Epoxysilane Rearrangement: Mechanistic Studies and Synthetic Applications

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Abstract: Mechanistic studies on and synthetic application of epoxysilane rearrangement, a novel synthetic use of α, β -epoxysilanes, in which an anion-induced ring-opening of epoxide and Brook rearrangement in the resulting α -silyl alkoxide occur in a tandem fashion to provide a β -siloxy allyl anion, are described.

1. Introduction:

Since the first synthesis of α, β -epoxysilanes reported by Eisch¹ more than forty years ago, many kinds of α, β -epoxysilanes have been synthesized and synthetic methodology based on their use has been developed.² The seminal work of Stork and co-workers,³ who showed that α, β -epoxysilanes can be converted to aldehydes and ketones via a ring-opening followed by desilylation, has stimulated considerable interest in their chemistry.

In this review we report a mechanistic aspect and synthetic applications of epoxysilane rearrangement, which is a novel synthetic use of α, β -epoxysilanes and features transformation of β -silyl- α, β -epoxy carbanion to β -siloxy allyl anion.

Thirteen years ago, we reported a new approach to the synthesis of highly functionalized cyclopentenol **5** using [3 + 2] annulation that involves a combination of (β -(trimethylsilyl)acryloyl)silane **1** as the three-carbon unit and lithium enolate **2** of alkyl methyl ketone as the two-carbon unit, which relies on the 1,3-sigmatropic shift in vinylcyclopropanolate **4** formed via a 1,2-anionic rearrangement of the silyl group (Brook rearrangement)⁴ in the 1,2-adduct **3** followed by internal carbonyl attack by the anion (Scheme 1).⁵

Scheme 1. Brook-rearrangement mediated [3 + 2] annulation.

During the course of extension of this methodology to asymmetric versions, we had occasion to examine the reaction of β -silyl- α, β -epoxyacrylsilanes **6** with enolate of alkyl methyl ketone **7**. Although we expected the formation of cyclopentenol derivatives **12** via a two-fold Brook rearrangement followed by an intramolecular aldol reaction, the major products were uncyclized enol silyl ether **10** and cyclopropanediol derivative **11**, the latter being formed as a result of an intramolecular allylic attack on the carbonyl group by a siloxy carbanion generated by the second Brook rearrange-

Scheme 2. Attempted asymmetric Brook-rearrangement mediated [3 + 2] annulation.

ment (**8** $\rightarrow$ **9**)(Scheme 2).

This result indicated the possibility of the reaction of an epoxysilane **13** bearing an anion-stabilizing electron-withdrawing group at the α -position with an amide base in the presence of an electrophile. If a tandem process that involves a base-promoted isomerization of the epoxide (**14** $\rightarrow$ **15**), Brook rearrangement (**15** $\rightarrow$ **16**), and a reaction of the resulting allylic anion with an electrophile (**16** $\rightarrow$ **17** $\rightarrow$ **18**) proceeds well, the epoxysilane **13** would function as a homoenolate equivalent⁶ with synthetically useful functionality (Scheme 3).

Scheme 3. Tandem base-promoted ring-opening/Brook rearrangement/allylic alkylation of α, β -epoxysilanes bearing an electron-withdrawing group at the γ -position.

2. Tandem Base-promoted Ring-opening/Brook Rearrangement/Allylic Alkylation of *O*-Silyl Cyanohydrins of β -Silyl- α,β -Epoxyaldehyde⁷

First, we chose *O*-silyl cyanohydrins of α,β -epoxyaldehydes **19** bearing a nitrile group as the electron-withdrawing group as a substrate and investigated its reaction with a base in the presence of alkylating agents. When **19a** and **19b** were treated with LDA (1.1 equiv) in THF at -80°C in the presence of MeI (1.2 equiv) for 5 min, α -methylated cyanohydrins **20**, products formed via a tandem sequence (**14** $\rightarrow$ **18**), were obtained in 82% and 84% yields, respectively (Table 1).

Table 1. Tandem base-promoted ring-opening/Brook rearrangement/allylic alkylation of *O*-silyl cyanohydrins of β -silyl- α,β -epoxyaldehyde.

RX	20, yield (%) (<i>E/Z</i>)	
	from 19a	from 19b
MeI	82 (2.5)	84 (22.0)
EtI	76 (2.9)	74 (28.0)
<i>i</i> -PrI	58 (2.8) ^a	74 (31.0)
PhCH ₂ Br	86 (2.7)	98 (47.0)
CH ₂ =CHCH ₂ Br	83 (3.4)	87 (40.0)

^a 12% yield of **20** (R = H) was obtained.

It is particularly noteworthy that (1) the reactions were completed within 5 min at -80°C and alkylation products of possible intermediates other than **20** were not detected and (2) *E/Z* ratios of **20** obtained from the two diastereomers were markedly different.

