Chiral Organosilicon Compounds in Asymmetric Synthesis

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Contents

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1. Introduction

The last two decades witnessed a tremendous development in the use of organosilicon compounds for organic synthesis.[1,2] It is fair to say that nowadays, in nearly every major synthesis, an organosilicon reagent of one type or another is used in the course of synthesis for C–C bond formation, functional group transformation, or protection. With the current challenge in synthesis being focused on enantio- and diastereoselectivity, it is not surprising that increasing attention has been directed toward the use of organosilicon compounds for asymmetric synthesis.[3]

In this review, we choose to limit the discussion to asymmetric synthesis in which the organosilicon moiety plays a critical role in controlling both the course of the reaction as well as the stereoselectivity. Not included in our discussion are reactions in which the silicon moiety may play an important role in controlling the course of the reaction, but the stereoselectivity of the reaction is controlled by other factors. An illustration of the distinction between these possibilities is the Lewis acid promoted condensation of allylsilanes with acetals (Scheme 1). While the silyl moiety in **1** is clearly necessary for the reaction to proceed, the enantioselectivity of the product **3** can be affected by the use of chiral Lewis acids,[4] chiral acetals,[5] or chiral organo-

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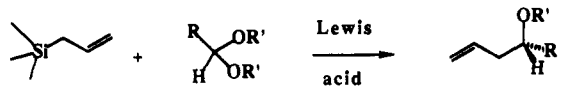
Scheme 1



1 2 3

silicon compounds.[6] Only the last possibility, the use of chiral organosilicon compounds for asymmetric synthesis, will be discussed in this review. Furthermore, in order for the reaction to be synthetically useful, the silyl moiety must be readily removable from the product targeted for synthesis. Reactions which lead only to the synthesis of chiral organosilicon compounds per se will not be considered.

In line with Paquette's suggestion,[6] chiral organosilicon compounds can be classified into two types: "Si-centered" and "C-centered", namely, chirality can reside on silicon or on the carbon of one of the substituents attached to silicon. Both types of chiral organosilicon compounds have been explored for asymmetric synthesis with varying degrees of success.

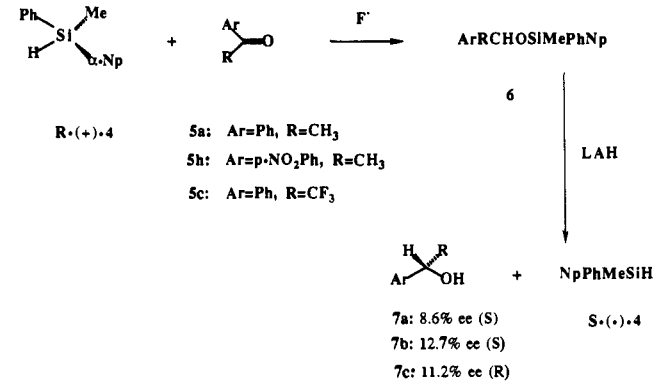
2. Si-Centered Chiral Organosilicon Compounds

Through the pioneering work of Sommer and his coworkers, optically active Si-centered chiral organosilicon compounds became available in the early 1960s.[7] A typical example is methyl-α-naphthylphenylsilane (4) and its derivatives. While much of the interest of Sommer and others have been directed toward probing the reaction mechanism of silicon compounds,[8] the potential of using this type of chiral organosilicon compounds for asymmetric synthesis was clearly recognized.

2.1. Enantioselective Reduction of Carbonyl Compounds

Hydrosilanes are useful reagent for the reduction of carbonyl compounds. The reactions can usually be carried out under relatively mild reaction conditions with a variety of catalysts. Recently, Fry and McAdam reported[9] that the fluoride ion catalyzed reaction between (*R*)-(+)-4 and the prochiral aromatic ketones 5 gave alkoxysilanes 6. Lithium aluminum hydride (LAH) reduction of 6 followed by hydrolysis gave the optically active alcohols 7 and the inverted, racemized hydride 4 (Scheme 2). The alcohols 7 were found to have enantiomeric excess (ee) in the range of 8.6–12.7%. The recovered hydride 4 from the LAH reduction had the opposite (*S*) configuration compared to the starting reagent, but extensive racemization was observed as well. Since it has been firmly established that LAH reduction of alkoxysilanes proceeds with a high degree of configuration retention at silicon, it follows that the formation of the alkoxysilane 6 from 5 must have occurred with inversion of configuration at silicon. The stereoselectivity however was relatively poor at both the carbon and the silicon. The low ee of the alcohol 7 obtained rendered the reaction not useful as a method for the asymmetric synthesis of alcohols. From our current understanding of the mechanism of fluoride ion catalysis, it is likely that hypervalent silicon intermediates are involved in the reaction.[10] The poor stereoselection observed at the carbon may be inherent

Scheme 2



in the reaction itself, or due to prior racemization of the chiral silane 4 via the pentacovalent intermediate 8 or the hexavalent intermediate 9. A better understanding of the reaction mechanism is required if one wishes to improve on the stereoselection of the reaction.

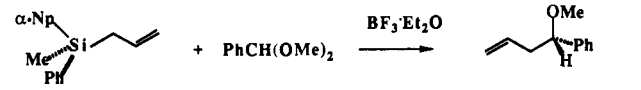
8 9

2.2. Reactions of Allylsilanes with Carbonyl Equivalents—The Sakurai Reaction

The reaction of carbonyl compounds or equivalents with allylsilanes under Lewis acid conditions to give homoallylic alcohols was first described by Sakurai and Hosomi.[11] The reaction has since been used extensively in synthesis for the formation of C–C bonds.[12] Naturally, the possibility of using this reaction for the asymmetric synthesis of homoallylic alcohols has been explored.

Allylmethyl-α-naphthylphenylsilane (10) has been used as the chiral organosilicon compound. Its reaction with a number of carbonyl compounds under Lewis acid conditions was found not to give the desired homoallylic alcohols in reasonable yield.[5] On the other hand, the reaction of 10 with the dimethyl acetal 11 and BF_3-Et_2O gave the homoallylic alcohol methyl ether 12 (Scheme 3) in modest yield with 3.9–5.5% ee. The

Scheme 3

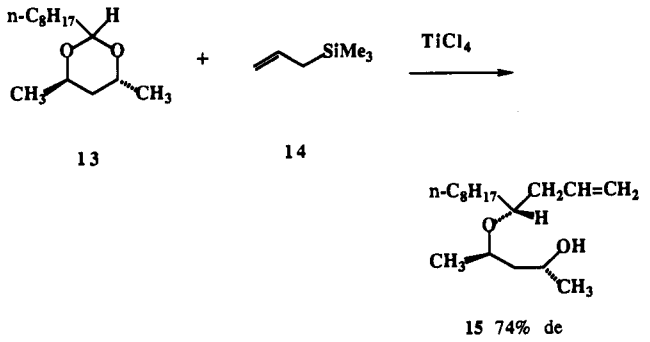


10 11 12 4-5%ee

20-30% yield

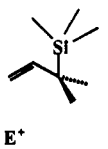
rather modest ee of the methyl ether 12 obtained should be contrasted with the results of Johnson et al. who found that the chiral acetal 13 condensed with allyltrimethylsilane (14) to give the ether 15 (Scheme 4) in high chemical as well as optical yields.[4] The difference in stereoselectivity can be understood in terms of the mechanism for the electrophilic reaction of allylsilanes. From the work of Kumada[13] and Fleming,[14] it has been concluded that the reaction of an electrophile E^+ with allylsilanes usually proceeds through a trans transition state 16. In 16, the silyl group and the electrophile E^+ are on the opposite sides of the plane defined by the

Scheme 4



13 14 15 74% de

allyl moiety. It is not surprising therefore to find that chirality at silicon has little influence on the stereochemical outcome of the new chiral center to be formed. Clearly, if enantioselectivity is to be improved, a structural feature must be designed into the silicon moiety that alters the course of reaction mechanism, bringing the influence of the silicon group to bear on the new chiral center (vide infra).



