (Scheme 407).[873]

Scheme 407



Hydrosilylation may sometimes follow a stereoselective carbometalation step when there is another double bond in the molecule, as in the reaction with the diene **1677**, which gave a cyclopentane, and hence a cyclopentylmethanol **1678** with the substituents *trans* on the ring (Scheme 408).[874]

Scheme 408



XVIII. A Silyl Group as a Removable Bridging Group Controlling Stereochemistry[3]

A silyl group can easily carry two functional arms, and act therefore as a bridge in bringing the two arms together, with the cyclic nature of the transition structure usually having substantial and often predictable stereochemical consequences. After it has been used to hold the bridge in place, the silyl group can be removed, usually by protodesilylation or by silyl-to-hydroxy conversion, reactions that have been mentioned several times already.

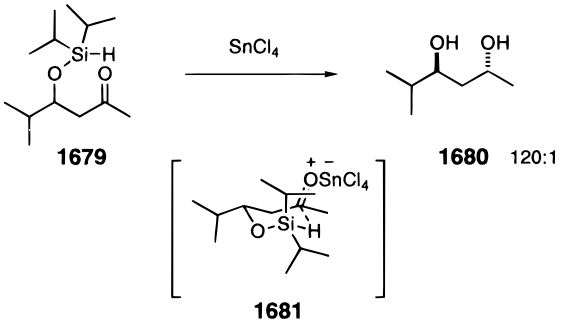
A few reactions that might equally have been included in this section have already been discussed in earlier sections, notably the reactions of silyl enol ethers (Schemes 132 and 148) and of allylsilanes (Schemes 207−210), in which the silyl group acted as the Lewis acid, coordinating to the electrophile. Somewhat related, but not actually the same, are those reactions in which the silyl group holds the substrate in a ring, ready for attack by an external reagent (Scheme 196).

A. Intramolecular Delivery of Hydride or Silicon

1. Intramolecular Hydride Delivery to Ketones and Carbocations

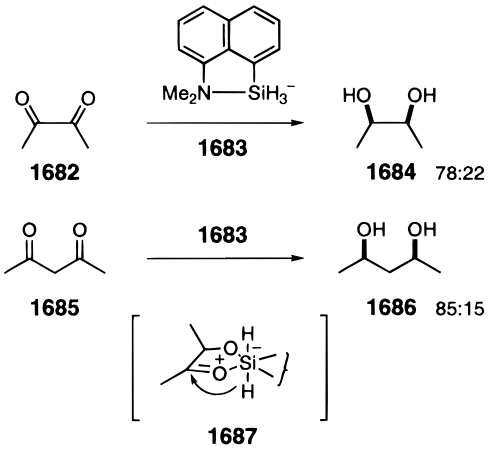
The silyl ether **1679** delivers hydride, in the presence of a Lewis acid, intramolecularly to the ketone group to give the 1,3-diol **1680** with very high levels of stereocontrol (120:1 for stannic chloride), presumably by way of a transition structure **1681**. The selectivity is sensitive to the choice of Lewis acid, at one extreme giving the opposite result, 71:29 in favor of the *syn* diastereoisomer, with zinc chloride.[875] However the stereoselectivity is relatively insensitive to the presence or configuration of a substituent on the methylene group between the silyl ether and ketone groups (Scheme 409).[876]

Scheme 409



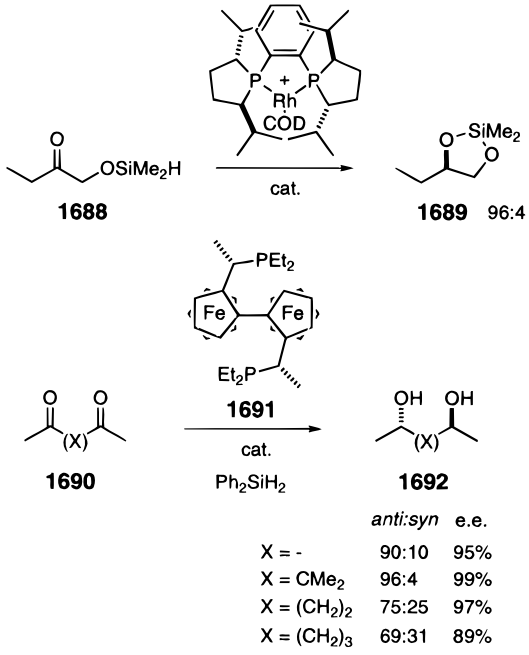
The 1,2- and 1,3-diketones **1682** and **1685** were reduced by the hypervalent silicon hydride **1683** directly to the *syn*-diols **1684** and **1686** with delivery of the second hydride in an intramolecular process **1687** (Scheme 410).[877] The silicon now provides the chelating group, and hydride is delivered to the less hindered side of the ring giving the opposite sense of reduction from that in Scheme 409.

Scheme 410



In the achiral ketone **1688**, intramolecular hydrosilylation was used with enantiocontrol from a cationic chiral rhodium-based catalyst to give the protected 1,2-diol **1689**,[878] and 1,2-, 1,3-, 1,4-, and 1,5-diols **1692** can be prepared from [1,*n*] diketones **1690** selectively in favor of the *anti* isomer, and enantiomerically enriched, with a homochiral catalyst **1691** with presumably intramolecular delivery of the second hydride (Scheme 411).[879]

Scheme 411

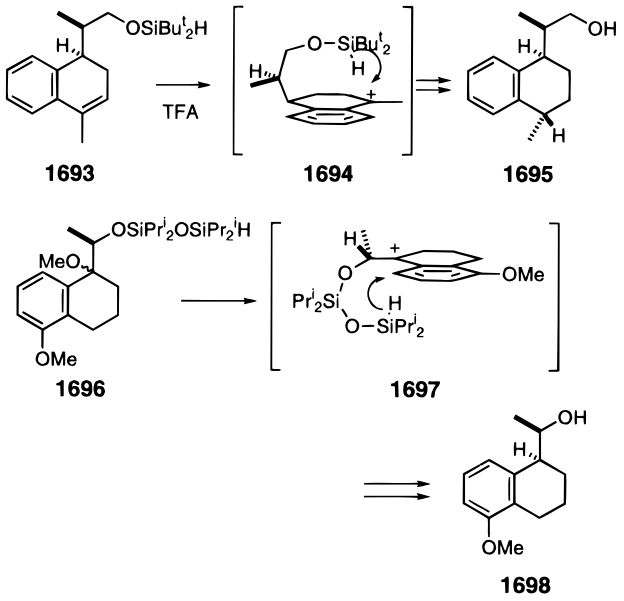


	anti:syn	e.e.
X = -	90:10	95%
X = CMe_2	96:4	99%
X = $(CH_2)_2$	75:25	97%
X = $(CH_2)_3$	69:31	89%

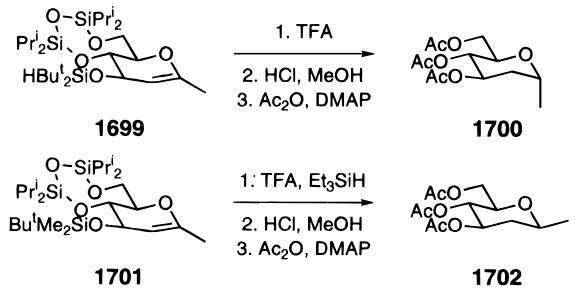
Intramolecular hydride delivery from silicon to carbon is also seen with the alkene **1693**[880] and with the alkyl ether **1696**,[881] giving the alcohols **1695** and **1698**, presumably by way of the cations **1694** and **1697** (Scheme 412).

Intramolecular hydride delivery also works at the anomeric position in sugars, and can lead to the opposite sense of reduction to the corresponding intermolecular process discussed in section XVII.A. Thus the 2-deoxy-*C*-methyl glucal **1699** gave the 1-β hydride **1700**, whereas the corresponding intermolecular reaction gave axial delivery to the glucal **1701**, and hence the 1-α hydride **1702** (Scheme 413).[881] A six- or seven-membered ring is needed for

Scheme 412



Scheme 413



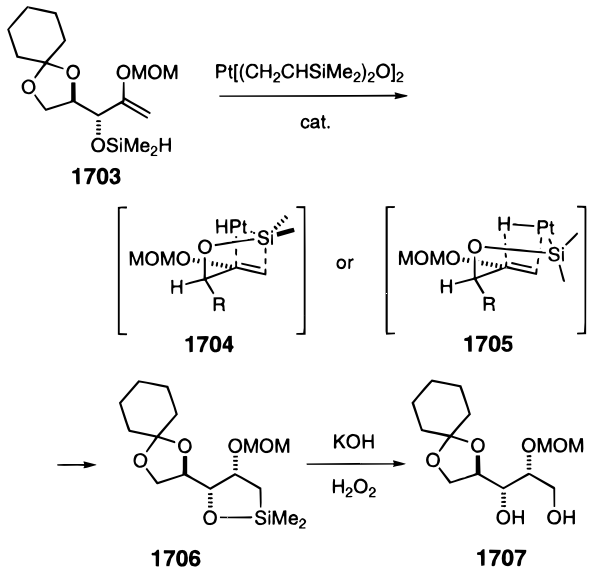
the intramolecular hydride transfer, with a five-membered ring failing.

2. Intramolecular Hydrosilylation of Alkenes

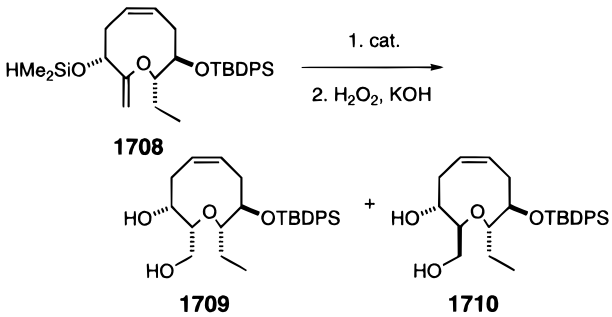
The allylic silyl ether **1703** induced hydrosilylation of the double bond with complete stereocontrol stemming from the configuration of the silicon-bearing oxygen, setting up a *syn*-1,2 relationship in the silyl ether **1706**. Silyl-to-hydroxy conversion[217] then gave the pentitol **1707** (Scheme 414).[882] The mechanistic detail in this type of reaction has been studied using deuterium labeling.[883] Two transition structures with the oxygen delivering the reagent to the terminus account for the selectivity, the first involving silylmetalation **1704** followed by a reductive elimination establishing the H−C bond, and the second involving hydrometalation **1705** followed by a reductive elimination establishing the Si−C bond. The stereochemistry is opposite in sense to the comparable, but intermolecular, hydroboration.[638,884] A similar reaction with intramolecular delivery from an aminosilane gave the *syn*-related amino alcohols,[885] and from dimethylsilyl 2-cyclopentenecarboxylate gave *cis*-2-hydroxycyclopentancarboxylic acid.[886]

The enol ether **1708** underwent a similarly selective hydrosilylation with the same catalyst to give, after silyl-to-hydroxy conversion, the *syn*-1,2-relationship of the incoming hydrogen and the resident hydroxyl group in the 1,3-diol **1709**. This reaction, however, could be tailored to give the other diastereoisomer **1710**, either by including a catalytic amount of the disilazane in the reaction mixture, or by changing to an alternative catalyst based on rhodium (Scheme 415).[887] Even better control in the formation

Scheme 414



Scheme 415

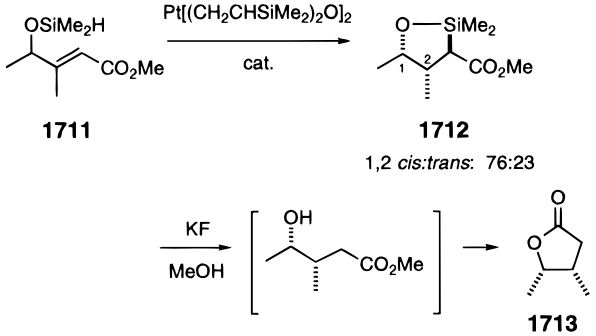


$Pt[(CH_2CHSiMe_2)_2O]_2$	84:16
$Pt[(CH_2CHSiMe_2)_2O]_2$, $(HMe_2Si)_2NH$	17:83
$Rh(acac)(C_7H_8)$	<5:95

of the diol **1709** could be gained by changing the silyl group from dimethylsilyl to diisopropylsilyl.

