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DEVELOPMENT OF EPOXYSILANE REARRANGEMENT AND ITS APPLICATION TO CHIRALITY TRANSFER

Michiko Sasaki, Hidaka Ikemoto, and Kei Takeda*

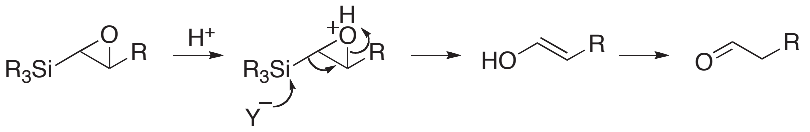
Department of Synthetic Organic Chemistry, Graduate School of Medical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-Ku, Hiroshima 734-8553, Japan. E-mail: takedak@hiroshima-u.ac.jp

Abstract – Development 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. Chirality transfer from epoxides to the position next to a nitrile group by taking advantage of the concerted process of the rearrangement is also reported.

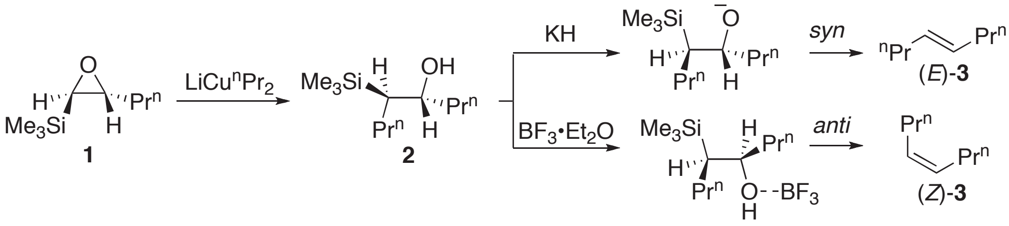
CONTENTS

1. INTRODUCTION

Although preparation of α,β-epoxysilanes was reported more than fifty years ago,[1] they had attracted little attention for use in synthetic applications until Stork and co-workers showed that α,β-epoxysilanes can be converted to aldehydes and ketones via a ring-opening followed by desilylation (Scheme 1).[2] Since then, they have been extensively used as versatile building blocks for organic synthesis.[3] Among those reported, one of the most synthetically useful reactions is a ring-opening process, in which attack of a nucleophile occurs in a regioselective manner to produce diastereomerically pure β-hydroxysilanes (Scheme 2, **1** → **2**).[4] The process with α-ring opening provides a highly stereospecific olefin synthesis coupled with the stereospecific syn- and anti-elimination depending on the reaction conditions (**2** → (*E*)- and (*Z*)-**3**).

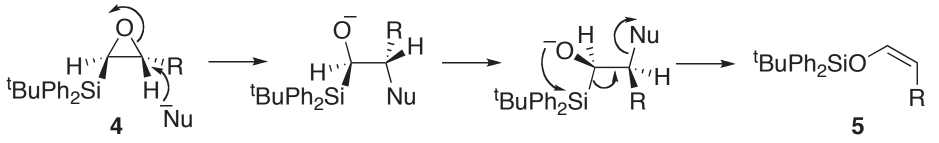


Scheme 1



Scheme 2

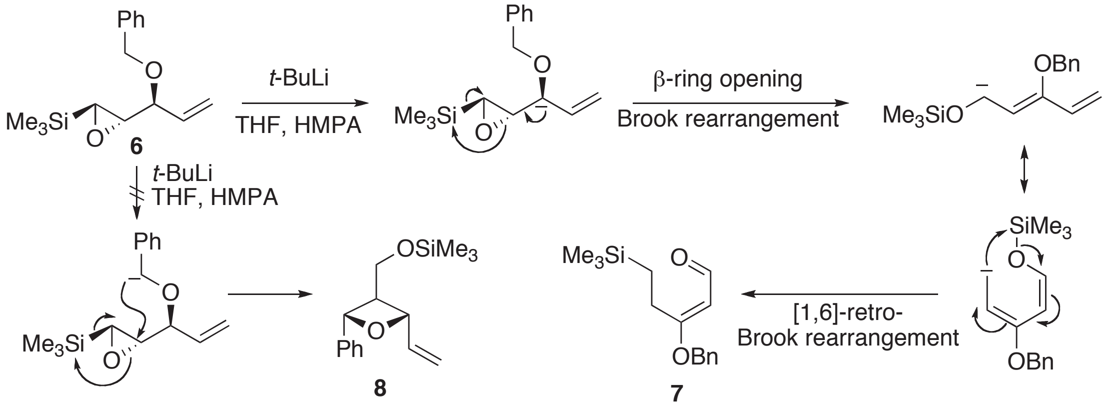
On the other hand, when a nucleophile is a heteroatom with a leaving ability and the silyl group is bulky enough to suppress the α-attack, β-ring opening in α,β-epoxysilane **4** occurs to provide an enol silyl ether **5** stereospecifically via a Brook rearrangemen[5] in the resulting α-oxidosilane followed by anti-elimination.[6]



$Nu^- = LiPPh_2, LiSPh$

Scheme 3

A similar type of reaction via Brook rearrangement in α,β-epoxysilanes was first observed by Jung and coworkers.[7] They found that treatment of epoxysilane **6** with *t*-BuLi produced aldehyde **7** via a tandem process that involves a base-induced β-ring opening followed by [1,2]- and [1,6]-silyl migration (Brook and [1,6]-retro-Brook rearrangement, respectively). This result was contrary to their expectation that oxetane derivative **8** would be obtained by 4-exo-epoxy mode cyclization.



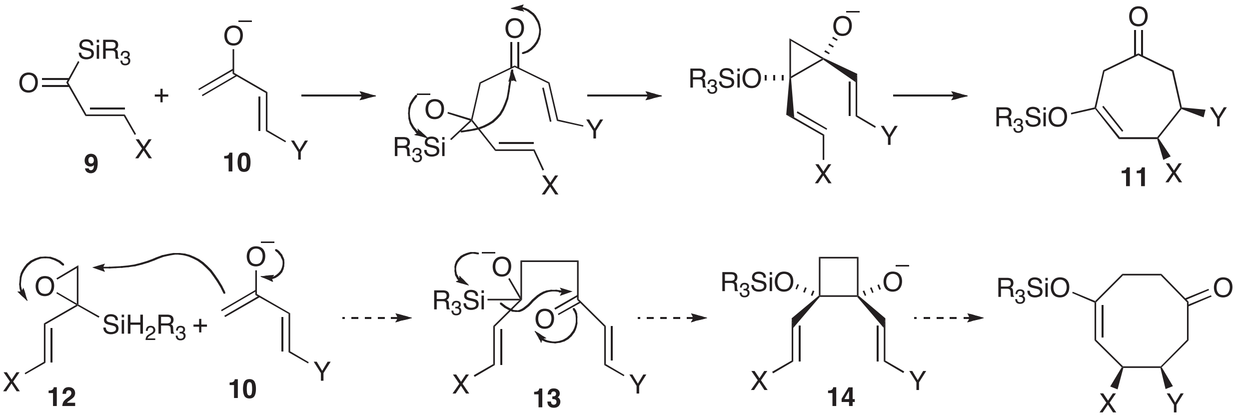
Scheme 4

Enantiomerically pure epoxides are now among the most important intermediates for organic synthesis because of their ready availability and high versatility.[8] Their chiralities have been extensively utilized for the establishment of one or more than two chiral centers via ring-opening reactions. However, when we started studies on α,β-epoxysilanes, there was no literature precedent for use of epoxides as a source for chiral carbanions.

In this review, we focus on 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, which we call epoxysilane rearrangement,[9] and its application to chirality transfer reactions.

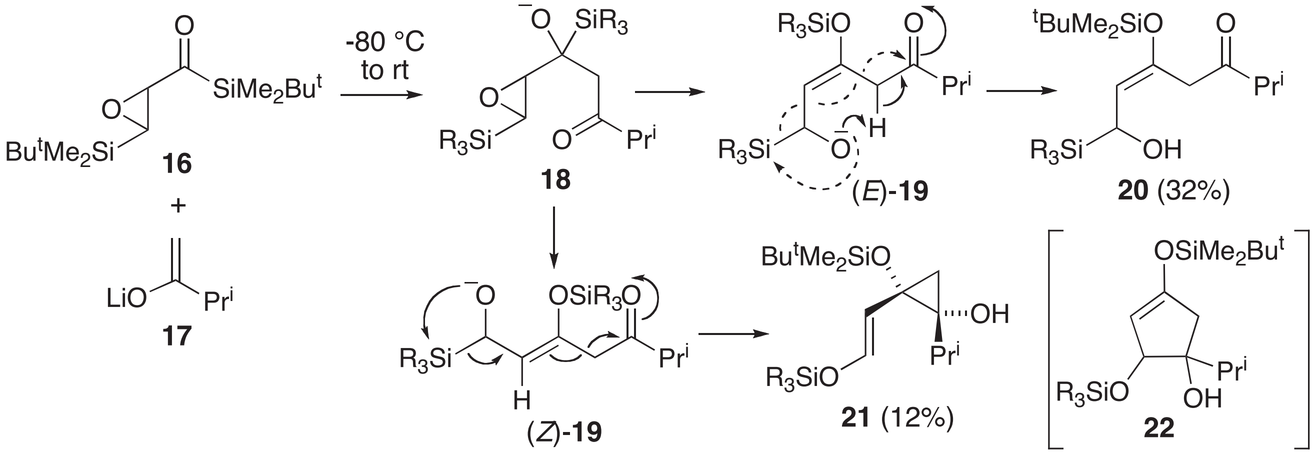
2. BACKGROUND

We conceived the idea of using α,β-epoxysilanes as a versatile building block, when trying to extend Brook rearrangement-mediated [3 + 4] annulation,[10] which uses a combination of acryloylsilanes **9** and methyl ketone enolates **10**, for the construction of eight-membered rings. Thus, we considered that the eight-membered ring **15** can be obtained by an anionic oxy-Cope rearrangement of divinylcyclobutanolate derivative **14**, which could be derived from **13** via Brook rearrangement followed by cyclization, which in turn was prepared by the reaction of epoxysilane **12** with alkenyl methyl ketone enolate **10**. We have tried a variety of combinations of an epoxysilane and a nucleophile, but almost all resulted in decomposition, recovery of the starting materials, or ring-opening on the undesired side.[11]