To obtain a better understanding of the reaction pathway, we first examined the effects of a cation and a base on the *E/Z* selectivity of the reaction using lithium hexamethyldisilazide (LHMDS), sodium hexamethyldisilazide (NaHMDS), and potassium hexamethyldisilazide (KHMDS) (Table 2). While the use of lithium hexamethyldisilazide (LHMDS, 1.0 M in THF) resulted in lower yields but improvement in *E/Z* ratios with **19a**, comparable yields of **20** were obtained with potassium hexamethyldisilazide (KHMDS, 0.5 M in toluene). It is notable that the increased formation of the *Z*-derivative with **19a** was observed in the case of the latter base. The best results, in terms of yield and *E/Z*-selectivity, were obtained with sodium hexamethyldisilazide (NaHMDS, 1.0 M in THF), allowing the formation of (*E*)-**20** in excellent yields.

Table 2. Effects of a cation and base on the *E/Z* selectivity.

base	20 yield (<i>E/Z</i>)	
	from 19a	from 19b
LHMDS	44 (23.0)	83 (31.0)
KHMDS	84 (0.9)	87 (9.7)
NaHMDS	96 (40.0)	98 (<i>E</i>)

Since increased formation of the (*Z*)-isomer was observed in the case of LDA and KHMDS, which contain hexane and toluene, respectively, we examined the effect of the counter cation⁸ using the same solvent system. However, the *E/Z* selectivity in the reaction does not seem to strongly depend on the counter cation. The relationship between polarity of the solvent⁹ and *E/Z* geometry of **20** was then investigated. The results are summarized in Table 3. The use of less-polar solvents resulted in a substantial enhancement of *Z*-selectivity, suggesting that the nature of the solvent plays an important role in determination of *E/Z* selectivity in the reaction.

Table 3. Effects of a solvent on the *E/Z* selectivity.

solvent	substrate	yield (%) <i>E/Z</i>
hexane	19a	93 1.5
	19b	78 6.0
toluene	19a	86 1.0
	19b	83 24.0
Et ₂ O	19a	84 1.9
	19b	77 28.0
THF	19a	85 28.0
	19b	84 52.0

One possible explanation of these results is that the internal chelated structure (*Z*)-**21'**, which involves M-O,¹⁰ is an immediate precursor to (*Z*)-**20** by alkylation. Thus, the poorer donor solvents help the intramolecular coordination of the siloxy group, therefore giving rise to the formation of (*Z*)-**20**. This is supported by the results showing that (*Z*)-selectivity in the methylation of **19a,b** with the bases was significantly lowered upon addition of HMPA, which can disrupt the chelated structure by solvating the cations (Table 4).

Table 4. Effects of addition of HMPA on the *E/Z* selectivity.

CH_3I
 base
 THF
 -80°C , 5 min

substrate	conditions		20		19
	base	HMPA	yield (%)	<i>E/Z</i>	yield (%)
19a	LDA	(-)	82	2.5	-
19a		(+)	61	28.0	26
19a	KHMDS	(-)	84	0.9	-
19a		(+)	92	15.0	-
19b	LDA	(-)	84	22.0	-
19b		(+)	85	<i>E</i>	8
19b	KHMDS	(-)	87	9.7	-
19b		(+)	84	<i>E</i>	-

Although the intermediacy of a chelated species such as (*Z*)-**21'** is consistent with the solvent effect on the *E/Z* ratio of the product, it can not explain the fact that **20** was

obtained from the two diastereomers **19a,b** in different *E/Z* ratios in the cases of LDA and KHMDS, unless it is assumed that (*E*)- and (*Z*)-**21** are formed from the starting cyanohydrins to a different extent depending on the stereochemistry of the starting cyanohydrins and on the solvent polarity and that they collapse to products before the establishment of an equilibrium. To determine whether alkylation occurs before equilibration, methyl iodide was added after addition of the base. The *E/Z* ratios changed only slightly (Table 5), suggesting two possibilities.

Table 5. Alkylation of pregenerated β -siloxy allyl anions.

	20 (from 19a)		20 (from 19b)	
base	yield (%)	<i>E/Z</i>	yield (%)	<i>E/Z</i>
LDA	76	2.9	69	38.0
LHMDS	36 ^a	39.0	68	54.0
NaHMDS	86	38.0	85	124.0
KHMDS	78	0.3	66	12.0

^a 56% of **19a** was recovered.

One possibility is that **21** is an immediate precursor for the alkylation, isomerization between (*E*)- and (*Z*)-**21** does not occur under the conditions, and the solvent effect for *E/Z* selectivity operates in the earlier steps. The other possibility is that **21** is not an immediate precursor and the alkylation can occur in a concerted manner from intermediates that preserve stereochemical information originating from the starting materials and form in a ratio depending on the solvent polarity. The former possibility can be ruled out if the *E/Z* isomerization between (*E*)- and (*Z*)-**21** is proved to occur under the conditions.

To verify whether isomerization between (*E*)- and (*Z*)-**21** occurs, carbanions were generated by deprotonation of (*E*)- and (*Z*)-**22**, which were prepared by quenching the reaction of **19b** with NaHMDS in THF and **19a** with KHMDS in Et₂O/toluene, respectively, by acetic acid (Scheme 4). No or only slight *E/Z*-isomerization was observed regardless of the order of addition of the reagents when (*E*)-**22** and (*Z*)-**22** were treated with a base and methyl iodide under similar conditions to those for **19**. These results cannot rule out the possibility of intermediacy of **21** in the reaction of **19**.