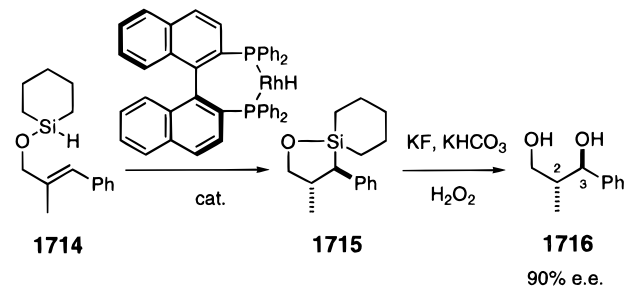
The α,β-unsaturated ester **1711** underwent moderately stereoselective hydrosilylation in favor of the 1,2-*syn*-relationship in the ether **1712**, but in this case the silyl group was removed by protodesilylation, easily since it was α to a carbonyl group, to give the lactone **1713** (Scheme 416).[888]

Scheme 416



A similar intramolecular attack diastereoselectively creating two stereogenic centers from an achiral substrate **1714** has, at the same time, been carried out enantioselectively using a homochiral catalyst (Scheme 417).[889] Silyl-to-hydroxy conversion[217] of the benzylsilane **1715** gave the 1,3-diol **1716** with high enantiomeric excess, but the 2,3 relationship had actually been controlled thermodynamically in favor of the *trans* relationship, and was not a consequence of *syn* stereospecificity in the hydrosilylation step.

Scheme 417

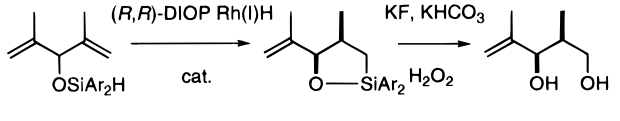


1714 **1715** **1716**

90% e.e.

Homochiral catalysis is especially effective in the case of an allylic alcohol with an enantiotopic pair of double bonds. In the event, the intramolecular hydrosilylation of the silyl ether **1717** gave the best result ever, after a little optimization tailoring the silicon substituents, with the silyl ether **1718**, and hence the diol **1719**, being completely *syn* and having a high enantiomeric excess (Scheme 418).[890]

Scheme 418



1717 **1718** **1719**

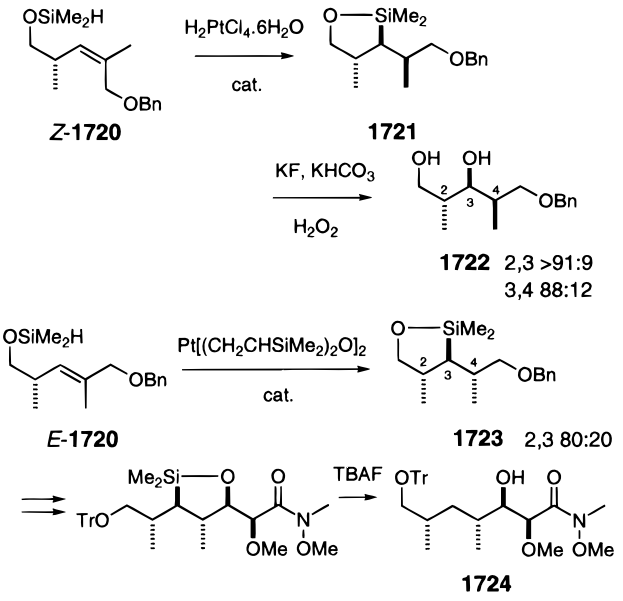
Ar = 3,5-$Me_2C_6H_3$

syn:anti >99:1

93% e.e.

Perhaps, even more powerful, homoallylic silyl ethers induce hydrosilylation of the alkene group, with complete *syn* stereospecificity with respect to the event taking place at the double bond, and with a high level of stereocontrol from the intervening stereogenic center. Thus the silyl ether (*Z*)-**1720** gave the silyl ether **1721**, and silyl-to-hydroxy conversion[217] gave the 1,3-diol **1722**, with three stereogenic centers set up from one (Scheme 419).[891] Similarly, the silyl ether (*E*)-**1720** with the opposite geometry in the double bond, gave the silyl ether **1723**, with the opposite relationship between C-3 and C-4, but in this case the silyl group was removed a few steps later by protodesilylation, in spite of the absence of anion-stabilizing groups on the carbon atom, to give the protected triol **1724**, designed for a synthesis of rapamycin (Scheme 419).[453] The selectivity could be increased from 80:20 to better than 95:5 by changing the substituents on the silyl group from dimethyl to spirocyclohexyl.[892]

Scheme 419



Z-**1720** **1721**

1722 2,3 >91:9
3,4 88:12

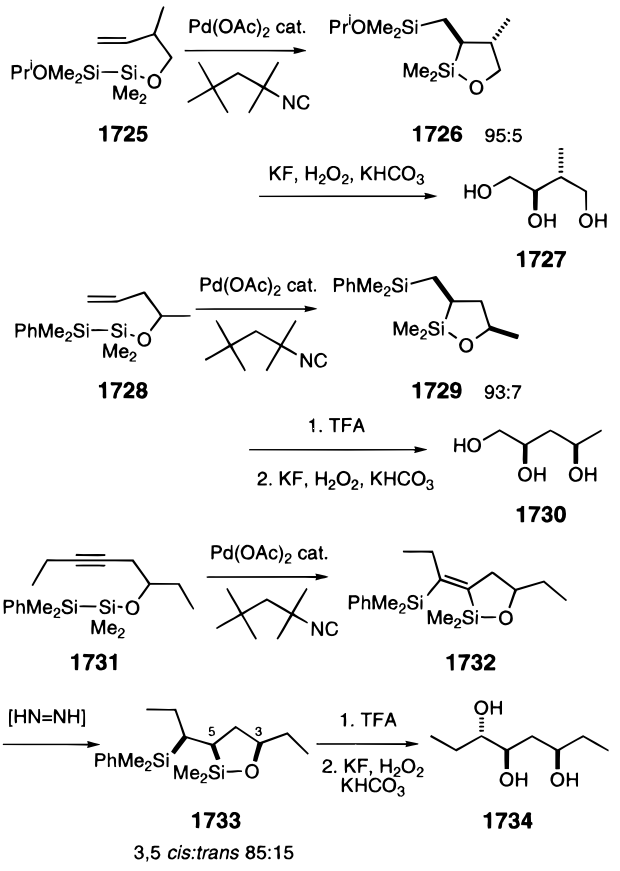
E-**1720** **1723** 2,3 80:20

1724

3. Intramolecular Silylsilylation of Alkenes

Although not a delivery of hydride, the silylsilylation of an alkene, catalyzed by a transition metal, is closely related. Carried out intramolecularly on the alkenes **1725** and **1728** it can give silyl ethers **1726** and **1729** with new silicon-bearing stereogenic centers with a 1,2- or 1,3-relationship to the existing stereocenter, and both silyl groups can be converted into hydroxyls to give the triols **1727** and **1730** (Scheme 420).[893] When carried out on a triple bond

Scheme 420



1725 **1726** 95:5

1727

1728 **1729** 93:7

1730

1731 **1732**

1733

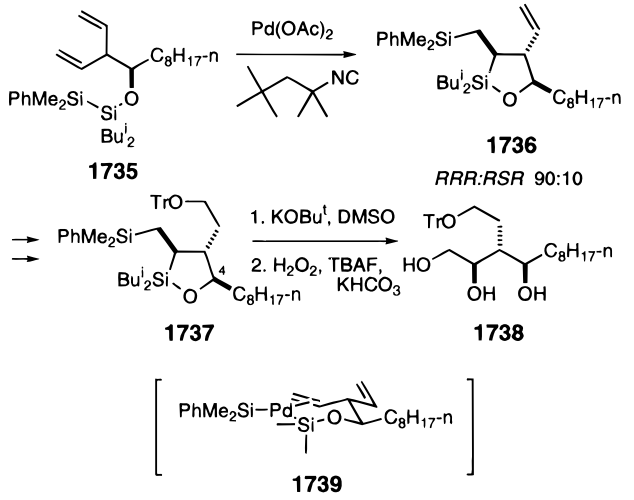
3,5 *cis:trans* 85:15

1734

in the alkyne **1731**, the resulting *Z*-vinyldisilane **1732** can be reduced *syn* stereospecifically with diimide to give the disilane **1733**, with fair diastereoselection with respect to the resident stereocenter, and then both silyl groups can be converted into hydroxyls to give the triol **1734** (Scheme 420).[894]

The silylsilylation of a double bond was used in a synthesis of (−)-avenaciolide, where the key stereochemistry-determining step was the selective reaction on one of the diastereotopic vinyl groups in the homochiral diene **1735**, giving the silyl ether **1736**. The stereochemistry was controlled by the preference for the all-equatorial arrangement of substituents in the transition structure **1739** (Scheme 421). The

Scheme 421



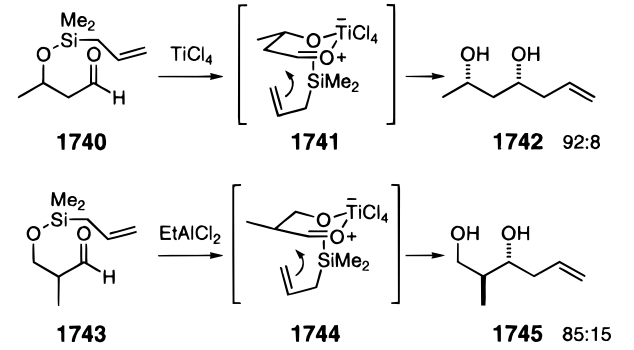
silyl-to-hydroxy conversion[217] **1737** → **1738** was carried out two steps later entirely under basic conditions, with the phenyl group on the silicon removed, in all probability, in the step using potassium *tert*-butoxide, and involving an alkoxide on C-4.[895]

B. Intramolecular Delivery of Carbon Nucleophiles

1. Intramolecular Delivery of an Allyl Group

The allyldimethylsilyl ether **1740** delivered the allyl group to the aldehyde selectively in favor of the *syn*-diol **1742** by way of a transition structure **1741** with the usual axial attack. In this case the intramolecularity was proved by a crossover experiment. An analogous stereochemical argument accounts for the corresponding reaction on the aldehyde **1743**, with 1,2-induction giving the diol **1745** (Scheme 422).[896] In this case, the methyl group is pseu-

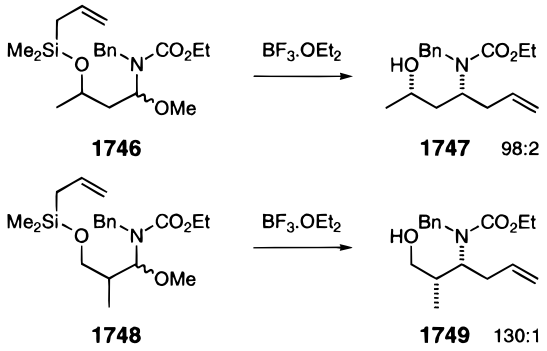
Scheme 422



doequatorial **1744**, and the selectivity is less. The diol **1742** is the opposite to that obtained by intermolecular attack on the corresponding benzyl ether in the presence of a chelating Lewis acid (Scheme 191), but the diol **1745** is the same.

