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Tandem Base-Promoted Ring Opening/Brook Rearrangement/Allylic Alkylation of *O*-Silyl Cyanohydrins of *β*-Silyl-α,*β*-epoxyaldehydes

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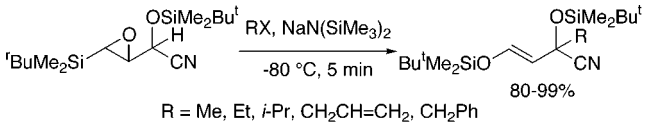
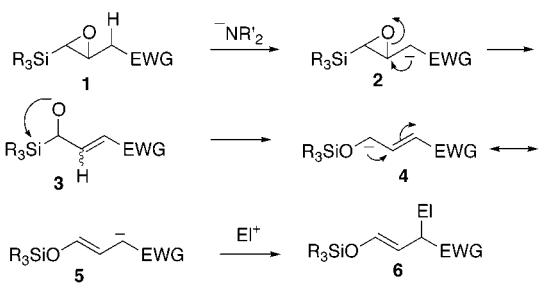
ABSTRACT



Metalated *O*-silyl cyanohydrins of *β*-silyl-α,*β*-epoxyaldehyde have been found to serve as functionalized homoenolate equivalents by a tandem sequence involving a base-promoted ring opening of the epoxide, Brook rearrangement, and alkylation of the resulting allylic anion.

Our continuing interest in the development of new synthetic reactions featuring a tandem bond formation[1] triggered by Brook rearrangement[2] led us to examine the reaction of epoxysilanes **1** bearing an anion-stabilizing electron-withdrawing group at the α-position with an amide base in the presence of an electrophile (Scheme 1). If the tandem process that involves a base-promoted isomerization of the epoxide (**2** → **3**), Brook rearrangement (**3** → **4**), and a reaction of the resulting allylic anion with an electrophile (**4** → **5** → **6**) proceeds well, the epoxysilane **1** would function as a homoenolate equivalent[3] equipped with a synthetically useful functionality. The internal quench conditions by alkylating agents were selected on the basis of the results of our previous study[1e] showing that α-cyano carbanions generated by Brook rearrangement in the reaction of acryl-

Scheme 1



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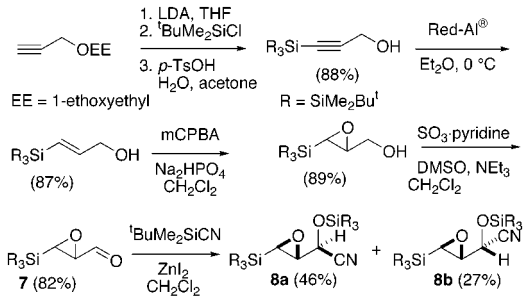
oylsilane with CN^-/18-crown-6 in the presence of MeI can undergo γ-alkylation without *O*-methylation and with the intention of ultimately extending the reaction to an asymmetric reaction by using homochiral epoxides.

Although base-promoted isomerization of epoxides to allylic alcohols has been well documented,[4] the only examples, to the best of our knowledge, of a tandem sequence involving a ring opening of expoxide followed by Brook rearrangement are two examples by González-Nogai and coworkers,[5] who succeeded in the generation of enol silyl ethers via cleavage of α,β-epoxysilanes with heteroatom nucleophiles. In this letter, we wish to report the results of our preliminary experiments on the tandem process.

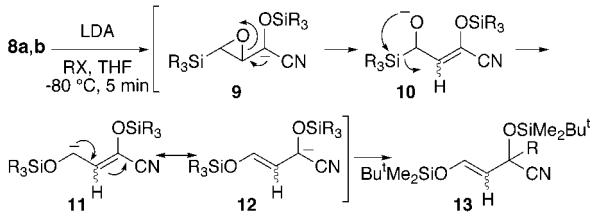
We focused on *O*-silyl cyanohydrins of α,β-epoxyaldehydes[6] **8** bearing a nitrile group as the electron-withdrawing group,[7] because **8** can be readily obtained from the corresponding aldehyde **7** and can provide functionalities useful for further synthetic elaboration. Epoxysilanes **8a** and **8b** were obtained as a diastereomeric mixture by the reaction of TBSCN with epoxyaldehyde **7**, which was derived from 3-(1-ethoxyethoxy)propyne[1f] via the sequence shown in Scheme 2.[8] The relative stereochemistry in **8a** and **8b** was determined on the basis of X-ray analysis of **8b**.

