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# Chirality Transfer from Epoxide to Carbanion: Base-Induced Alkylation of *O*-Carbamoyl Cyanohydrins of β-Silyl-α,β-epoxy Aldehyde

Michiko Sasaki,[a] Eiji Kawanishi,[a] Yuri Shirakawa,[a] Masatoshi Kawahata,[b] Hyuma Masu,[b] Kentaro Yamaguchi,[b] and Kei Takeda*[a]

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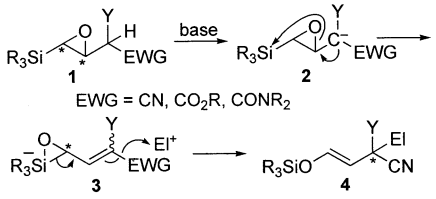
Enantioselective C–C bond formation at an α-position of a nitrile group with an external electrophile can be realized, although in modest *ee*, with the aid of both the concerted process of an epoxysilane rearrangement and a carbamoyl group.



## Introduction

Enantioselective formation of a chiral carbanion followed by stereospecific reaction with an electrophile is one of the most powerful and efficient methods in asymmetric carbon–carbon bond-forming reactions. Although recent developments in methods for generating a chiral carbanion by using chiral ligands such as sparteine have provided relatively ready access to chiral carbanions and a better understanding of the process, they have usually been applied for the generation of less-stable carbanions such as benzyl and allyl anions, which often have α-heteroatoms or dipole-stabilizing and directing groups.[1] 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 coworkers, who found that a chiral cyclopropyl nitrile derivative could be enantiospecifically deuterated in basic $CH_3OD$ is the only example.[2] They also found that the corresponding chiral aliphatic nitrile derivative suffered extensive racemization under the same conditions.

We recently reported that epoxide chirality can be transferred to a carbanion through epoxysilane rearrangement[3] and trapped intramolecularly almost without racemization by [2,3]-Wittig rearrangement.[4] We also demonstrated that the chirality can be transferred to remote positions without complete racemization through an intramolecular tandem process that involves epoxysilane rearrangement and Brook rearrangement-mediated [3+4] annulation.[5] On the basis of these findings we became interested to determine whether a more stable carbanion such as an α-nitrile carbanion[6] generated by epoxysilane rearrangement (Scheme 1) could participate in the enantioselective formation with an electrophile intermolecularly through a concerted process involving Brook rearrangement[7] via silicate intermediate **3** without the involvement of a free α-nitrile carbanion.




Scheme 1. Epoxysilane rearrangement.

## Results and Discussion

First we examined the reaction of enantiomerically enriched epoxysilane **5**[8] with a base in the presence of benzyl bromide (Scheme 2). Unfortunately, benzylated rearrangement products (*E*)- and (*Z*)-**6**[3] obtained under a variety of conditions were completely racemic. The cause of the unsuccessful result could be ascribed to several factors, including the existence of equilibrium between silicate **3** and another silicate intermediate involving the siloxy group at the α-position of the nitrile group. We next examined the reaction with the use of the corresponding *O*-benzylcyanohydrin derivative, in which the formation of a chelation structure at the position is impossible; this results in low chemical yield as well as complete racemization again.

[a] Graduate School of Medical Sciences, Hiroshima University
1-2-3 Kasumi, Minami-Ku, Hiroshima 734-8553, Japan
Fax: +81-82-257-5184
E-mail: takedak@Hiroshima-u.ac.jp
[b] Tokushima Bunri University
1314-1 Shido, Sanuki, Kagawa, 769-2193, Japan
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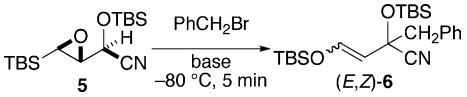
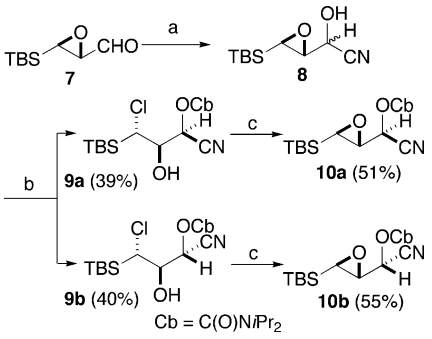



Scheme 2. Epoxysilane rearrangement with the use of enantiomerically enriched **5**.