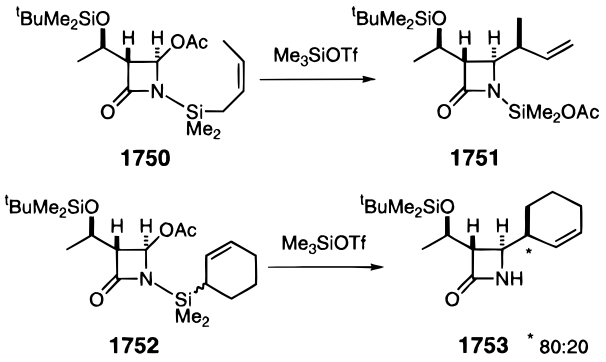
A selective intramolecular delivery to the iminium ions derived from the azaacetals **1746** and **1748** gave the *syn* hydroxyamine derivatives **1747** and **1749**, without the benefit of chelation by a Lewis acid. In this case the 1,2-induction giving the hydroxyamine **1749** was selective for the *syn* isomer (Scheme 423).[897]

Scheme 423



Intramolecular delivery of the allylsilane group in the *β*-lactam **1750** was selective for attack on the iminium ion *anti* to the silyloxyethyl side chain, and in favor of the *syn* arrangement of the substituents at the two new stereogenic centers **1751**, setting up the *β*-methyl group for a 1*β*-methylcarbapenem synthesis (Scheme 424).[898] A similar reaction was also

Scheme 424

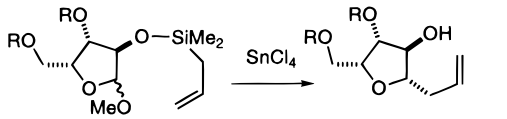


successful between the same, homochiral *β*-lactam portion attached to a racemic 2-cyclohexenylsilane **1752**, where chiral recognition took place, only one diastereoisomer of the allylsilane **1752** reacted, and largely one diastereoisomer **1753** was formed in nearly 50% yield (Scheme 424).[899]

An allyl group can be delivered intramolecularly from a C-2 silyloxy group **1754** to the anomeric position of sugars to make *C*-glycosides **1755**. The seven-membered ring transition structure allows the incoming allyl group to be largely *anti* to the delivering silyloxy group (Scheme 425).[900]

An allyl group can also be delivered from silicon in an ene reaction **1756** → **1757** and **1758** → **1759**, with the silyl group simply tethering the central carbon atom and restricting the geometry much as

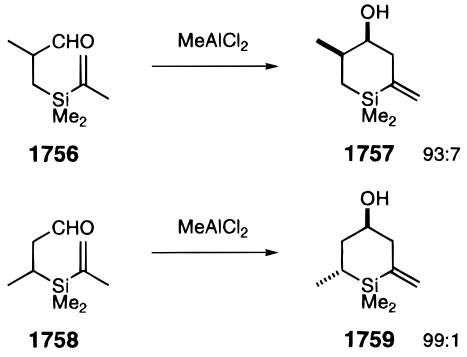
Scheme 425



1754 R = $CH_2C_6H_4Cl$-*p* **1755** 83:17

the all-carbon chain does in otherwise similar reactions (Scheme 426).[901]

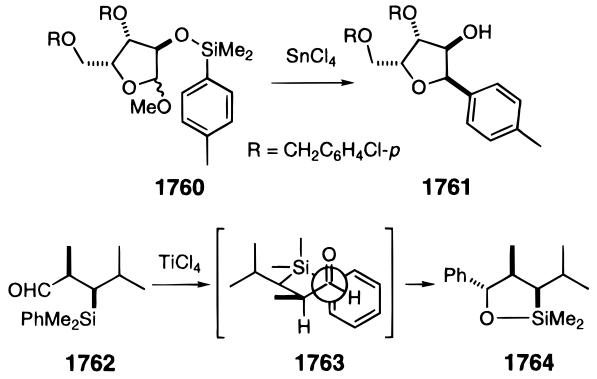
Scheme 426



2. Intramolecular Delivery of a Phenyl or Vinyl Group

An aryl group can be delivered from an arylsilane if a suitable electrophile is held at the right distance, as in the reaction of the acetal **1760**, in which a tolyl group was delivered intramolecularly and, because the transition structure only has a five-membered ring, *syn* to the delivering silyloxy group to give the *C*-glycoside **1761** (Scheme 427).[900] A vinyl group was

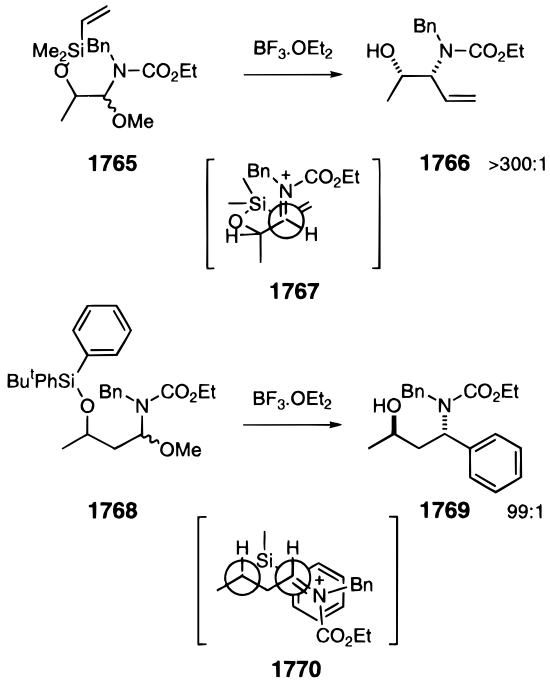
Scheme 427



similarly transferred *syn* to the anomeric carbon. In an open-chain system, a phenyl group was inadvertently delivered intramolecularly to an aldehyde group during a failed attempt to persuade the aldehyde **1762** to react with an allenylsilane in the same type of reaction as worked with the closely related aldehyde **1302** in Scheme 320. The first-formed product was the silyl ether **1764**, reasonably accounted for by delivery *anti* to the methyl group in the conformation **1763**. Because delivery is intramolecular, this product has the opposite relative configuration to that produced by direct, Cram-controlled attack of the phenyl Grignard reagent on the aldehyde (Scheme 427).[902]

A phenyl and a vinyl group have also been delivered intramolecularly, both 1,5 and 1,6, from silyloxy groups to an iminium ion. 1,5-Vinyl migration is illustrated with the vinylsilane **1765**, and 1,6-phenyl migration illustrated for the phenylsilane **1768**, but both combinations were successful. In contrast to the corresponding allylsilane reaction (Scheme 422), the major product in both cases had the *anti* arrangement **1766** and **1769**, reasonably by way of the transition structures **1767** and **1770** (Scheme 428).[903]

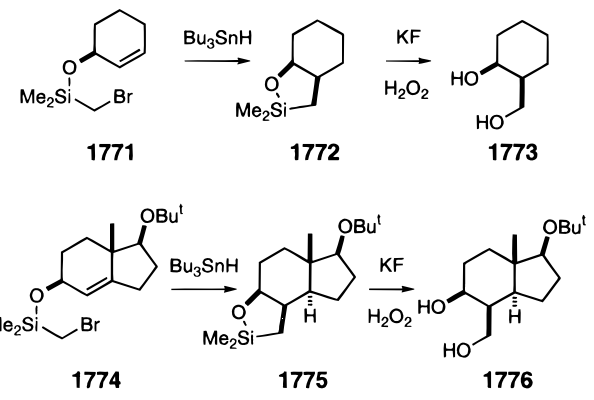
Scheme 428



C. Radical-Initiated Cyclizations

The bromine atom in the (bromomethyl)silyl ether **1771** is a source of a radical that cyclizes to give a *cis*-bicyclic silyl ether **1772**, with the new C−C bond delivered *syn* to the Si−O bond. Subsequently, the C−Si bond was cleaved oxidatively to give the diol **1773** (Scheme 429).[904] In a somewhat more compli-

Scheme 429

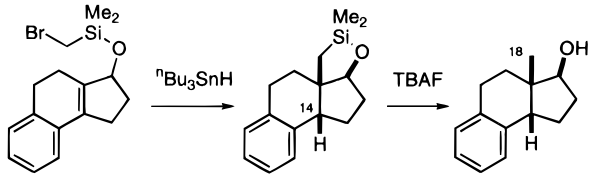


cated system starting from the silyl ether **1774**, designed to solve the problem of preparing a steroidal CD *trans*-hydrindan, the intermediate radical picked up a hydrogen atom selectively on the α-face to give the silyl ether **1775**, because the silicon-containing bridge and the *tert*-butoxy and methyl groups sterically shielded the *β*-face. Again, the C−Si bond was cleaved oxidatively[217] to give the corresponding diol

1776, which was used to synthesize 19-nortestosterone (Scheme 429).[905]

A similar transformation from the bromide **1777** was used to make a functionalized steroidal C-18 by silyl-to-hydroxy conversion of the silyl ether **1778**. Alternatively protodesilylation set up the unsubstituted C-18 methyl group **1779**. The relative stereochemistry at the new C−C bond was completely controlled, but the transfer of the hydrogen atom to C-14 was selective for the *cis* ring junction (Scheme 430).[906]

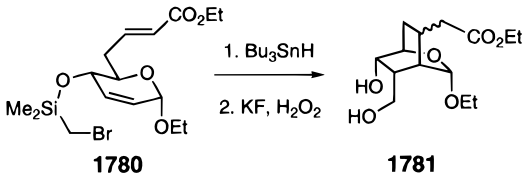
Scheme 430



Other reactions of the same kind forming a five-membered ring have been used with silyl-to-hydroxy conversion in syntheses of deoxyisoamijiol,[907] a homochiral diphosphine ligand,[908] a sugar-derived cyclohexenol,[909] some carbocyclic pseudo-sugars,[910] and a brassinolide,[911] and with protodesilylation to set up a β-methyl group on C-4 of a steroid,[451] and either α- or β-steroidal C-21 methyl groups.[912]

The intermediate radical can undergo a second ring-forming reaction if a suitably placed and suitably functionalized double bond is held nearby, as in the step **1780** → **1781** used in a synthesis of reserpine (Scheme 431).[913] Similarly, the radical can attack a