Scheme 4. Base-induced alkylation of **22**.

As a reaction pathway that can explain the above results, we propose a pathway in which a pentacoordinate silicate species, (*E*)- and (*Z*)-**23**, are formed first via addition of oxyanion, generated by ring-opening of the epoxide, to the

silicon center, and then transformed into alkylation products (*E,Z*)-**20** in a concerted manner or via allyl anion intermediates **21** (Scheme 5). Silicate (*E*)-**23** can be formed via *syn*-elimination of **19a** or *anti*-elimination of **19b**, and (*Z*)-**23** can be formed via *anti*-elimination of **19a** or *syn*-elimination of **19b**. After rotation around the C3-C4 bond in such a way that the C4-Si bond can adopt a parallel arrangement with the π orbitals of the double bond, (*E*)- and (*Z*)-**23** are converted to silicates (*E*)-**23a,b** and (*Z*)-**23a,b**, respectively, among which only (*Z*)-**23a** can form an internally chelated structure with a metal cation. Consequently, if the chelated intermediate is responsible for the formation of (*Z*)-**23**, the mode of ring-opening should be *anti* because (*Z*)-**20** is formed in a higher ratio from **19a** than from **19b** (see Table 1).

To determine the mode of ring-opening of the epoxide, we designed the following competitive experiment that relies on the fact that the conformational preference in *syn*- and *anti*-elimination acts in an opposite sense in the reaction of **19a** and **19b**. Thus, while the transition state from **19a** is more favorable than that from **19b** in the *syn*-elimination in terms of less repulsive interactions between H-4 and the *O*-silyl cyanohydrin moiety (*A*-value¹¹ for OSiMe₂: 0.74; for CN: 0.2), in the case of *anti*-elimination, the transition state from **19b** is more favorable. When a mixture of **19a** (1 equiv) and **19b** (1 equiv) in THF was treated with LDA (1 equiv) in the presence of MeI (1 equiv) at -80 °C for 5 min, a 1.0:0.7 mixture of **19a** and **19b** was obtained in 40% yield together with 35% of **20** (*E/Z* = 6.6), indicating that **19b** is more reactive than is **19a** (Table 6). These results are consistent with *anti*-elimination, thus supporting the pathway described above. Furthermore, the concerted *anti*-deprotonation and ring-opening process was supported by the fact that the reactivities of **19a** and **19b** were not affected by the addition of HMPA.

Further support for the proposed *anti*-elimination was also provided by reactions using *cis*-epoxysilanes, in which the difference between reactivities of the two diastereomers was expected to increase because of more severe steric repulsion between the siloxy and silyl groups in a transition state for *anti*-elimination.

The key question that needed to be addressed is why the mode of elimination in the case of **19** is *anti*, which is in sharp contrast to the widely accepted chelation-assisted *syn*-elimination mechanism for a base-promoted ring-opening.^{12,13} We speculated that the intramolecular chelated structure for the *syn*-elimination is less favorable because partial formation of an oxygen-silicon bond occurs in the transition state leading to **23** from **19**. To test this, we carried out a competitive experiment using **19b** and **24b**, which bear electronically and sterically different silyl groups, anticipating that if the formation of the oxygen-silicon bond occurs after complete formation of the double bond, a difference between reactivities of **19b** and **24b** would not be observed (Table 7). When **19b** (1 equiv) and **24b** (1 equiv) were treated with LDA (1.4 equiv) in the presence of CH₃I (1.4 equiv) in THF for 5 min, methylated derivatives (*E*)-**20** and (*E*)-**25** were obtained in a ratio of 3.1:1 together with recovery of the starting materials, **19b** (18%) and **24b** (40%), indicating that **19b** is more reactive than **24b**. This result can be understood by assuming that O-Si bond formation is involved in the rate-determining

Scheme 5. A plausible reaction pathway.

Table 6. Competition reaction between **19a** and **19b**.

anti-elimination

syn-elimination

transition state and is more favorable in the *t*-butyldimethylsilyl group than in the *t*-butyldiphenylsilyl counter part, due to a steric factor rather than an electronical one, which would reflect the stabilization of the silicate ion by the phenyl group on the silyl group. Increased steric repulsion between a base and the silyl group in the proton abstraction, which is another possible factor explaining the result, proved to be less important on the basis of results of competitive experiments using less and more hindered bases, LiNEt₂ and lithium 2,2,6,6-tetramethylpiperidide (LTMP). Thus, reaction with LiNEt₂ resulted in almost the same ratio of (*E*)-**20**/*(E)*-**25**, while the ratio was decreased in the reaction

Table 7. Competitive reaction between **19b** and **24b**.

base	yield (%)			yield (%)	
	(<i>E</i>)- 20	(<i>E</i>)- 25	(<i>E</i>)- 20 / <i>(E)</i> - 25	19b	24b
LDA	22	7	3.1	18	40
LiNEt ₂	19	6	3.2	24	39
LTMP	22	15	1.5	19	30

with LTMP. Therefore, the partial formation of an O-Si bond in the transition state can make the *syn*-elimination less favorable in the case of α -silyl epoxide relative to substrates lacking an α silyl group.