16

2.3. Addition Reactions of Chiral Acylsilanes

Chiral acylsilanes **17** reacted readily with nucleophilic reagents such as organolithiums or hydrides to give the addition products **18** as a mixture of two diastereomers (Scheme 5).[15] The diastereoselectivity of the addition reaction was usually modest with de ranging between 0 to 50%. The silylcarbinol adducts **18** (R = Ph, R′ = D) can undergo rearrangement to the corresponding alkoxysilanes **19** with complete stereospecificity. Since the silyl moiety in **19** can be removed easily by hydrolysis, the overall process can be considered as a method for the stereoselective synthesis of alcohols.

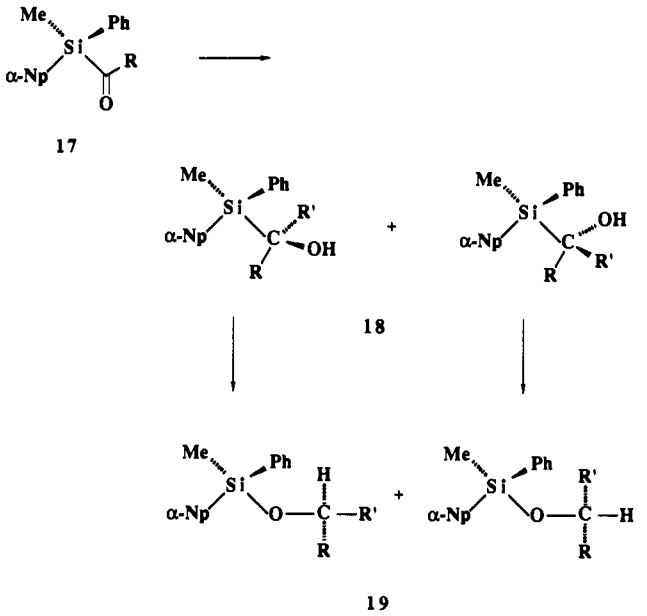
Recently, addition reactions of phenyllithium or sodium borohydride to the acylsilanes **20** were studied (Scheme 6). It was found that the diastereoselectivity of the addition was greatly enhanced (up to 78% de) relative to the same reactions for **17**. The improved stereoselectivity was attributed to the chelation of the alkoxy group with the organometallic reagent prior to the attack of the nucleophile on the carbonyl function.[16] Even though the diastereoselectivity was demonstrated only on the racemic acylsilanes **20**, one would expect that similar reactions using optically active **20** combining with the stereospecific Brook's rearrangement can lead to optically active carbinols with good ee.

2.4. Addition Reactions of Chiral α-Silyl Thione

The optically active α-silyl thione **21** was prepared from the corresponding α-silyl ketone **22** by acid catalyzed reaction with hydrogen sulfide. Diels–Alder cycloaddition of **21** with 1,3-butadiene gave the adduct **23** as a 75:25 mixture of two diastereomeric thiodihydropyrans (de 50%). Interestingly, the silyl moiety can be removed by treatment of **23** with tetrabutylammonium fluoride (TBAF) in aqueous tetrahydrofuran (THF) to give the protodesilylated product **24** with 51% ee (Scheme 7). This suggests that the protodesilylation reaction is a stereospecific process.[17]

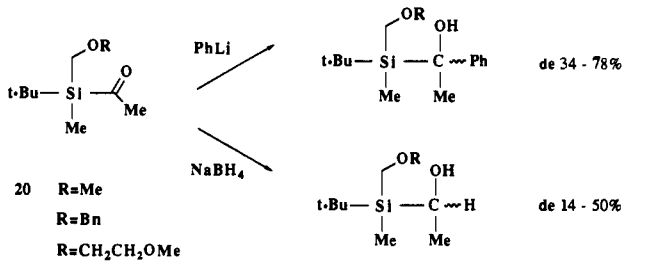
Compound **21** also reacted with methyllithium in THF at −78 °C followed by quenching with methanol to give the sulfide **25** as a mixture of two diastereomers (de 40%) (Scheme 7). It was argued that the chiral information was transmitted in the addition step, with the probable formation of two diastereomeric intermediates **26**. In terms of the utility of this reaction in asymmetric synthesis, it has been demonstrated that the silyl moiety in **25** can be protodesilylated stereospecifically with TBAF in THF/H(D)$_2$O.[18]

Scheme 5



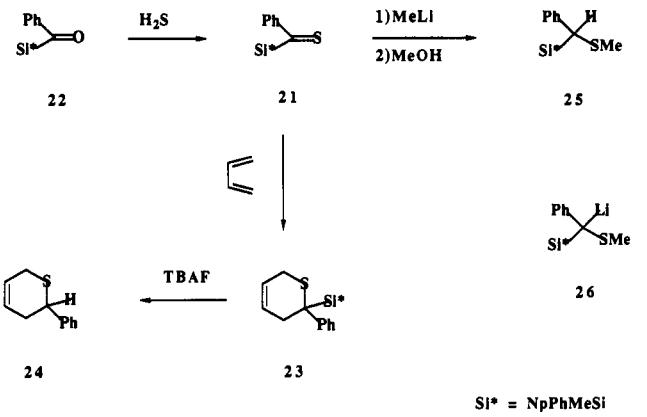
17 18 19

Scheme 6



20 R=Me R=Bn R=CH_2CH_2OMe

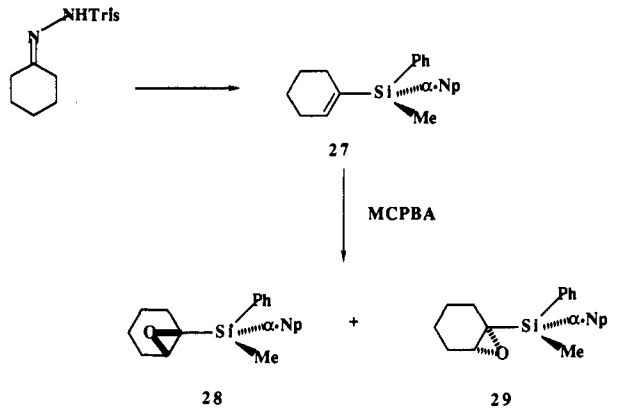
Scheme 7



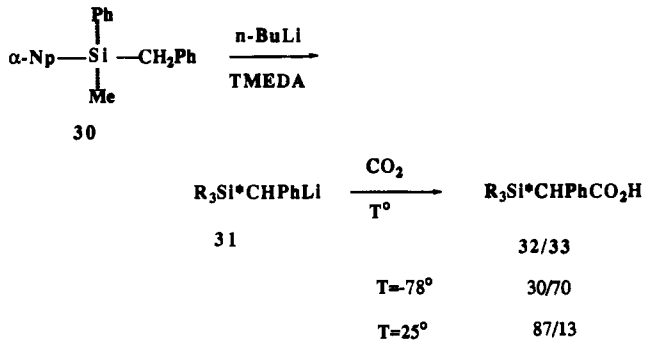
22 21 25 26 24 23

Si* = NpPhMeSi

Scheme 8



Scheme 9



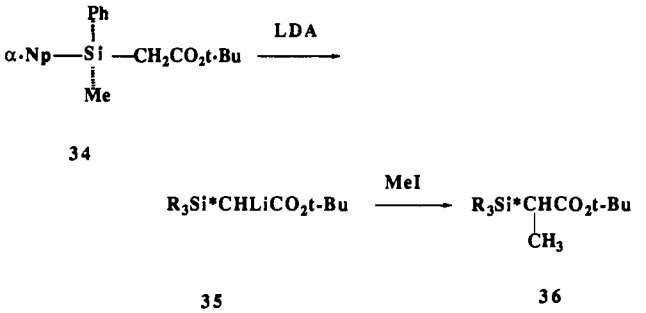
2.5. Epoxidation of Alkenylsilanes

The optically active alkenylsilane **27**, cyclohexenylmethyl-α-naphthylphenylsilane, was prepared from the 2,4,6-triisopropylphenylsulfonyl hydrazone of cyclohexanone via the Shapiro–Bond reaction.[19] Epoxidation of **27** with *m*-chloroperbenzoic acid (MCPBA) gave the epoxides **28** and **29** in a ratio of 43:57 (Scheme 8).[20] While the level of asymmetric induction is relatively poor (14% de), the reaction is of potential interest. It is known that protodesilylation of epoxysilane can be achieved with a high degree of retention of configuration to give the corresponding epoxide.[21] If better stereoselection in the epoxidation step can be realized through, for example, a template effect using a coordinating group attached to silicon, the reaction may well be useful for the asymmetric synthesis of chiral epoxides.