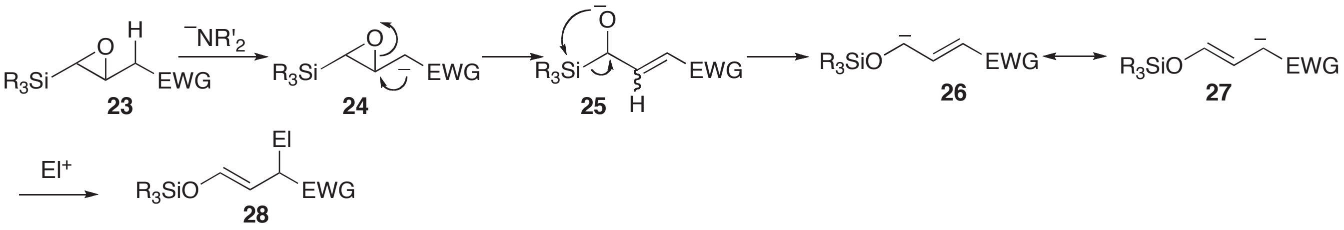
Scheme 5

Although we could not establish the viability of the tandem sequence that involves β-ring opening followed by a Brook rearrangment in the reaction of α,β-epoxysilanes with a nucleophile, the idea has been realized in a different form. During the course of extension of Brook rearrangement-mediated [3 + 2] annulation[12] to asymmetric versions, we had occasion to examine the reaction of β-silyl-α,β-epoxyacylsilanes **16** with enolate of alkyl methyl ketone **17**. Although we expected the formation of cyclopentenol derivatives **22** via a two-fold Brook rearrangement followed by an intramolecular nucleophilic addition ((*E*)-**19** → **22**, dashed arrow), the major products were uncyclized enol silyl ether **20** and cyclopropanediol derivative **21**.[13] The former is formed by intramolecular proton transfer before a second Brook rearrangement in (*E*)-**19**, while the latter is formed as a result of an intramolecular allylic attack on the carbonyl group by a siloxy carbanion generated by the second Brook rearrangement in (*Z*)-**19** (Scheme 6).



Scheme 6

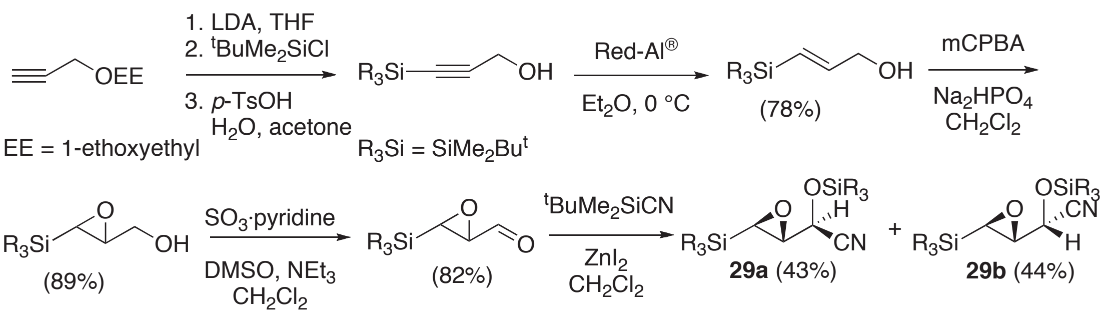
This result indicates the possibility of the reaction of an epoxysilane **23** bearing an anion-stabilizing electron-withdrawing group at the α-position with an amide base in the presence of an electrophile. If a tandem process that involves a base-promoted isomerization of the epoxide (**24** → **25**), Brook rearrangement (**25** → **26**), and a reaction of the resulting allylic anion with an electrophile (**26** → **27** → **28**) proceeds well, the epoxysilane **23** would function as a homoenolate equivalent[14] with synthetically useful functionality (Scheme 7).



Scheme 7

3. TANDEM BASE-PROMOTED RING-OPENING/BROOK REARRANGEMENT/ALLYLIC ALKYLATION OF *O*-SILYL CYANOHYDRINS OF β-SILYL-α,β-EPOXYALDEHYDE

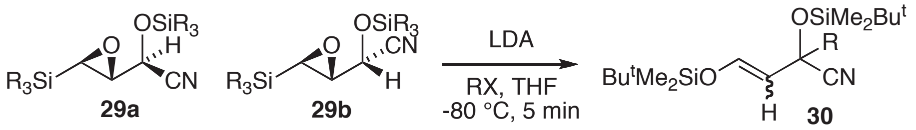
We first focused on *O*-silyl cyanohydrins of β-silyl-α,β-epoxyaldehydes **29a**,**b** as a precursor for the species of **27**, in which a nitrile group is an electron-withdrawing group, because of its ease of preparation. The preparation of **29a** and **29b** was shown in Scheme 8.



Scheme 8

When **29a** and **29b** 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 **30**, products formed via a tandem sequence (**24** → **28**), were obtained in 82% and 84% yields, respectively (Table 1).[9]

Table 1



RX	**30**, yield (%) (*E*/*Z*)			
	from **29a**		from **29b**	
MeI	82	(2.5)	84	(22.0)
EtI	76	(2.9)	74	(28.0)
i-PrI	58	(2.8)	74	(31.0)
$PhCH_2Br$	86	(2.7)	98	(47.0)
$CH_2=CHCH_2Br$	83	(3.4)	87	(40.0)

It is particularly noteworthy that (1) the reactions were completed within 5 min at –80 °C and alkylation products of possible intermediates other than **30** were not detected and (2) *E*/*Z* ratios of **30** obtained from the two diastereomers were markedly different. These facts prompted us to conduct stereochemical and mechanistic studies on the reaction. Summarizing the results obtained from the studies, (1) the mode of ring opening of the epoxide is anti,[15] which is based on competitive experiments using the diastereomeric cyanohydrins **29a** and **29b**, (2) experiments using epoxysilanes with a different silyl group showed that silicon-oxygen bond formation is involved in the rate-determining transition state **31**, and (3) there is no equilibrium between (*E*)- and (*Z*)-siloxyallyl anions **32**, which are candidates for immediate precursors for the alkylation.

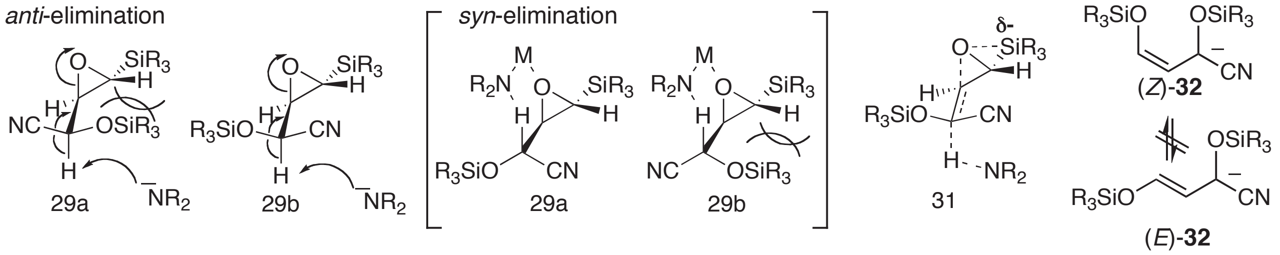
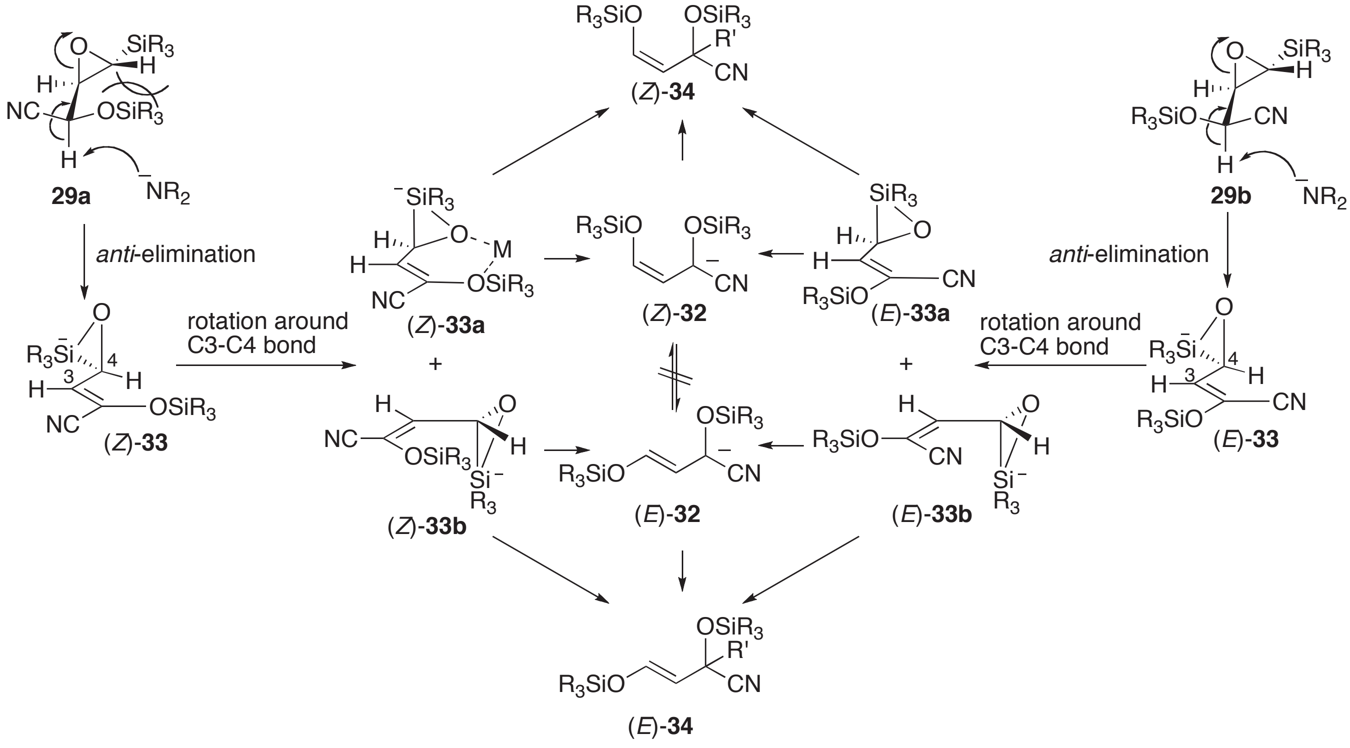


