CHEMISTRY LETTERS, pp. 829 - 832, 1984.

AN ASYMMETRIC TRANSFORMATION OF CYCLOHEXENE OXIDE TO (S)-2-CYCLOHEXEN-1-OL BY CHIRAL LITHIUM AMIDES

Masatoshi ASAMI
Department of Chemistry, Faculty of Education,
Yokohama National University,
Tokiwadai, Hodogaya-ku, Yokohama 240

(S)-2-Cyclohexen-1-ol is prepared in 92% ee from cyclohexene oxide by using chiral lithium amides, prepared from butyllithium and (S)-2-(disubstituted aminomethyl)pyrrolidines, as bases.

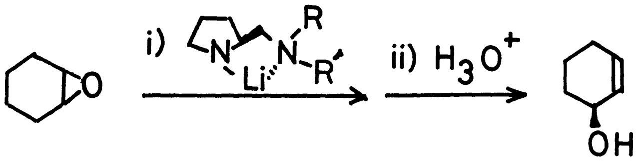
A variety of highly stereoselective asymmetric reactions has already been known for the synthesis of optically active compounds. Most of those reactions are diastereo- or enantioface-differentiating reactions,[1)] and only a few reactions which show high selectivity for diastereotopos or enantiotopos differentiation are known.[2)] We recently reported an asymmetric synthesis of bicyclic lactones by diastereotopically selective reduction of cyclic imides, prepared from meso-dicarboxylic acids.[3)]

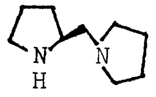
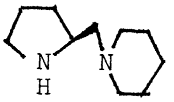
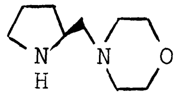
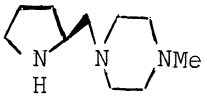
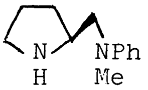
The transformation of epoxides to allylic alcohols by the use of lithium dialkylamides is well known.[4)] It is possible to apply this reaction to the asymmetric reaction by the selective deprotonation of enantiotopically related protones in the symmetrical epoxides. Whitesell and Felman reported the first example of such reaction by treating cyclohexene oxide with a number of chiral mono- and dialkyl lithium amides, but the optical yield of the resulting 2-cyclohexen-1-ol was not high (≦31% ee).[5)]

We have already reported several highly stereoselective asymmetric reactions using chiral diamines, easily prepared from (S)-proline.[6)] In those reactions, the formation of the tight complex between organometallic reagents and the diamines by coordinations is assumed to play an important role for the high selectivities. In this communication, we wish to describe a highly stereoselective transformation of cyclohexene oxide to (S)-2-cyclohexen-1-ol using chiral lithium amides, prepared from (S)-2-(disubstituted aminomethyl)pyrrolidine (1a-f).[7)]

Initially, we attempted the asymmetric reaction in tetrahydrofuran (THF) at -78 °C using several diamines 1a-f in order to investigate the effect of the disubstituted aminomethyl group of the diamine 1, and it was found that the best result was obtained when the diamine 1a was used (90% ee). Next, the reaction was carried out at 0 °C using 1a or 1c, and almost the same results were obtained even at 0 °C. (Entries 1,2 and 4,5). These facts are interesting because asymmetric reactions often need to be carried out at low temperature to obtain high selectivities. These results are summarized in Table 1.