Scheme 2



When **8a** and **8b** were treated with LDA (1.05 equiv) in THF at −80 °C in the presence of MeI (1.2 equiv) for 5 min, α-methylated cyanohydrins **13**, products formed via the tandem sequence (**9** → **10** → **11** → **12**), were obtained in 82% and 84%, respectively (Table 1).

Table 1



	13, yield (%) (*E*/*Z*)	
RX	from **8a**	from **8b**
MeI	82 (2.5)	84 (22.0)
EtI	76 (2.9)	74 (28.0)
i-PrI	58 (2.8)[a]	74 (31.0)
$PhCH_2Br$	86 (2.7)	98 (47.0)
$CH_2{=}CHCH_2Br$	83 (3.4)	87 (40.0)

[a] 12% yield of **13** (R = H) was obtained.

Methylation products of intermediates **9** or **10** were not detected. Similar results were obtained for other alkylating agents (Table 1). Although almost the same yields were obtained from **8a** and **8b**, the *E*/*Z* ratios of the two isomers were markedly different, suggesting that the reactions from **8a** and **8b** do not share common intermediates in their major reaction pathways. Also, the addition of an alkylating agent after treatment with a base did not markedly affect the yield or *E*/*Z* ratio.

Next, we examined the effectiveness of other amide bases to improve the *E*/*Z*-selectivity. While the use of lithium hexamethyldisilazide (LHMDS, 1.0 M in THF) resulted in lower yields but improvement in *E*/*Z* ratios with **8a**, comparable yields of **13** were obtained with potassium hexamethyldisilazide (KHMDS, 0.5 M in toluene). It is notable that the increased formation of the *Z*-derivative with **8a** 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 (NHMDS, THF solution), allowing the formation of (*E*)-**13** in excellent yields. It is particularly noteworthy that the alkylation proceeds rapidly under much milder conditions than those for *O*-trimethylsilyl cyanohydrins of α,β-unsaturated aldehydes.[9]

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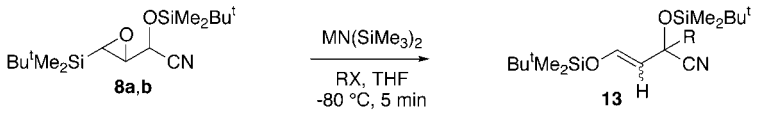
(8) For preparation of trimethylsilyl derivatives of **7** (R = Me), see: Urabe, H.; Matsuka, T.; Sato F. *Tetrahedron Lett*. **1992**, *33*, 4179−4182.

Table 2

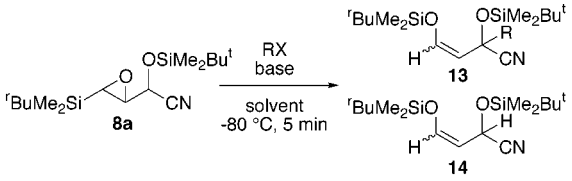


	13, yield (%) (*E*/*Z*)					
	from **8a**			from **8b**		
RX	LHMDS[a]	KHMDS[b]	NHMDS[a]	LHMDS[a]	KHMDS[b]	NHMDS[a]
MeI	44 (23.0)	84 (0.9)	96 (40.0)	83 (31.0)	87 (9.7)	98 (E)
EtI	24 (16.0)	76 (0.7)	90 (42.0)	64 (28.0)	81 (16.0)	89 (42.0)
i-PrI	15 (14.0)	42 (2.1)	80 (62.0)	44 (37.0)	73 (83.0)	89 (75.0)
$PhCH_2Br$	56 (30.0)	83 (0.8)	98 (65.0)	75 (82.0)	88 (13.0)	99 (67.0)
$CH_2{=}CHCH_2Br$	45 (31.0)	80 (1.1)	91 (39.0)	80 (89.0)	83 (14.0)	92 (41.0)

[a] 1.0 M solution in THF was used. [b] 0.5 M solution in toluene was used (THF/toluene = ca. 2:3).