Chart 1

Based on these and other results, we have proposed a reaction pathway that involves silicate intermediates (*Z*)-**33** and (*E*)-**33**, which are formed from **29a** and **29b**, respectively, by an anti ring-opening followed by the formation of an oxygen-silicon bond (Scheme 9). The silicates are converted into rotamers (*Z*)-**33a**,**b** and (*E*)-**33a**,**b**, respectively, after rotation around the C_3-C_4 bond in such a way that the C_4-silicon bond can adopt a parallel arrangement with the π orbitals of the double bond. They are transformed into the products (*E*)- and (*Z*)-**34** directly via concerted alkylation and/or via allyl anion intermediates (*Z*)-**32** and (*E*)-**32**. Among silicates (*Z*)-**33a**, **33b** and (*E*)-**33a**, **33b**, only (*Z*)-**33a** can form an internally chelated structure with a metal cation. This pathway can explain the fact that (*Z*)-isomer is obtained in higher ratio from diastereomer **29a**.

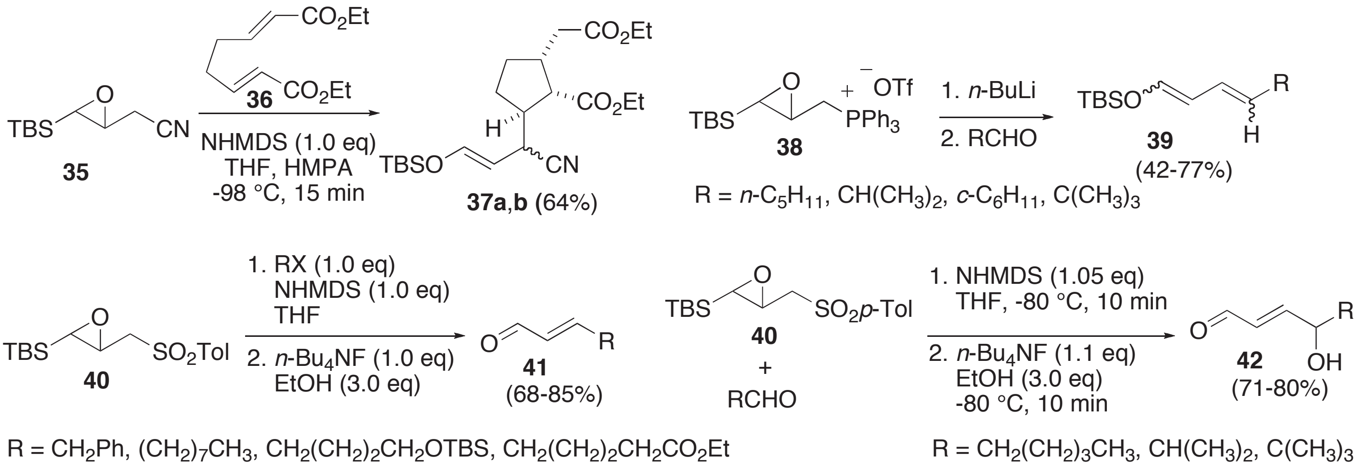


Scheme 9

4. SYNTHETIC APPLICATION OF THE EPOXYSILANE REARRANGEMENT

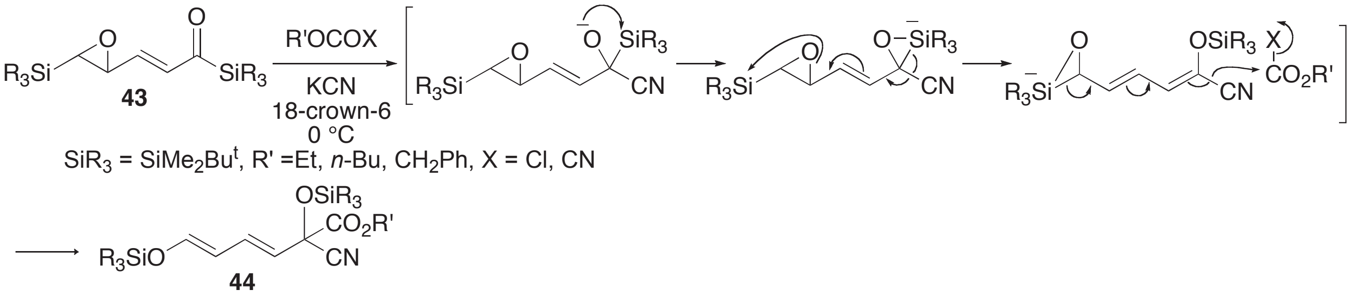
Since we have published a review on mechanistic studies of epoxysilane rearrangements and their application as synthetic reactions,[16,17] we will touch upon the title subject in this section only briefly. For the generation of an anion at the γ-position of α,β-epoxysilanes that triggers the tandem process, we devised three methods, (1) deprotonation, (2) reaction of acylsilanes with a nucleophile followed by Brook rearrangement, and (3) a conjugate addition of a nucleophile to an enoate system bearing an epoxysilane moiety at the α-position.

A β-siloxy carbanion generated in the nitrile derivative **35** can participate in a Michael-Initiated-Ring-Closure type reaction with bisenoate **36** to give **37a**,**b** (Scheme 10).[18] The use of phosphonio group instead of a nitrile group as the electron-withdrawing group resulted in the formation of siloxydiene derivatives **39** via Wittig reaction (**38** → **39**).[19] When the group next to the epoxysilane moiety is an anion-stabilizing leaving group such as tosyl, the epoxysilane **40** can function as an acrolein β-anion equivalent to give β-substituted acrolein derivatives **41** and **42**.[20]



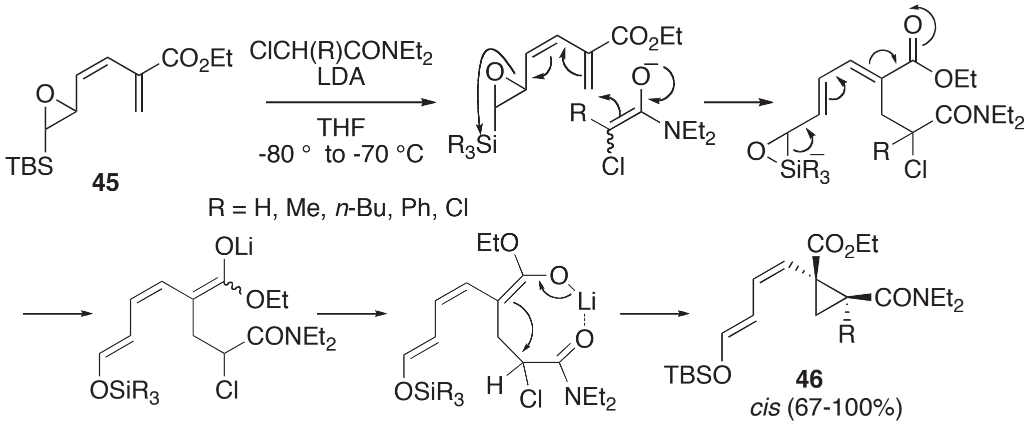
Scheme 10

We previously reported that reactions of acylsilanes with KCN under phase-transfer catalytic conditions proceeded smoothly via Brook rearrangement to produce *O*-silylated cyanohydrin derivatives in excellent yields.[21] These results prompted us to focus our attention on the reaction of acylsilanes with cyanide ion as a method for the generation of a carbanion at the γ-position to the epoxysilane. Reaction of δ-silyl-γ,δ-epoxy-α,β-unsaturated acylsilanes **43** with KCN in the presence of chloro- or cyanoformates and 18-crown-6 gave highly functionalized dienol silyl ether derivatives **44** via a two-fold Brook rearrangement-induced tandem sequence (Scheme 11).[22]



Scheme 11

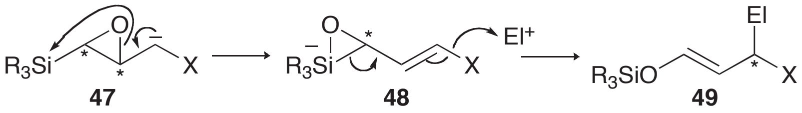
A carbanion generated by Michael addition of a lithium enolate of α-chloroacetamide to enoate **45** bearing an epoxysilane moiety at the α-postion can also participate via the same type tandem sequence to give **46** with stereoselectivity that can be explained by the formation of chelation structures (Scheme 12).[23]



Scheme 12

5. CHIRALITY TRANSFER USING EPOXYSILANE REARRANGEMENT

As mentioned above, epoxysilane rearrangement was discovered during extension of the Brook rearrangement-mediated [3 + 2] annulation to its enantioselective version. The key of the idea is to use the epoxide chirality as a precursor for chiral carbanions via a concerted process involving Brook rearrangement (**47** → **48** → **49**), which would allow enantioselective C-C bond formation in the reaction with an electrophile (Scheme 13).