Table 1. An Asymmetric Transformation of Cyclohexene Oxide



Entry	Diamine	Temp /°C	Yield/%$^{a)}$	$[\alpha]_D$(c, $CHCl_3$)	ee/%$^{b)}$
1	 (1a)	-78	78	$[\alpha]_D^{18}$ -100.8 ° (0.65)	90
2	1a	0	77	$[\alpha]_D^{20}$ -102.6 ° (0.61)	92
3	 (1b)	-78	71	$[\alpha]_D^{20}$ -90.6 ° (0.46)	81
4	 (1c)	-78	70	$[\alpha]_D^{17}$ -95.9 ° (0.61)	86
5	1c	0	72	$[\alpha]_D^{20}$ -98.9 ° (0.62)	88
6	 (1d)	-78	67	$[\alpha]_D^{17}$ -76.3 ° (0.60)	68
7	 (1e)	-78	69	$[\alpha]_D^{18}$ -93.3 ° (0.61)	83
8	 (1f)	-78	55	$[\alpha]_D^{18}$ -53.0 ° (0.54)	47

a) Isolated yield after benzoylation.

b) Absolute configuration and ee are based on $[\alpha]_D$ -112 ° (c 0.6, $CHCl_3$) for optically pure (S)-2-cyclohexen-1-ol.8)

A typical experimental procedure is as follows; to a THF (10 ml) solution of the diamine 1 (3.3 mmol) was added a hexane (2 ml) solution of butyllithium (3 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 30 min and then cooled to -78 °C (except Entries 2 and 5). Then a THF (5 ml) solution of cyclohexene oxide (2 mmol) was added to the reaction mixture and the reaction temperature was gradually warmed to room temperature. Saturated ammonium chloride solution was added and the reaction mixture was extracted with ether. The organic layer was washed with 2% HCl (10 ml), water, and brine, successively, and dried over anhydrous Na_2SO_4. The solvent was removed and the resulting crude 2-cyclohexen-1-ol was benzoylated with benzoyl chloride (4 mmol) and pyridine (8 mmol) in dichloromethane. After an addition of water and ether, the organic layer was washed with 2 mol dm^{-3} HCl (10 ml), water, and brine.

After drying (anhydrous Na_2SO_4) and evaporation of the solvent *in vacuo*, the oily substance was purified by preparative tlc on silica gel to give 2-cyclohexenyl benzoate. To determine the absolute configuration and ee of the resulting 2-cyclohexen-1-ol, the benzoate was hydrolysed with sodium hydroxide in methanol.$^{9)}$ After usual work-up, 2-cyclohexen-1-ol was purified by Kugelrohr distillation and the optical rotation was measured.

As it is known that the deprotonation of cyclohexene oxide is highly selective for the *syn* proton that occupies the quasiaxial orientation,$^{4)}$ it becomes necessary to be distinguished the equilibrating enantiomeric conformations I and II by chiral lithium amide to obtain optically active 2-cyclohexen-1-ol (Fig. 1).

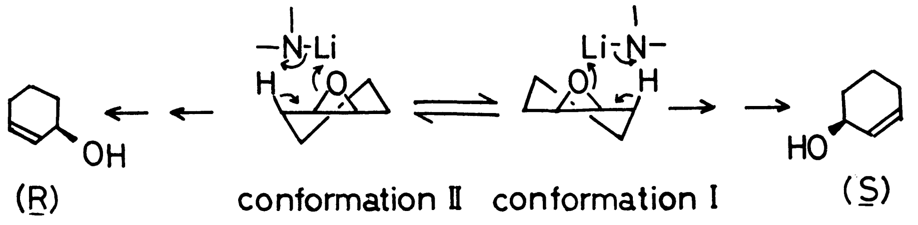


Fig. 1.

In the present study, the selectivity may be accounted for by assuming the cyclic six-membered transition state suggested by Thummel and Rickborn.$^{4)}$ In the transition state A (the conformation of cyclohexene oxide is I), there is no steric interaction between cyclohexane ring and the diamine because the cyclohexane ring is located as being apart from the diamine, by the molecular model study. On the other hand, in the transition state B (the conformation of cyclohexene oxide is II), the steric repulsion arises because the cyclohexane ring is located as being close to the diamine (Fig. 2). Thus, the transition state A is favorable and the alcohol having *S*-configuration is obtained.