2.6. Reactions of Chiral α-Silylcarbanions

α-Silylcarbanions are useful intermediates in organic synthesis. As early as 1970, Brook and his co-workers studied the reactions of chiral α-silylcarbanions where the chirality resided on silicon.[22] Metalation of benzylmethyl-α-naphthylphenylsilane (**30**) using *n*-butyllithium/tetramethylethylenediamine (TMEDA) complex gave the carbanion **31**. Carbonation of **31** with carbon dioxide gave two diastereomeric carboxylic acids **32** and **33** (Scheme 9). The relative proportion of these two diastereomers depended quite markedly on the condition used for the carbonation. At room temperature, the ratio of **32**/**33** was 30:70, but at −78 °C, the ratio was 87:13.

Scheme 10



Scheme 11

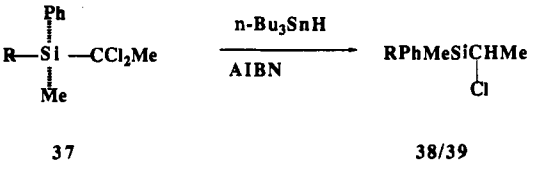


Table 1. Ratio of Diastereomers 38/39 in the Reduction of 37

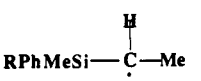
R	ratio of 38/39	de, %
α-Np	50/50	0
c-C_6H_{11}	47/53	6
i-Pr	51/49	2
t-Bu	52/48	4
mesityl	40/60	20

Similarly, the α-silyl ester **34** could be deprotonated with lithium diisopropylamide (LDA) to give the carbanion **35**. Methylation of **35** gave the ester **36** in 81% yield and 80% de (Scheme 10).[23]

The relatively high asymmetric induction observed in these reactions of α-silylcarbanions suggests that these reactions could be synthetically useful. Even though the silyl moiety had not been removed from the products of these reactions, one can confidently expect that the silyl group can be cleaved oxidatively with high retention of configuration on the basis of known chemistry.[24] These reactions can therefore serve as a useful way to synthesize optically active α-hydroxy acids and esters.

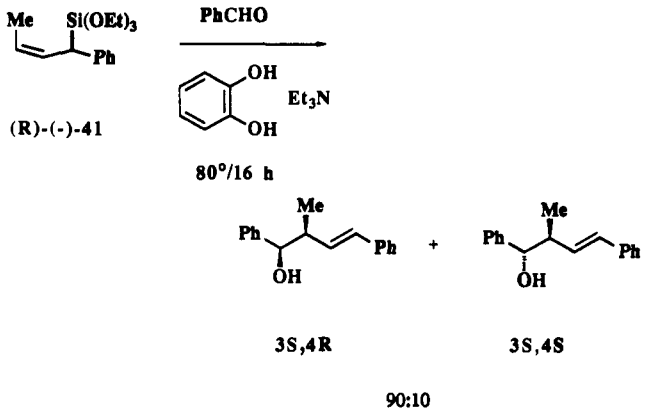
2.7. Radical Reduction of α-Halo Silanes

Monoreduction of a series of chiral α,α-dichloro silanes **37** was accomplished with tributyltin hydride in benzene in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) (Scheme 11).[25] The reduction products were a pair of diastereomers **38** and **39**, the ratio of the two depending on the groups attached to silicon (Table 1). Judging from the data in Table 1, it seems that as the R group in **37** increased in steric bulk, the selectivity increased also. However, even with the mesityl group, the diastereomeric excess in the reduction was still a modest 20%. Since the tin hydride reduction of halo compounds is known to proceed with a radical mechanism,[26] the results suggest that the radical intermediate **40** does not abstract a hydrogen



40

Scheme 12



atom from the tin hydride with high selectivity. In contrast, a similar carbanion intermediate, **26** or **31** or **35**, can be protonated, carbonated, or methylated with a fairly high degree of stereoselectivity. A possible difference could be that in the carbanion case, aggregation of the carbanion–counterion complex reinforces the steric effect of each of the silyl moiety and therefore leads to greater stereoselection.

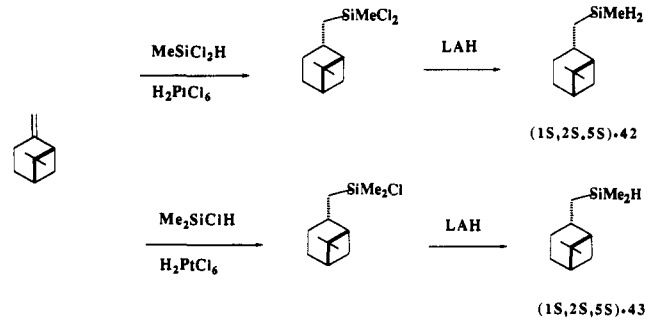
2.8. Conclusion Regarding the Use of Si-Centered Chiral Organosilicon Compounds in Asymmetric Synthesis

It is clear from the above that the Si-centered chiral organosilicon compounds used so far have been fairly limited in structural variation. Most of the compounds are derivatives of the methyl-α-naphthylphenylsilyl system. Its influence on stereoselectivity appears to be mainly steric in origin. With the exception of the reactions of α-silylcarbanions, the level of stereoselectivity is modest. Other factors such as electronic or template effects, in addition to steric effects, will have to be brought to bear on the reaction if stereoselectivity is to be improved. The enhanced diastereoselectivity observed in the addition reactions of **20** offers some hope that simple structural modifications of the chiral Si center by introducing alkoxy group or other ligands can be beneficial in many of these reactions.

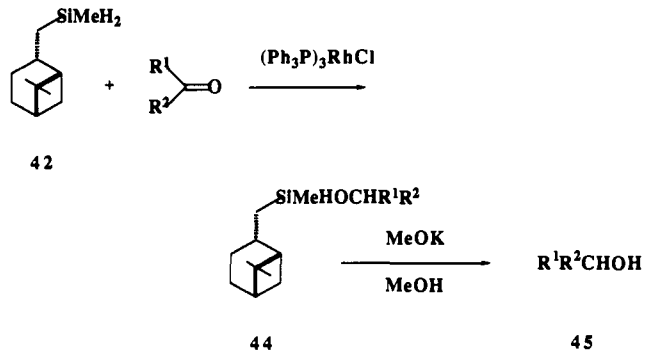
3. C-Centered Chiral Organosilicon Compounds

One of the limitations in using Si-centered chiral organosilicon compounds is the need to secure these compounds by optical resolution. Furthermore, since organosilicon compounds can undergo racemization in many of the reaction conditions, recovery and recycling of the valuable optically active silicon compounds with its optical purity intact cannot be guaranteed. All these factors conspire to limit the potential of using Si-centered chiral organosilicon compounds for asymmetric synthesis in any practical manner. In the last few years, increasing attention has been focused on the use of C-centered chiral organosilicon compounds where the chiral moiety, while attached to a silicon, is located at a carbon center. It is expected that such compounds can be prepared in synthetically useful quantities from readily available optically active natural products. Racemization at silicon would not constitute a problem as long as the stereochemical integrity at the carbon center remains intact.