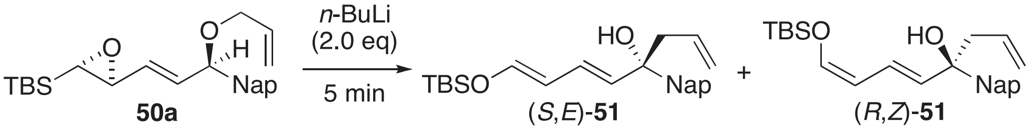
Scheme 13

We recognized the possibility of its application to chirality transfer from the fact that the diastereomeric epoxysilanes **29a** and **29b** give **34** in markedly different *E*/*Z* ratios in the reaction with a base in the presence of an electrophile. Preliminary experiments using a combination of homochiral epoxysilane **29a**, LDA, and benzyl bromide resulted in complete racemization. We attributed this failure to the slower reaction of a generated chiral carbanion with an electrophile because the process involves a configurationally extremely unstable α-nitrile carbanion and the process is an intermolecular one.

5.1. INTRAMOLECULAR TRAPPING OF CHIRAL CARBANIONS GENERATED VIA EPOXYSILANE REARRANGEMENT BY [2,3]-WITTIG REARRANGEMENT

We next changed the reaction with an electrophile from an intermolecular process to an intramolecular one with the expectation of acceleration of the trapping reaction of the carbanion and then focused on [2,3]-Wittig rearrangement.[24] After extensive examination of various substrates, we chose the 2-naphthyl (Nap) derivatives **50a** and **50b**, which were obtained from the corresponding epoxy aldehyde and provided the best results in terms of separability of diastereomers. When enantiomerically enriched **50a** was treated with *n*-BuLi (2.0 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*)-**51** were obtained in 46% yield and in racemic form (Table 2, entry 1). Although the asymmetric induction remained poor in the solvent at higher temperatures (entry 3), change in the solvent to other ethereal solvents resulted in dramatic improvement in asymmetric induction (entries 5-8). The use of 1,4-dioxane provided excellent enantiomeric purity (entries 7 and 8).[25]

Table 2. [2,3]-Wittig rearrangement of **50a**

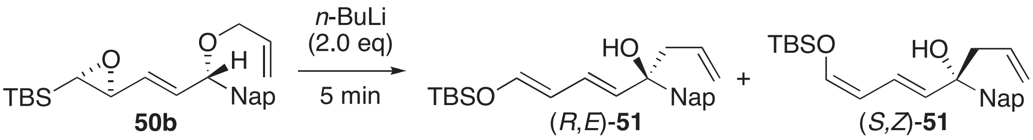


entry	solvent	temperature	yield (%)	recovered SM[a] (%)	*E*:*Z*	ee (%)[b]	
						E	*Z*
1	THF	–80 ° to –75 °C	46	45	5.3:1	0	0
2	THF	–35 ° to –30 °C	88	-	2.4:1	0	0
3	THF	25 ° to 30 °C	80	-	1.2:1	7	0
4	Et_2O	–80 ° to –75 °C	0	94	-	-	-
5	Et_2O	–35 ° to –30 °C	45	35	1:9.5	81	74
6	Et_2O	25 ° to 30 °C	72	-	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 the ee of the starting material (90% ee).

Reaction of diastereomer **50b** proceeded in a similar manner to give (*R*,*E*)- and (*S*,*Z*)-**51**, which are enantiomeric to those obtained from **50a**, respectively (Table 3).

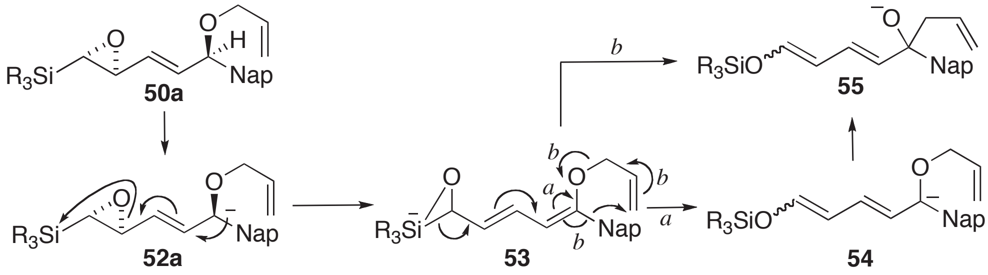
Table 3



entry	solvent	temperature	yield (%)	recovered SM[a] (%)	*E*:*Z*	ee (%)[b]	
						E	*Z*
1	THF	–80 ° to –75 °C	54	36	*E*	0	-
2	THF	–35 ° to –30 °C	91	-	*E*	0	-
3	THF	25 ° to 30 °C	90	-	15.4:1	5	0
4	Et_2O	–80 ° to –75 °C	0	84	-	-	-
5	Et_2O	–35 ° to –30 °C	51	41	12.0:1	90	36
6	Et_2O	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 the ee of the starting material (91% ee).

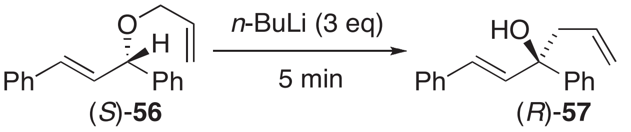
Particularly noteworthy is that chirality of a carbanion derived from the epoxide, conjugated with both a naphthyl group and a double bond, can be retained even above room temperature. The observed stereospecificity suggests (1) the formation of a carbanion precursor in a concerted manner followed by [2,3]-Wittig rearrangement before racemization (Scheme 14, **52a** → **53** → **54** → **55**) or (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 (**52a** → **53** → **55**)(Scheme 14).



Scheme 14

To obtain information about the configurational stability of a carbanion between an aryl group and a double bond, we examined [2,3]-Wittig rearrangement of enantiomerically enriched (*S*)-**56**, in which racemization may be more facile. Although no asymmetric induction was observed in THF, reactions in 1,4-dioxane were found to show the best enantioselectivity again to give (*R*)-**57** (Table 4, entries 1 and 4). It is notable that less enantioselectivity was observed at a lower temperature in Et_2O (entries 2 and 3), suggesting that the loss of chirality is at least partly attributed to the racemization due to decreased rate of the [2,3]-Wittig rearrangement at a lower temperature. These results are consistent with the former possibility, although the latter possibility of tandem epoxysilane rearrangement/[2,3]-Wittig rearrangement cannot be ruled out.

Table 4



entry	solvent	temperature	additive	yield (%)	ee (%)[c]
1	THF	30 ° to 34 °C	-	95	0
2	Et_2O	30 ° to 34 °C	-	76	35
3	Et_2O[a]	–80 °C	-	39	9
4	1,4-dioxane	30 ° to 34 °C	-	70	71
5	1,4-dioxane	30 ° to 34 °C	HMPA	50[b]	0
6	1,3-dioxane	30 ° to 34 °C	-	96	0

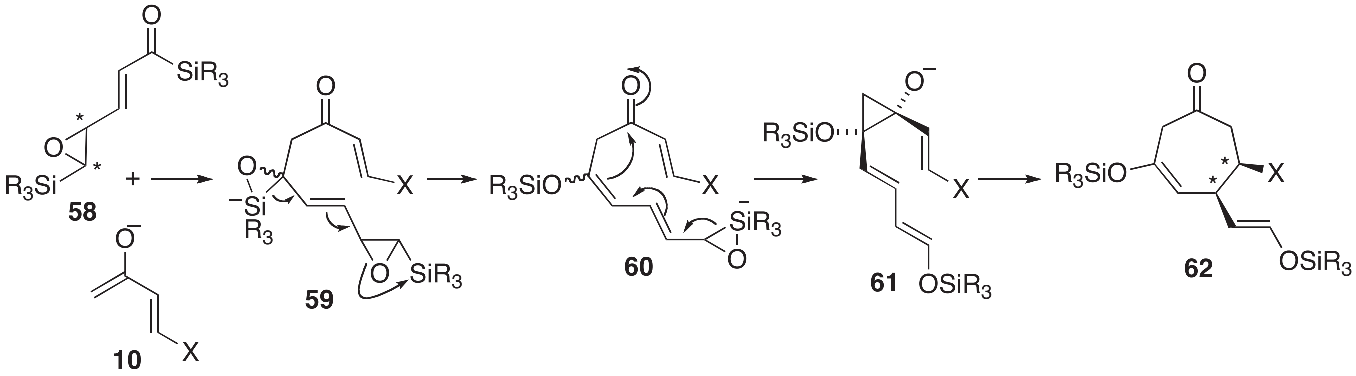
[a] *t*-BuLi was used [b] 40% of (*S*)-**56** was recovered

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

The origin of the excellent enantioselectivity observed in 1,4-dioxane is unclear at present, but it may 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.

