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# An Asymmetric Transformation of Symmetrical Epoxides to Both Enantiomers of Allylic Alcohols by Chiral Lithium Amides#

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Both enantiomers of several optically active allylic alcohols are obtained from cyclic and acyclic symmetrical epoxides by using chiral lithium amides, i.e., lithium cyclohexyl[(S)-1-ethylpyrrolidin-2-yl]methylamide or lithium (S)-2-[(pyrrolidin-1-yl)methyl]pyrrolidide, as bases.

Asymmetric synthesis starting from symmetrical compounds has become one of attractive approaches for the preparation of synthetically useful chiral compounds. Recently, various highly stereoselective reactions have been developed employing biochemical[1] or chemical[2-4] methods for such a type of the reaction.

In the previous paper, we reported an asymmetric transformation of cyclohexene oxide to (S)-2-cyclohexen-1-ol by highly enantioselective deprotonation reaction employing the chiral lithium amide, prepared from butyl lithium and (S)-2-[(pyrrolidin-1-yl)methyl]pyrrolidine (1) (Figure 1).[3a] The reaction was successfully applied to the synthesis of an optically active cis-2-cyclopenten-1,4-diol derivative, versatile intermediate for prostagrandin synthesis.[3b] It is of value to develop a new and efficient chiral amine which shows the opposite selectivity to 1, since 1 is prepared from (S)-proline, and (R)-proline is not easily available.

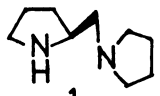

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Fig. 1.

In this communication, we wish to report that cyclohexyl[(S)-1-ethylpyrrolidin-2-yl]methylamine (2c),[5] also prepared from easily available (S)-proline, shows the opposite selectivity to 1 to provide (R)-2-cyclohexen-1-ol in a good optical yield. Furthermore, syntheses of both enantiomers of several cyclic and acyclic optically active allylic alcohols by the enantioselective deprotonation of symmetrical epoxides using the chiral lithium amides prepared from the diamine 1 or 2c are demonstrated.

At first, the reaction was carried out in tetrahydrofuran (THF) using lithium cyclohexyl[(S)-1-methylpyrrolidin-2-yl]methylamide (3a), and (R)-2-cyclohexen-1-ol was obtained in 52% ee (enantiomeric excess). To improve the optical yield, the reaction was carried out in the presence of an additive, which can coordinate to lithium ion. Among additives examined, hexamethylphosphoric triamide (HMPA) was the best and the optical yield was increased to 62% ee (Table 1, entries 1-5).

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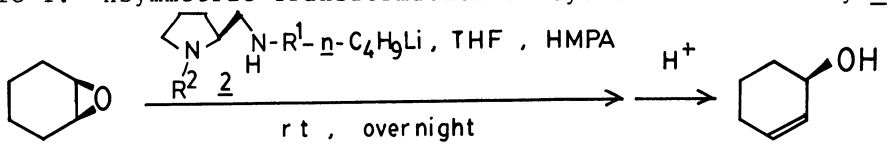
# Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.

Table 1. Asymmetric Transformation of Cyclohexene Oxide by 3[a)]




| Ent. | Diamine | $R^1$ | $R^2$ | Yield/%[b)] | $[\alpha]_D$ ($CHCl_3$) /° (c, temp /°C) | ee/%[c)] |
|---|---|---|---|---|---|---|
| 1 | 2a | c-$C_6H_{11}$(cyclohexyl) | $CH_3$ | 85(85)[d)] | +69.4 (0.61, 15) | 62(52)[d)] |
| 2[e)] | 2a | | | 78 | +60.0 (0.50, 16) | 54 |
| 3[f)] | 2a | | | 80 | +59.1 (0.64, 16) | 53 |
| 4[g)] | 2a | | | 81 | +58.7 (0.60, 16) | 52 |
| 5[h)] | 2a | | | 81 | +55.1 (0.60, 19) | 49 |
| 6 | 2b | (S)-$C_6H_5(CH_3)CH$ | $CH_3$ | 80(66)[d)] | +42.7 (0.63, 18) | 42(58)[d)] |
| 7 | 2c | c-$C_6H_{11}$ | $C_2H_5$ | 80 | +87.4 (0.60, 17) | 78 |
| 8 | 2d | c-$C_6H_{11}$ | $(CH_3)_2CH$ | 75 | +64.0 (0.45, 21) | 57 |
| 9 | 2e | c-$C_6H_{11}$ | $(CH_3)_2CHCH_2$ | 63 | -43.3 (0.62, 18) | 39[i)] |
| 10 | 2f | c-$C_6H_{11}$ | $(CH_3)_3CCH_2$ | 77 | -69.8 (0.65, 22) | 62[i)] |