3. Synthetic Application of the Epoxysilane Rearrangement

Based on the above described results showing that an α , β -epoxysilane with an anion at the γ -position can function as an efficient trigger in cascade reactions, we decided to extend this tandem sequence to several synthetically useful reactions. We devised three different methods for the generation of a carbanion at the γ -position of the epoxysilanes, (1) deprotonation, (2) reaction of acylsilanes with a nucleophile

Scheme 6. Methods for the generation of a carbanion at the γ -position of the epoxysilanes.

followed by Brook rearrangement, and (3) a conjugate addition of a nucleophile to an enoate system bearing an epoxysilane moiety at the α -position (Scheme 6).

3.1 Reaction of **26** with Bis-electrophile¹⁴

During the investigation of the mechanism of the epoxysilane rearrangement using **26**, an epoxysilane derivative bearing a nitrile group as an electron-withdrawing group and lacking a siloxy group, we observed that the reactions of **26** with MeI (1 equiv) in the presence of a base (1 equiv) afforded dimethylated enol silyl ethers as a major product, suggesting that the second deprotonation and methylation are very fast processes probably because of the small steric demand of the nitrile group. These results prompted us to examine the reaction with bis-electrophiles.¹⁵ When **26** was treated with NaHMDS in the presence of 1,4-dibromobutane at -80°C , five-membered annulation product **27** was obtained in excellent yield. A similar result was obtained for the six-membered ring. Since the intramolecular alkylation proceeded well, we next examined the possibility of an annulation reaction using ω -bromo- α,β -unsaturated esters. In the reaction leading to six- and seven-membered rings, the expected reaction, which involves a proton transfer in the Michael adducts followed by an intramolecular alkylation,¹⁶ occurred to give **28**. In contrast, in the reaction leading to a five-membered ring, instead, a Michael-Initiated-Ring-Closure, so-called MIRC reaction,^{17,18} involving conjugate addition to the enolate followed by an intramolecular alkylation before proton transfer, occurred to give **29** in 66% yield as a single diastereomer. The above results led us to examine the MIRC reaction of **26** with α,ω -bisenoates.¹⁹ When a mixture of **26** and **30** in THF-HMPA was treated with NaHMDS at -98°C for 15 min, MIRC products **31a,b** were obtained as a diastereomeric mixture (8:3) in 64% yield. This MIRC reaction seems to be affected by a subtle conformational difference; in fact, reaction of **26** with α,ω -bisenoates that would lead to a six-membered ring afforded only Michael addition products (Scheme 7).

3.2 Nitrile Anion Cyclization with Epoxysilanes²⁰

We became interested in determining whether epoxysilane **32**, a substrate in which one more carbon atom is introduced between the epoxide and the nitrile group in **26**, could undergo the same type of reaction as that of **26**. If so, epoxy nitrile

Scheme 7. Reaction of **26** with bis-electrophiles.

derivative **32** by reaction with a base would afford **36** via a tandem process that involves the formation of cyclopropane derivative **34** by epoxy nitrile cyclization followed by Brook rearrangement and an anion-induced cleavage of the cyclopropane ring. In this case, the nucleophilic characters of the α -nitrile carbanions **33** and **35** might be critical factors in controlling the reaction. In contrast to the case of **19**, in which a base-promoted ring-opening proceeds in a concerted process via an *anti*-opening of the epoxide followed by the formation of an O-Si bond, the three processes, cyclopropane formation from **33** (**33** $\rightarrow$ **34**), carbanion-mediated ring-opening of the cyclopropane (**34** $\rightarrow$ **35**), and alkylation (**35** $\rightarrow$ **36**), should be affected more by the nature of the carbanions. Thus, the ring-opening of the epoxide and the alkylation can be facilitated by increasing the nucleophilicity of the carbanions, whereas the cyclopropane ring cleavage can be enhanced by increasing the stability of the anion in **35**.

Scheme 8. Nitrile anion cyclization with epoxysilanes followed by Brook rearrangement/ring-opening of cyclopropane nitriles/alkylation.

When *trans*-**37** (X = H, Ph (diastereomeric mixture)) was treated with NaHMDS followed by the addition of MeI at -15°C , methylated enol silyl ether (*Z*)-**38** was exclusively obtained (Scheme 9). The fact that the reaction of an α -phenyl derivative required more forcing conditions suggests that the ring-opening of the epoxide is the slowest step. This is supported by the finding that treatment of one

Scheme 9. Methylation of *trans*-37.

diastereomer of *trans*-37 (X = Ph) with *n*-BuLi at -80 °C afforded a 1:1 mixture of the diastereomers in 87% yield.

