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Catalytic Enantioselective Deprotonation of *meso*-Epoxides by the Use of Chiral Lithium Amide

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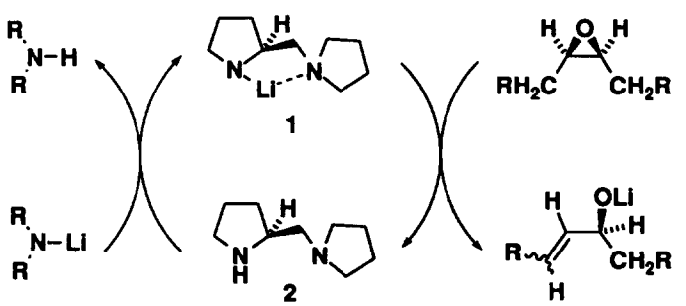
Abstract: Catalytic enantioselective deprotonation of *meso*-compound is achieved for the first time by the combined use of a catalytic amount of chiral lithium amide, lithium (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidide, and excess lithium diisopropylamide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene.

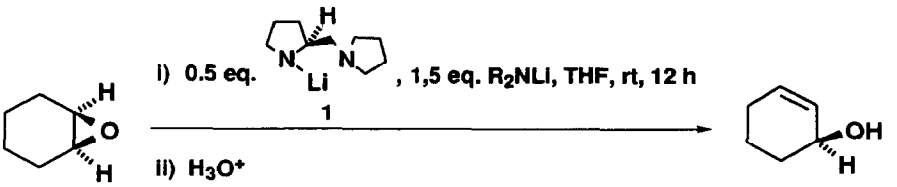
Asymmetric synthesis by the use of chiral lithium amide is emerging as a useful method for the preparation of non-racemic compounds.[1] We have reported the enantioselective transformation of *meso*-epoxides to chiral allylic alcohol derivatives using lithium (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidide (**1**).[2] The reactions, which use chiral lithium amides so far reported, all require more than a stoichiometric amount of chiral auxiliary although the catalytic asymmetric synthesis is of current interest. Here we wish to describe an efficient catalytic enantioselective deprotonation of *meso*-epoxide using chiral lithium amide **1**.

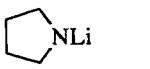
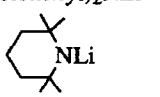
It is necessary to regenerate chiral lithium amide **1** from the resulting chiral diamine, (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**2**), in the reaction mixture in order to achieve the catalytic reaction. As we observed in the course of our investigation using chiral lithium amide **1** that **1** was more reactive toward epoxides than usual lithium amides such as lithium diethylamide or lithium diisopropylamide (LDA), we anticipated that the catalytic cycle shown in Scheme 1 is possible by employing a suitable achiral lithium amide to regenerate **1** in the reaction mixture.



Scheme 1

Table 1. Catalytic Enantioselective Deprotonation of Cyclohexene Oxide



Entry	Achiral Lithium Amide	Additive	Yield/%[a]	ee/%[b]
1[c]	–	DBU	80	81
2	Et_2NLi	–	81	37
3		–	59	37
4	LDA	–	63	48
5	$(cyclohexyl)_2NLi$	–	38	4
6		–	72	2
7	LDA	TMEDA[d]	67	43
8	LDA	HMPA[d]	63	54
9	LDA	DBU[d]	71	61
10	LDA	DBU[e]	79	68
11	LDA	DBU[f]	81	72
12	LDA	DBU[g]	82	74

[a] Isolated yield after benzoylation. [b] Determined by the specific rotation value of 2-cyclohexen-1-ol.[3,5b] [c] Stoichiometric amount of **1** (1.5 equiv) and DBU (1.65 equiv) were used. [d] 2.0 equiv to cyclohexene oxide. [e] 4.0 equiv to cyclohexene oxide. [f] 6.0 equiv to cyclohexene oxide. [g] 10.0 equiv to cyclohexene oxide.

In the first place, asymmetric transformation of cyclohexene oxide was investigated using 0.5 equiv of **1** and 1.5 equiv of various achiral lithium amides in THF at rt for 12 h. As shown in Table 1, regeneration and reuse of chiral lithium amide **1** were realized when lithium diethylamide, lithium pyrrolidide, or LDA was used as the achiral lithium amide (entries 2–4) though the ee of the product was not so high as the case when a stoichiometric amount of **1** was used (entry 1). Hindered lithium amides such as lithium dicyclohexylamide and lithium 2,2,6,6-tetramethylpiperidide gave almost racemic product (entries 5, 6). Thus those bases seemed to be more reactive than lithium amide **1**, and **1** was hardly concerned in the reaction.

Several additives (2.0 equiv to cyclohexene oxide) were examined under the same reaction conditions mentioned above to improve the ee of the product by increasing the difference of the reactivities of **1** and LDA. A cyclic amidine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), was more effective than *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and hexamethylphosphoric triamide (HMPA) similar to the case when stoichiometric amount of **1** was used,[2d] and the ee of the product was increased to 61% (entries 7–9). The ee was further improved by using a large excess of DBU (entries 9–12).