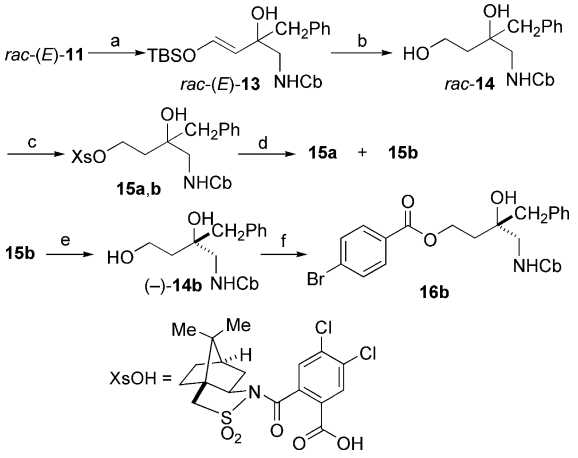
These results led us to consider that the concerted alkylation from silicate intermediate **3** is not the sole product-forming reaction pathway and that a pathway via an α-nitrile-stabilized carbanion intermediate could also be operative. Next, we decided to change the siloxy group into a carbamoyloxy group,[9] which would decelerate the rate of racemization of the generated α-nitrile allylic carbanion by its strong chelating ability. Carbamoyl derivatives **10a** and **10b** were prepared according to the route shown in Scheme 3. Reaction of cyanohydrin **8**, derived from **7** (94% *ee*),[3,10] with carbamoyl chloride resulted in ring opening of the epoxide to chlorohydrins **9a** and **9b**, which were converted into epoxides **10a** and **10b** by treatment with DBU after separation. Stereostructures of **10a** and **10b** were determined on the basis of X-ray analysis of **9b**.




Scheme 3. Synthesis of **10a** and **10b**. Reagents and conditions: (a) TMSCl, KCN, $n$Bu$_4$PBr, $CH_2Cl_2$; then $H_2SiF_6$, room temp., 94%; (b) ClCON$i$Pr, pyridine, 90 °C, 8 h; then separation; (c) DBU, $CH_2Cl_2$, 0 °C, 1.5 h.

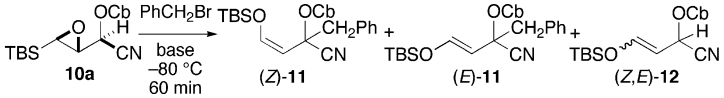
First, exploratory experiments to find conditions allowing the successful chirality transfer shown in Scheme 1 were carried out by using **10a** and benzyl bromide as an electrophile with bases in several solvents for 60 min (Table 1). The best result in terms of chemical and optical yields was obtained with LDA in the presence of benzyl bromide in $Et_2O$ or toluene at –80 °C, which gave benzylated products (*Z*)-**11** in 23%*ee* and 35%*ee*, respectively.[11] In contrast, reactions in THF, the most common solvent for carbanion reactions, resulted in complete racemization. The use of sodium or potassium amide bases and the addition of TMEDA were not effective.

Although determination of the absolute configurations of (*Z*)-**11** and (*E*)-**11** proved difficult and required extensive investigation, they were eventually determined by chemical correlation shown Scheme 4. Thus, *rac*-(*E*)-**11**[12] was transformed into diol derivative *rac*-**14** by $LiAlH_4$ reduction followed by desilylation and $NaBH_4$ reduction of the resulting aldehyde. Most attempts at separation of *rac*-**14** after derivatization to diastereomers as well as separation of *rac*-**14** itself by using preparative chiral HPLC failed. The only successful separation was achieved by preparative chiral HPLC after conversion to diastereomeric camphorsultum[13] derivatives **15a**,**b**. Because suitable crystals of **15a** and **15b** for X-ray analysis could not be obtained, they were




Scheme 4. Determination of the absolute configurations of (*Z*)- and (*E*)-**11**. Reagents and conditions: (a) $LiAlH_4$, THF, room temp., 1 h, 52%; (b) $n$Bu$_4$NF, THF, 0 °C, 30 min; EtOH; then $NaBH_4$, room temp., 1 h, 94%; (c) XsOH, EDC·HCl, DMAP, $CH_2Cl_2$, room temp., 17 h, 85%; 8d) separation with a chiral HPLC column; 8e) $K_2CO_3$, MeOH, room temp.; 8f) $p$-Br$C_6H_4$COCl, $NEt_3$, DMAP, $CH_2Cl_2$.