Scheme 431

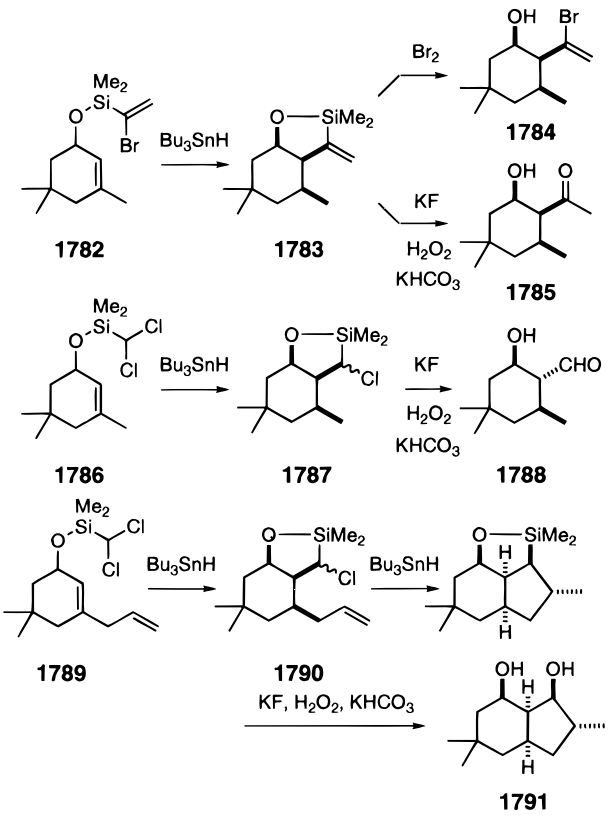


triple bond followed by a double bond, and a highly functionalized diquinane set up.[914]

The atom carrying the radical center may be more functionalized, either as a double bond **1782**[915] or by having a second halogen **1786**,[916] allowing the carbon group to be delivered to the neighboring double bond at a higher oxidation level but with similar stereocontrol (Scheme 432). The vinylsilane **1783** can be treated with bromine to give the vinyl bromide **1784**, or subjected to silyl-to-hydroxy conversion[217] to give the ketone **1785**, and the same reaction on the chloride **1787** gave the aldehyde **1788**, with epimerization of the aldehyde group to give mainly (85:15) the *trans*-aldehyde. The atom carrying the radical center may also be stereogenic, as in the chloride **1789**. The reaction of the radical derived from the chloride **1790** with another double bond was also stereoselective with five stereogenic centers created in the diol **1791** from the one stereogenic center in the silyl ether **1789** (Scheme 432).[916]

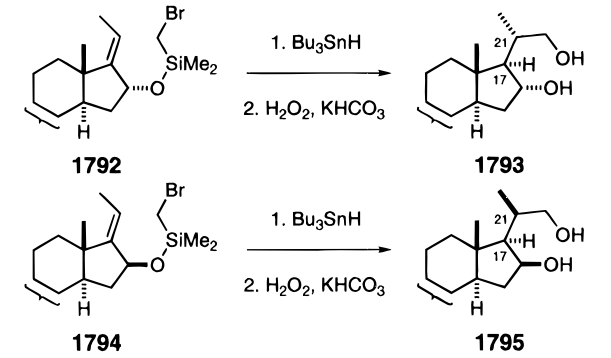
The radical cyclization also works for six-membered ring formation and has been used to control stereospecifically the configuration at C-21 in a steroid

Scheme 432



using the allylic alcohol derivatives **1792** and **1794** (Scheme 433).[917] In this type of radical cyclization,

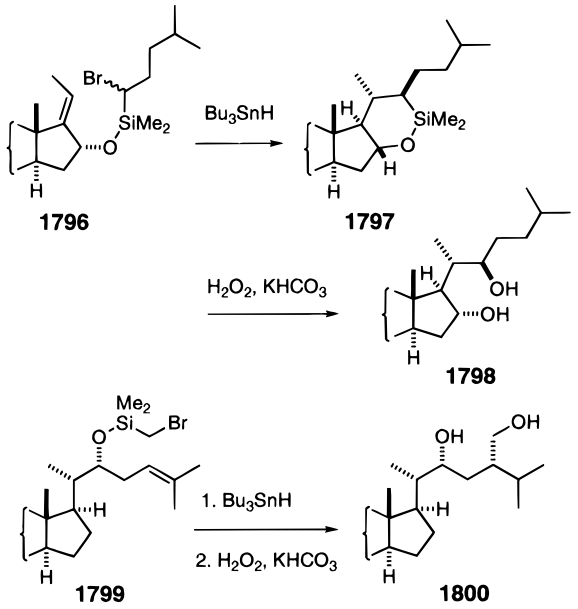
Scheme 433



the presence of the silyl group acts not only as a bridge to restrain the conformation, but also to encourage 6-*endo* cyclization, which is not the normal path for a 5-hexenyl radical. Even with the silyl group present in the ring, the cyclization in this type of reaction is not always 6-*endo*.[918] Because these reactions form a six-membered ring, the intermediate radical that picks up the hydrogen atom on C-17 can give a *trans* ring junction in the intermediate, and does so in the ring derived from the silyl ether **1792**. In the intermediate derived from the silyl ether **1794**, however, the ring junction is *cis*, with the result that the side chain in both products, **1793** and **1795**, is 17β in both cases.

The steroidal side chain can be attached to the carbon atom that is the radical center with good stereoselectivity **1796** → **1797** for it to be *trans* to the neighboring substituent (Scheme 434).[919] The stereocontrol is also good within the steroidal side chain itself, with the homoallylic alcohol derivative **1799**

Scheme 434

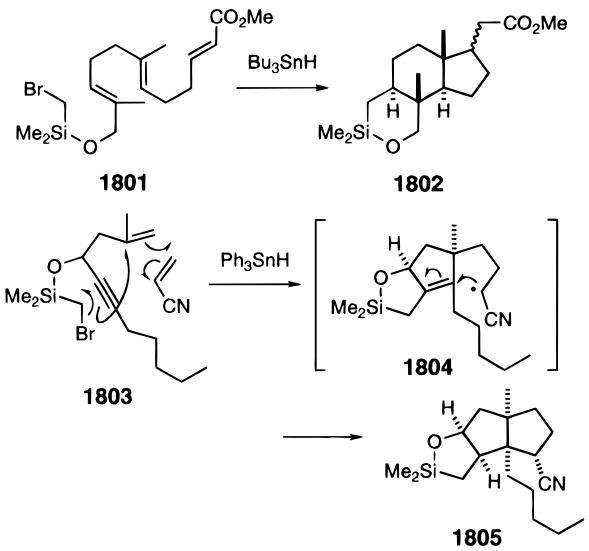


1796 1797 1798 1799 1800

giving good 1,3-stereoselection in favor of the *syn* arrangement in the formation of the diol **1800** (Scheme 434).[920]

The stereochemistry of polyene cyclization, however, is less well controlled in radical reactions than it is in ionic reactions, although the two products most easily isolated, in 28% yield, from a mixture of many products in the tricyclization of the triene **1801** were the silyl ethers **1802** with *trans*-fused rings differing only in the configuration of the acetate sidechain (Scheme 435).[921] However, with a judicious

Scheme 435

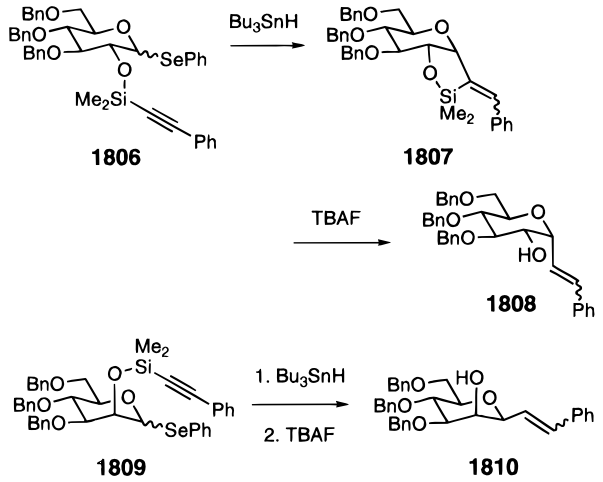


1801 1802 1803 1804 1805

choice of alkynes and alkenes, their placing, and their substituents, a long sequence of intramolecular and intermolecular steps can be combined in one operation to set up several stereocenters effectively,[922] as in the cyclization of the silyl ether **1803** in the presence of acrylonitrile giving the tricyclic nitrile **1805** (Scheme 435).[923]

The radical center does not need to be adjacent to the silyl group. The anomeric radical derived from the selenide **1806** attacked the triple bond attached to the silicon, to give a vinylsilane **1807** (Scheme 436).

Scheme 436

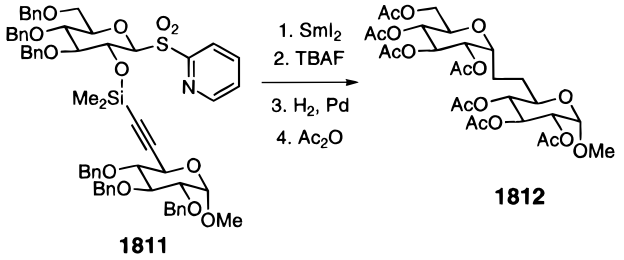


1806 1807 1808 1809 1810

Protodesilylation then removed the temporary silicon tether both from carbon and oxygen to give the *C*-styryl glucoside **1808** with the styryl group *cis* to the delivering group. The equivalent mannose-derived selenide **1809** is complementary, delivering the styryl group to the β surface **1810** (Scheme 436), and also works from the glucose 6-hydroxyl, or the 2-, 3-, or 5-hydroxyl of pentoses.[924]

There is also a samarium iodide-based version of the initiation step in this type of reaction, which was used, with a sugar attached through oxygen to the silylacetylene **1811**, in a synthesis of a *C*-maltoside **1812** (Scheme 437).[925]

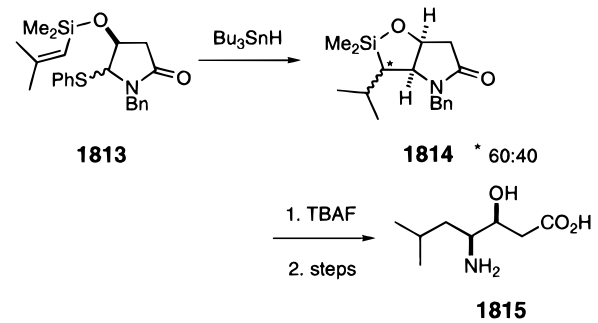
Scheme 437



1811 1812

The vinylsilane **1813** was attacked with a low level of control by the radical generated from the phenylthio group, but the ring fusion was, as usual, entirely *cis*, enabling the product **1814** to be used, with protodesilylation, in a synthesis of statine **1815** (Scheme 438).[452]

Scheme 438

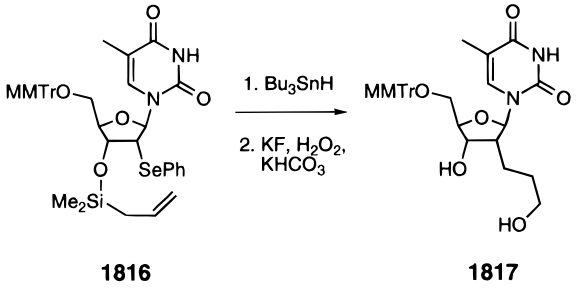


1813 1814 * 60:40 1815

An allylsilane can effectively deliver a propanol chain *syn* to a neighboring radical site, in a 7-*endo* cyclization **1816** → **1817**, although the yields are only