It should be noted that (*E*)-38 could not be detected even with addition of HMPA, suggesting that an internal chelation structure 39 is not responsible for the formation of the (*Z*)-isomer. The observed *Z*-selectivity can be explained by assuming the formation of silicate intermediate 40^{21,22} via backside displacement of the epoxide by the α -nitrile carbanion and the O-Si bond formation followed by concerted processes involving Brook rearrangement and the *anti*-mode of eliminative ring fission of the cyclopropane from the rotamer 40' (Scheme 10),²³ in which the C4-Si bond can adopt a coplanar arrangement with the C2-C3 bond. In this case, Brook rearrangement should occur with retention of configuration at the silyl-bearing carbon atom, because the (*E*)-derivative should be obtained if the rearrangement proceeds with inversion of configuration.^{24,25} If our analysis for the stereoselectivity is correct, the use of *cis*-epoxide *cis*-37 should provide (*E*)-enol silyl ether via 41'. To confirm this, we decided to examine the reaction of *cis*-37.

In fact, exposure of *cis*-37 to NaHMDS followed by methylation gave (*E*)-38 in 71% yield (Scheme 11). No

Scheme 10. Stereochemical processes of base-mediated isomerization of *trans*- and *cis*-37.

(*Z*)-enol silyl ether derivative was detected. The observed stereospecificity is compatible with the concerted pathway shown in Scheme 10.

Scheme 11. Methylation of *cis*-37.

3.3 γ -*p*-Toluenesulfonyl- α,β -Epoxy-silane as an Acrolein β -Anion Equivalent²⁶

α,β -Unsaturated aldehyde is an important structural moiety as a synthetic intermediate in a variety of chemical transformations as well as in diverse classes of bioactive organic molecules. Consequently, much effort has been devoted to the development of synthetic methods for the functionality. Among these, the most general and commonly used methods include Wittig-type homologation reaction²⁷ and the use of β -acyl vinyl anion equivalents.²⁸ Most of these methods, however, require relatively harsh reaction conditions to unmask the α,β -unsaturated aldehyde. We envisioned that introduction of a leaving group that can stabilize a carbanion instead of the nitrile group would produce 42, which can be easily transformed into conjugate aldehyde 44 via desilylation with concomitant elimination of the leaving group in 43 (Scheme 12).

Scheme 12. Epoxysilanes 42 as an acrolein β -anion equivalent.

We examined a variety of leaving groups, including pyridin-2-sulfinyl, phenylsulfonyl and *p*-toluenesulfonyl. Among them, *p*-toluenesulfonyl derivative 46, which was prepared from the known epoxy silane 45 readily derived from propargyl alcohol, was found to provide the best result.²⁹ When NaHMDS was added to a cooled (-80 °C) solution of 46 and benzyl bromide and the reaction mixture was allowed to warm to -60 °C over a period of 30 min, enol silyl ether 47 was obtained in 93% yield. Conversion of 47 to conjugate aldehyde 48a was carried out by treatment with *n*-Bu₄NF in 86% yield (Scheme 13). It should be noted that 46 does not need chromatographic purification and possesses excellent shelf stability at room temperature.

Scheme 13. Preparation of 46 and its reaction with PhCH₂Br followed by demasking to 48.

The entire reactions could be carried out in a one-pot process by the addition of ethanol, which can enhance the

solubility of TBAF at a lower temperature and lower the nucleophilicity of the resulting sulfinate derivatives. The reaction was also successful with alkyl halides bearing functional groups such as siloxy and ester and with an aldehyde to give α, β -unsaturated aldehydes **48** and **49** (Tables 8, 9).

Table 8. One-pot synthesis of **48**.

RX	conditions	yield (%)
BrCH ₂ Ph	1. -80 ° to -60 °C, 30 min 2. -80 ° to -70 °C, 15 min	85
ICH ₂ (CH ₂) ₆ CH ₃	1. -80 ° to -50 °C, 40 min 2. -80 ° to -70 °C, 20 min	84
BrCH ₂ CH=CH(CH ₂) ₄ CH ₃	1. -80 ° to -50 °C, 30 min 2. -80 ° to -70 °C, 15 min	82
ICH ₂ CH ₂ CH ₂ CH ₂ OSiMe ₂ Bu ^t	1. -80 to -40 °C, 45 min 2. -80 ° to -70 °C, 15 min	68
ICH ₂ CH ₂ CH ₂ CO ₂ Et	1. -80 °C, 5 min; then RX -80 ° to -40 °C, 45 min 2. -80 ° to -70 °C, 20 min	74

Table 9. One-pot synthesis of **49**.

$\text{1BuMe}_2\text{Si}$ **46** $\text{SO}_2\text{p-Tol}$

+ RCHO

1. NaHMDS (1.05 eq)
 THF,
 -80 °C, 10 min
 2. $n\text{-Bu}_4\text{NF}$ (1.1 eq)
 EtOH (3.0 eq)
 -80 °C, 10 min

49a-c

RCHO	yield (%)
$\text{CH}_3(\text{CH}_2)_4\text{CHO}$	77 ^a
$(\text{CH}_3)_2\text{CHCHO}$	71
$(\text{CH}_3)_3\text{CCHO}$	80

^aCH₃COOH (1.0 eq) was added in the desilylation.