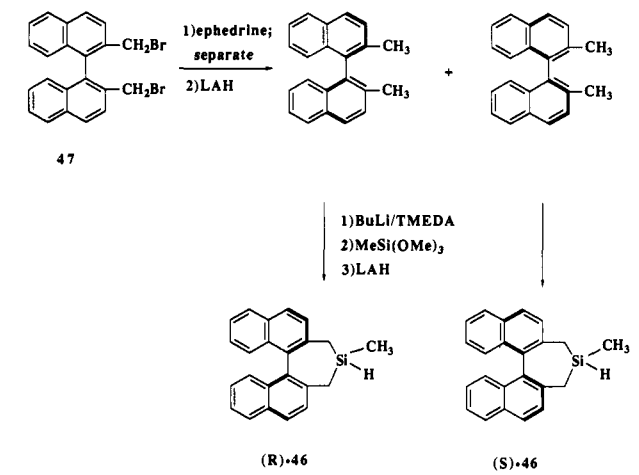
Scheme 13



Scheme 14



Scheme 15



At this point, a distinction should be made between C-centered chiral organosilicon compounds where the chiral center is a nonreactive substituent on silicon (and are the subject of this review) and organosilicon compounds where the chiral carbon center is also the reactive component. An example of the latter is the reaction of the optically active allylsilane (*R*)-(−)-**41** with a carbonyl electrophile (Scheme 12).[27] A number of such reactions have been extensively studied and will not be covered in this review.

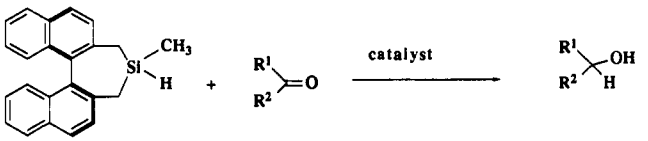
3.1. Enantioselective Reduction of Ketones

Some of the early examples of the C-centered chiral organosilicon compounds are the optically active silanes **42** and **43**, prepared by the hydrosilylation of (−)-β-pinene with dichloromethylsilane or chlorodimethylsilane, followed by LAH reduction (Scheme 13).[28] Reduction of prochiral ketones with the silane **42** using the Wilkinson catalyst $(Ph_3P)_3RhCl$ was examined. The

Table 2. Chirality Transfer with Binaphthylic Silane (*S*)-46

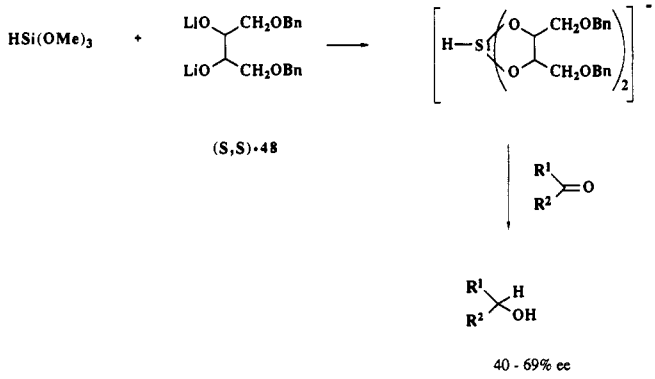
ketone	catalyst	conditions	yield, %	% ee (chirality)
$PhCOCH_3$	$(Ph_3P)_3RhCL$	PhH/80 °C/14 h	70	11.9 (+) (*R*)
$MeCO(CH_2)_5CH_3$	$TiCl_4$	CH_2Cl_2/−78 °C/4 h	75	15.3 (+) (*S*)
$MeCO(CH_2)_2COOEt$	$TiCl_4$	CH_2Cl_2/−11 °C/69 h	71	16.8 (−) (*S*)
$MeCOC(CH_3)_2COOEt$	$TiCl_4$	CH_2Cl_2/−30 to −11 °C/72 h	97	22.8 (+) (*S*)

Scheme 16



(S)-46

Scheme 17



(S,S)-48

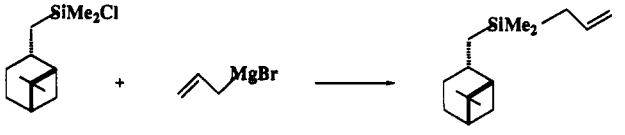
siloxy products **44** was hydrolyzed to give the alcohols **45** (Scheme 14) which had 8.9–25.7% ee.

These results should be compared with that obtained by Jung.[29] The optically active silanes (*R*)-**46** and (*S*)-**46** were obtained from the C_2 chiral binaphthyl compound **47** according to Scheme 15. Reduction of prochiral ketones with the silane **46** using either the Wilkinson catalyst or the Lewis acid $TiCl_4$ yielded optically active alcohols in 11.9–25.6% ee (Table 2; Scheme 16).

Recently, it has been demonstrated that hypervalent silicon hydrides can reduce aldehydes and ketones efficiently to the corresponding alcohols.[30] The hypervalent silicon species can often be formed in situ from tetravalent silicon compounds with fluoride or alkoxide ions. Enantioselective hydrosilylation of ketones was reported by the use of trimethoxysilane and an optically active lithium alcoholate **48** derived from diethyl L-(+)-tartrate (Scheme 17).[31] The enantioselectivity of the reaction was in the range of 40–69% ee.

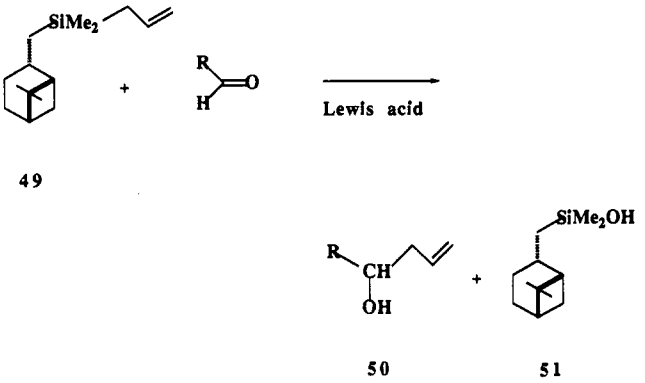
Some preliminary conclusions can be drawn by comparing these results with those obtained from the Si-centered chiral organosilicon compounds discussed in section 2.1. In the case of Si-centered chiral compound **4**, even though the center of chirality is in closer proximity to the site of reaction (the Si–H bond), it does not confer a greater degree of asymmetric induction in the alcohols obtained. Furthermore, the silane **4** was extensively racemized upon recovery whereas the C-centered chiral organosilicon compounds **42** and **46** could be recovered with their optical purities essentially intact, and in the case of **48**, it could in fact be used in catalytic amount and recycled.