5.2. CHIRALITY TRANSFER IN THE CONSTRUCTION OF SEVEN-MEMBERED CARBOCYCLES USING A COMBINATION OF BROOK REARRANGEMENT-MEDIATED [3 + 4] ANNULATION AND EPOXYSILANE[26]

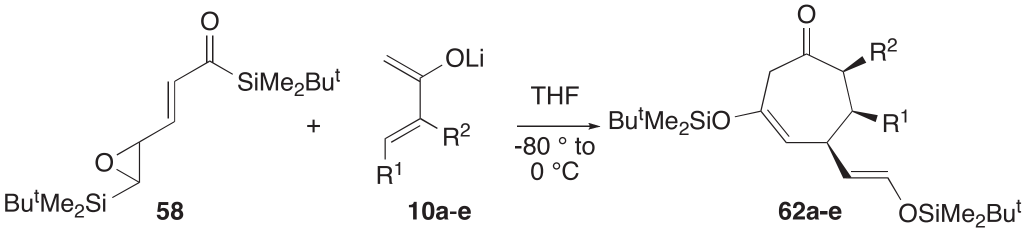
The fact that the chirality of the epoxides can be trapped intramolecularly without complete racemization even through allyl rearrangement prompted us to examine the construction of seven-membered ring systems using a combination of Brook rearrangement-mediated [3 + 4] annulation and epoxysilane rearrangement. Thus, [3 + 4] annulation using **58** instead of acryloylsilane **9** (Scheme 5) as a three-carbon unit would afford highly functionalized cycloheptenone derivatives **62** via a tandem process that involves a two-fold Brook rearrangement (**59** → **60** and **60** → **61**) as shown in Scheme 15. The strategy relies on our findings that once the divinylcyclopropanediolate is formed, the next anionic oxy-Cope rearrangement proceeds very rapidly and that vinylcyclopropanol **21** is formed in the reaction of **16** with methyl ketone enolate **17**. In the annulation, we expected remote chirality transfer from the epoxide to the seven-membered ring by taking advantage of the concerted nature of the processes.



Scheme 15

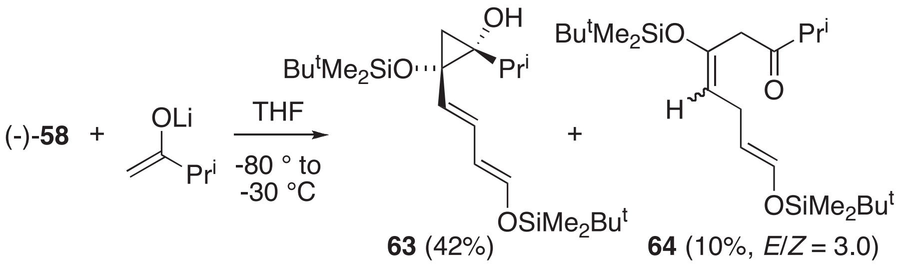
When lithium enolate **10a**-**e** was added to a THF solution of racemic **58** at –80 °C and the mixture was allowed to warm to 0 °C, the expected [3 + 4] annulation product **62a**-**e** was isolated in 31-60% yields as a single diastereomer (Table 5).

Table 5



entry		R^1	R^2	yield
1	**10a**	$CHMe_2$	H	60
2	**10b**	$(CH_2)_4$	H	45
3	**10c**	OMe	H	38
4	**10d**	Bn	H	31
5	**10e**	$-(CH_2)_4-$		55

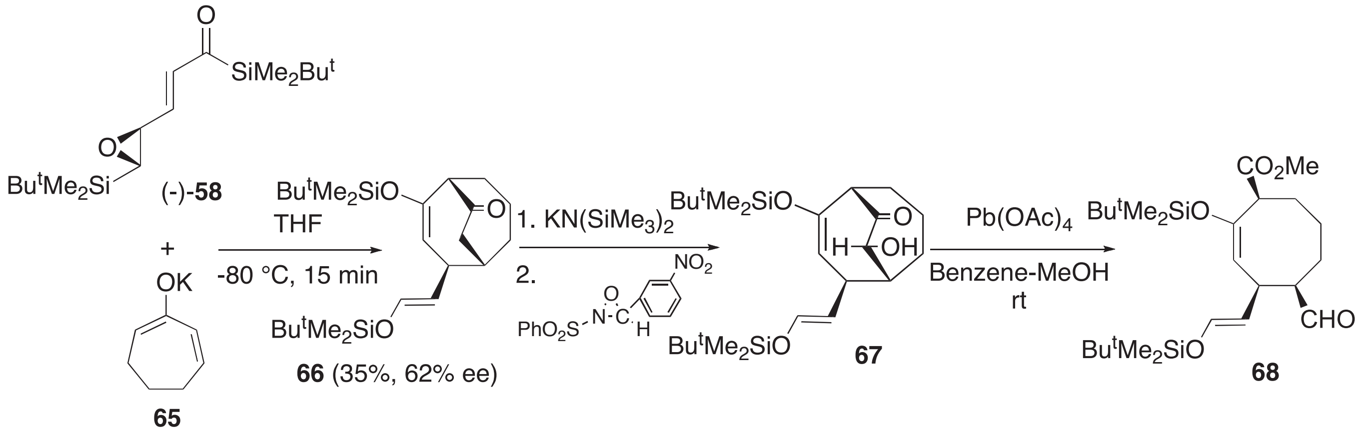
We first conducted [3 + 4] annulation using enantiomerically enriched (-)-**58** (90% ee) and **10a** under the same conditions as those employed for the racemic one to give **62a** with 19% ee. This result suggests that the epoxide chirality can be transferred to remote positions without complete racemization via an intramolecular process. One of the origins of the low enantioselectivity was thought to be partial racemization in **61** via ring opening-closure of the cyclopropane, because we have observed that a ring-opening and ring-closing process is quite facile and competes with anionic oxy-Cope rearrangement.[10] Therefore, we verified this by the reaction of (-)-**58** with lithium enolate of isopropyl methyl ketone, in which anionic oxy-Cope rearrangement cannot occur. The reaction resulted in complete racemization to give vinylcylopropandiolate **63** in 42% yield together with uncyclized enol silyl ethers **64** (Scheme 16). This result suggests that the acceleration of anionic oxy-Cope rearrangement could suppress the racemization.



Scheme 16

Our previous observation that the use of enolate of cycloalkenone in [3 + 4] annulation accelerates the anionic oxy-Cope rearrangement because of its fixed conformation, which is suitable for the rearrangement,[27] led us to examine [3 + 4] annulation using an enolate of cycloalkenone. When (-)-**58** was treated with potassium enolate **65** of 2-cycloheptenone, [3 + 4] annulation proceeded to give **66** in 35% yield with 62% ee (Scheme 17). As expected, the enantiomeric excess was greatly improved.

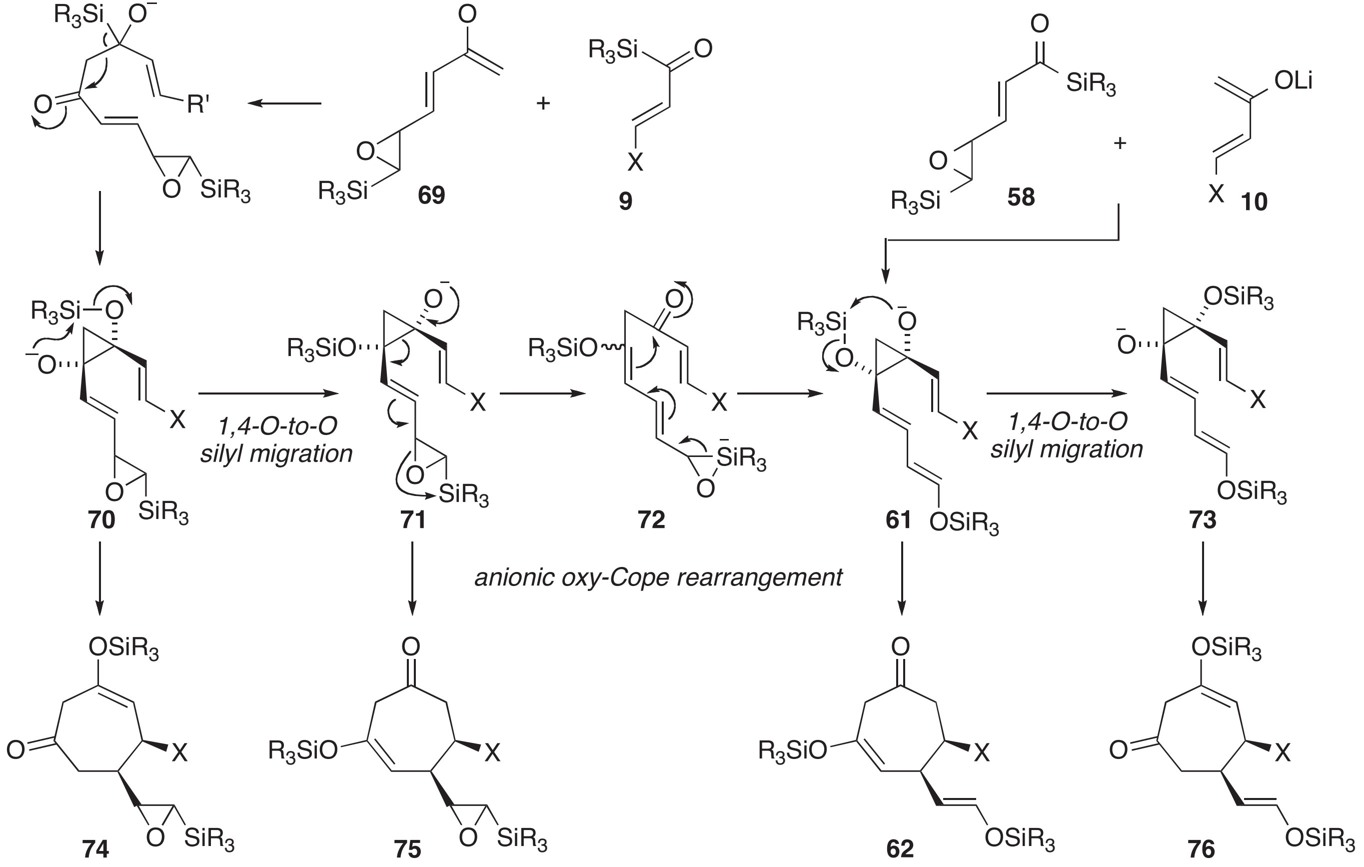
Transformation of **66** into a functionalized eight-membered carbocycle **68** could be achieved in a manner similar to that reported previously.[27]