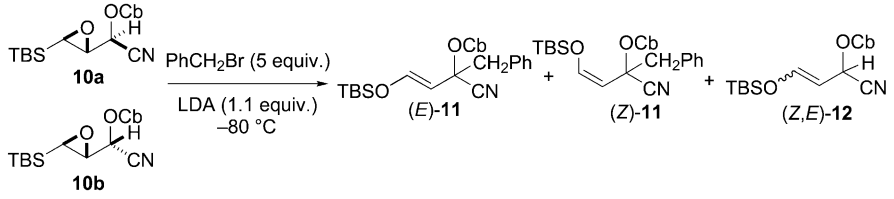
Table 1. Reaction of enantiomerically enriched **10a** with a base in the presence of BnBr.




| Solvent | Base | (*Z*)-**11** Yield [%] | (*Z*)-**11** *ee* [%] | (*E*)-**11** Yield [%] | (*Z*,*E*)-**12** Yield [%] |
|---|---|---|---|---|---|
| THF | LDA | 36 | 0 | 30 | 9 |
| $Et_2O$ | LDA | 47 | 23 | 8 | 6 |
| $Et_2O$ | LDA (TMEDA) | 25 | 0 | 8 | 21 |
| Toluene | LDA | 39 | 35 | 14 | 19 |
| Toluene | LDA (TMEDA) | 29 | 0 | 25 | 11 |
| $Et_2O$ | LHMDS | 35 | 23 | 22 | 7 |
| $Et_2O$ | NaHMDS | 33 | 4 | 33 | 0 |
| $Et_2O$ | KHMDS | 24 | 0 | 50 | 0 |

Table 2. Reaction of enantiomerically enriched **10a** and **10b** with LDA in the presence of BnBr.




| | Solvent | Time [min] | (*Z*)-**11** Yield [%] | (*Z*)-**11** *ee* [%][a] | (*E*)-**11** Yield [%] | (*E*)-**11** *ee* [%] | **12** Yield [%] |
|---|---|---|---|---|---|---|---|
| **10a** | $Et_2O$ | 1 | 22 | 39 (*R*) | 5 | 40 (*R*) | 47 |
| **10a** | $Et_2O$ | 60 | 47 | 23 (*R*) | 8 | 35 (*R*) | 6 |
| **10a** | toluene | 1 | 39 | 29 (*R*) | 13 | 21 (*R*) | 21 |
| **10a** | toluene | 60 | 39 | 35 (*R*) | 14 | 20 (*R*) | 19 |
| **10b** | $Et_2O$ | 1 | – | – | 27 | 7 (*R*) | 44 |
| **10b** | $Et_2O$ | 60 | 5 | 10 (*S*) | 45 | 5 (*R*) | 7 |
| **10b** | toluene | 1 | 5 | 9 (*S*) | 47 | 10 (*R*) | 16 |
| **10b** | toluene | 60 | 6 | 15 (*S*) | 42 | 11 (*R*) | 18 |

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

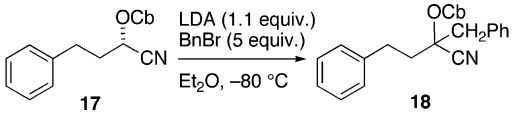
further transformed into *p*-bromobenzoate derivatives **16a** and **16b**. Absolute configurations of **16b**, whose crystal was suitable for X-ray analysis, were determined by X-ray crystallographic analysis by using the anomalous dispersion technique. Comparison of chiral HPLC of (–)-**14b** derived from **15b** with **14** derived from (*E*)-**11** and (*Z*)-**11** obtained in the reaction of **10a**, respectively, showed that both of the absolute configurations of the major enantiomers of (*E*)- and (*Z*)-**11** are *R*.

Having established the absolute configurations, we next decided to examine the reactions of **10a** and **10b** with LDA in the presence of BnBr in $Et_2O$ and toluene with reaction times of 60 min and 1 min (Table 2). The latter reaction time was selected by considering the possibility of a relatively slow reaction rate of the silicate intermediate and/or the chiral carbanion with benzyl bromide. In $Et_2O$, the *ee* values of (*R*,*Z*)-**11** and (*R*,*E*)-**11** were improved by quenching for 1 min, but at the expense of the chemical yield, whereas in toluene the chemical and optical yields were not greatly affected by the reaction time. The 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 **10b** were lower than those in the reaction of **10a**.