Scheme 18



(1S,2S,5S)-49

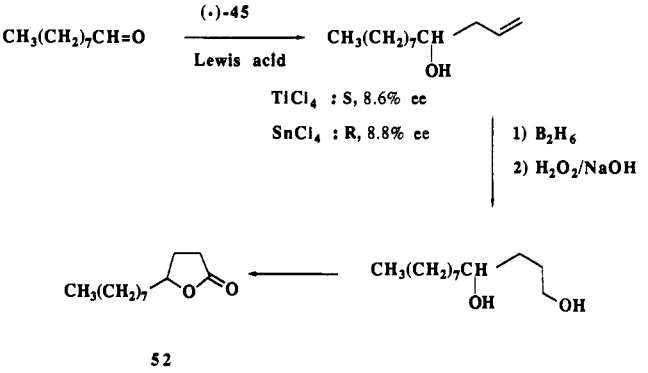
Scheme 19



49

50 51

Scheme 20

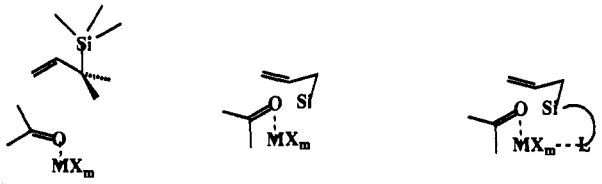


52

3.2. Asymmetric Synthesis Using C-Centered Chiral Allylsilanes

Starting from (−)-β-pinene, optically active α-pinanyldimethylallylsilane (**49**) was prepared according to Scheme 18. The reaction of **49** with aldehydes under Lewis acid conditions gave the homoallylic alcohols **50** in good yields but with a modest enantioselectivity of between 4 to 15% ee (Scheme 19).[32] The silicon-containing product, α-pinanyldimethylsilanol (**51**) and its disiloxane could be readily recovered from the reaction mixture with the same optical purity as the starting material **49** and could be recycled if necessary. The reaction has been applied to the synthesis of the γ-lactone **52** (Scheme 20), a component of the sex pheromone of rove beetle. Even though the lactone **52** had only 8.8% ee, the synthesis nonetheless demonstrated the synthetic potential of such asymmetric synthesis, and it underscores the importance to improve the enantioselectivity of these kinds of reactions.

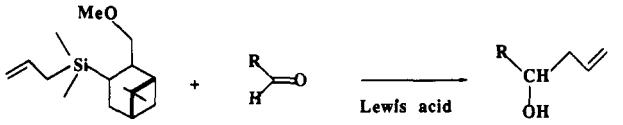
As we mentioned earlier, the modest stereoselectivity obtained in this and similar reactions is not totally unexpected if one considers the mechanism generally accepted for the reaction of allylsilanes with carbonyl compounds under Lewis acid conditions. With the trans transition state **16**, the chiral moiety, whether it is on silicon, or C-centered but attached to silicon, will have little influence on the stereochemical outcome of the new chiral center to be formed. On the other hand, the recent work by Denmark[33] suggests that the synclinal transition state **53** may also be operative under certain conditions. It is possible that in **53**, the silyl group may have a greater influence on the stereochemistry of the reaction. Attempts to improve the stereoselectivity must be aimed at introducing structural features or reaction conditions that favor the synclinal transition state **53**. One way to do this is to introduce on the silyl moiety ligands which can coordinate with the Lewis acid, as illustrated in **54**.



53 **54**

In this connection, Taddei et al. prepared the chiral allylsilane **55** starting from (1*R*)-myrtenal. The methoxy group in **55** presumably provided the coordination with the Lewis acid. When silane **55** reacted with carbonyl compounds in the presence of Lewis acids, the homoallylic alcohols **50** obtained showed ee varying between 21 to 56% (Scheme 21).[34]

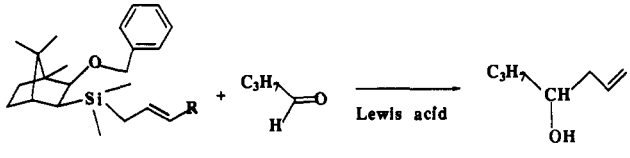
Scheme 21



55 **50** 21-56% ee

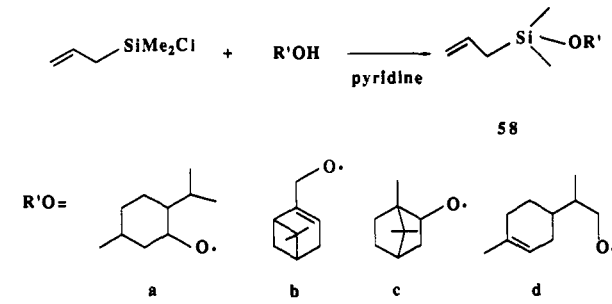
Comparing these results with the case of **49**, it is clear that the presence of a methoxy group dramatically enhanced the enantioselectivity of the reactions. On the other hand, the chiral silane **56**, with an alkoxy group directly attached to the bornane skeleton, reacted with butyraldehyde and Lewis acid to give the homoallylic alcohol **57** with a much lower ee (18%).[35] It is argued that in the case of **56**, the alkoxy group does not appear to be in position for an efficient coordination with a Lewis acid to induce the reaction toward the synclinical transition state (Scheme 22).

Scheme 22



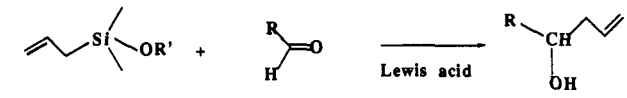
56 (R=H) **57** 18% ee

Scheme 23



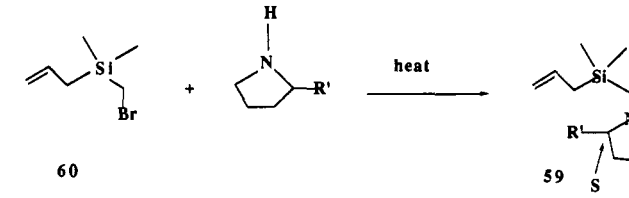
58

Scheme 24



58 **50** 18-23 % ee

Scheme 25

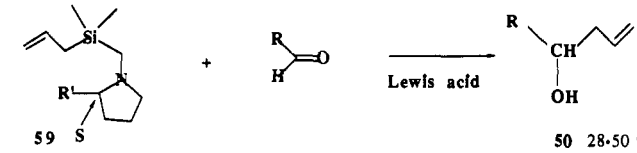


60 **59**

a: R'= CH_2OMe
b: R'= CO_2Me
c: R'= $CH_2OCONHPh$
d: R'= H

(S)-

Scheme 26



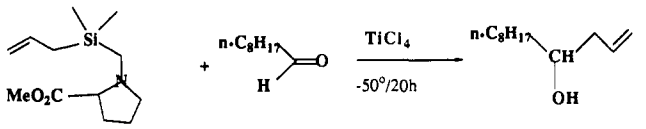
59 **50** 28-50 % ee

Alternative approaches were provided by using alkoxyallylsilanes where the alkoxy group was derived from readily available optically active alcohols. Thus, the chiral alkoxyallylsilanes **58** were prepared from allyldimethylchlorosilane according to Scheme 23. Reactions of **58** with a number of aldehydes and BF_3-etherate gave the homoallylic alcohols **50** with ee in the range of 18–23% (Scheme 24).[36] The improved selectivity in the reactions of **58** compared to that of **49** was attributed to the coordinating ability of the alkoxy group with the Lewis acid used.

Better coordinating ligands were introduced onto the silyl moiety in the form of a series of chiral (pyrrolidinylmethyl)allylsilanes **59** prepared from the (bromomethyl)allylsilane **60** and optically active compounds derived from (*S*)-proline (Scheme 25). The ee of the homoallylic alcohols **50** from the reaction of **59** with aldehydes (Scheme 26) was much improved (up to 50%)[37] relative to those from **49** and **58**.