Scheme 17

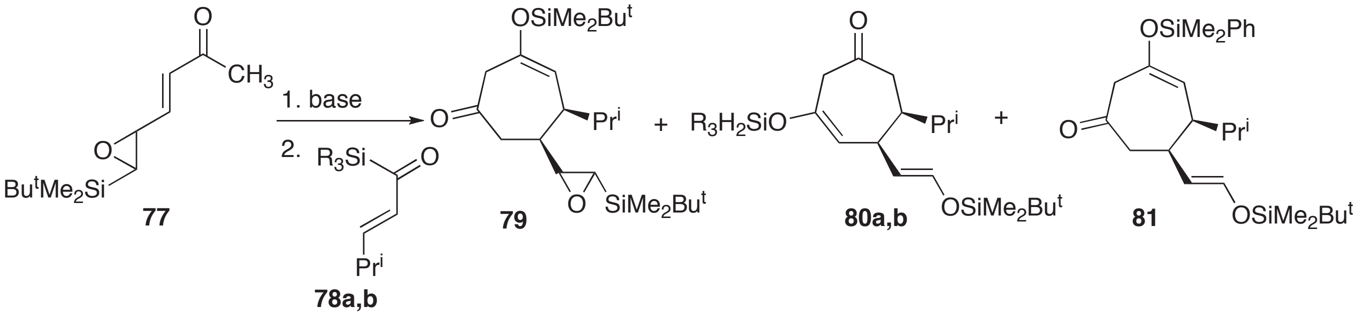
We next became interested in a new variation of the [3 + 4] annulation using an opposite combination of the three and the four carbon units (**69** + **9**), in which an epoxysilane moiety is incorporated in four-carbon unit **69**, because the epoxysilane can be prepared more easily than **58** (Scheme 18). The crucial step of this strategy should be 1,4-*O*-to-*O* silyl migration in **70**, which allows the formation of the intermediate **61**, which is exactly the same as that obtained from the normal version of [3 + 4] annulation (**58** + **10**), via epoxysilane rearrangement (**71** → **72**). We have also observed a similar 1,4-*O*-to-*O* migration of silyl group.[28] This annulation, in principle, generates four types of divinylcyclopropanolates, **70**, **71**, **61** and **73**, depending on the timing of the epoxysilane rearrangement and the 1,4-*O*-to-*O* silyl migration, which should provide seven-membered carbocycles **74**, **75**, **62**, **76**, respectively, via an anionic oxy-Cope rearrangement.

When lithium enolate of **77** was treated with **78a** at –80 °C and allowed to warm to 0 °C, **79** (a 1:1 diastereomeric mixture), an oxy-Cope rearrangement product of **70** before 1,4-*O*-to-*O* silyl migration, was obtained as a sole identifiable product in 50% yield (Table 6, entry 1). On the other hand, the use of sodium enolate prepared with NaHMDS resulted in the formation of desired cycloheptenone **80a** in 43% yield in addition to **79** (16%) (Table 6, entry 2). Since this result can be interpreted as the consequence of acceleration of the 1,4-*O*-to-*O* silyl migration by an increase in the ionic character of a counter cation, we examined the reaction using **78b** (R_3Si = $PhMe_2Si$) with the expectation of further acceleration of the 1,4-*O*-to-*O* silyl migration by introduction of a phenyl group to the silyl group. Treatment of sodium enolate of **77** with **78b** under the same conditions afforded **80b** in an improved yield, 65% (Table 6, entry 3). Although formation of **79** could not be detected, instead **81**, a two-fold 1,4-*O*-to-*O* silyl migration product, was formed in 11% yield. These results indicate that the product distributions are a subtle balance among the relative rates of epoxysilane rearrangement, anionic oxy-Cope rearrangement and 1,4-*O*-to-*O* silyl migration in **70** and **61**.



Scheme 18

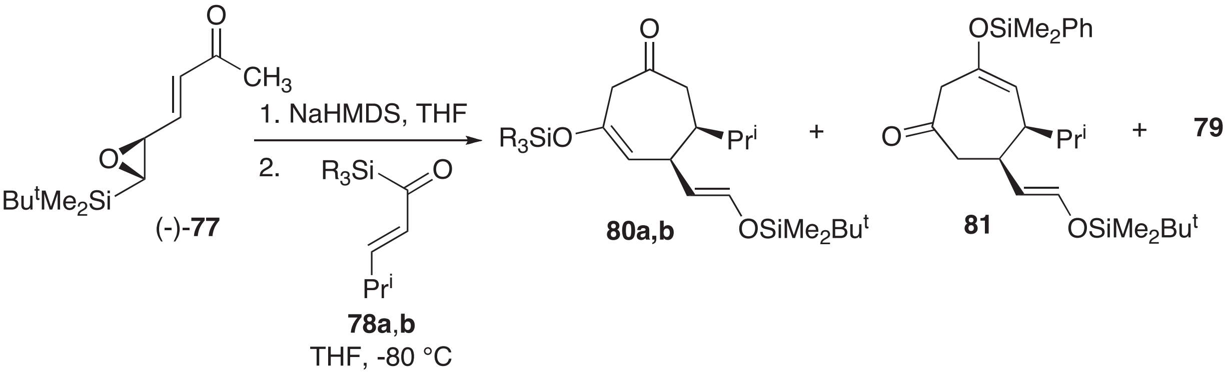
Table 6



entry		R$_3$Si	base	yield (%)		
				79	**80**	**81**
1	**78a**	^{t}BuMe$_2$Si	LDA	50	-	-
2	**78a**	^{t}BuMe$_2$Si	NaHMDS	16	43	-
5	**78b**	PhMe$_2$Si	NaHMDS	-	65	11

A relay of stereochemistry in the second version of the [3 + 4] annulation provided better ee than those obtained with the normal version of [3 + 4] annulation in the case of TBS derivative **78a**, the origin of which is not clear at present (Table 7).

Table 7



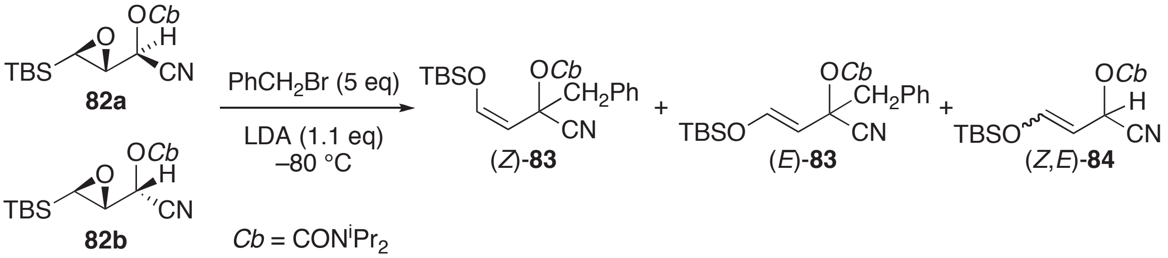
	R$_3$Si	80		81		79
		yield	ee (%)	yield	ee (%)	yield
78a	^{t}BuMe$_2$Si	43	37	-	-	16
78b	PhMe$_2$Si	65	17	11	14	-

5.3. CHIRALITY TRANSFER FROM EPOXIDE TO α-NITRILE CARBANION

Based on the above findings, we next proceeded to examine intermolecular trapping of chiral α-nitrile carbanions generated via Brook rearrangement using *O*-carbamoyl cyanohydrins **82**. We attributed the unsuccessful result in the chirality transfer using enantioenriched **29a** to the intervention of a pathway via an α-nitrile-stabilized carbanion intermediate. Chiral carbanions that are conjugated with carbon-oxygen or carbon-nitrogen multiple bonds have been considered to be extremely difficult to generate due to their high proclivity toward racemization. To the best of our knowledge, reports by Walborsky and co-workers, who found that a chiral cyclopropyl nitrile derivative could be enantiospecifically deuterated in basic CH_3OD, are the only example.[29] They also found that the corresponding chiral aliphatic nitrile derivative suffered extensive racemization under the same conditions. We envisioned that the carbamoyloxy group (*Cb*)[30] would decelerate the rate of racemization of the α-nitrile allylic carbanion by its strong chelating ability.

On the basis of exploratory experiments to find conditions in which the best result in terms of chemical and optical yields is obtained with LDA in the presence of benzyl bromide in Et_2O or toluene at -80 °C, we examined the reactions of **82a** and **82b** with LDA in the presence of BnBr in Et_2O and toluene with reaction times of 1 min and 60 min (Table 8).[31] The latter reaction time was selected considering the possibility of a relatively slow reaction rate of the silicate intermediate and/or the chiral carbanion with benzyl bromide. The ees of (*R*,*Z*)-**83** and (*R*,*E*)-**83** in the reactions in Et_2O were improved by quenching for 1 min, but at the expense of the chemical yield, while in toluene the chemical and optical yields were not greatly affected by the reaction time. This result can be interpreted in terms of a relatively slow reaction rate of the silicate intermediate and/or the chiral carbanion with benzyl bromide in Et_2O. The optical yields in the reaction of **82b** were lower than those in the reaction of **82a**.