3.4 Two-fold Brook Rearrangement-mediated Tandem Reactions of δ -Silyl- γ, δ -Epoxy- α, β -Unsaturated Acylsilanes with a Cyanide Ion^{30,21}

We previously reported that the reaction of acylsilanes with a cyanide ion produces an α -siloxy nitrile carbanion via Brook rearrangement.³¹ The rearrangement is a very facile process because of the anion-stabilizing nature of a cyano group. We conceived the idea that the α -cyano carbanion could induce epoxysilane rearrangement and focused on epoxysilane **50** because the parent compound, lacking the double bond between acylsilane and epoxysilane moieties, could not be prepared in reasonable yield.

First, to test the feasibility of this approach, we examined the reaction with KCN in CH₂Cl₂-H₂O on the basis of the previous result. When acryloylsilane **50** was treated with KCN in the presence of *n*-Bu₄PBr in CH₂Cl₂-H₂O, *O*-silyl cyanohydrin derivative **55** was obtained together with α -silyl alcohol **54**, a product that was protonated before the formation of the second silicate intermediate **53** (Table 10).³² The fact that **50** can undergo a two-fold Brook rearrangement in the presence of water to give **55** as a major product without interception of intermediates such as **51** by water prompted us to examine the reaction of **50** with electrophiles in non-hydroxylic solvents.

Table 10. Reaction of **50** with KCN under liquid-liquid phase-transfer catalytic conditions.

Reaction scheme showing the conversion of epoxysilane **50** to products **54** and **55** via intermediates **51**, **52**, and **53**.

Epoxysilane **50** (1-(tert-butyl(dimethyl)silyl)-2-(trimethylsilyl)oxirane-2-carbaldehyde) reacts with KCN (3 eq) and $n\text{-Bu}_4\text{PBr}$ in $\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$ at 0°C to form intermediate **51** (1-(tert-butyl(dimethyl)silyl)-2-(trimethylsilyl)-2-cyanoethoxy-1-silane).

Intermediate **51** proceeds via two pathways:

- Pathway 1: Intermediate **51** is converted to intermediate **52** (1-(tert-butyl(dimethyl)silyl)-2-(trimethylsilyl)-2-cyanoethoxy-1-silane, deprotonated form). Intermediate **52** then yields product **54** (1-(tert-butyl(dimethyl)silyl)-2-(trimethylsilyl)-2-cyanoethoxy-1-silane, deprotonated form).
- Pathway 2: Intermediate **51** is converted to intermediate **53** (1-(tert-butyl(dimethyl)silyl)-2-(trimethylsilyl)-2-cyanoethoxy-1-silane, deprotonated form). Intermediate **53** then yields product **55** (1-(tert-butyl(dimethyl)silyl)-2-(trimethylsilyl)-2-cyanoethoxy-1-silane, deprotonated form).

Products **54** and **55** are shown as **54** (1-(tert-butyl(dimethyl)silyl)-2-(trimethylsilyl)-2-cyanoethoxy-1-silane, deprotonated form) and **55** (1-(tert-butyl(dimethyl)silyl)-2-(trimethylsilyl)-2-cyanoethoxy-1-silane, deprotonated form).

			products (%)	
catalyst	mol%	time (h)	54	55 (<i>E/Z</i>)
$n\text{-Bu}_4\text{PBr}$	0.5	7.5	42	34 (only <i>E</i>)
$n\text{-Bu}_4\text{PBr}$	5	1.5	32	31 (6.75)
$n\text{-Bu}_4\text{PBr}$	50	5 (min)	5	50 (0.72)

Among the electrophiles in combination with KCN tested, cyanofornates³³ provided the best results in terms of reaction rate and yield (Table 11). Thus, treatment of **50** with cyanofornate in the presence of catalytic amounts of KCN and 18-crown-6 afforded highly functionalized dienol silyl ether derivatives via a tandem sequence featuring a two-fold Brook rearrangement.

Table 11. Reaction of **50** with cyanofornates.

time yield (%)		
EtOCOCN	1	93
<i>n</i> -BuOCOCN	1.5	89
BnOCOCN	0.25	81

SiR₃ = SiMe₂Bu^t

3.5 Formation of Functionalized Cyclopropane Derivatives via Epoxysilane Rearrangement Induced by a Carbanion Generated by Conjugate Addition of Enolates of Chloroacetate and α -Chloroacetamide³⁴

The third method for generating a carbanion at the neighboring position of the epoxysilanes involves the Michael addition of nucleophile onto enoates bearing an epoxysilane moiety at the α -position. After an extensive search for the combination of an enoate with a nucleophile, we found that an enoate **57**, which has a double bond between an epoxysilane and an enoate moiety, is a suitable substrate in terms of the ease of preparation. Also, an internal nucleophile-electrophile such as an enolate of α -haloester, which can trap the anion generated by the epoxysilane rearrangement before decomposition, was found to serve as an effective nucleophile. Treatment of **57** with the potassium enolate³⁵ of ethyl chloroacetate in THF at -80 °C to -60 °C afforded cyclopropanediolate derivatives **58a** and **58b** with predominant formation of a *cis*-isomer (Table 12).