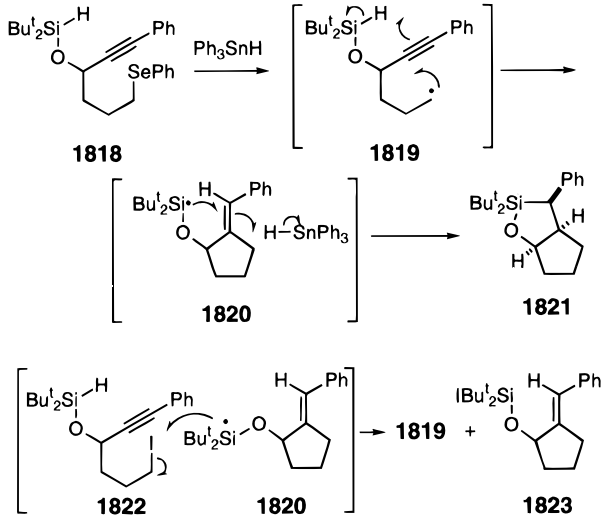
in the 45−56% range, and on the more hindered β-surface the reactions are unreliable (Scheme 439).[926]

Scheme 439



Even the silyl radical itself **1820** can participate in cyclizations as in the longer sequence initiated by removing a phenylselenenyl group from the selenide **1818** and culminating in the formation of the silyl ether **1821** (Scheme 440).[927] If the iodo compound

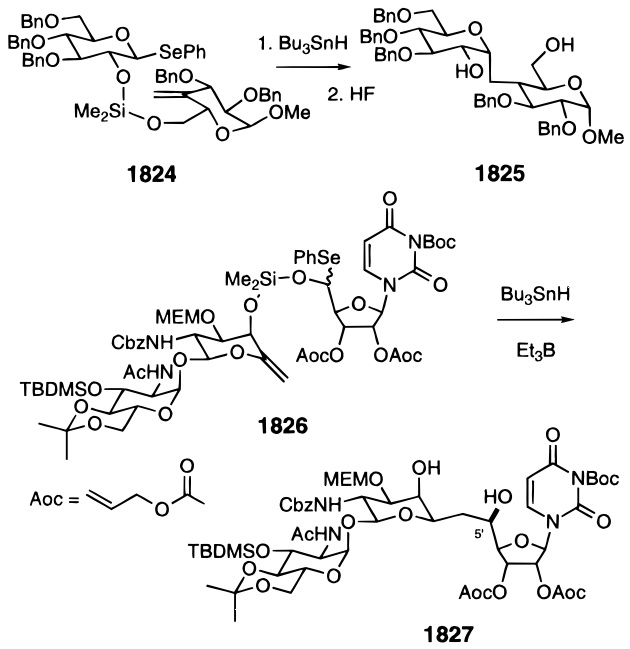
Scheme 440



1822 is used in place of the phenyl selenide **1818**, the silyl radical **1820** does not attack the double bond in the intermediate, but removes the iodine atom instead, making the reaction catalytic in tin hydride, and giving the alkene **1823** with the stereochemistry of the exocyclic double bond controlled by the overall *anti* addition (Scheme 440).[928]

The formation of the interglycosidic links in disaccharides is difficult to control stereochemically. In addition to the method seen in Scheme 437, where one of the carbon groups on the silicon is transferred to the anomeric position to make a *C*-glycoside, holding the two components together with a temporary silicon connection through *two* oxygens is also promising. Examples using ionic chemistry for *O*-linked disaccharides are discussed in the next section, but radicals have been used for *C*-linked sugars, as in the coupling of the glucoselenide to the exomethylene glucose derivative linked through the 6-position in the double silyl ether **1824** (Scheme 441).[929] The reaction took place remarkably through a nine-membered ring to give the *C*-maltoside **1825**, as the only diastereoisomer that could be isolated, although only in 40% yield. The yield can be improved to 50% by using a sulfone in place of the selenide and samarium iodide in place of the tin hydride.[930]

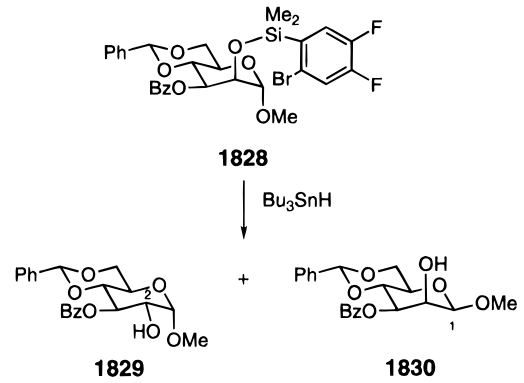
Scheme 441



However, this comparatively well-behaved reaction needs to be compared to the superficially similar reaction of the corresponding exomethylene glucose linked through the 3-position, requiring an 8-*endo* cyclization, which gave a mixture of products with little stereoselectivity. A two-carbon bridge was similarly established, with a 7-*endo* cyclization using the double silyl ether **1826** in a synthesis of some tunicamycin antibiotics (Scheme 441).[931] A substantial amount of fine tuning of the conditions of this reaction led to the product **1827** in 60% yield, with the major byproduct being the C-5′ diastereoisomer.

A completely different use of a radical reaction is the stereochemical equilibration in the reaction of the α-maltoside derivative **1828**, where the aryl radical abstracted the hydrogen atom to some extent on C-2, and the rest on C-1, and the radicals so produced took a hydrogen atom from the tin hydride mainly from the axial direction, to give a 50:50 mixture of the α-glucoside derivative **1829**, and the β-mannoside **1830**, where C-1 had inverted (Scheme 442).[932]

Scheme 442

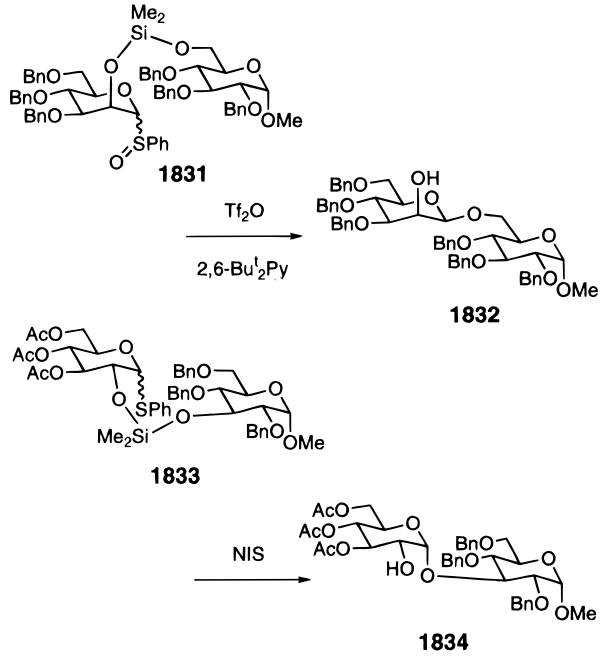


D. Silicon-Bridged Disaccharide Formation

The silyl group, bridged through two oxygen atoms, can deliver one sugar *syn* to the anomeric position of another, simply by holding the nucleophile on the desired surface and completely controlling the regio-

and stereochemistry. Thus the mannoside **1831**, in the very situation where it is most difficult, gave the β-glycoside **1832** (Scheme 443), whereas intermolecular reaction favors the formation of the α-anomer.[933] A similar reaction with the glucose derivative **1833** was complementary in its anomeric selectivity, giving the α-glycoside **1834** linked to the β-3-hydroxy group of another glucose (Scheme 443).[934]

Scheme 443

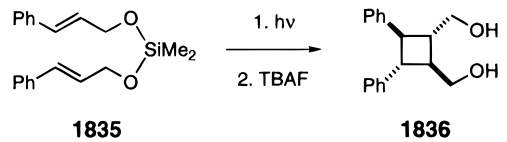


E. Silicon-Bridged Cycloadditions

Silicon tethers have been used to control the regio- and stereochemistry in three kinds of cycloadditions, where the intramolecularity changes the regio- and stereochemistry relative to those of the usual intermolecular reactions. As usual, the silicon can easily be removed oxidatively or by protodesilylation, if one of the links to silicon is through oxygen and one through carbon, or by hydrolysis if both links are through oxygen.

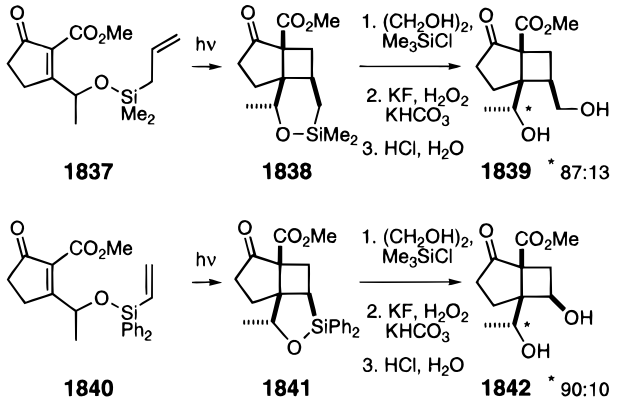
A photochemical [2+2] cycloaddition with both links from cinnamyl alcohol through oxygen **1835** allowed the cyclobutane **1836** to be made in nearly quantitative yield as a single diastereoisomer (Scheme 444).[935]

Scheme 444



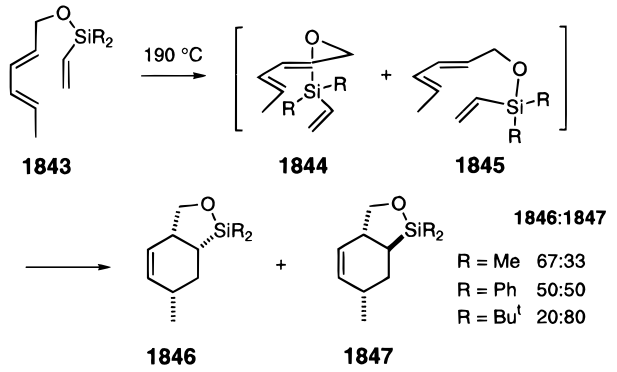
An enone cycloaddition with an alkene partner was highly controlled with one link to the silicon through carbon in the allylsilane **1837** and the vinylsilane **1840**, where the products **1838** and **1841**were oxidized[217] to the diols **1839** and **1842** (Scheme 445).[936] In contrast, the corresponding intermolecular reaction with allyl alcohol gave eight diastereoisomeric [2+2] products.

Scheme 445



In Diels−Alder reactions, both components can be relied upon to react suprafacially. The choice in the most simple system using a vinylsilane as the dienophile **1843** was therefore between the *endo* and the *exo* transition structures **1844** and **1845**. With a dimethylsilyl link, the *endo* product **1846** was preferred by a small margin, but making the silyl groups larger made the transition structure with the silyl groups *endo* too crowded, and favored the *exo* structure **1845** (Scheme 446).[937] Unfortunately the di-*tert*-butylsilyl group was too hindered to be oxidized to an alcohol, although new methods[457] may overcome this limitation.