Table 8

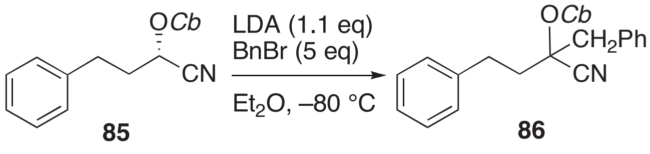


	solvent	Time (min)	(*Z*)-**83** yield (%)	(*Z*)-**83** *ee* (%)[a]	(*E*)-**83** yield (%)	(*E*)-**83** *ee* (%)[a]	**84** yield (%)
82a	Et_2O	1	22	39 (*R*)	5	40 (*R*)	47
82a	Et_2O	60	47	23 (*R*)	8	35 (*R*)	6
82a	toluene	1	39	29 (*R*)	13	21 (*R*)	21
82a	toluene	60	39	35 (*R*)	14	20 (*R*)	19
82b	Et_2O	1	-	-	27	7 (*R*)	44
82b	Et_2O	60	5	10 (*S*)	45	5 (*R*)	7
82b	toluene	1	5	9 (*S*)	47	10 (*R*)	16
82b	toluene	60	6	15 (*S*)	42	11 (*R*)	18

[a] Corrected for the ee of the starting material (94% ee)

To examine the possibility of the intermediacy of a discrete chiral α-nitrile carbanion in the reaction of **82a**,**b**, we performed benzylation reaction of *O*-carbamoyl cyanohydrin **85**. When LDA was added to a solution of **85** and benzyl bromide in Et_2O at –80 °C and then quenched for 1 min, benzylated product **86** was obtained in 35% chemical yield and 5% ee (Table 9). While prolongation of the reaction time to 60 min gave almost the same ee, the use of toluene as a solvent gave somewhat higher ee (11%). These results suggest the intermediacy of a discrete chiral α-nitrile carbanion that can be trapped intermolecularly with an electrophile without complete racemization, although the ees were low. Consequently, the partial chirality transfer observed in the above epoxysilane rearrangement should be based on both a concerted alkylation process from the silicate intermediate and the presence of the carbamoyl group, although the former process should be mainly responsible for the chirality transfer.

Table 9

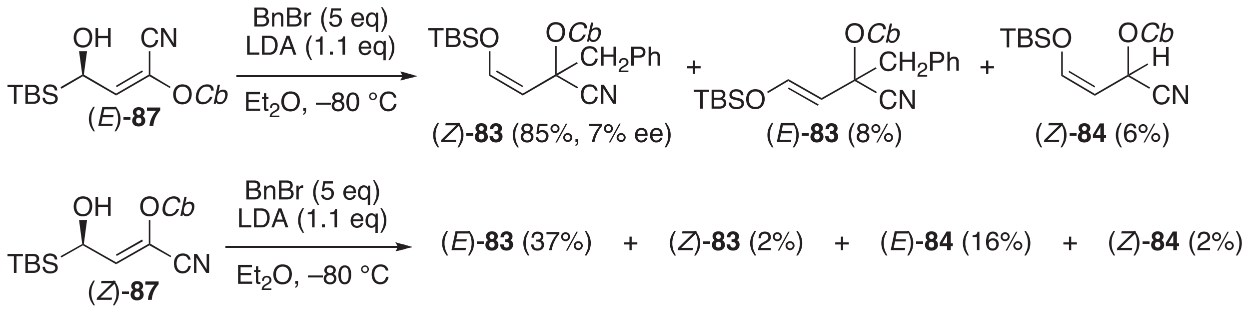


Solvent	Time (min)	yield (%)	*ee* (%)
Et_2O	1	35	5
Et_2O	60	84	3
toluene	1	40	11
toluene	60	71	9
THF	1	85	0
THF	60	80	0

To gain further insight into the stereochemical course of this reaction, particularly alkylation of silicates **33** (**33** → **34**, Scheme 9), we trapped the α-silyl alkoxide intermediates corresponding to **25** (Scheme 7).[32]

We envisioned that clarification of the correlation between the double bond geometry of **87** and the double bond geometry and absolute stereochemistry at the C-2 position of **83** is essential for understanding the chirality transfer observed. After extensive experimentation, we were able to isolate (*E*,*Z*)-**87** by performing the reaction in Et_2O at a lower temperature. We have sometimes observed that the rate of Brook rearrangement in Et_2O is much slower than that in THF. Treatment of **82a** with LDA at –98 °C in Et_2O afforded (*E*)-**87** in 59% yield. A similar result was obtained with **82b** to give (*Z*)-**87**. The observed stereospecificity was consistent with a syn-mode ring opening of the epoxide, although we have suggested an anti-mode ring opening for similar reactions using the corresponding OTBS derivatives in THF.

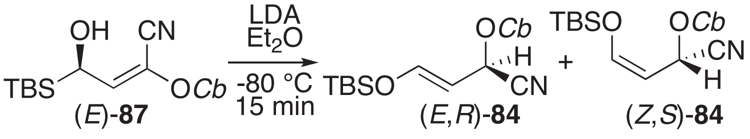
When LDA (1.1 equiv) was added to an Et_2O solution of (*E*)-**87** at –80 °C in the presence of BnBr and the reaction was quenched after 1 h, (*Z*)-**83** and (*E*)-**83** were obtained in 85% and 8% yields, respectively, together with protonated product (*Z*)-**84** (Scheme 19). In contrast to the results obtained in the reaction of **82a** (30-40% ee), the ees of all products were low. Reaction of (*Z*)-**87** provided (*E*)- and (*Z*)-**83** with low ees in a reversed ratio.

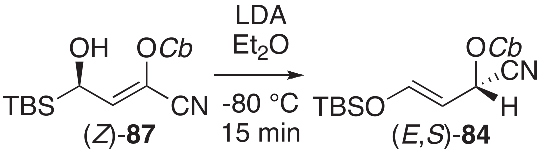


Scheme 19

The observed lower asymmetric induction in comparison with the cases in **82a**,**b** can be rationalized by assuming competitive *C*-protonation at the C-2 position by **87** with benzylation. This hypothesis led us to examine proton transfer reactions using substoichiometric amounts of LDA. The results are shown in Table 10.

Table 10





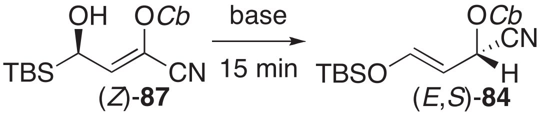
LDA	(*E*,*R*)-**84**		(*Z*,*S*)-**84**		(*E*)-**87**
(eq)	yield	ee (%)	yield	ee (%)	yield
0.1	5	69	4	35	33
0.3	20	29	34	9	-
0.6	13	25	32	8	-
1.0	7	0	38	0	-

LDA	(*E*,*S*)-**84**		(*Z*)-**87**
(eq)	yield	ee	yield
0.1	54	68	25
0.3	77	55	-
0.6	78	38	-
1.0	18	4	13

As expected, the enantiomeric excess increased with decreasing amount of LDA in the reactions of both (*E*)-and (*Z*)-**87**; thus, use of 0.1 equiv and 1.0 equiv of LDA gave the best and poorest results in terms of ee, respectively, and the best result with regard to chemical yield was obtained when 0.3 equiv of the base was used. The lower chemical yields when using stoichiometric amounts of the base may stem from base-induced decomposition in **84**.

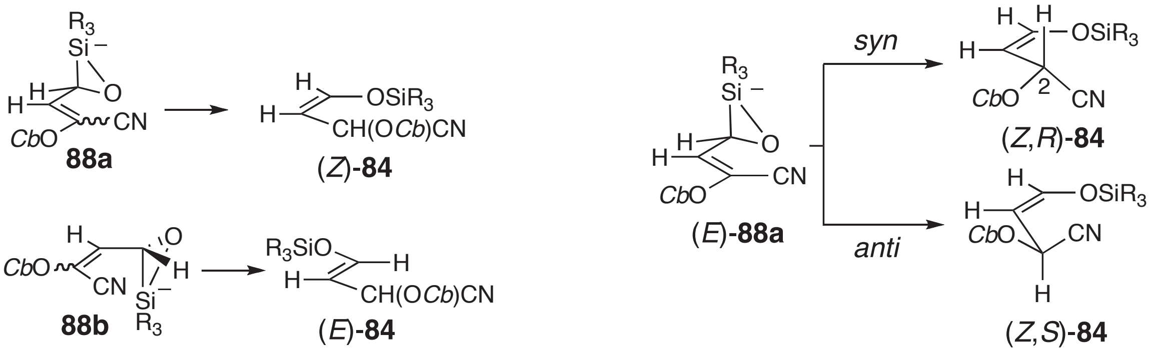
The above results prompted us to examine the reaction using much weaker bases than LDA in protic solvents, which would suppress base-induced decomposition and allow a rapid capture of the resulting anions. The best result was obtained by treating (Z)-**87** with *t*-BuOLi in *t*-BuOH at room temperature, giving (*E*,*S*)-**84** in 86% yield and 75% ee (Table 11, entry 8).