The varying yields and *E*/*Z* ratios depending on the bases used prompted us to investigate the reaction pathway. First, we examined several solvent systems, considering the possibility that the increased formation of the (*Z*)-isomer in the case of KHMDS may be due to the lower polarity of toluene than that of THF. The results are summarized in Table 3. The use of less-polar solvents resulted in a substantial enhancement of the *Z*-selectivity, suggesting that the nature of the solvent, not the countercation, plays an important role in determination of *E*/*Z* selectivity in the reaction.[10]

Table 3



			yield (%), (*E*/*Z*)	
base	solvent	RX	**13**	**14**
LDA	hexane−tolene (1:1)	CH_3I	27 (0.1)	21 (0.06)
KHMDS	hexane−tolene (1:1)	CH_3I	24 (1.1)	43 (0.19)
NHMDS	hexane−THF (8.2:1)	$PhCH_2Br$	93 (1.5)	
NHMDS	toulene−THF (82:1)	$PhCH_2Br$	86 (1.0)	
NHMDS	Et_2O−THF (82:1)	$PhCH_2Br$	84 (1.9)	

We were also interested in the difference between the *E*/*Z* ratios of the diastereomers **8a** and **8b** in the reaction with LDA and KHMDS. Fleming and co-workers reported that the lithium amide base-promoted ring opening of *β*,*γ*-epoxynitrile proceeds by syn-elimination via a six-membered transition state in which the lithium ion coordinates the oxygen atom of the epoxide, on the basis of the slow ring opening of a substrate in which intramolecular chelation is geometrically precluded.[7a] We decided to compare the relative rates of ring opening of the diastereomers **8a** and **8b**. When a mixture of **8a** (1 equiv) and **8b** (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 **8a** and **8b** was obtained in 40% yield together with 35% of **13** (R = Me) (*E*/*Z* = 6.6), indicating that **8b** is more reactive than is **8a**. The difference in reactivities can be rationalized by invoking a concerted anti-deprotonation and ring opening, in which the transition state from **8b** is more favorable than that from **8a** in terms of less repulsive interactions between H-4 and the *O*-silyl cyanohydrin moiety (*A*-value[11] for $OSiMe_3$, 0.74; for CN, 0.2) (Figure 1).

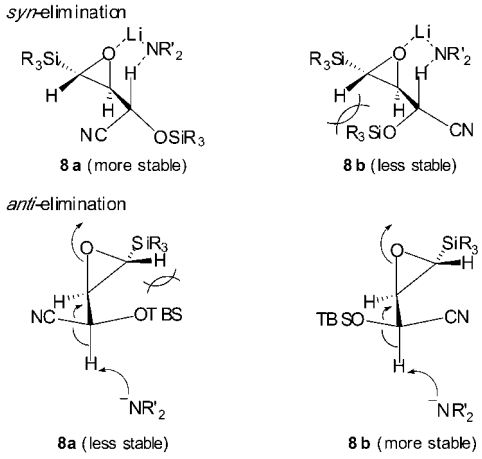


Figure 1.

This is in sharp contrast to the widely accepted chelation-assisted syn-elimination mechanism for a base-promoted ring

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(11) Eliel, E.; Wilen, S. H. In *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; p 696.

opening,[4,7] in which the pathway from **8a** is sterically preferable to that from **8b** owing to the repulsive interaction shown in Figure 1. Furthermore, the concerted anti-deprotonation and ring opening process was supported by the fact that the reactivities of **8a** and **8b** were not affected by the addition of HMPA, which can disrupt the chelated structure by solvating the lithium cation.

In conclusion, we have found that *O*-silyl cyanohydrins of β-silyl-α,β-epoxyaldehyde can function as a highly functionalized homoenolate equivalent via the tandem sequence involving base-promoted ring opening, Brook rearrangement, allylic rearrangement, and alkylation. Although a full understanding of the actual mechanism of the entire process, including the stereochemistries of the Brook rearrangement and subsequent allylic rearrangement and alkylation, must await further detailed mechanistic experimentation, a number of mechanistically interesting issues seems to be embedded in the synthetically useful reactions. More detailed mechanistic investigation and attempts at extension of the process to an asymmetric reaction using homochiral epoxides will be reported in a forthcoming paper.

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Supporting Information Available: Full experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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