The more favorable formation of the *cis*-isomer can be explained as being a consequence of chelation in which the two ester groups are involved, since addition of HMPA

Table 12. Reaction of **57** with the potassium enolate of ethyl chloroacetate.

conditions	yield (%) (58a/58b)
-80 °C to -60 °C	75 (1.0:0.5)
-98 °C	85 (1.0:0.2)
HMPA (10%), -80 °C to -60 °C	76 (0.7:1.0)

resulted in a reversal of selectivity. We speculated that stabilization of the chelation structure would enhance the selectivity, and we focused on the use of lithium enolate of chloroacetamides from the point of view that the higher reactivity of the enolates and the stronger chelating ability of the amide function and of the lithium cation are sufficient to compensate for the lower reactivity of lithium enolates relative to potassium enolates. When **57** was treated with the lithium enolate of *N,N*-diethylchloroacetamide, the corresponding cyclopropane derivative **59a** was obtained as a single diastereomer in an excellent yield (Table 13).

Table 13. Reaction of **57** with the lithium enolate of *N,N*-diethylchloroacetamide.

R	yield (%)
a H	100
b Me	82
c <i>n</i> -Bu	67
d Ph	74
e Cl	86

A plausible reaction pathway that accounts for the stereochemical outcome of the reaction of **57** is outlined in Scheme 14. The exclusive formation of the internal (*Z*)-olefin in the reactions of both ester and amide enolates can be understood by assuming that silicate intermediate **61** reacts in a *s*-cis diene conformation and faster than the change in the conformation of the diene moiety in **61** to give **62**. The enolate **62** can undergo either or both of two reaction pathways, intramolecular alkylation to give **58a** and **58b** and formation of the chelation structures **63** and **64**, depending on the stability of the chelation structures. The fact that reactions with lithium enolate of α -chloroacetamide give the *cis*-derivative exclusively can be understood in terms of the stronger chelating ability of the lithium cation and of the amide function.

4. Chirality Transfer from Epoxide to Carbanion³⁶

Enantiomerically pure chiral epoxides are now among the most important intermediates for organic synthesis because of their ready availability and high versatility.³⁷ Their chiralities have been extensively utilized for the establishment of one or more than two chiral centers via ring-opening reactions. During the mechanistic studies on epoxysilane rear-

Scheme 14. Plausible reaction pathway.

rangement,^{7b} we became interested in the novel use of epoxide as a chiral source, in which the chirality can be transferred to remote positions via a cascade sequence triggered by chirality transfer of epoxide into a formal carbanion.

First, we examined the reaction of enantiomerically enriched epoxysilane **19a** with a base in the presence of benzyl bromide, anticipating direct alkylation from an allylsilicate derivative **23** (Scheme 5), a possible intermediate in the epoxysilane rearrangement, without involvement of a carbanion intermediate **21**. Unfortunately, benzylated rearrangement products (*E*)- and (*Z*)-**20** obtained under a variety of conditions were completely racemic (Scheme 15).

Scheme 15. Epoxysilane rearrangement using optically enriched **19a**.

We attributed the racemization to the slower reaction with an electrophile because of the intermolecular process. We therefore decided to change the reaction with an electrophile from an intermolecular to intramolecular process and focused on trapping of the generated carbanion by [2,3]-Wittig rearrangement³⁸ as shown in Scheme 16.

Scheme 16. Tandem epoxysilane rearrangement/[2,3]-Wittig rearrangement.

First, we examined the reaction under a variety of conditions using a model compound **65**, but the starting material was recovered. Since the failure of the reaction was attributed to insufficient acidity of the proton at C-1 and a sterically congested environment around the proton, we attempted to introduce a double bond between the epoxysilane moiety and the aryl substituent. Among the substrates examined, the 2-naphthyl derivatives **66a** and **66b** provided the best results in terms of separability of diastereomers (Figure 1).

When optically enriched **66a** was treated with *n*-BuLi (2.0

Figure 1

equiv) in THF, the most common solvent for [2,3]-Wittig rearrangement, for 5 min at -80° to -75°C , the tandem rearrangement products (*E*)- and (*Z*)-**67** were obtained in 46% yield and in racemic form (Table 14, entry 1). The fact that the asymmetric induction was observed in the solvent at higher temperatures, albeit in poor yield, (entry 3) prompted us to change the solvent to other ethereal solvents, resulting in dramatic improvement in the asymmetric induction (entries 5–8). The use of 1,4-dioxane³⁹ provided excellent enantiomeric purity (entries 7 and 8).