Although a mechanistic rationalization of the observed partial asymmetric induction and of the stereochemical outcome cannot be made at the present time and must await further studies, it is noteworthy, considering the fact that a chiral α-nitrile carbanion has never been generated due to its low inversion barrier except Walborsky's substrate,[14] that a chiral carbanion in an α-position of the nitrile group can be generated and trapped by an intermolecular process without complete racemization, with a maximum *ee* value of 40%, regardless of whether a discrete chiral α-nitrile carbanion is involved. Carlier reported that the calculated inversion barrier for lithioacetonitirile is 0.45 kcal/mol,[15,16] and X-ray analysis of lithiophenylacetonitrile indicated that the geometry is planar.[17] The formation of enantiomerically enriched products by change in the *O*-substituent of the cyanohydrin from TBS to carbamoyl seems to be consistent with a pathway that involves an α-nitrile carbanion. Carlier also predicted increased configurational stabilization of an α-nitrile carbanion by a directing group such as a carbamoyl group based on calculation for lithiated β-formylcyclopropylnitriles.

To examine the possibility of the intermediacy of a discrete chiral α-nitrile carbanion in the reaction of **10a**,**b**, we decided to perform benzylation reaction of *O*-carbamoyl cyanohydrin **17**,[18] which was prepared from *O*-acetyl cyanohydrin of 3-phenylpropanal by lipase-mediated kinetic resolution[19] followed by carbamoylation. When LDA was added to a solution of **17** and benzyl bromide in $Et_2O$ at –80 °C and then quenched for 1 min, benzylated product **18**[20] was obtained in 35% chemical yield and 5%*ee* (Table 3). Although prolongation of the reaction time to 60 min gave almost the same *ee* value, the use of toluene as a solvent gave a somewhat higher *ee* value (11%).[21] These results suggest the intermediacy of a discrete chiral α-nitrile carbanion that can be trapped intermolecularly with an

Table 3. Reaction of enantiomerically enriched **17** with LDA in the presence of BnBr.




| Solvent | Time [min] | Yield [%] | *ee* [%][c] |
|---|---|---|---|
| $Et_2O$ | 1 | 35[a] | 5 |
| $Et_2O$ | 60 | 84 | 3 |
| Toluene | 1 | 40[b] | 11 |
| Toluene | 60 | 71 | 9 |
| THF | 1 | 85 | 0 |
| THF | 60 | 80 | 0 |

[a] 39% of **17** was recovered. [b] 27% of **17** was recovered. [c] Corrected for the *ee* of the starting material (98%*ee*).

electrophile without complete racemization, although the *ee* values 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.

## Conclusions

The overall stereochemical process of the chirality transfer through an epoxysilane rearrangement is much more complicated than it may appear and involves subtle interplay of many factors that are not easy to estimate. Thus, at least the mode of ring opening of the epoxide (*syn*/*anti*), stereochemistry of the Brook rearrangement (retention/inversion), and the stereochemistry (*syn*/*anti*) of the SE′ reaction in silicate intermediate **3** should be clarified. Further work along these lines is currently under way, and the results will be the subject of a forthcoming full paper.

## Experimental Section

To a cooled (–80 °C) solution of **10a** (100 mg, 0.294 mmol) and benzyl bromide (0.175 mL, 1.47 mmol) in $Et_2O$ (2.4 mL) was added dropwise a solution of lithium diisopropylamide (0.4 M in $Et_2O$, 0.808 mL, 0.323 mmol) over a period of 2 min. After stirring at the same temperature for 1 min, the reaction mixture was poured into saturated ammonium chloride solution (5 mL) and then extracted with $Et_2O$ (3 × 10 mL). The combined organic phase was washed with water (10 mL) and saturated brine (10 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel 15 g; hexane/$Et_2O$, 5:1) to give a mixture of (*E*)-**11**, (*Z*)-**11**, (*E*)-**12**, and (*Z*)-**12** (81.1 mg).

**Supporting Information** (see footnote on the first page of this article): Full experimental details and spectroscopic data.

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[20] The absolute configuration of **18** was not determined.

[21] We believe that the *ee* values are meaningful because they were reproducible.

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