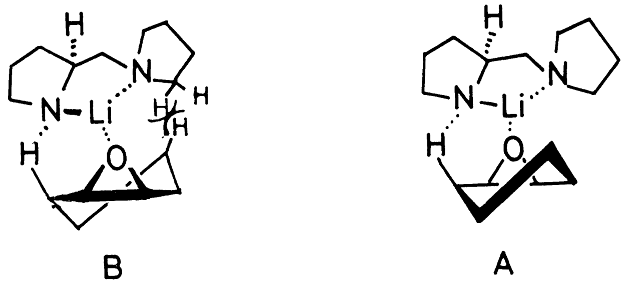


Fig. 2.

It is noteworthy that highly selective deprotonation of enantiotopically related protones was first achieved by using the chiral lithium amide prepared from (*S*)-2-(disubstituted aminomethyl)pyrrolidine, and (*S*)-2-cyclohexen-1-ol, a useful synthetic intermediate for the synthesis of some sesquiterpenes such as (+)-2-carene$^{8)}$ and (4*S*)-*trans*-β-elemenone, was obtained in 92% ee starting from cyclohexene oxide at 0 °C. Further application of this reaction to other symmetrical epoxides and other asymmetric reactions using the chiral lithium amide are now in progress.

This work was partially supported by a Grant in Aid for Scientific Research from the Ministry of Education, Science and Culture (No. 58540302).

References

1) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N.J. (1971); H. B. Kagan and J. C. Fiaud, Top. Stereochem., 10, 175 (1978); D. Valentine and J. W. Scott, Synthesis, 1978, 329; J. W. ApSimon and R. P. Seguin, Tetrahedron, 35, 2797 (1979).

2) Except the reactions using enzymes; U. Eder, G. Sauer, and R. Wiechert, Angew. Chem., Int. Ed. Engl., 10, 496 (1971); Z. G. Hajos and D. R. Parrish, J. Org. Chem., 39, 1615 (1974); E. Fujita, Y. Nagao, K. Seno, S. Takao, T. Miyasaka, M. Kimura, and W. H. Watson, J. Chem. Soc., Perkin Trans. 1, 1981, 914; Y. Nagao, T. Ikeda, M. Yagi, E. Fujita, and M. Shiro, J. Am. Chem. Soc., 104, 2079 (1982); T. Mukaiyama, I. Tomioka, and M. Shimizu, Chem. Lett., 1984, 49.

3) T. Mukaiyama, H. Yamashita, and M. Asami, Chem. Lett., 1983, 385.

4) R. P. Thummel and B. Rickborn, J. Am. Chem. Soc., 92, 2064 (1970).

5) J. K. Whitesell and S. W. Felman, J. Org. Chem., 45, 755 (1980).

6) T. Mukaiyama, Tetrahedron, 37, 4111 (1981) and references cited therein; N. Iwasawa and T. Mukaiyama, Chem. Lett., 1982, 1441; M. Asami and T. Mukaiyama, Chem. Lett., 1983, 93; N. Iwasawa and T. Mukaiyama, Chem. Lett., 1983, 297; R. W. Stevens and T. Mukaiyama, Chem. Lett., 1983, 1799.

7) The diamines 1a-e were easily prepared according to the reported method,11) and 1f was prepared from N-benzyloxycarbonyl-(S)-proline as follows; i)coupling with N-methylaniline using dicyclohexylcarbodiimide, ii)selective reduction of amide to amine with diborane, iii) removal of benzyloxycarbonyl group by catalytic hydrogenolysis.

8) S. Yamada, N. Takamura, and T. Mizoguchi, Chem. Pharm. Bull., 23, 2539 (1975).

9) K. Mashimo and Y. Seno, Tetrahedron, 26, 803 (1970).

10) T. Sato, Y. Gotoh, M. Watanabe, and T. Fujisawa, Chem. Lett., 1983, 1533.

11) T. Sone, K. Hiroi, and S. Yamada, Chem. Pharm. Bull., 21, 2331 (1973).

(Received February 29, 1984)