Table 14. Tandem epoxysilane rearrangement/[2,3]-Wittig rearrangement of **66a**.

entry	solvent	temperature	yield (%)	recovered SM ^a (%)	<i>E</i> : <i>Z</i>	ee (%) ^b <i>E</i> / <i>Z</i>
1	THF	-80° to -75°C	46	45	5.3:1	0/0
2	THF	-35° to -30°C	88	-	2.4:1	0/0
3	THF	25° to 30°C	80	-	1.2:1	7/0
4	Et ₂ O	-80° to -75°C	0	94	-	-/-
5	Et ₂ O	-35° to -30°C	45	35	1:9.5	81/74
6	Et ₂ O	25° to 30°C	72	-	1:6.8	84/80
7	1,4-dioxane	25° to 30°C	85	-	1:2.6	96/74
8	1,4-dioxane	50° to 60°C	82	-	1:2.6	91/82

^a SM = starting material.

^b Corrected for ee of the starting material (90% ee).

Reaction of diastereomer **66b** proceeded in a similar manner to give (*R,E*)- and (*S,Z*)-**67**, which are enantiomeric to those obtained from **66a**, respectively (Table 15).

Table 15. Tandem epoxysilane rearrangement/[2,3]-Wittig rearrangement of **66b**.

entry	solvent	temperature	yield (%)	recovered SM ^a (%)	<i>E</i> : <i>Z</i>	ee (%) ^b <i>E</i> / <i>Z</i>
1	THF	-80° to -75°C	54	36	<i>E</i>	0/-
2	THF	-35° to -30°C	91	-	<i>E</i>	0/-
3	THF	25° to 30°C	90	-	15.4:1	5/0
4	Et ₂ O	-80° to -75°C	0	84	-	-/-
5	Et ₂ O	-35° to -30°C	51	41	12.0:1	90/36
6	Et ₂ O	25° to 30°C	71	-	2.6:1	91/58
7	1,4-dioxane	25° to 30°C	92	-	8.1:1	97/45
8	1,4-dioxane	50° to 60°C	81	-	5.3:1	96/49

^a SM = starting material.

^b Corrected for ee of the starting material (91% ee).

It should be noted that chirality of a carbanion derived from the epoxide, conjugated with both a naphthyl group and a double bond, can be retained even at above room temperature. The results are consistent with two reaction pathways, (1) the formation of a carbanion precursor in a concerted manner followed by [2,3]-Wittig rearrangement before racemization (**66** → **68** → **69** → **67**) and (2) the direct formation of [2,3]-Wittig rearrangement products from a silicate derivative, a possible intermediate in the Brook rearrangement, without involvement of a carbanion intermediate (**66** → **68** → **67**) (Scheme 17).

Scheme 17. Possible reaction pathways for the tandem epoxysilane rearrangement/[2,3]-Wittig rearrangement.

To obtain insight into the reaction pathway, we decided to examine [2,3]-Wittig rearrangement of optically enriched (*S*)-**70**,⁴⁰ in which a carbanion is generated by direct protonation and racemization may be more facile. If the reaction of **70** results in complete racemization, the possibility of a pathway involving a carbanion intermediate would be ruled out. Although no asymmetric induction was observed in THF, reactions in 1,4-dioxane were found to show the best enantioselectivity again to give (*R*)-**71** (Table 16, entries 1 and 4). It is notable that less enantioselectivity was observed at a lower temperature in Et₂O (entries 2 and 3), suggesting that the loss of chirality is at least partly attributed to racemization due to the decreased rate of the [2,3] Wittig rearrangement at a lower temperature. These results are consistent with the intermediacy of a chiral carbanion, although the possibility of epoxysilane rearrangement/[2,3]-Wittig rearrangement in a concerted manner cannot be ruled out. The origin of the excellent enantioselectivity observed in 1,4-dioxane is unclear at present, but it might be due to the decreased rate of racemization by chelation of the lithium cation with the two oxygens. This is supported by the fact that the addition of HMPA in 1,4-dioxane (entry 5) and the use of 1,3-dioxane (entry 6) resulted in complete racemization.

5. Conclusion

In this account, we have demonstrated the development of epoxysilane rearrangement, results of its mechanistic studies and synthetic application. The rearrangement could trigger a reaction cascade that eventually can achieve a large increase in complexity in one operation and in a stereoselective manner. Moreover, results of mechanistic studies on the rearrangement led to a conceptually novel approach to the chirality transfer in which epoxide chirality can be transferred into carbanion.

Table 16. [2,3]-Wittig rearrangement of (S)-70.

entry	solvent	additive	yield (%)	ee (%) ^c
1	THF	-	95	0
2	Et ₂ O	-	76	35
3	Et ₂ O ^a	-	39	9
4	1,4-dioxane	-	70	71
5	1,4-dioxane	HMPA	50 ^b	0
6	1,3-dioxane	-	96	0

^a *n*-BuLi was used at -80 °C. ^b 40% of (S)-70 was recovered.

^c Corrected for ee of the starting material (99% ee)

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sequence: (1) PhLi, (2) kinetic resolution according to the pro-
tocol of Sharpless, and (3) BrCH₂CH=CH₂.

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