Table 11



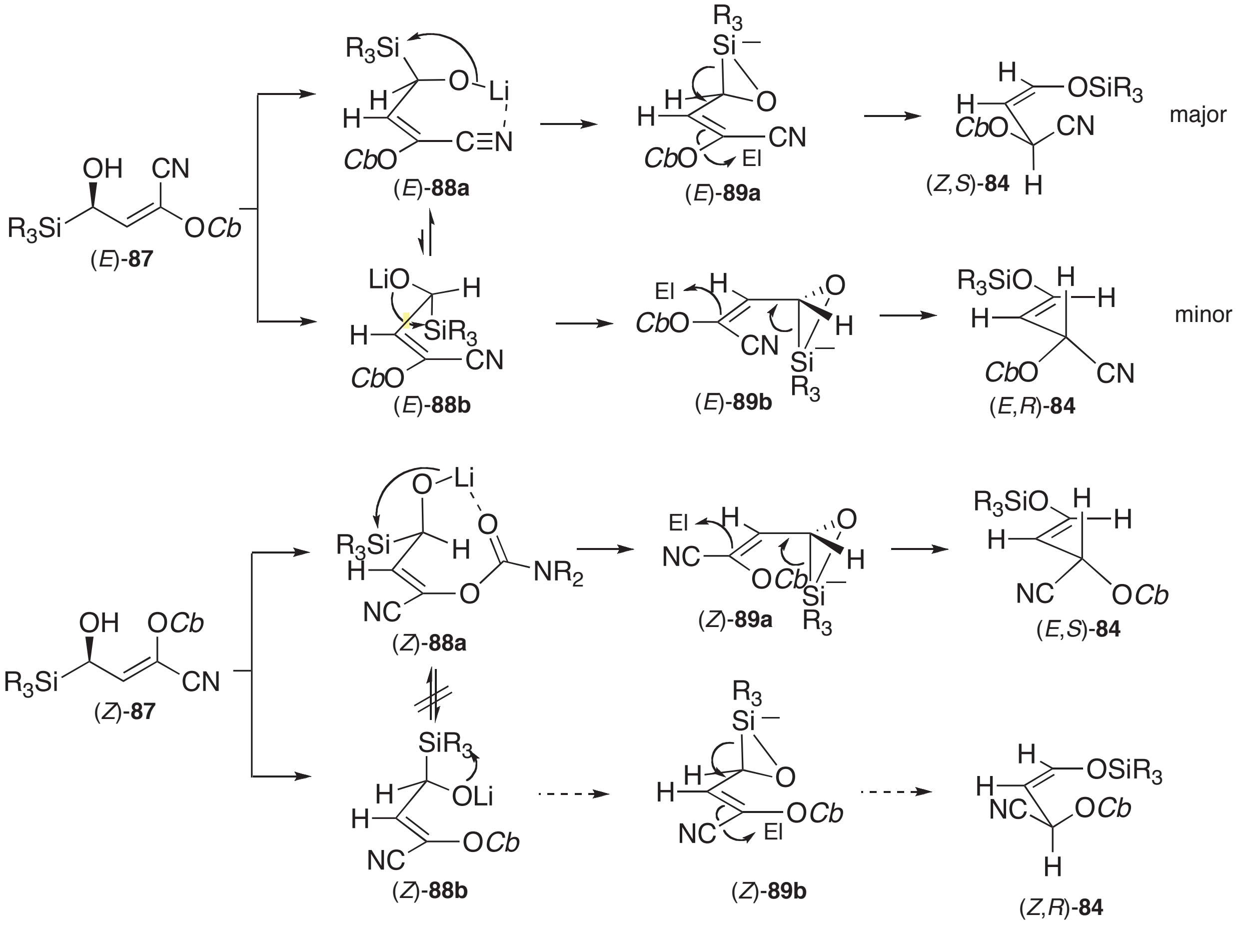
entry	base (equiv)	solvent	temp.	(*E*,*S*)-**84** yield (%)	(*E*,*S*)-**84** ee (%)	(*Z*)-**87** yield (%)
1	LDA (0.1)	Et_2O-hexane (1:1)	–80 °C	20	77	72
2	LDA (0.1)	Et_2O-hexane (1:2)	–80 °C	25	77	56
3	DBU (0.1)	DMSO	rt	14	74	10
4	*t*-BuOLi (0.1)	Et_2O	–80 °C	25	61	64
5	*t*-BuOLi (0.1)	Et_2O-hexane (1:1)	–80 °C	36	76	50
6	*t*-BuOLi (0.1)	Et_2O-hexane (1:1)	0 °C	64	70	20
7	*t*-BuOLi (0.1)	Et_2O-hexane (1:1)	rt	85	52	-
8	*t*-BuOLi (0.05)	*t*-BuOH	rt	86	75	-

In order to understand the stereochemical outcome in the reactions of (*E*)- and (*Z*)-**87**, the origin of the stereospecificity depending on the *E*/*Z*-geometry of **87** should be rationalized. The *E*/*Z*-geometry in **84** would be solely controlled by the conformation of silicate intermediates **88a**,**b**, which are generated via deprotonation by a base followed by attack of the oxyanion on the silicon atom, assuming that no *E*/*Z* isomerization occurs in the products **84** under the conditions and that C-Si bond cleavage in the silicates occurs in a concerted fashion while keeping a parallel alignment between the C-Si bond and the π-orbital (Scheme 20). On the other hand, the stereochemistry at the C-2 position would be regulated by both the double bond geometry and a syn/anti mode protonation to the C-Si bond in **88**. For example, (*E*)-**88a** would afford (*Z*,*R*)-**84** and (*Z*,*S*)-**84** in syn- and anti-protonation, respectively.



Scheme 20

The findings that (*Z*,*S*)-**84** and (*E*,*S*)-**84** were obtained from (*E*)-**87** and (Z)-**87** as a major product and as a sole product, respectively, can be explained on the basis of the results of ab initio calculations at the RI-MP2/6-31+G* level of theory (Scheme 21). Thus, an internally chelated conformation (*E*)-**88a** was found to be more stable than (*E*)-**88b**, while in the case of (*Z*)-derivatives, a local minimum identified was only (*Z*)-**88a** in which the lithium ion was chelated with the carbonyl oxygen. On the basis of the absolute configuration of the products **84**, which were determined by the modified Mosher method, (*E*)-**87** affords (*Z*,*S*)-**84** and (*E*,*R*)-**84** via anti-mode protonation of silicate intermediates (*E*)-**89a** and (*E*)-**89b** derived from (*E*)-**88a** and (*E*)-**88b**, respectively, according to the least motion principle, while (*Z*)-**87** gives only (*E*,*S*)-**84** via (*Z*)-**89a** derived from (*Z*)-**88a**. The origin for the observed anti-mode protonation might be related to steric effects of the bulky silyl group, to steroelectronic effects in the concerted process involving Brook rearrangement and protonation, and to electronic effects of the carbamoyloxy group.



Scheme 21

The above results obtained with (*E*)- and (*Z*)-**87** seem to provide us with a clear view of the mechanism of the second half of the tandem process in the reaction of **82a**,**b**. However, the fact that (*E*)-**83** and (*Z*)-**83** that were obtained from (*E*)-**82a** have the same (*R*)-configuration at C-2 cannot be explained on the basis of the exclusive formation of (*E*)- or (*Z*)-**88** from **87** via *syn*-ring opening of the epoxide. Assuming that the anti-mode protonation observed in the reactions of **87** is also applicable to the benzylation of **82a**,**b**, both syn- and anti-mode ring-opening should occur in **82a**,**b**. Since we have found that the mode of ring-opening depends on the solvent and temperature, a more definitive elucidation of the overall stereochemical process of the chirality transfer via the epoxysilane rearrangement must await more detailed mechanistic study, particularly for the first half of the process.

6. CONCLUSION

We have shown that epoxysilanes are useful and versatile building blocks in organic synthesis in combination with Brook rearrangement. Furthermore, the newly found rearrangement will provide a conceptually novel approach that allows construction of stereogenic centers at the position next to conjugative electron-withdrawing groups such as nitrile via a chiral carbanion.

ACKNOWLEDGEMENTS

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15. While the transition state from **29a** is more favorable than that from **29b** in the *syn*-elimination in

terms of less repulsive interactions between H-4 and the *O*-silyl cyanohydrin moiety (A-value for $OSiMe_3$: 0.74; for CN: 0.2), in the case of anti-elimination, the transition state from **29b** is more favorable. When a mixture of **29a** (1 equiv) and **29b** (1equiv) 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 **29a** and **29b** was obtained in 40% yield together with 35% of **30** (R = Me), indicating that **29b** is more reactive than is **29a**. These results are consitent with anti-elimination.

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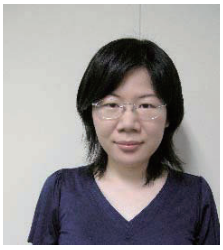

Michiko Sasaki is an assistant professor of organic chemistry at Hiroshima University. She obtained her B.S. degree (2002), M.S. degree (2003), and Ph.D. degree (2006) from Hiroshima University under the direction of Professor Kei Takeda. Her current research interests lie in the area of development of new synthetic reactions. She was the recipient of the Chugoku-Shikoku Branch of Pharmaceutical Society of Japan Award for Young Scientists (2007).

Hidaka Ikemoto is a 1st year PhD candidate and a research associate of organic chemistry at Hiroshima University. He obtained his B.S. degree (2007) and M.S. degree (2009) from Hiroshima University under the direction of Professor Kei Takeda. His current research interests lie in the area of chiral carbanion chemistry. He was the recipient of the Chugoku-Shikoku Branch of Pharmaceutical Society of Japan Award for Students (2008).

Kei Takeda is professor of organic chemistry at Hiroshima University. He was born in 1952 and received both his B.S. degree (1975) and M.S. degree (1977) from Toyama University (Professor Eiichi Yoshii) and his Ph.D. degree from the University of Tokyo (1980), where he studied with Professor Toshihiko Okamoto. In 1980, he joined the faculty at Toyama Medical and Pharmaceutical University (Prof. Yoshii's group). After working as a visiting scientist at MIT with Professor Rick L. Danheiser (1988-1989), he was promoted to Lecturer (1989) and then to associate professor (1996). He became a professor of Hiroshima University in 2000. His research interests are in the invention of new synthetic reactions and their application to complex organic molecules. He was the recipient of the Sato Memorial Award (1998) and the 41st Senji Miyata Foundation Award.