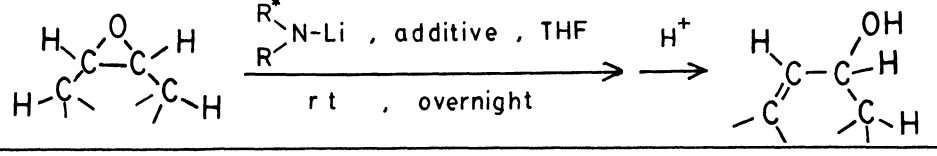
a) Cyclohexene oxide : butyllithium : 2 : HMPA = 1.00 : 1.50 : 1.65 : 1.65. b) Isolated yield after benzoylation. c) Absolute configuration and ee were determined based on $[\alpha]_D$ -112°(c 0.6, $CHCl_3$) for (S)-2-cyclohexen-1-ol.[6)] d) The figure in parenthesis refer to result without HMPA. e) Pyridine was used in place of HMPA. f) Triethylamine was used in place of HMPA. g) N,N,N',N'-Tetramethylethylenediamine was used in place of HMPA. h) 1,8-Diazabicyclo-[5.4.0]undec-7-ene (DBU) was used in place of HMPA. i) (S)-2-Cyclohexen-1-ol was obtained.

Next, various chiral lithium amides 3 prepared from alkyl[(S)-1-alkylpyrrolidin-2-yl]methylamine (2)[5)] were examined in THF in the presence of HMPA (Table 1, entries 6-10). As shown in Table 2, the substituent of the nitrogen atom of the pyrrolidine ring ($R^2$) was found to have a noticeable effect on the selectivity. The best result was obtained when the diamine 2c ($R^1$=c-$C_6H_{11}$, $R^2$=$C_2H_5$) was used, and (R)-2-cyclohexen-1-ol was obtained in 78% ee (entry 7). On the contrary, (S)-2-cyclohexen-1-ol was obtained predominantly in the cases that 2e ($R^1$=c-$C_6H_{11}$, $R^2$=$(CH_3)_2CHCH_2$) or 2f ($R^1$=c-$C_6H_{11}$, $R^2$=$(CH_3)_3CCH_2$) was used (entries 9,10).

Thus it has become possible to prepare the both enantiomers of 2-cyclohexen-1-ol in high ee from cyclohexene oxide employing the diamines 1[3a)] or 2c, the reaction was applied to several cyclic and acyclic symmetrical epoxides (Table 2). As shown in Table 2, both enantiomers were obtained in every case as expected. Even in the cases of acyclic symmetrical epoxides, good selectivities were achieved, though the enantioselective deprotonation reaction was known only for 5- or 6-membered cyclic compounds so far.[3,4)]

A typical experimental procedure is as follows: To a THF (2.5 ml) solution of 1 (254 mg, 1.65 mmol) was added a hexane (1.0 ml) solution of butyllithium (1.50 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at

Table 2. Asymmetric Transformation of Symmetrical Epoxides to Allylic Alcohols[a)]




| Epoxide | Method[b)] | Yield/%[c)] | $[\alpha]_D$(c, solv) | ee/%[d)] |
|---|---|---|---|---|
| cyclopentene oxide | A | 49[e,f)] | $[\alpha]_D^{30}$-55.0°(1.35, $CCl_4$) | 31(S)[g)] |
| | B | 48[e,f)] | $[\alpha]_D^{25}$+22.3°(1.63, $CCl_4$) | 15(R)[g)] |
| cyclooctene oxide | A | 45[h)](84)[e)] | $[\alpha]_D^{22}$+30.4°(1.14, $CHCl_3$) | 58[i)](50)[e)] |
| | B | 56[j)](61)[e)] | $[\alpha]_D^{29}$-19.3°(1.40, $CHCl_3$) | 42[i)](34)[e)] |
| (Z)-2-butene oxide | A | 60[f)] | $[\alpha]_D^{31}$+32.3°(1.01, $CHCl_3$)[k)] | 70(S)[1)] |
| | B | 58[f)] | $[\alpha]_D^{29}$-28.4°(1.05, $CHCl_3$)[k)] | 62(R) |
| (Z)-4-octene oxide | A | 66 | $[\alpha]_D^{27}$-3.63°(1.94, $CHCl_3$) | 60(S)[m)] |
| | B | 66 | $[\alpha]_D^{28}$+3.47°(2.96, $CHCl_3$) | 59(R) |