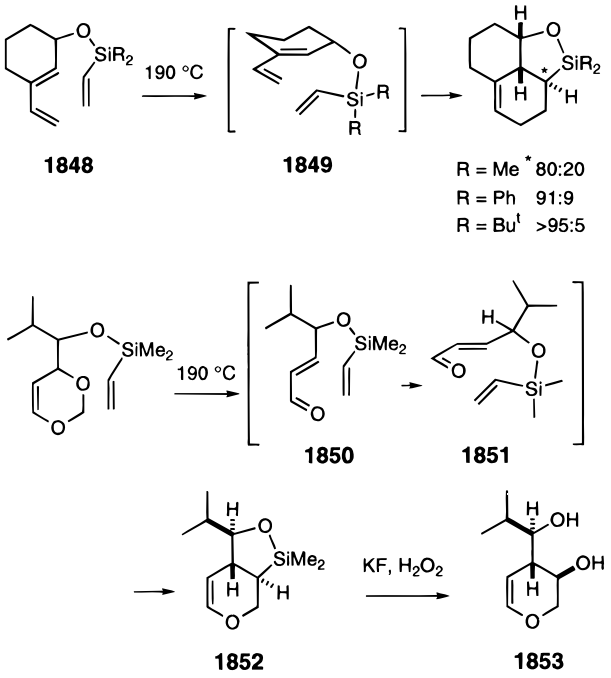
Scheme 446



Attaching the link to a hydroxyl group on a stereogenic center, as in the silyl ether **1848**, gave only *syn* delivery with respect to the hydroxyl group, and the *exo* transition structure **1849** favored with any of the silyl groups (Scheme 447). A hetero-Diels−Alder reaction with the α,β-unsaturated aldehyde **1850** with a stereogenic center on the open chain was also selective for *syn* delivery with the hydrogen on the stereogenic center inside, and only the product **1852** of an *exo* transition structure **1851** was detected (Scheme 447).[937] In most of these reactions, the silyl group was converted into a hydroxyl,[217] as in the reaction **1852** → **1853**.

The suprafacial nature of the reaction can be exploited when the vinylsilane is substituted as in the reaction of the vinylsilane ester (*E*)-**1854**, giving only the adduct **1855**, which follows from an *endo* transition structure with respect to the ester group

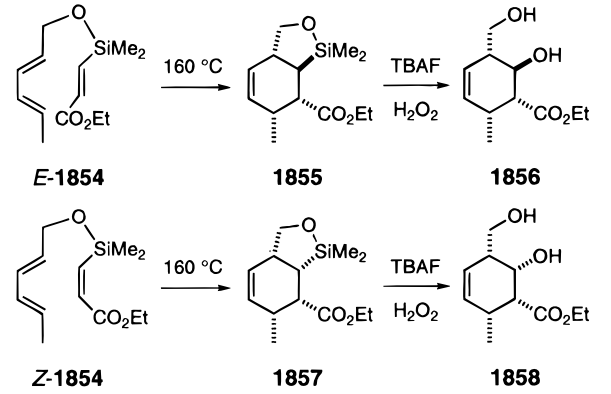
Scheme 447



1848 1849 1850 1851 1852 1853

and *exo* with respect to the silyl group. Alternatively, the *Z* isomer (*Z*)-**1854** gave only the adduct **1857** which follows from an *endo* transition structure with respect to both substituents. The silyl groups were converted into hydroxyls[217] to give the esters **1856** and **1858** with all four stereogenic centers controlled (Scheme 448).[454]

Scheme 448

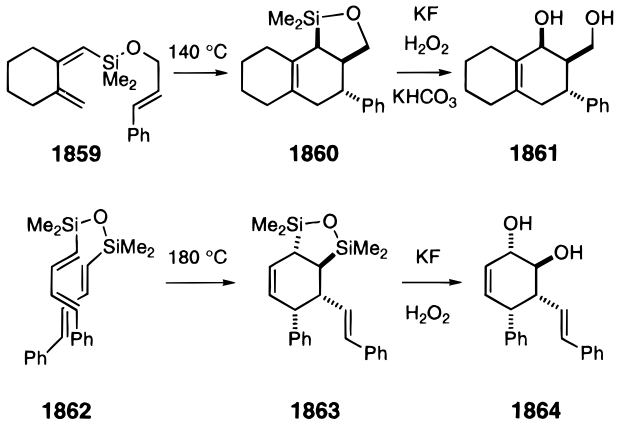


E-1854 1855 1856 *Z*-1854 1857 1858

The silyl group can also be attached directly to the diene component, as in the cycloaddition **1859** → **1860** and hence the diol **1861** (Scheme 449),[938] and even to both the diene and dienophile components, as in the reaction of the symmetrical bis-diene **1862**, which cyclized to give only the adduct **1863**, and hence the diol **1864** after silyl-to-hydroxy conversion[217] (Scheme 449).[939]

More commonly the silicon bridge has been attached through two oxygen atoms, and the oxidation step has not been needed to make diol products. Furthermore, using the di-*tert*-butylsilyl group, which can help in stereocontrol, is no longer a problem, since di-*tert*-butylsilyl groups can be hydrolyzed when they could not be oxidized. The enol silyl ether **1865**

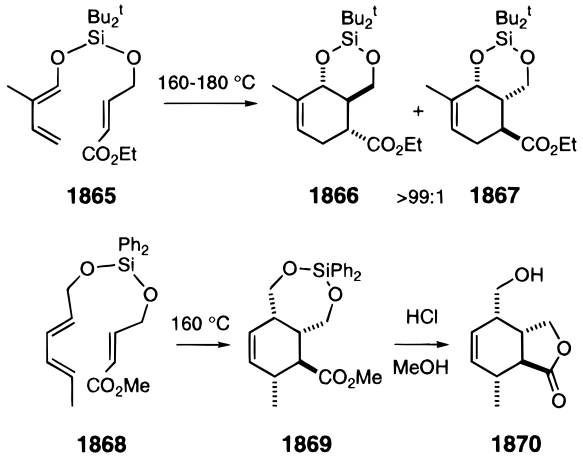
Scheme 449



1859 1860 1861 1862 1863 1864

gave the adduct **1866**, *endo* with respect to the ethoxycarbonyl group, as the major product (Scheme 450), the main achievement being the reversal of the normal regiocontrol.[940] Similarly the allylic silyl ether **1868** gave only the adduct **1869**, corresponding to an *exo* transition structure with respect to the methoxycarbonyl group, and hence the lactone **1870** after hydrolysis of the silyl ether bonds (Scheme 450).[941] The corresponding intermolecular reaction

Scheme 450

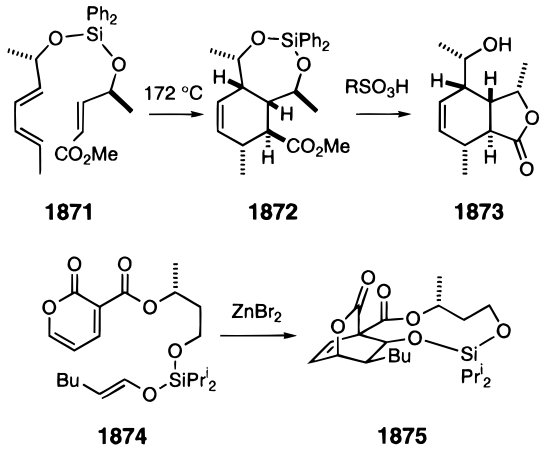


1865 1866 1867 1868 1869 1870

gave all four possible all-suprafacial diastereoisomers with the one corresponding to **1869** the least abundant.

The last reaction, with a methylene group placed between the silyloxy group and both the diene and dienophile components, gives opportunities for a stereogenic center on either of these methylene groups to control the sense in which the four new centers are created in the cycloaddition step. In practice this works well, with the dienophile center the more powerful.[942] There are also opportunities for the two stereogenic centers to be matched or mismatched, with the matched pair illustrated by the cycloaddition of the silyl ether **1871**, which gave only one adduct **1872** and hence the lactone **1873** (Scheme 451).[942] An even longer tether carrying a stereogenic center allows a well-controlled cycloaddition of the silyl enol ether **1874**, but it appears to be a stepwise reaction rather than a Diels−Alder reaction with inverse electron demand, because the major adduct

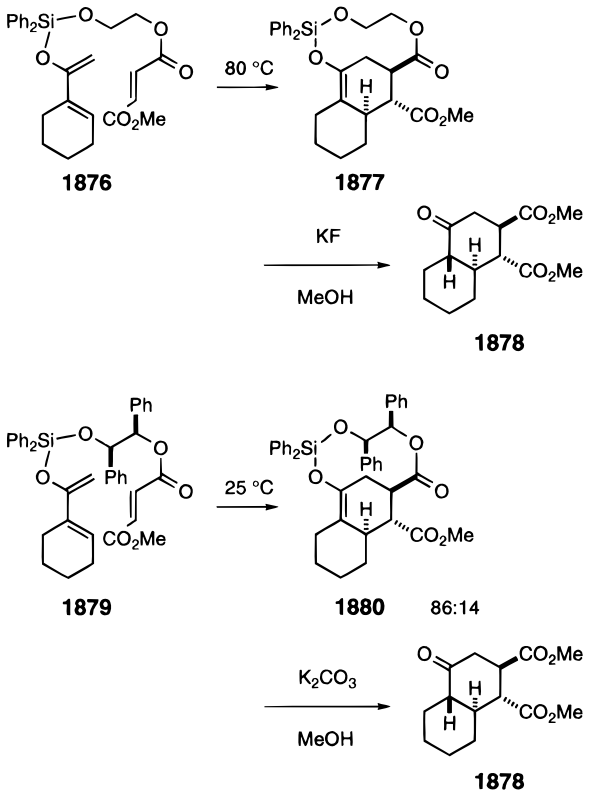
Scheme 451



1875 corresponds to that from the (*Z*)-silyl enol ether (Scheme 451).[943]

The silyl groups can even be connected to the 2-position of the diene, as in the silyl enol ether **1876**, with a necessarily long tether to allow the adduct **1877**, which has a bridgehead double bond, to be feasible (Scheme 452).[944] A homochiral version of the

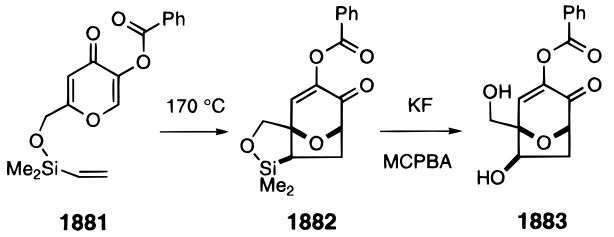
Scheme 452



same reaction, with a homochiral tether in the diene **1879**, gave the adduct **1880** with good diastereoselectivity. After separation of the major adduct from its diastereoisomer and removal of the tether, the ketone **1878** was obtained enantiomerically pure (Scheme 452).[945] This reaction has since been developed into a synthesis of androsterone.[946]

In addition to Diels–Alder reactions there is also the possibility of a silicon-containing tether between the components of other cycloadditions, as in the [5+2] pyrone–vinylsilane combination **1881** → **1882**, where the silyl group took up the *exo* orientation, and silyl-to-hydroxy conversion[217] gave the diol **1883** (Scheme 453).[947]

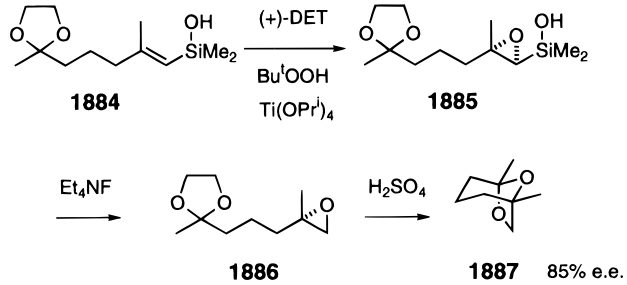
Scheme 453



F. Silicon-Bridged Epoxidation

One of the few limitations of the Sharpless asymmetric epoxidation reaction is that it requires the allylic hydroxyl group to direct the reagent to the double bond. A vinylsilanol has such an allylic alcohol group, and the silyl group can be removed later. The problem is that, with the long C–Si and Si–O bonds, it is not clear that replacing the carbon atom by silicon will be otherwise benign. In practice the idea does work. The silanol **1884** gave the epoxide **1885** in moderately high enantiomeric excess, and the reaction was used, with subsequent protodesilylation, for a synthesis of frontalin **1887** (Scheme 454).[948] The same type of reaction was used in the

Scheme 454



kinetic resolution of a chiral silyl compound (Scheme 459).