Table 2. Examination of the Molar Ratio of **1** and LDA

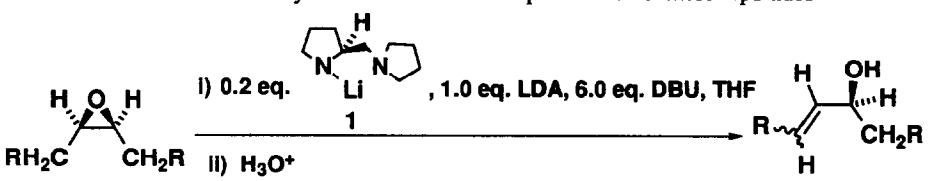
Entry	**1**[a]	LDA[a]	Yield/%[b]	ee/%[c]
1	0.5	1.5	81	72
2	0.33	1.67	83	73
3	0.2	1.8	69	68
4	0.1	1.9	76	68
5	0.05	1.95	65	59
6	0.2	1.0	71	75
7	0.12	1.08	75	69
8	0.06	1.14	61	59

[a] Equivalent to cyclohexene oxide. [b] Isolated yield after benzoylation. [c] Determined by the specific rotation value of 2-cyclohexen-1-ol.[5b]

Next, the reaction was examined with various molar ratios of **1** : LDA (1 : 3 – 1 : 39) using 2.0 equiv of the total amount of lithium amide and 6.0 equiv of DBU to make this catalytic system more effective (Table 2, entries 1–5). It is remarkable that almost the same selectivity was obtained in the molar ratio range of **1** : LDA between 1 : 3 – 1 : 19. The selectivity was further increased to 75% ee by decreasing the total amount of lithium amide to 1.2 equiv in the presence of 6.0 equiv of DBU (Table 2, entries 6).

The catalytic system was then applied to (Z)-4-octene oxide and cyclooctene oxide using 0.2 equiv of **1**, 1.0 equiv of LDA and 6.0 equiv of DBU in THF. The catalytic reaction proceeded without significant loss of the selectivity as shown in Table 3.

Table 3. Catalytic Enantioselective Deprotonation of *meso*-Epoxides



Epoxide	Reaction Conditions	Yield/%	ee/%[a]
(Z)-4-octene oxide	rt, 3 days	54[b] (66)[c]	60 (60)[c]
cyclooctene oxide	rt, 3 days	27[d] (45)[c]	54 (58)[c]
cyclooctene oxide	refl., 7 h	86[d] (84)[c]	45 (50)[c]

[a] Determined by ^{1}H-NMR of the corresponding acetate in the presence of Eu(hfc)$_3$.[2d] [b] Isolated yield after benzoylation. [c] Data in parentheses are the results obtained by using 1.5 equiv of **1** and 1.65 equiv of DBU.[2d] [d] Isolated yield of the alcohol.

It is noteworthy that the first catalytic enantioselective deprotonation of *meso*-compounds was achieved effectively in the reaction of chiral lithium amide **1** and *meso*-epoxides by the combined use of a catalytic amount of the chiral auxiliary and excess LDA in the presence of DBU.

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3. In the previous papers,[2a,c,d] we determined the ee of 2-cyclohexen-1-ol based on the optical rotation value reported in the literature ($[\alpha]_D^{20}$ −112 (*c* 0.6, $CHCl_3$)).[4] As the optical rotation values of high ee of 2-cyclohexen-1-ol confirmed by ^{1}H-NMR of the corresponding MTPA ester ($[\alpha]_D$ −125 (*c* 6.4, $CHCl_3$))[5a] or HPLC of the precursor ($[\alpha]_D$ +130.6 (*c* 1.21, $CHCl_3$))[5b] were reported recently, we also examined ^{1}H-NMR study by deriving our sample ($[\alpha]_D^{18}$ −105.2 (*c* 0.61, $CHCl_3$) obtained in entry 1 in Table 1) to MTPA ester. The ee was 80–83% which was in good accordance with the reported value,[5b] therefore the ee's of the other samples were determined based on the optical rotation ($[\alpha]_D$ +130.6 (*c* 1.21, $CHCl_3$) for >99% ee of (*R*)-2-cyclohexen-1-ol).

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6. Representative experimental procedure is described for entry 6 in Table 2: To (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (62 mg, 0.4 mmol) and diisopropylamine (202 mg, 2.0 mmol) in THF (10 ml) was added a hexane solution of butyllithium (1.6 ml, 2.4 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred at 0 °C for 0.5 h and THF (6 ml) solution of DBU (1.815 g, 12 mmol) was added to the reaction mixture at 0 °C. After stirring at 0 °C for 0.5 h, cyclohexene oxide (196 mg, 2.0 mmol) in THF (6 ml) was added to the reaction mixture at 0 °C. The reaction temperature was warmed to room temperature and then stirring was continued at the temperature for 12 h. Saturated ammonium chloride solution and ether were added to the reaction mixture. The organic layer was washed successively with 1 M HCl and brine and dried over anhyd $MgSO_4$. The solvent was removed at atmospheric pressure and the resulting crude 2-cyclohexen-1-ol was benzoylated with benzoyl chloride (3.4 mmol) and pyridine (3.4 mmol) in dichloromethane (10 ml) for 2 h. After addition of water and ether, the organic layer was washed with 1 M HCl and brine. After drying (anhyd $MgSO_4$) and evaporation of the solvent *in vacuo*, the oily substance was purified by column chromatography (silicagel/hexane:ether=10:1) to give 2-cyclohexenyl benzoate (288 mg, 71 %). Then the resulting 2-cyclohexenyl benzoate was hydrolyzed with sodium hydroxide (0.4 g, 10 mmol) in methanol (10 ml) by stirring overnight at room temperature. After removal of the methanol at atmospheric pressure, ether and water were added to the mixture. The organic layer was washed with water and brine, then dried over anhyd $MgSO_4$. The solvent was removed at atmospheric pressure, and resulting crude 2-cyclohexen-1-ol was purified by bulb-to-bulb distillation (150 °C/20 mmHg); $[\alpha]_D^{25}$ −97.3 (*c* 0.96, $CHCl_3$).

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