Coordination of the oxygen function was critical to the success of the reaction. Compound **59d** which lacks the oxygen function, failed to give any homoallylic alcohol product under identical reaction conditions. Another interesting observation is that as the ratio of

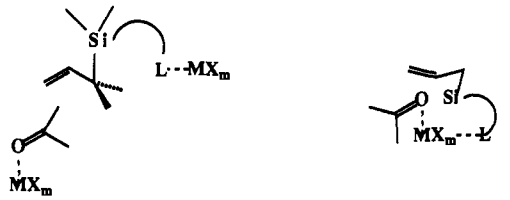
Table 3. Reaction of 59b with Nonanal under Lewis Acid Conditions



59b

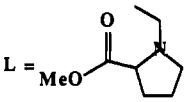
ratio: Lewis acid/ aldehyde	chemical yield of product, %	optical yield of product, % ee	absolute configuration
1:1	<5		
2:1	60	43	(*S*)
3:1	61	43	(*S*)
10:1	79	28	(*S*)

Lewis acid (e.g. $TiCl_4$) to aldehyde was increased from 1 to 10 equiv, the chemical yield of the product, within a fixed period of time, was increased, but the optical yield was decreased (Table 3). This observation was consistent with the possibility that at lower Lewis acid concentrations, the Lewis acid coordinates with both the oxygen ligand in **59** and with the aldehyde, leading to more of the synclinal transition state **61**.



62

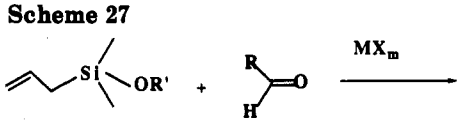
61



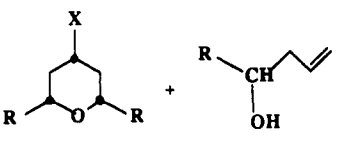
At higher Lewis acid concentrations, the antiperiplanar transition state **62** predominates with different molecules of the Lewis acid coordinating separately with the oxygen ligand and with aldehyde, thus accounting for a faster rate of reaction but a lower ee of the product. If this interpretation is correct, further improvement in stereoselectivity can be expected by the design of better ligands.

In addition to the synthesis of homoallylic alcohols, allylsilanes can be used in other contexts. It was found that the condensation of alkoxyallylsilanes **58** with aldehydes could give 2,4,6-trisubstituted tetrahydropyrans **63** instead of the homoallylic alcohols **50** (Scheme 27). The relative distribution of the two products, **63**

Scheme 27

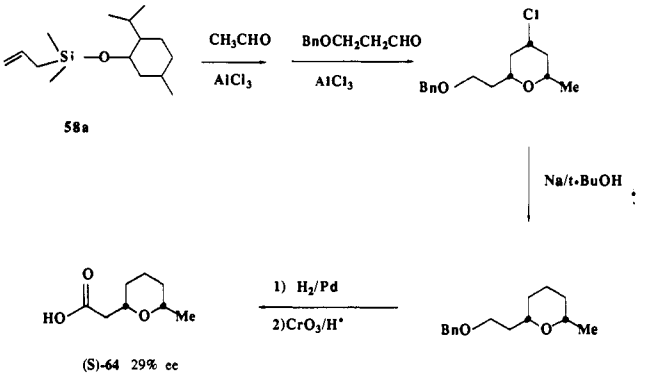


58



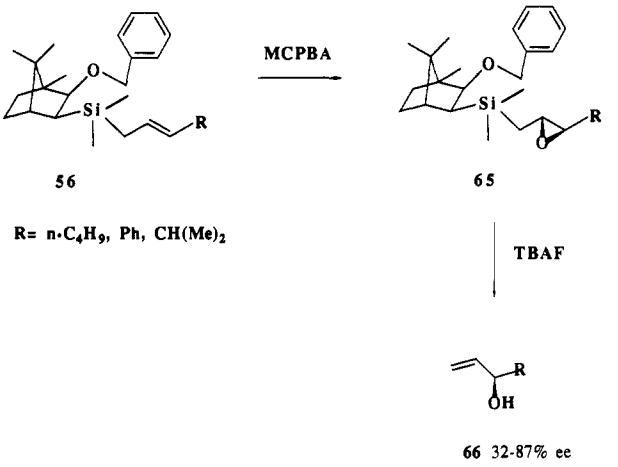
63 50

Scheme 28



58a

Scheme 29



56

R= n-C_4H_9, Ph, $CH(Me)_2$

65

66 32-87% ee

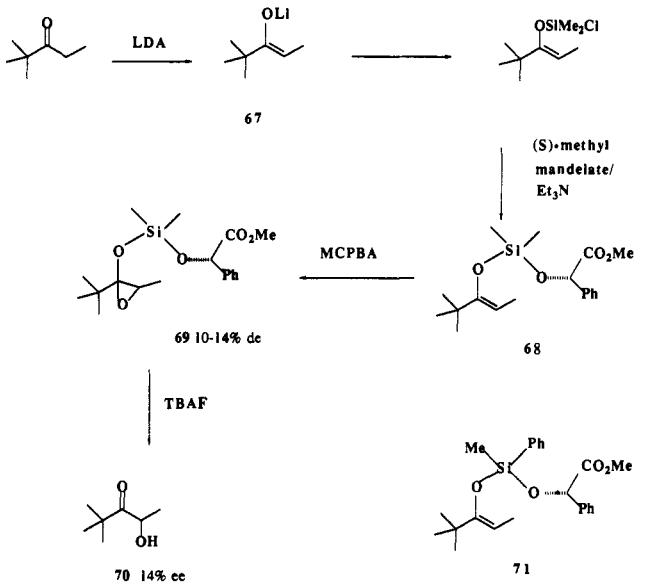
versus **50**, could be selectively controlled, depending on the nature of the alkoxy group OR, the nature and quantity of the Lewis acid used, and the temperature of the reaction. When two different aldehydes were used, unsymmetrically substituted tetrahydropyrans could be prepared. The reaction can therefore serve as a way to synthesize chiral tetrahydropyrans by using chiral alkoxyallylsilanes.[36] This was demonstrated by the synthesis of compound **64**, a natural compound that was isolated from the glandular secretion of the civet cat according to Scheme 28. In this case, (*S*)-**64** with 29% ee was prepared in 38% overall yield starting from the chiral alkoxyallylsilane **58a** (Scheme 28).

Another application of allylsilanes in asymmetric synthesis is the epoxidation reaction. The chiral allylsilanes **56** were treated with MCPBA to give the epoxysilanes **65** with 85–95% de. β-Elimination of the silyl moiety from **65** by TBAF gave the allylic alcohols **66** with 32–87% ee in 49–70% yield (Scheme 29).[38] Application of this reaction in asymmetric synthesis would be considerably enhanced if the chiral auxiliary in **56** could be prepared easily.

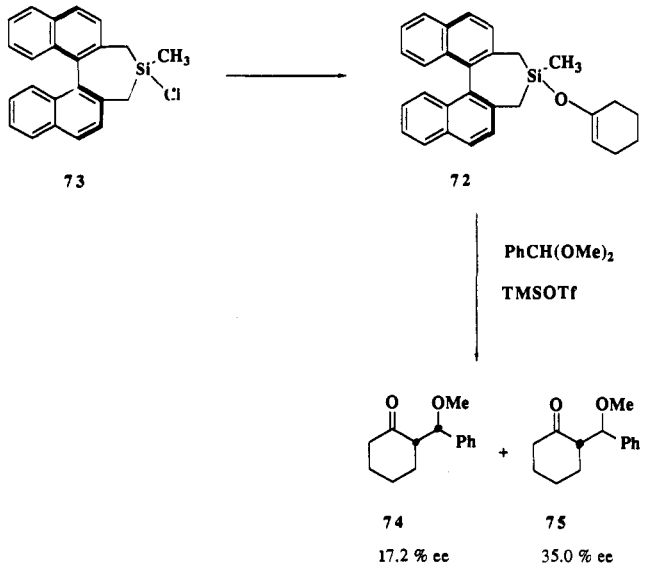
3.3. Reactions of Chiral Enol Silyl Ethers

Enol silyl ethers have become quite useful intermediates in synthesis.[39] Recently, enol silyl ethers with a chiral moiety attached to silicon have been synthesized. The lithium enolate **67** was reacted with dichlorodimethylsilane followed by condensation with (*S*)-methyl mandelate to give the chiral enol silyl ether **68** (Scheme 30).[40] Epoxidation of **68** with MCPBA gave the epoxide **69** in 10–14% de. Desilylation of **69** with

Scheme 30



Scheme 31



TBAF gave the hydroxy ketone **70** with 14% ee. Similar epoxidation of the enol silyl ether **71**, where chirality resided on silicon as well, gave the corresponding epoxide with the same de. It was thus concluded that the stereoselectivity of the epoxidation reaction was controlled by the chiral alkoxy group and not by the chiral silicon center.