XIX. Stereocontrol Transferred from Chiral Silyl Groups and Silyl Groups Carrying Chiral Substituents

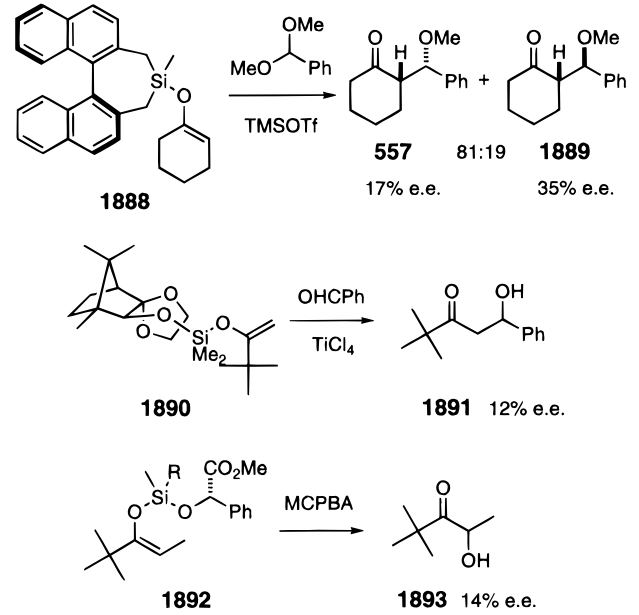
Most of the reaction types in this section have been discussed already, and even some reactions, such as those in Schemes 451 and 452, might have been as appropriately discussed here. The distinctive feature in this section is that the stereochemistry stems from the silyl group or its substituents, and the controlling feature does not appear in the final product after the removal of the silyl group. As with any chiral auxiliary, this device allows the transfer of stereochemical information from one molecule to another, or from one part of a molecule to another, with the possibility in the latter case, either actually carried out or potentially available, of removing the silyl group and recycling it. The chirality may reside at the tetrahedral silicon atom, building on Sommer's

pioneering work,[949] or in one or more of the substituents attached to the silyl group. There is a fundamental difficulty in achieving high levels of stereocontrol with a chiral auxiliary attached through silicon, because the long bonds to silicon are inherently apt to separate the chiral information and the reaction site. Nevertheless the idea has now worked in a number of cases, and the levels of stereocontrol are going up year by year. The topics discussed here are in the same order as the corresponding reactions in sections VI−XVIII.

A. Silyl Enol Ethers

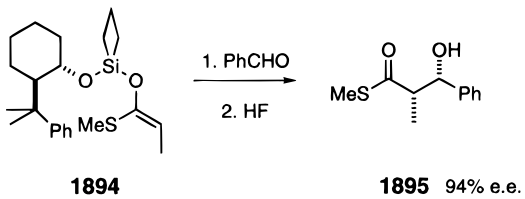
Silyl enol ethers carrying a chiral silyl group have given rather low levels of asymmetric induction, as in the Lewis acid-catalyzed reactions with an acetal **1888** → **557** + **1889**,[950] and with an aldehyde **1890** → **1891**,[951] and in epoxidation **1892** → **1893** (Scheme 455).[364] In the case of the silyl enol ether **1892** (R = Ph), where there is the possibility of using a stereogenic silyl group as well as the side-chain stereogenic center, neither diastereoisomeric silyl enol ether was able to add any useful selectivity to that already coming from the side chain of the silyl enol ether **1892** (R = Me).

Scheme 455



In spite of these unpromising beginnings, silyl enol ethers that allow chelated transition structures, like that in Scheme 132 but with stereogenic centers in the silyl substituents, have given good asymmetric induction in uncatalyzed Mukaiyama aldol reactions. The silyl enol ether **1894** gives aldols **1895** in high enantiomeric excess (Scheme 456).[952]

Scheme 456

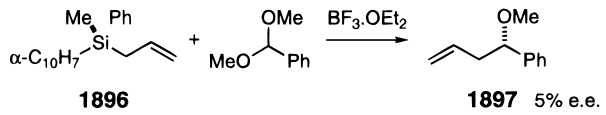


The reaction illustrated in Scheme 148 might equally have been placed in this section.

B. Allylsilanes

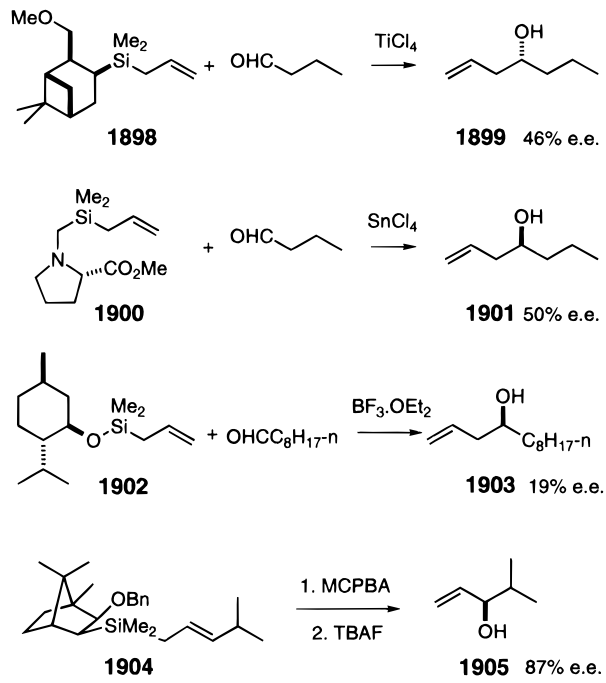
An allylsilane stereogenic at the silicon atom gave low levels of asymmetric induction **1896** → **1897**, presumably because the three substituents on the silyl group were not different enough (Scheme 457).[953]

Scheme 457



On the other hand, when the stereogenic centers are in one of the substituents on the silyl group, some surprisingly good results have been obtained, as in the Lewis acid-catalyzed reactions with aldehydes **1898** → **1899**,[954] **1900** → **1901**,[955] and **1902** → **1903**,[956] and in the epoxidation **1904** → **1905** (Scheme 458).[957]

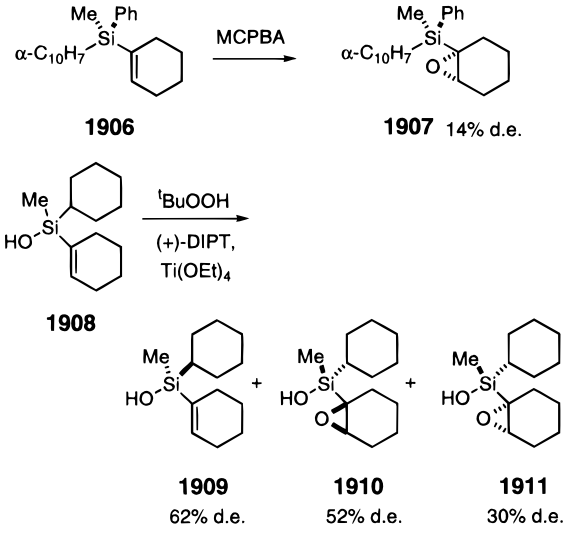
Scheme 458



C. Vinylsilanes

The epoxidation of a vinylsilane with an adjacent stereogenic silyl group **1906** → **1907** is poorly selective,[958] but if the chiral silyl group carries a hydroxyl group **1908**, substantial kinetic resolution using Sharpless asymmetric epoxidation (see section XVI-II.F) is moderately effective both for the unchanged enantiomer **1909** and for both diastereoisomeric epoxides **1910** and **1911** (Scheme 459).[959]

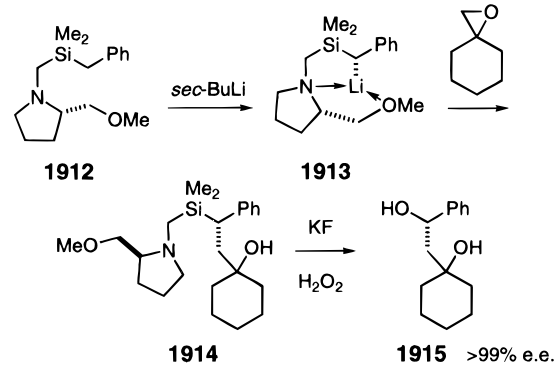
Scheme 459



D. α-Silyl Anions[4]

Anions adjacent to the silyl group are themselves stereogenic centers inherently close to the stereochemical information held in the silyl group, especially when the anions have been generated with coordination sites present in the chiral auxiliary. This area is one of the few so far to have given high asymmetric induction. The benzylsilane **1912** allows metalation to give a chelated organolithium species **1913**, which reacts with electrophiles such as alkyl halides[960] and epoxides,[961] to give a new stereogenic center. The silyl group in the product **1914**, although substituted with all-carbon ligands, is however directly available for silyl-to-hydroxy conversion,[217] as in the formation of the diol **1915** (Scheme 460). This

Scheme 460

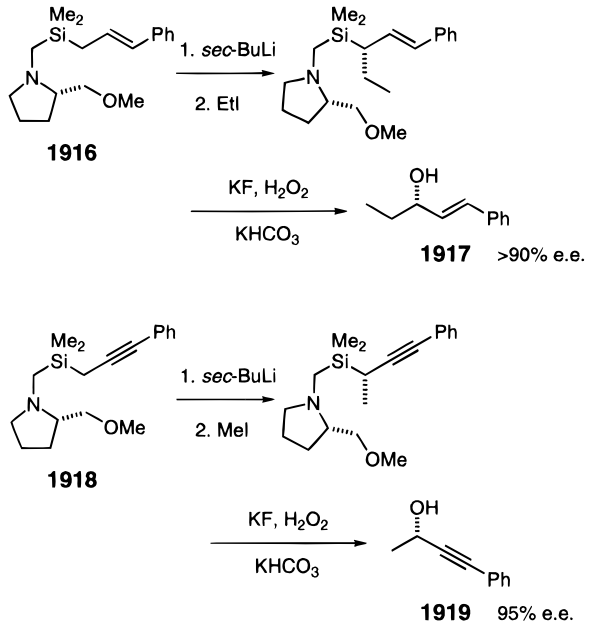


reaction must begin by oxidation of the amino group followed by a Polonovsky-type of reaction, in order to functionalize the silyl group for the oxidative rearrangement.

A similar level of control was found for the allylsilane **1916**[962] and the propargylsilane **1918**[963] carrying the same proline-derived auxiliary, and which gave the allylic and propargylic alcohols **1917** and **1919**, respectively (Scheme 461).