a) Epoxide : butyllithium : diamine : additive = 1.00 : 1.50 : 1.65 : 1.65. b) Method A: The reaction was carried out using diamine 1 in the presence of DBU.[7)] Method B: The reaction was carried out using diamine 2c in the presence of HMPA. c) Isolated yield. d) Determined by $^1$H NMR taken in the presence of $Eu(hfbc)_3$ after conversion to corresponding acetates. e) The reaction was carried out under reflux for 1.5-4 h. f) Isolated yield after benzoylation. g) Configuration was determined based on reported value for (R)-2-cyclopenten-1-ol ($[\alpha]_D^{21}$+22.8° (c 5, $CCl_4$).[8)] h) Cyclooctene oxide was recovered (50%). i) Configuration was not determined. j) Cyclooctene oxide was recovered (34%). k) Optical rotation value of the benzoate. 1) Configuration was determined by conversion of the product to 1,2-propanediol ($[\alpha]_D^{27}$+14.5°(c 2.4, $H_2O$); lit[9)] $[\alpha]_D^{23}$+20.1°(c 7.5, $H_2O$) for (S)-1,2-propanediol). m) Configuration was determined by conversion of the product to 1,2-pentanediol ($[\alpha]_D^{30}$-8.66°(c 3.65, $C_2H_5OH$); lit.[10)] $[\alpha]_D^{20}$+16.2°(c 8.00, $C_2H_5OH$) for (R)-1,2-pentanediol).

0 °C for 30 min and a THF (2.0 ml) solution of DBU (251 mg, 1.65 mmol) was added at this temperature. After 30 min, a THF (2.0 ml) solution of (Z)-4-octene oxide (128 mg, 1.00 mmol) was added and the reaction mixture was stirred for overnight at room temperature. Saturated ammonium chloride solution was added and the reaction mixture was extracted with ether. The organic layer was washed with 2% HCl, water, and brine, successively, and dried over anhydrous $Na_2SO_4$. After the removal of the solvent, the residue was purified by column chromatography to afford (S)-3-octen-5-ol (84.5 mg, 66%): $[\alpha]_D^{27}$-3.26°(c 1.94, $CHCl_3$).

As lithium amide promoted transformation of epoxides to allylic alcohols is supposed to proceed in a cyclic concerted manner,[11)] we presume the transition states as shown in Figure 2-4 to account for the stereoselectivities of the reactions. In the cases that the diamine 1

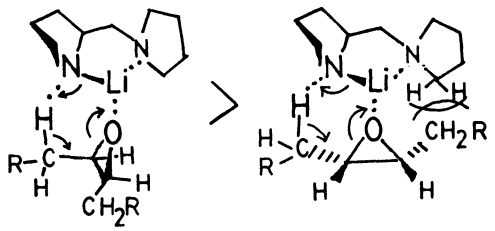



Fig. 2.

is used, the reaction proceeds via transition state $T_1$ in preference to transition state $T_2$, in which steric repulsion between the diamine and the epoxide arises. Consequently, the alcohol having S-configuration is obtained (Figure 2). In cases of the diamine 2a-d, epoxide approaches the lithium amide from the less hindered side (side B) in such a way that the steric repulsion can be avoided. Thus transition state $T_3$ is favored over transition state $T_4$, and the alcohol having R-configuration is obtained (Figure 3). When $R^2$ is bulky (2e,f), epoxide approaches from side A in a manner shown in transition state $T_5$ to yield the alcohol having S-configuration (Figure 4).

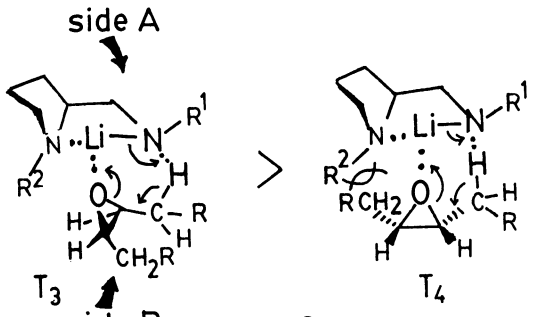



Fig. 3.

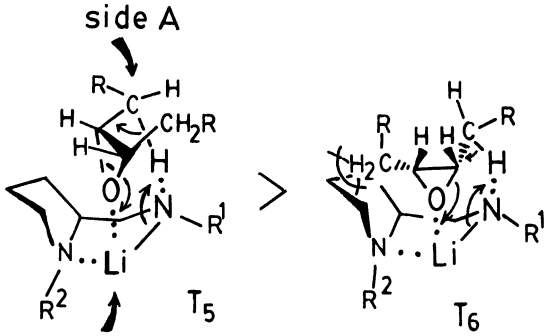



Fig. 4.

It should be noted that the both enantiomers of several cyclic and acyclic allylic alcohols were obtained from symmetrical epoxides by the enantioselective deprotonation employing the chiral diamines 1 or 2c, both derived from easily available (S)-proline.

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