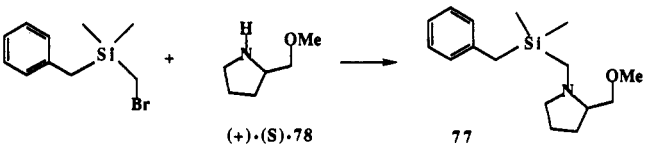
The chiral enol silyl ether **72** was prepared by the reaction of cyclohexanone with the binaphthyl silyl chloride **73** (Scheme 31).[29] Condensation of **72** with the methyl acetal of benzaldehyde under Mukaiyama aldol conditions[41] gave in 78% yield, a 4.4:1 mixture of the separable erythro **74** and threo **75** isomers. The enantioselectivity was 17.2% for **74** and 35.0% for **75**.

At the present time, the mechanism of the reactions of enol silyl ethers with electrophiles has not been delineated. It is known that in certain cases,[42] the reaction proceeds by addition of the electrophile E+ to form the intermediate carbocation **76**. If analogy to the allylsilane reaction is used, the transition state to the formation of **76** may well have an anti stereochemistry as well. Any effort to improve the stereoselection of these reactions will have to take such mechanistic implication into consideration.

3.4. Reactions of Chiral α-Silylcarbanions

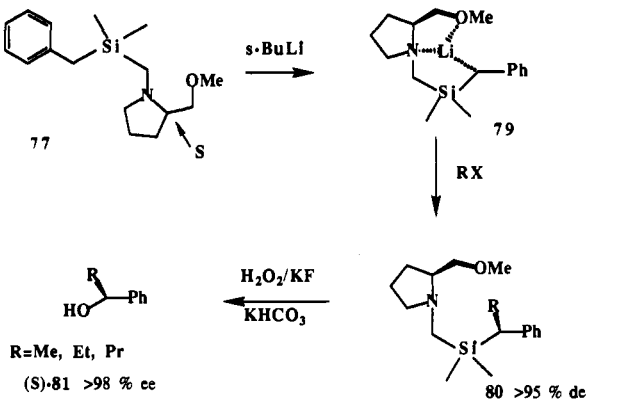
α-Silylcarbanions are useful intermediates in organic synthesis. Recently, the chiral organosilicon compound **77** was prepared from benzyl(bromomethyl)dimethylsilane and (*S*)-(+)-2-(methoxymethyl)pyrrolidine (**78**) (Scheme 32). Treatment of **77** with *sec*-butyllithium

Scheme 32

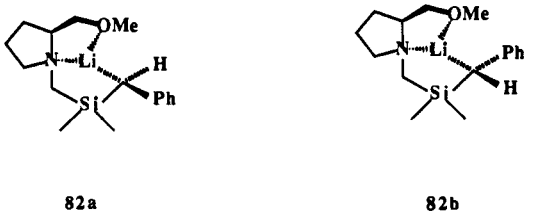


gave the α-silylcarbanion **79**. Reaction of **79** with alkyl halides in ether gave the alkylated products **80** in good yield and high diastereoselectivity (>95% de) (Scheme 33).[43] Oxidative cleavage[44] of the C–Si bond in **80** with

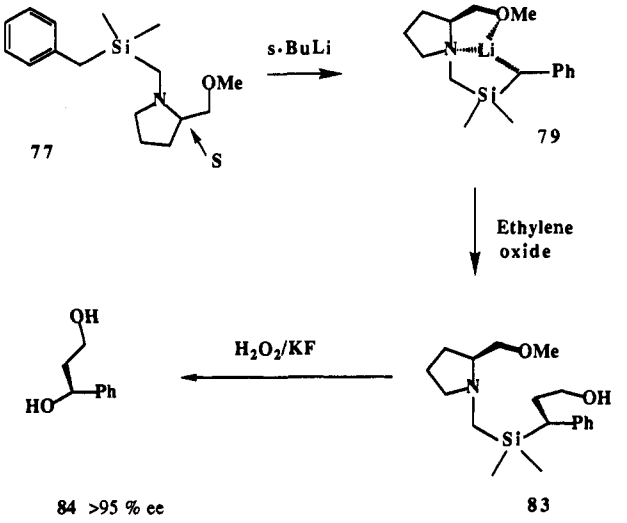
Scheme 33



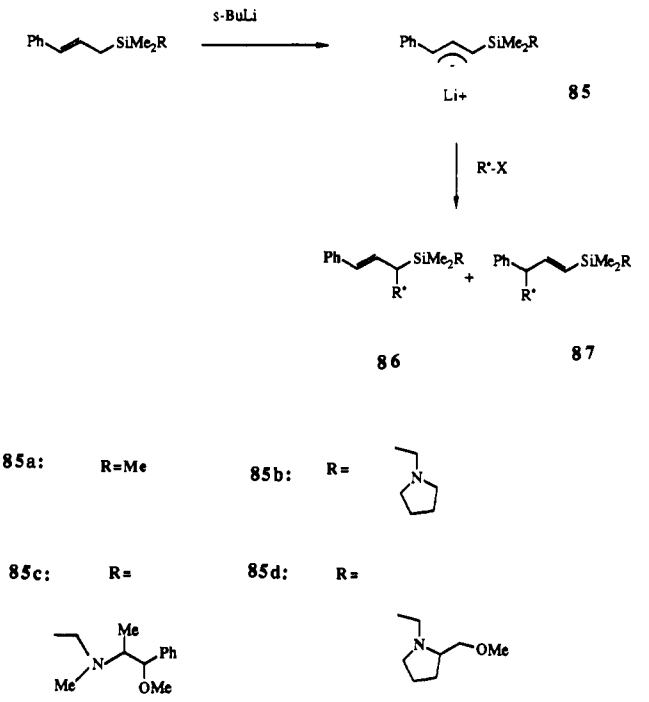
H_2O_2 and $KHCO_3$ gave chiral (*S*)-α-phenylcarbinols **81** with high optical purity (>98% ee). In addition to its synthetic potential, this reaction has several interesting features in terms of its contribution to our understanding of stereoselectivity. The de of the alkylation products **80** was greatly diminished if the alkylation was carried out in THF. It has been postulated that the high degree of asymmetric induction observed in ether is due to the formation of internal chelation of the chiral ligand with the lithium ion as depicted by **82a** or **82b**. Since it is fairly well established that



Scheme 34



Scheme 35



oxidative cleavage of C–Si bond proceeds with retentioin of configuration, it follows that **80** has the absolute configuration as indicated. What is not clear at this time is the exact structure of the carbanion **79** (**82a** or **82b**?) and the stereochemistry of the alkylation step (retention via **82a** or inversion via **82b**?). In spite of the mechanistic uncertainty, the high asymmetric induction observed in the reaction suggests that chiral organosilicon compounds can be profitably exploited for the synthesis of enantiomerically highly enriched compounds.