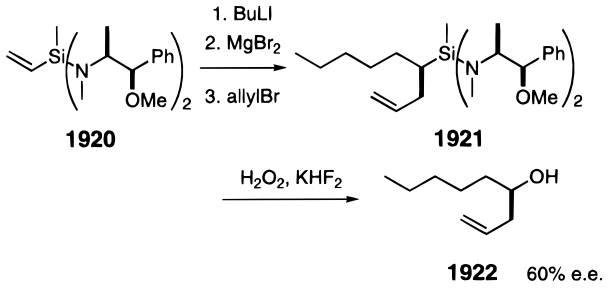
Nucleophilic attack on the vinylsilane **1920** gave a chelated α-silyl anion, which showed only moderately good levels of asymmetric induction in allylation reactions giving the homoallylsilane **1921**, and less good levels with other electrophiles. Silyl-to-hydroxy

Scheme 461



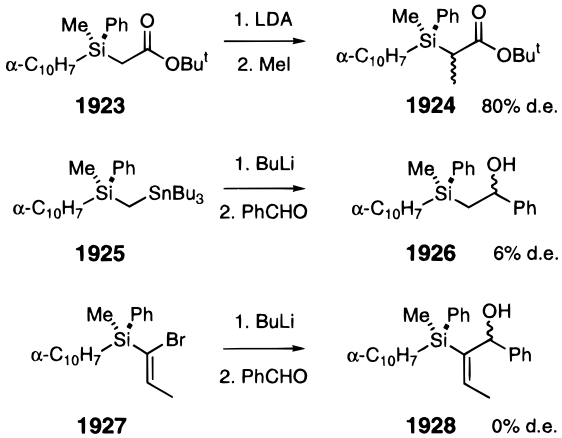
conversion[217] gave the homoallylic alcohol **1922** (Scheme 462).[964]

Scheme 462



In enolate reactions, but with chiral silicon, a surprisingly high level of control has been found in the methylation **1923** → **1924** (Scheme 463).[965] On

Scheme 463



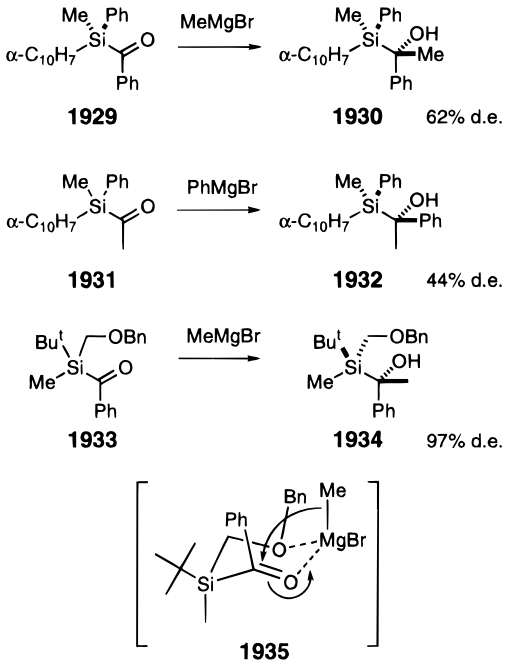
the other hand, the unsubstituted α-silyl anion derived from the stannane **1925** is not usefully selective with respect to the stereogenic center created in the product **1926** of its reaction with aldehydes,[966] and the vinyllithium reagent derived from the bromide **1927** was completely unselective (Scheme 463). However, the 50:50 mixture of diastereoisomers **1928** could be separated into the alcohol **80** and

its diastereoisomer and used to make homochiral allenes as shown in Scheme 17.[68]

E. Acylsilanes

Cram's rule does not uniformly apply to acylsilanes bearing stereogenic centers on silicon, because the C−Si bond is so much longer than the corresponding C−C bond of the compounds in Cram's studies.[967] Nevertheless, there has been some success with nucleophilic attack on a carbon atom adjacent to a stereogenic silicon atom, with the acylsilane **1929** having been known for a long time to give a high level of diastereocontrol in the Cram sense in favor of the diastereoisomer **1930** in its reaction with the methyl Grignard reagent. The corresponding acetylsilane **1931**, recently studied in more detail, gave the complementary result (Scheme 464).[968,969] The acylsilane **1933**, with better designed substituents, generally shows even higher levels of induction, much affected by reagent and choice of solvent, with Grignard reagents in ether the best, as in the example giving the diastereoisomer **1934** (Scheme 464). The

Scheme 464

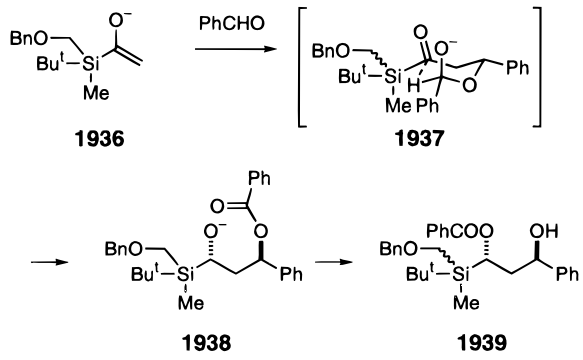


reaction is probably controlled by chelate formation to the alkoxy group deliberately built into the auxiliary, and delivery of the reagent complexed to this feature in the sense **1935**.[970]

However, nucleophilic attack by the enolate **1936** of a similar acylsilane was unselective with respect to the relative stereochemistry of the stereogenic silicon center and the new stereocenters in the product **1939**, but the intramolecular Cannizzaro reaction **1937** took place with high selectivity for the formation of the 1,3-related centers *anti* (Scheme 465).[971]

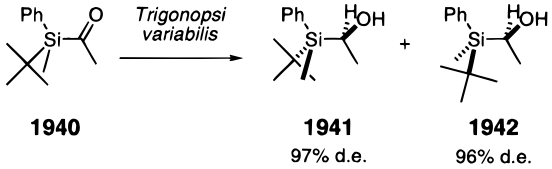
Bioreduction of the racemic acetylsilane **1940** gave the pair of diastereoisomeric alcohols **1941** and **1942**, enantiomerically highly enriched in each case, with the organism controlling the absolute configuration

Scheme 465



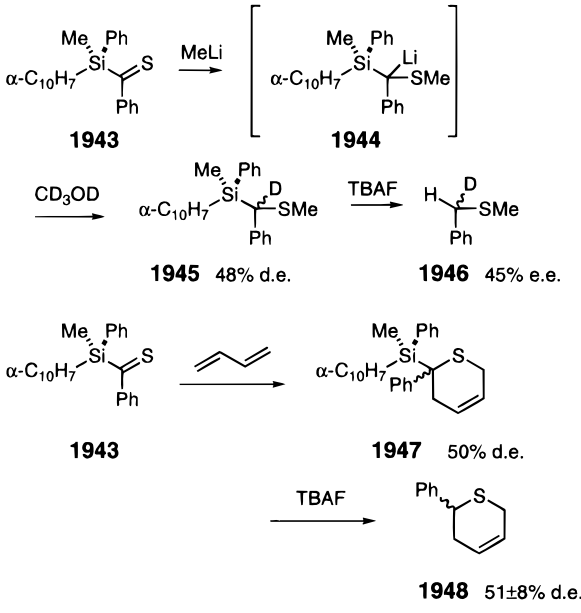
at the carbinol carbon (Scheme 466).[972] The result is effectively the resolution of a chiral silyl group, which can be added to other biologically based methods.[973]

Scheme 466



Nucleophilic attack on a thioacylsilane takes place on sulfur **1943** → **1944**, and subsequent protonation or deuteronation on carbon gives the sulfide **1945**. The silyl group can be removed stereospecifically by protodesilylation to give the silicon-free sulfide **1946**, probably with retention of configuration, but the stereochemical sense of the reaction was not proved (Scheme 467).[974] Similarly thioacylsilanes undergo

Scheme 467

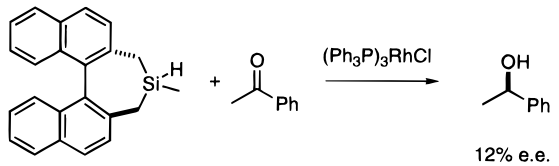


cycloadditions **1943** → **1947** with fairly good asymmetric induction, and protodesilylation to give the dihydrothiopyran **1948** was again stereospecific.[975]

F. Silicon Hydrides

The silyl hydride **1949**, chiral at silicon by virtue of a BINAP system, reduces ketones with low levels of enantioselectivity (Scheme 468).[950]

Scheme 468

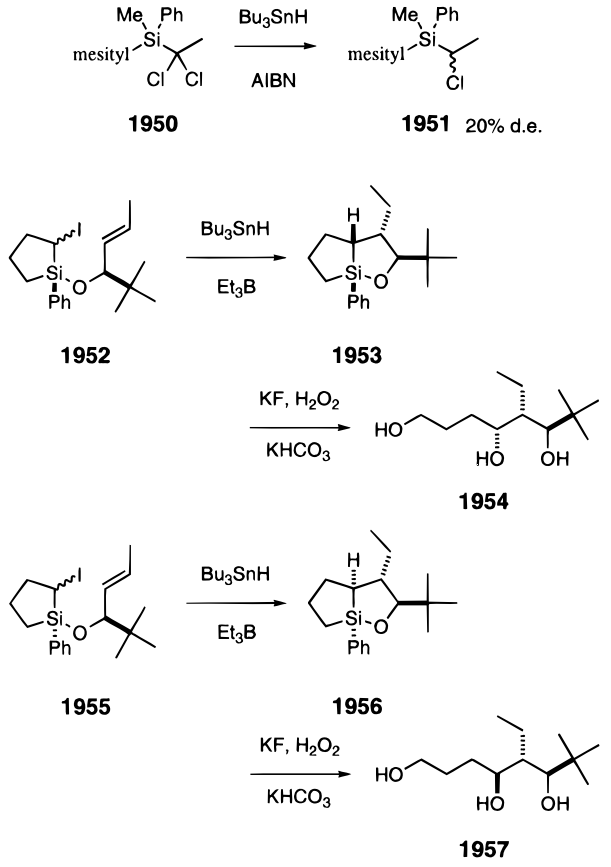


1949

G. α-Silyl Radicals

A radical reduction adjacent to stereogenic silicon **1950** → **1951** shows only a low level of diastereoselectivity, even with a silyl group having rather better differentiated substituents than the usual (Scheme 469).[976] On the other hand, an α-silyl radical in a

Scheme 469



ring attacking a double bond intramolecularly is subject to the normal constraints, and the stereochemistry can be controlled, with the diastereoisomeric silyl ethers **1952** and **1955** giving diastereoisomeric products **1953** and **1956**, respectively, and hence diastereoisomeric triols **1954** and **1957** after silyl-to-hydroxy conversion[217] (Scheme 469).[977]

XX. Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	(*tert*-butyloxy)carbonyl
BOM	(benzyloxy)methyl
Bu	*n*-butyl (unless otherwise stated)
Bz	benzoyl
CAN	ceric ammonium nitrate
cat.	a less than equimolar quantity
Cbz	(benzyloxy)carbonyl
COD	cyclooctadiene
Cp	cyclopentadienyl
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
DAM	di-*p*-anisylmethyl
DBU	diazabicyloundecene
DDQ	dichlorodicyanobenzoquinone
DET	diethyl tartarate
DIBAL	diisobutylaluminum hydride
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane
DIPT	diisopropyl tartarate
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
FVP	flash vacuum pyrolysis
HMPA	hexamethylphosphoramide
IPC	isopinocampheyl
KHMDS	potassium hexamethyldisilazide
L-Selectride	lithium tri-*sec*-butylborohydride
LDA	lithium diisopropylamide
LDEA	lithium diethylamide
LHMDS	lithium hexamethyldisilazide
MABR	methylbis(4-bromo-2,6-di-*tert*-butylphenoxy-)aluminum
MCPBA	*m*-chloroperoxybenzoic acid
MOM	methoxymethyl
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMMO	*N*-methylmorpholine *N*-oxide
PCC	pyridinium chlorochromate
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PNB	*p*-nitrobenzyl
Py	pyridinyl or pyridine
SEM	2-(trimethylsilyl)ethyl
TASF	tris(dimethylamido)sulfur trimethylsilyl difluoride
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMEDA	tetramethylethylenediamine
Tol	4-methylphenyl
Tr	triphenylmethyl
Ts	toluene-*p*-sulfonyl

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