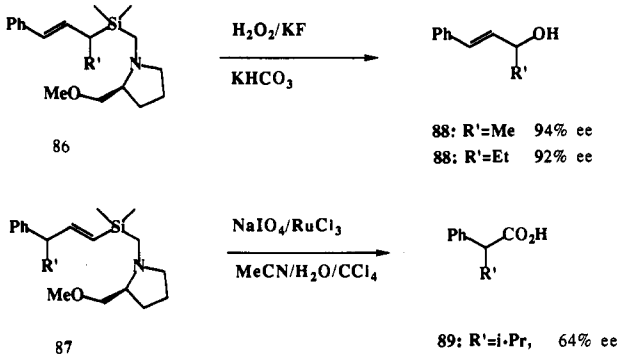
Reaction of the α-silylcarbanion **79** with ethylene oxide proceeded with high yield to give the compound **83** with high diastereoselectivity as well.[45] Oxidative cleavage of the C–Si bond of **83** gave the diol **84** with high ee (>95%) and the same (*S*) configuration at the benzylic carbon position (Scheme 34). The stereochemical course was presumably the same as the alkylation reaction. This reaction offers an attractive entry into optically active 1,3-diols.

In order to probe the factors controlling the stereoselectivity and to extend the synthetic utility to other silylcarbanions, the reactions of silylcinnamyl carbanions **85** have been examined carefully (Scheme 35).[46] The control of stereoselectivity in this allylic system is particularly challenging because of the additional complication due to regioselectivity. From the results summarized in Table 4, it is clear that when the silyl moiety contained only alkyl (methyl) substituents, alkylation of the cinnamyl anion **85a** with methyl iodide in ether gave a 1:1 mixture of the α- and γ-isomers (**86** and **87**, respectively). Replacement of one of the methyl groups by a pyrrolidinylmethyl substituent as in **85b** did not significantly affect the α/γ ratio in ether or THF. On the other hand, replacement of the pyrrolidinyl group by a bidentate ligand such as *O*-methyl-(–)-ephedrinyl as in **85c** changed significantly the α/γ ratio in favor of the α-isomer when the alkylation was carried out in ether. It has been previously established that α-regioselection is favored by similar bidentate ligand in the alkylation of simple α-silylallylic carbanions.[47] Internal chelation of the lithium counterion with the bidentate ligand has been suggested as the cause in favoring α-alkylation. Internal chelation most likely existed then in **85c**, at least in ether. However, the stereoselection in the alkylation of **85c** was not high, with de in the range of 6 to 14%. Using the bidentate ligand (methoxymethyl)pyrrolidinyl system as in **85d**, both α-regioselection and stereoselection were improved. With toluene as the solvent and methyl iodide as the electrophile, the α-alkylation product was formed in high yield with a high degree of asymmetric induction

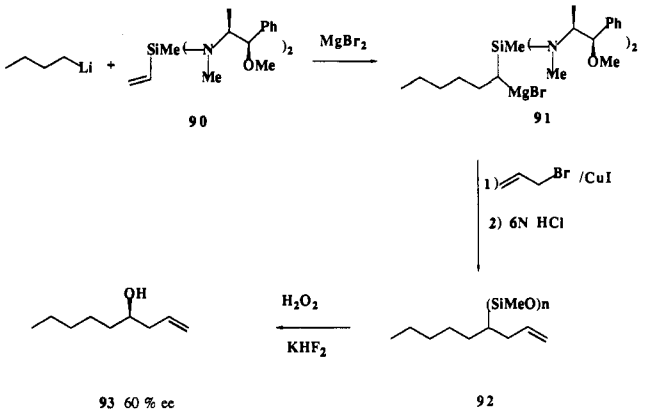
Table 4. Regio- and Stereoselection in the Alkylation of Silylcinnamyl Carbanions 85

carbanion	alkyl halide	solvent	chemical yield, %	regioselection α:γ (86/87)	stereoselection α(86): % de, conformation	stereoselection γ(87): % de, conformation
85a	MeI	ether		50:50		
85b	MeI	THF	82	46:53		
85b	MeI	ether	76	40:46		
85c	MeI	THF	92	39:41	6, (*S*)	
85c	MeI	ether	98	81:19	14, (*R*)	
85d	MeI	THF	99	46:52	18, (*R*)	17, (*S*)
85d	MeI	ether	92	88:7	>90, (*S*)	
85d	MeI	toluene	89	90:9	>90, (*S*)	
85d	EtI	THF	92	40:60	10, (*R*)	
85d	EtI	ether	99	68:19	92, (*S*)	
85d	EtI	toluene	81	79:20	>90, (*S*)	
85d	HexI	ether	74	84:9	>90, (*S*)	
85d	*i*-PrI	toluene	89	8:85		78, (*R*)

Scheme 36

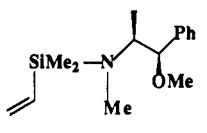


Scheme 37



(95% de). Similar stereoselectivity was observed for other alkyl halides as well. From a synthetic point of view, since the α- and γ-isomers could be separated by column chromatography, the present reactions offer a facile method for the enantioselective synthesis of these chiral molecules. The carbon–silicon bond can be cleaved under oxidative conditions to give the corresponding alcohols **88** or carboxylic acids **89** with the optical purity intact (Scheme 36).

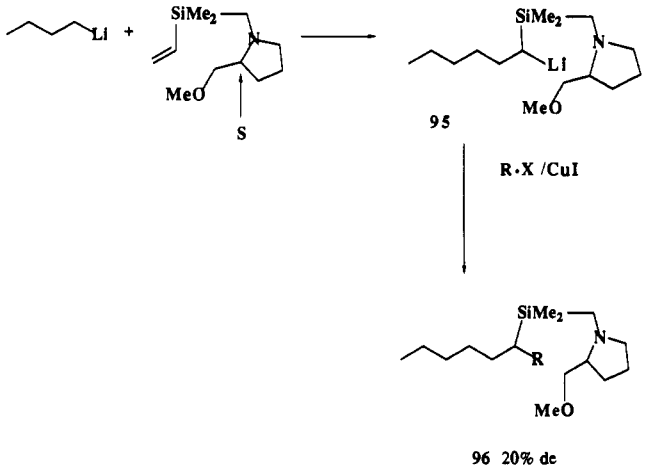
α-Silylalkyl carbanion could be generated by the addition of organolithium to vinylsilanes. Recently, chiral vinylsilane **90** was prepared in situ by treatment of vinylmethyldichlorosilane with the *N*-lithio derivative of (−)-ephedrine (Scheme 37). Addition of *n*-butyllithium to **90** followed by coupling of the carbanion **91** with allyl bromide gave the alkylated product **92** which on oxidative cleavage gave the chiral alcohol **93** with up to 60% ee.[48] Monoaminosilyl derivative **94** also gave (*R*)-**93** of 51% ee, indicating that only one



94

chiral ligand was sufficient for reasonably asymmetric induction. In this respect, it was rather surprising to find that similar reaction with the chiral α-silylalkyl carbanion **95**, using (*S*)-(methoxymethyl)pyrrolidinyl moiety as the chiral auxiliary and generated according to Scheme 38, gave the alkylated product **96** with a much lower stereoselectivity (20% de).[49] At this time, we cannot offer any reasonable explanation.

Scheme 38



4. Conclusion

It is clear that we are only in the beginning phase of the use of chiral organosilicon compounds in asymmetric synthesis. We are beginning to understand some of the limitations and potentials of this area of fascinating chemistry. Better knowledge of the mechanism of reactions of organosilicon compounds will be required if we wish to design synthetic reactions with greater stereoselectivity. The lesson we have learned so far is that steric effect alone is insufficient to provide the necessary stereocontrol. Other effects, such as stereoelectronic effect, or ligand coordination, will have to be utilized. In this respect, our exploration on the chemistry of organosilicon compounds is barely beginning and the scope for improvement is vast. It will be a rewarding area of research for those with the patience and ingenuity to meet the challenge.

5. References

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